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CONFIRMATION NO. 9254

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PATREA L. PABST
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400 COLONY SQUARE
SUITE 1200
ATLANTA, GA 30361

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PATENT DEPT.

FILING RECEIPT

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Receipt is acknowledged of this provisional Patent Application. It will not be examined for patentability and will become abandoned not later than twelve months after its filing date. Be sure to provide the U.S. APPLICATION NUMBER, FILING DATE, NAME OF APPLICANT, and TITLE OF INVENTION when inquiring about this application. Fees transmitted by check or draft are subject to collection. Please verify the accuracy of the data presented on this receipt. **If an error is noted on this Filing Receipt, please write to the Office of Initial Patent Examination's Filing Receipt Corrections, facsimile number 703-746-9195. Please provide a copy of this Filing Receipt with the changes noted thereon. If you received a "Notice to File Missing Parts" for this application, please submit any corrections to this Filing Receipt with your reply to the Notice. When the USPTO processes the reply to the Notice, the USPTO will generate another Filing Receipt incorporating the requested corrections (if appropriate).**

Applicant(s)

Nachiappan Chidambaram, High Point, NC;
Aqeel A. Fatmi, Greensboro, NC;

Power of Attorney: The patent practitioners associated with Customer Number 23579.

If Required, Foreign Filing License Granted: 03/23/2005

The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is US60/659,679

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Non-Publication Request: No

Early Publication Request: No

Title

Solvent system for enhancing the solubility of pharmaceutical agents

Docketed for
By: QS
Date: 4-5-05

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Title 35, United States Code, Section 184
Title 37, Code of Federal Regulations, 5.11 & 5.15

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ASSIGNMENT

We, Nachiappan Chidambaram of 4001 River Pointe Place, Apt. 3D, High Point, North Carolina 27265, and Aqeel A. Fatmi of 3809 Camden Falls Court, Greensboro, North Carolina 27410, in consideration of ten dollars and other valuable consideration paid to us by Banner Pharmacaps, Inc., a corporation of the State of Delaware, having its principal place of business at 4125 Premier Drive, High Point, North Carolina 27265 (hereinafter "said Assignee"), the receipt of which is hereby acknowledged, do hereby sell, assign and transfer unto said Assignee, its successors and assigns, the entire interest for the United States of America, and its territories and all foreign countries and jurisdictions, including all rights of priority under the International Convention for the Protection of Industrial Property, in a certain invention or improvement in *"SOLVENT SYSTEM FOR ENHANCING THE SOLUBILITY OF PHARMACEUTICAL AGENTS"* described in U.S. Serial No. 60/659,679 filed in the United States Patent and Trademark Office on March 8, 2005, by Nachiappan Chidambaram and Aqeel Fatmi, and in all Letters Patent of the United States and its territories and all foreign countries and jurisdictions which may or shall be granted on said invention, or any parts thereof, or on said application, or any provisional, divisional, continuation, continuation-in-part, reissue, or other applications based in whole or in part thereon. And we agree, for ourselves and our executors and administrators, with said Assignee and its successors and assigns, but at its or their expense or charges, hereafter to execute all applications, amended specifications, deeds or other instruments, and to do all acts necessary or proper to secure the grant of Letters Patent in the United States and its territories and in all other foreign countries and jurisdictions to said Assignee, with specifications and claims in such form as shall be approved by the counsel of said Assignee, and to vest and confirm in said Assignee, its successors and assigns, the legal title to all such patents.

Title: *"SOLVENT SYSTEM FOR ENHANCING THE SOLUBILITY OF PHARMACEUTICAL AGENTS"*
By: Nachiappan Chidambaram and Aqeel A. Fatmi
Filed: March 8, 2005
ASSIGNMENT

And we do hereby authorize and request the Commissioner of Patents and Trademarks of the United States to issue such Letters Patent as shall be granted upon said application or applications based thereon to said Assignee, its successors and assigns.

WITNESS my hand and seal this 23rd **day of** March **, 2005.**

Nachiappan Chidambaram

State **of** North Carolina)
County of Guilford)

Then personally appeared the above named Nachiappan Chidambaram and acknowledged the foregoing instrument to be his/her free act and deed, before me this 23rd **day of** March **, 2005.**

Notary Public

My Commission expires: 6/25/2006

OPHELIA M. MOORE NOTARY PUBLIC GUILFORD COUNTY, NC

Title: *"SOLVENT SYSTEM FOR ENHANCING THE SOLUBILITY OF PHARMACEUTICAL AGENTS"*
By: Nachiappan Chidambaram and Aqeel A. Fatmi
Filed: March 8, 2005
ASSIGNMENT

WITNESS my hand and seal this 21st **day of** March **, 2005.**

Aqeel A. Fatmi

State **of** North Carolina)
County of Randolph)

Then personally appeared the above named Aqeel A. Fatmi and acknowledged the foregoing instrument to be his/her free act and deed, before me this 21st **day of** March **, 2005.**

Phyllis E. Harden
Notary Public

My Commission expires: July 29, 2009

PCT/US06/07788

SOLVENT SYSTEM FOR ENHANCING THE SOLUBILITY OF PHARMACEUTICAL AGENTS

FIELD OF THE INVENTION

This invention is in the field of fill materials encapsulated in soft gelatin capsules.

This application claims priority under 35 U.S.C. 119 to U.S.S.N. 60/659,679 filed March 8, 2005.

BACKGROUND OF THE INVENTION

Filled one-piece soft gelatin capsules ("softgels") have been widely used for years to encapsulate consumable materials such as vitamins and pharmaceuticals in a liquid vehicle or carrier. Because softgels have properties which are quite different from two-piece hardshell capsules, softgels are more capable of retaining a liquid fill material.

Not all liquids may be enclosed in a softgel capsule. Liquids containing more than about 20% water by weight are generally not enclosed in softgels, because the water tends to dissolve the gelatin shell. Other solvents such as propylene glycol, glycerin, low molecular weight alcohols, ketones, acids, amines, and esters all tend to degrade or dissolve the gelatin shell to some extent.

Softgels are also somewhat sensitive to pH, and generally require a pH in the encapsulated liquid from about 2.5 to about 7.5. Highly acidic liquids may hydrolyze the gelatin, resulting in leaks, while basic liquids may tan the gelatin, resulting in decreased solubility of the gelatin shell.

Pharmaceutical liquids are usually enclosed in softgels as either viscous solutions or suspensions. Suspensions are pharmaceutically less desirable because they can settle during manufacture, which leads to a less uniform product. In contrast, solutions provide the best liquid form for obtaining optimal "content uniformity" in a batch. Further, solutions typically provide a faster and more uniform absorption of an active agent than do suspensions.

Suitable softgel solutions, however, can be difficult to achieve. One constraint is size. Many pharmaceutical agents require volumes of solvent

too large to produce a softgel capsule small enough to be taken by patients. The solvent must also have sufficient solvating power to dissolve a large amount of the pharmaceutical agent to produce a concentrated solution and yet not dissolve, hydrolyze or tan the gelatin shell.

Concentrated solutions of pharmaceutical agents for use in softgel capsules have been described. Most of these systems involve ionizing the free pharmaceutical agent *in situ* to the corresponding salt. For example, U.S. Patent No. 5,360,615 to Yu *et al.* discloses a solvent system for enhancing the solubility of acidic, basic, or amphoteric pharmaceutical agents. The solvent system comprises polyethylene glycol, an ionizing agent, and water. The ionizing agent functions by causing the partial ionization of the free pharmaceutical agent. U.S. Patent No. 6,383,515, U.S. Patent Application Publication No. 2002/0187195, and U.S. Patent Application Publication No. 2001/0007668 to Sawyer *et al.* discloses pharmaceutically acceptable solutions containing a medicament suitable for filling softgel capsules comprising a polymer such as polyethylene glycol and an acid salt of a compound having three or more carbon atoms, such as sodium propionate. The salt helps to ionize the medicament without relying on the use of strong acids or bases. U.S. Patent No. 6,689,382 to Berthel *et al.* describes a pharmaceutical formulation suitable for filling softgel capsules comprising (a) a therapeutically effective amount of a non-steroidal anti-inflammatory drug (NSAID); and (b) a solvent system comprising 40% to 60% by weight a polyoxyethylene ether, 15% to 35% by weight of glycerin and 15% to 35% by weight water. In cases where the NSAID has a carboxyl or an acidic functional group, the solvent system also includes hydroxide ions. U.S. Patent No. 5,505,961 to Shelley *et al.* describes a method for increasing the solubility of acetaminophen alone or in combination with other pharmaceutically active agents to form a clear solution for encapsulation into a softgel capsule. The method comprises solubilizing acetaminophen in a mixture of propylene glycol, polyethylene glycol, water, polyvinylpyrrolidone and sodium or potassium acetate.

The previously described methods all involve the conversion of the free pharmaceutical agent to the corresponding salt. In cases where the free pharmaceutical agent is acidic, the resulting anion can react with the polyethylene glycol in the fill to produce polyethylene glycol esters, thus reducing the amount of available pharmaceutical agent.

There is a need for a solvent system containing a medicament, which can be encapsulated in a softgel capsule, wherein the formation of PEG esters is minimized.

Therefore it is an object of the invention to provide a stable solvent system for pharmaceutical agents, which is suitable for encapsulation in a softgel capsule, wherein the formation of PEG esters is minimized.

BRIEF SUMMARY OF THE INVENTION

Liquid and semi-solid pharmaceutical compositions, which can be administered in liquid form or can be used for preparing capsules, are described herein. The composition comprises the salt of one or more active agents, and 0.2-1.0 mole equivalents of a de-ionizing agent per mole of active agent. The pH of the composition is adjusted within the range of 2.5 – 7.5. The de-ionizing agent causes partial de-ionization (neutralization) of the salt of the active agent resulting in enhanced bioavailability of salts of weakly acidic, basic or amphoteric active agents as well as decreased amounts of polyethylene glycol (PEG) esters.

DETAILED DESCRIPTION OF THE INVENTION

I. Composition

A. Fill Materials

1. Drugs to be Formulated

The formulation can contain any therapeutic, diagnostic, prophylactic or nutraceutical agent. Exemplary agents include, but are not limited to, analeptic agents; analgesic agents; anesthetic agents; antiasthmatic agents; antiarthritic agents; anticancer agents; anticholinergic agents; anticonvulsant agents; antidepressant agents; antidiabetic agents; antidiarrheal agents; antiemetic agents; antihelminthic agents; antihistamines; antihyperlipidemic agents; antihypertensive agents; anti-infective agents; anti-inflammatory

agents; antimigraine agents; antineoplastic agents; antiparkinson drugs; antipruritic agents; antipsychotic agents; antipyretic agents; antispasmodic agents; antitubercular agents; antiulcer agents; antiviral agents; anxiolytic agents; appetite suppressants (anorexic agents); attention deficit disorder and attention deficit hyperactivity disorder drugs; cardiovascular agents including calcium channel blockers, antianginal agents, central nervous system ("CNS") agents, beta-blockers and antiarrhythmic agents; central nervous system stimulants; diuretics; genetic materials; hormonolytics; hypnotics; hypoglycemic agents; immunosuppressive agents; muscle relaxants; narcotic antagonists; nicotine; nutritional agents; parasympatholytics; peptide drugs; psychostimulants; sedatives; sialagogues, steroids; smoking cessation agents; sympathomimetics; tranquilizers; vasodilators; beta-agonist; and tocolytic agents.

A first class of drugs is selected based on inclusion in the molecule of a weakly acidic, basic or amphoteric group that can form a salt. Any drug that bears an acidic or a basic functional group, for example, an amine, imine, imidazoyl, guanidine, piperidinyl, pyridinyl, quaternary ammonium, or other basic group, or a carboxylic, phosphoric, phenolic, sulfuric, sulfonic or other acidic group, can react with the de-ionizing agent.

Some specific drugs that bear acidic or basic functional groups and thus may be converted to the corresponding salt for use in the described formulations include, but are not limited to, Acetaminophen, Acetylsalicylic acid, Alendronic acid, Alosetron, Amantadine, Amlopidine, Anagrelide, Argatroban, Atomoxetine, Atrovastatin, Azithromycin dehydrate, Balsalazide, Bromocriptan, Bupropion, Candesartan, Carboplatin, Ceftriaxone, Clavulonic acid, Clindamycin, Cimetadine, Dehydrocholic (acid), Dexmethylphenidate, Diclofenac, Dicyclomine, Diflunisal, Diltiazem, Donepezil, Doxorubicin, Doxepin, Epirubicin, Etodolic acid, Ethacrynic acid, Fenoprofen, Fluoxetine, Flurbiprofen, Furosemide, Gemfibrozil, Hydroxyzine, Ibuprofen, Imipramine, Indomethacin, Ketoprofen, Levothyroxine, Maprolitline, Meclizine, Methadone, Methylphenidate, Minocycline, Mitoxantone, Moxifloxacin, Mycophenolic

acid, Naproxen, Niflumic acid, Ofloxacin, Ondansetron, Pantoprazole, Paroxetine, Pergolide, Pramipexole, Phenytoin, Pravastain, Probenecid, Rabeprazole, Risedronic acid, Retinoic acid, Ropinirole, Selegiline, Sulindac, Tamsulosin, Telmisertan, Terbinafine, Theophyline, Tiludronic Acid, Tinzaparin, Ticarcillin, Tometin, Valproic acid, Salicylic acid, Sevelamer, Ziprasidone, Zoledronic acid, Acetophenazine, Albuterol, Almotriptan, Amitriptyline, Amphetamine, Atracurium, Beclomethasone, Benztropine, Biperiden, Bosentan, Bromodiphenhydramine, Brompheniramine carbinoxamine, Caffeine, Capecitabine, Carbergoline, Cetirizine, Chlocylizine, Chlorpheniramine, Chlorphenoxamine, Chlorpromazine, Citalopram, Clavunate potassium, Ciprofloxacin, Clemastine, Clomiphene, Clonidine, Clopidogrel, Codeine, Cyclizine, Cyclobenzaprine, Cyproheptadine, Delavirdine, Diethylpropion, Divalproex, Desipramine, Dexmethylphenidate, Dexbrompheniramine, Dexchlopheniramine, Dexchlor, Dextroamphetamine, Dexedrine, Dextromethorphan, Fiflunisal, Diphemanil methylsulphate, Diphenhydramine, Dolasetron, Doxylamine, Enoxaparin, Ergotamine, Ertepenem, Eprosartan, Escitalopram, Esomeprazole, Fenoldopam, Fentanyl, Fexofenadine, Flufenamic acid, Fluvastatin, Fluphenazine, Fluticasone, Fosinopril, Frovatriptan, Gabapentin, Galatamine, Gatifloxacin, Gemcitabine, Haloperidol, Hyalurondate, Hydrocodone, Hydroxychloroquine, Hyoscyamine, Imatinib, Imipenem, Ipatropin, Lisinopril, Leuprolide, Levopropoxyphene, Losartan, Meclofenamic acid, Mefanamic acid, Mesalamine, Mepenzolate, Meperidine, Mephentermine, Mesalimine, Mesoridazine, Metaproteranol, Metformin, Methdialazine, Methscopolamine, Methysergide, Metoprolol, Metronidazole, Mibefradil, Montelukast, Morphine, Mometasone, Naratriptan, Nelfinavir, Nortriptylene, Noscapine, Nylindrin, Omeprazole, Orphenadrine, Oseltamivir, Oxybutynin, Papaverine, Pentazocine, Phendimetrazine, Phentermine, Pioglitazone, Pilocarpine, Prochloroperazine, Pyrilamine, Quetapine, Ranitidine, Rivastigmine, Rosiglitazone, Salmetrol, Sertaline, Sotalol, Sumatriptan, Tazobactam, Tacrolimus, Tamoxifen, Ticlopidine, Topiramate, Tolterodine,

Triptorelin, Triplennamine, Triprolidine, Tramadol, Trovofloxacin, Ursodiol, Promazine, Propoxyphene, Propanolol, Pseudoephedrine, Pyrilamine, Quinidine, Oxybate sodium, Sermorelin, Tacrolimus, Tegaseroid, Teriparatide, Tolterodine, Triptorelin pamoate, Scoplolamine, Venlafaxine, Zamivir, Aminocaproic acid, Aminosalicylic acid, Hydromorphone, Isosuprine, Levorphanol, Melhalan, Nalidixic acid, and Para-aminosalicylic acid.

2. Deionizing Agent

The deionizing agent functions by causing partial deionization (neutralization) of the salt of one or more pharmaceutically active agents. When the active agent is the salt of a weak acid and a strong base, the deionizing agent is preferably a hydrogen ion species. When the active agent is the salt of a weak base and a strong acid, the deionizing agent is preferably a hydroxide ion species. The deionizing agent is preferably present in an amount between 0.2 to 1.0 mole equivalents per mole of the pharmaceutically active agent.

Exemplary hydrogen ion species useful as de-ionizing agents described herein, include, but are not limited to, hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, fumaric acid, maleic acid, tartaric acid, methane-, ethane-, and benzene sulfonates, citric acid, malic acid, acetic acid, proprionic acid, pyruvic acid, butanoic acid, and lactic acid.

Exemplary hydroxide ion species useful as de-ionizing agents described herein, include, but are not limited to, metal hydroxides such as sodium hydroxide, potassium hydroxide, ammonium hydroxide, calcium hydroxide, aluminum hydroxide, and magnesium hydroxide.

Additional acid or base can be added to adjust the pH of the fill composition. In a preferred embodiment, the pH of the fill composition is from about 2.5 to about 7.5.

3. Excipients

Formulations may be prepared using a pharmaceutically acceptable carrier composed of materials that are considered safe and effective and may be administered to an individual without causing undesirable biological side

effects or unwanted interactions. The carrier is all components present in the pharmaceutical formulation other than the active ingredient or ingredients. As generally used herein "carrier" includes, but is not limited to, plasticizers, crystallization inhibitors, wetting agents, bulk filling agents, solubilizers, bioavailability enhancers, solvents, pH-adjusting agents and combinations thereof.

In a preferred embodiment, a mixture of polyethylene glycol and water is used as a solvent for the salt of the active agent and the de-ionizing agent. Polyethylene glycol is present in an amount from about 10% to about 80% by weight. Water is present in an amount from about 1% to 18% by weight. The molecular weight of polyethylene glycol is between 300 and 1500. Other suitable solvents include surfactants and copolymers of polyethylene glycol. Optionally, glycerin, polyvinyl pyrrolidone (PVP) or propylene glycol (PPG) can be added to enhance the solubility of the drug agent.

B. Shell Composition

1. Gelatin

Gelatin is the product of the partial hydrolysis of collagen. Gelatin is classified as either Type A or Type B gelatin. Type A gelatin is derived from the acid hydrolysis of collagen while Type B gelatin is derived from alkaline hydrolysis of collagen. Traditionally, bovine bones and skins have been used as raw materials for manufacturing Type A and Type B gelatin while porcine skins have been used extensively for manufacturing Type A gelatin. In general acid-processed gelatins form stronger gels than lime-processed gelatins of the same average molecular weight.

2. Other Shell Additives

Other suitable shell additives include plasticizers, opacifiers, colorants, humectants, preservatives, flavorings, and buffering salts and acids.

Plasticizers are chemical agents added to gelatin to make the material softer and more flexible. Suitable plasticizers include glycerin, sorbitol

solutions which are mixtures of sorbitol and sorbitan, and other polyhydric alcohols such as propylene glycol and maltitol or combinations thereof.

Opacifiers are used to opacify the capsule shell when the encapsulated active agents are light sensitive. Suitable opacifiers include titanium dioxide, zinc oxide, calcium carbonate and combinations thereof.

Colorants can be used to for marketing and product identification/differentiation purposes. Suitable colorants include synthetic and natural dyes and combinations thereof.

Humectants can be used to suppress the water activity of the softgel. Suitable humectants include glycerin and sorbitol, which are often components of the plasticizer composition. Due to the low water activity of dried, properly stored softgels, the greatest risk from microorganisms comes from molds and yeasts. For this reason, preservatives can be incorporated into the capsule shell. Suitable preservatives include alkyl esters of p-hydroxy benzoic acid such as methyl, ethyl, propyl, butyl and heptyl (collectively known as "parabens") or combinations thereof.

Flavorings can be used to mask unpleasant odors and tastes of fill formulations. Suitable flavorings include synthetic and natural flavorings. The use of flavorings can be problematic due to the presence of aldehydes which can cross-link gelatin. As a result, buffering salts and acids can be used in conjunction with flavorings that contain aldehydes in order to inhibit cross-linking of the gelatin.

II. Method of Making

A. Fill Material

The fill material is prepared by mixing the agent (such as a salt of the drug), the deionizing agent, water, and polyethylene glycol at a temperature of 50°C to 70°C. The resulting solution is encapsulated using the appropriate gel mass. The pharmaceutical agent is present in an amount from about 10% to about 50% by weight. The deionizing agent is present in an amount from about 0.2 to 1.0 mole per mole of the pharmaceutical agent. Water is present in an amount from about 1% to about 20% by weight and polyethylene glycol is present in amount from about 10% to about 80% by weight.

Optionally, propylene glycol and/or polyvinyl pyrrolidone are present in an amount from about 1% to about 10%.

B. Gel Mass

The main ingredients of the softgel capsule shell are gelatin, plasticizer, and purified water. Typical gel formulations contain (w/w) 40-50% gelatin, 20-30% plasticizer, and 30-40% purified water. Most of the water is subsequently lost during capsule drying. The ingredients are combined to form a molten gelatin mass using either a cold melt or a hot melt process. The prepared gel masses are transferred to preheated, temperature-controlled, jacketed holding tanks where the gel mass is aged at 50-60°C until used for encapsulation.

1. Cold Melt Process

The cold melt process involves mixing gelatin with plasticizer and chilled water and then transferring the mixture to a jacket-heated tank. Typically, gelatin is added to the plasticizer at ambient temperature (18-22°C). The mixture is cooked (57-95°C) under vacuum for 15-30 minutes to a homogeneous, deaerated gel mass. Additional shell additives can be added to the gel mass at any point during the gel manufacturing process or they may be incorporated into the finished gel mass using a high torque mixer.

2. Hot Melt Process

The hot melt process involves adding, under mild agitation, the gelatin to a preheated (60-80°C) mixture of plasticizer and water and stirring the blend until complete melting is achieved. While the hot melt process is faster than the cold melt process, it is less accurately controlled and more susceptible to foaming and dusting.

C. Softgel Capsule

Softgel capsules are typically produced using a rotary die encapsulation process. The gel mass is fed either by gravity or through positive displacement pumping to two heated (48-65°C) metering devices. The metering devices control the flow of gel into cooled (10-18°C), rotating casting drums. Ribbons are formed as the cast gel masses set on contact with the surface of the drums.

The ribbons are fed through a series of guide rolls and between injection wedges and the capsule-forming dies. A food-grade lubricant oil is applied onto the ribbons to reduce their tackiness and facilitate their transfer. Suitable lubricants include mineral oil, medium chain triglycerides, and soybean oil. Fill formulations are fed into the encapsulation machine by gravity. In the preferred embodiment, the softgels contain printing on the surface, optionally identifying the encapsulated agent and/or dosage.

III. Method of Use

The softgels may be used to encapsulate a wide range of pharmaceutically active agents, nutritional agents and personal care products. Softgel capsules may be administered orally to a patient to deliver a pharmaceutically active agent.

Examples

In the following examples, the fill material can be prepared by mixing the salt of one or more pharmaceutically active agents, the deionizing agent, water and polyethylene glycol at a temperature of 50°C to 70°C. The resulting solution can be encapsulated in a softgel capsule using the appropriate gel mass.

Example 1. Naproxen Sodium with Acetic Acid as the Deionizing Agent

Fill Material:

Ingredients	% (by weight)
Naproxen Sodium	25.50
Acetic Acid	3.00
PVP	1.85
PEG 400	62.30
Water	7.40

Example 2. Naproxen Sodium with Citric Acid as the Deionizing Agent

Fill Material:

Ingredients	% (by weight)
Naproxen Sodium	25.50
Citric Acid	4.75
PVP	1.85
PEG 400	60.50
Water	7.40

Example 3. Naproxen Sodium with Hydrochloric Acid as the Deionizing Agent

Fill Material:

Ingredients	% (by weight)
Naproxen Sodium	25.50
Hydrochloric Acid	4.72
PVP	1.85
PEG 400	63.52
Water	7.40

Example 4. Naproxen Sodium with Acetic Acid as the Deionizing Agent

Fill Material:

Ingredients	% (by weight)
Naproxen Sodium	25.50
Acetic Acid	3.00
PVP	1.85
PEG 400	31.15
Water	7.40
PEG 600	31.15

Example 5. Naproxen Sodium with Citric Acid as the Deionizing Agent

Fill Material:

Ingredients	% (by weight)
Naproxen Sodium	25.50
Citric Acid	4075
PVP	1.85
PEG 400	30.25
Water	7.40
PEG 600	30.25

Example 6. Naproxen Sodium with Hydrochloric Acid as the Deionizing Agent

Fill Material:

Ingredients	% (by weight)
Naproxen Sodium	25.50
Hydrochloric Acid	4072
PVP	1.85
PEG 400	30.25
Water	7.40
PEG 600	30.25

Example 7. Naproxen Sodium with Lactic Acid as the Deionizing Agent

Fill Material:

Ingredients	% (by weight)
Naproxen Sodium	27.50
Lactic Acid	5.27
Propylene Glycol	2.00
PEG 400	64.64
Water	0.60

Example 8. Naproxen Sodium with Lactic Acid as the Deionizing Agent

Fill Material:

Ingredients	% (by weight)
Naproxen Sodium	25.00
Lactic Acid	0.24-0.35 M
Propylene glycol	2.00
PEG 600.	q.s.

Example 9. Naproxen Sodium with Lactic Acid as the Deionizing Agent

Fill Material:

Ingredients	% (by weight)
Naproxen Sodium	25.00
Lactic Acid	5.00
Propylene glycol	2.00
PEG 600	61.2
PEG 1000	6.80

Example 10. Naproxen Sodium with Lactic Acid as the Deionizing Agent

Fill Material:

Ingredients	% (by weight)
Naproxen Sodium	25.00
Lactic acid	5.00
Propylene glycol	2.00
PEG 600	51.00
PEG 1000	17.00

Example 11. Naproxen Sodium with Lactic Acid as the Deionizing Agent

Fill Material:

Ingredients	% (by weight)
Naproxen Sodium	25.00
Lactic Acid	5.00
Propylene glycol	2.00
PEG 600	34.00
PEG 1000	34.00

Example 12. Naproxen Sodium with Lactic Acid as the Deionizing Agent

Fill Material:

Ingredients	% (by weight)
Naproxen Sodium	25.00
Lactic acid	5.00
Propylene glycol	2.00
PEG 600	17.00
PEG 1000	51.00

It is understood that the disclosed invention is not limited to the particular methodology, protocols, and reagents described as these may vary. It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments only, and is not intended to limit the scope of the present invention which will be limited only by the appended claims.

Unless defined otherwise, all technical and scientific terms used herein have the same meanings as commonly understood by one of skill in the art to which the disclosed invention belongs. Although any methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present invention, the preferred methods, devices, and materials are as described. Publications cited herein and the materials

for which they are cited are specifically incorporated by reference. Nothing herein is to be construed as an admission that the invention is not entitled to antedate such disclosure by virtue of prior invention.

We claim:

1. A pharmaceutical composition comprising

(a) a salt of one or more pharmaceutically active agents; and

(b) a deionizing agent.

2. The composition of claim 1 wherein the pharmaceutically active agent is selected from the group consisting of therapeutically active agents, diagnostic agents, and prophylactic agents.

3. The composition of claim 1 wherein the deionizing agent is present in an
amount from about 0.2 to 1.0 mole equivalents per mole of the pharmaceutically active agent(s).

4. The composition of claim 1 wherein the deionizing agent is selected from the group consisting of hydrogen ion and hydroxide ion.

5. The composition of claim 1 further comprising polyethylene glycol.

6. The composition of claim 5 wherein polyethylene glycol is present in an amount from about 10% to about 80% by weight

7. The composition of claim 5 wherein polyethylene glycol is one or more polyethylene glycols with a molecular weight between 300 and 1500.

8. The composition of claim 1 further comprising water.

9. The composition of claim 8 wherein water is present in an amount from about 1% to about 18% by weight.

10. The composition of claim 1 further comprising one or more excipients.

11. The composition of claim 7 wherein the excipients are selected from the group consisting of plasticizers, crystallization inhibitors, wetting agents, bulk filling agents, solubilizers, bioavailability enhancers, solvents, pH-adjusting agents, dyes, preservatives, solvents, surfactants, and combinations thereof.

12. The composition of claim 11 wherein the solubilizer is selected from the group consisting of glycerin, polyvinylpyrrolidone, propylene glycol and combinations thereof.

13. The composition of claim 12 wherein the solubilizer is present in amount from about 1% to about 10% by weight.

14. A method of making the composition of any of claims 1-13 comprising

(a) mixing the salt of one or more pharmaceutically active agents, and the deionizing agent at an appropriate temperature; and

(b) encapsulating the mixture in a softgel capsule.

15. The method of claim 14 further comprising polyethylene glycol.

16. The method of claim 14 further comprising water.

17. The method of claim 14 wherein the appropriate temperature is from about 50°C to about 70°C.

18. A method of using the composition of any of claims 1-13 comprising

administering to a patient in need thereof the salt of one or more pharmaceutically active agents.

19. A softgel capsule comprising a fill material wherein the fill material comprises

(a) a salt of one or more pharmaceutically active agents; and

(b) a deionizing agent.

20. The capsule of claim 19 wherein the pharmaceutically active agent is selected from the group consisting of therapeutically active agents, diagnostic agents, and prophylactic agents.

21. The capsule of claim 19 wherein the deionizing agent is present in an

amount from about 0.2 to 1.0 mole equivalents per mole of the pharmaceutically active agent(s).

22. The capsule of claim 19 wherein the deionizing agent is selected from the group consisting of hydrogen ion and hydroxide ion.

23. The capsule of claim 19 further comprising polyethylene glycol.

24. The capsule of claim 23 wherein polyethylene glycol is present in an amount from about 10% to about 80% by weight

25. The capsule of claim 23 wherein polyethylene glycol is one or more polyethylene glycols with a molecular weight between 300 and 1500.

26. The capsule of claim 19 further comprising water.

27. The capsule of claim 26 wherein water is present in an amount from about 1% to about 18% by weight.

28. The capsule of claim 19 further comprising one or more excipients.

29. The capsule of claim 28 wherein the excipients are selected from the group consisting of plasticizers, crystallization inhibitors, wetting agents, bulk filling agents, solubilizers, bioavailability enhancers, solvents, pH-adjusting agents, dyes, preservatives, solvents, surfactants, and combinations thereof.

30. The capsule of claim 29 wherein the solubilizer is selected from the group consisting of glycerin, polyvinylpyrrolidone, propylene glycol and combinations thereof.

31. The capsule of claim 29 wherein the solubilizer is present in amount from about 1% to about 10% by weight.

PCT/US06/07788

SOLVENT SYSTEM FOR ENHANCING THE SOLUBILITY OF PHARMACEUTICAL AGENTS

ABSTRACT OF THE DISCLOSURE

Liquid and semi-solid pharmaceutical compositions, which can be administered in liquid form or can be used for preparing capsules, are described herein. The composition comprises the salt of one ore more active agents, polyethylene glycol, 0.2-1.0 mole equivalents of a de-ionizing agent per mole of active agent, and water. The pH of the composition is adjusted within the range of 2.5 – 7.5. The de-ionizing agent causes partial de-ionization (neutralization) of the salt of the active agent resulting in enhanced bioavailability of salts of weakly acidic, basic or amphoteric active agents as well as lesser amounts of polyethylene glycol (PEG) esters.

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(54) Title: SOLVENT SYSTEM FOR ENHANCING THE SOLUBILITY OF PHARMACEUTICAL AGENTS

(57) Abstract: Liquid and semi-solid pharmaceutical compositions, which can be administered in liquid form or can be used for preparing capsules, are described herein. The composition comprises the salt of one ore more active agents, polyethylene glycol, 0.2-1.0 mole equivalents of a de-ionizing agent per mole of active agent, and water. The pH of the composition is adjusted within the range of 2.5 - 7.5. The de-ionizing agent causes partial de- ionization (neutralization) of the salt of the active agent resulting in enhanced bioavailability of salts of weakly acidic, basic or amphoteric active agents as well as lesser amounts of polyethylene glycol (PEG) esters.

WO 2006/096580 A1

SOLVENT SYSTEM FOR ENHANCING THE SOLUBILITY OF PHARMACEUTICAL AGENTS

FIELD OF THE INVENTION

This invention is in the field of fill materials encapsulated in soft gelatin capsules.

This application claims priority under 35 U.S.C. 119 to U.S.S.N. 60/659,679 filed March 8, 2005.

BACKGROUND OF THE INVENTION

Filled one-piece soft gelatin capsules ("softgels") have been widely used for years to encapsulate consumable materials such as vitamins and pharmaceuticals in a liquid vehicle or carrier. Because softgels have properties which are quite different from two-piece hardshell capsules, softgels are more capable of retaining a liquid fill material.

Not all liquids may be enclosed in a softgel capsule. Liquids containing more than about 20% water by weight are generally not enclosed in softgels, because the water tends to dissolve the gelatin shell. Other solvents such as propylene glycol, glycerin, low molecular weight alcohols, ketones, acids, amines, and esters all tend to degrade or dissolve the gelatin shell to some extent.

Softgels are also somewhat sensitive to pH, and generally require a pH in the encapsulated liquid from about 2.5 to about 7.5. Highly acidic liquids may hydrolyze the gelatin, resulting in leaks, while basic liquids may tan the gelatin, resulting in decreased solubility of the gelatin shell.

Pharmaceutical liquids are usually enclosed in softgels as either viscous solutions or suspensions. Suspensions are pharmaceutically less desirable because they can settle during manufacture, which leads to a less uniform product. In contrast, solutions provide the best liquid form for obtaining optimal "content uniformity" in a batch. Further, solutions typically provide a faster and more uniform absorption of an active agent than do suspensions.

Suitable softgel solutions, however, can be difficult to achieve. One constraint is size. Many pharmaceutical agents require volumes of solvent

too large to produce a softgel capsule small enough to be taken by patients. The solvent must also have sufficient solvating power to dissolve a large amount of the pharmaceutical agent to produce a concentrated solution and yet not dissolve, hydrolyze or tan the gelatin shell.

Concentrated solutions of pharmaceutical agents for use in softgel capsules have been described. Most of these systems involve ionizing the free pharmaceutical agent *in situ* to the corresponding salt. For example, U.S. Patent No. 5,360,615 to Yu *et al.* discloses a solvent system for enhancing the solubility of acidic, basic, or amphoteric pharmaceutical agents. The solvent system comprises polyethylene glycol, an ionizing agent, and water. The ionizing agent functions by causing the partial ionization of the free pharmaceutical agent. U.S. Patent No. 6,383,515, U.S. Patent Application Publication No. 2002/0187195, and U.S. Patent Application Publication No. 2001/0007668 to Sawyer *et al.* discloses pharmaceutically acceptable solutions containing a medicament suitable for filling softgel capsules comprising a polymer such as polyethylene glycol and an acid salt of a compound having three or more carbon atoms, such as sodium propionate. The salt helps to ionize the medicament without relying on the use of strong acids or bases. U.S. Patent No. 6,689,382 to Berthel *et al.* describes a pharmaceutical formulation suitable for filling softgel capsules comprising (a) a therapeutically effective amount of a non-steroidal anti-inflammatory drug (NSAID); and (b) a solvent system comprising 40% to 60% by weight a polyoxyethylene ether, 15% to 35% by weight of glycerin and 15% to 35% by weight water. In cases where the NSAID has a carboxyl or an acidic functional group, the solvent system also includes hydroxide ions. U.S. Patent No. 5,505,961 to Shelley *et al.* describes a method for increasing the solubility of acetaminophen alone or in combination with other pharmaceutically active agents to form a clear solution for encapsulation into a softgel capsule. The method comprises solubilizing acetaminophen in a mixture of propylene glycol, polyethylene glycol, water, polyvinylpyrrolidone and sodium or potassium acetate.

The previously described methods all involve the conversion of the free pharmaceutical agent to the corresponding salt. In cases where the free pharmaceutical agent is acidic, the resulting anion can react with the polyethylene glycol in the fill to produce polyethylene glycol esters, thus reducing the amount of available pharmaceutical agent.

There is a need for a solvent system containing a medicament, which can be encapsulated in a softgel capsule, wherein the formation of PEG esters is minimized.

Therefore it is an object of the invention to provide a stable solvent system for pharmaceutical agents, which is suitable for encapsulation in a softgel capsule, wherein the formation of PEG esters is minimized.

BRIEF SUMMARY OF THE INVENTION

Liquid and semi-solid pharmaceutical compositions, which can be administered in liquid form or can be used for preparing capsules, are described herein. The composition comprises the salt of one or more active agents, and 0.2-1.0 mole equivalents of a de-ionizing agent per mole of active agent. The pH of the composition is adjusted within the range of 2.5 – 7.5. The de-ionizing agent causes partial de-ionization (neutralization) of the salt of the active agent resulting in enhanced bioavailability of salts of weakly acidic, basic or amphoteric active agents as well as decreased amounts of polyethylene glycol (PEG) esters.

DETAILED DESCRIPTION OF THE INVENTION

I. Composition

A. Fill Materials

1. Drugs to be Formulated

The formulation can contain any therapeutic, diagnostic, prophylactic or nutraceutical agent. Exemplary agents include, but are not limited to, analeptic agents; analgesic agents; anesthetic agents; antiasthmatic agents; antiarthritic agents; anticancer agents; anticholinergic agents; anticonvulsant agents; antidepressant agents; antidiabetic agents; antidiarrheal agents; antiemetic agents; antihelminthic agents; antihistamines; antihyperlipidemic agents; antihypertensive agents; anti-infective agents; anti-inflammatory

agents; antimigraine agents; antineoplastic agents; antiparkinson drugs; antipruritic agents; antipsychotic agents; antipyretic agents; antispasmodic agents; antitubercular agents; antiulcer agents; antiviral agents; anxiolytic agents; appetite suppressants (anorexic agents); attention deficit disorder and attention deficit hyperactivity disorder drugs; cardiovascular agents including calcium channel blockers, antianginal agents, central nervous system ("CNS") agents, beta-blockers and antiarrhythmic agents; central nervous system stimulants; diuretics; genetic materials; hormonolytics; hypnotics; hypoglycemic agents; immunosuppressive agents; muscle relaxants; narcotic antagonists; nicotine; nutritional agents; parasympatholytics; peptide drugs; psychostimulants; sedatives; sialagogues, steroids; smoking cessation agents; sympathomimetics; tranquilizers; vasodilators; beta-agonist; and tocolytic agents.

A first class of drugs is selected based on inclusion in the molecule of a weakly acidic, basic or amphoteric group that can form a salt. Any drug that bears an acidic or a basic functional group, for example, an amine, imine, imidazoyl, guanidine, piperidinyl, pyridinyl, quaternary ammonium, or other basic group, or a carboxylic, phosphoric, phenolic, sulfuric, sulfonic or other acidic group, can react with the de-ionizing agent.

Some specific drugs that bear acidic or basic functional groups and thus may be converted to the corresponding salt for use in the described formulations include, but are not limited to, Acetaminophen, Acetylsalicylic acid, Alendronic acid, Alosetron, Amantadine, Amlopidine, Anagrelide, Argatroban, Atomoxetine, Atrovastatin, Azithromycin dehydrate, Balsalazide, Bromocriptan, Bupropion, Candesartan, Carboplatin, Ceftriaxone, Clavulonic acid, Clindamycin, Cimetadine, Dehydrocholic (acid), Dexmethylphenidate, Diclofenac, Dicyclomine, Diflunisal, Diltiazem, Donepezil, Doxorubicin, Doxepin, Epirubicin, Etodolic acid, Ethacrynic acid, Fenoprofen, Fluoxetine, Flurbiprofen, Furosemide, Gemfibrozil, Hydroxyzine, Ibuprofen, Imipramine, Indomethacin, Ketoprofen, Levothyroxine, Maprolitline, Meclizine, Methadone, Methylphenidate, Minocycline, Mitoxantone, Moxifloxacin, Mycophenolic

acid, Naproxen, Niflumic acid, Ofloxacin, Ondansetron, Pantoprazole, Paroxetine, Pergolide, Pramipexole, Phenytoin, Pravastain, Probenecid, Rabeprazole, Risedronic acid, Retinoic acid, Ropinirole, Selegiline, Sulindac, Tamsulosin, Telmisertan, Terbinafine, Theophyline, Tiludronic Acid, Tinzaparin, Ticarcillin, Tometin, Valproic acid, Salicylic acid, Sevelamer, Ziprasidone, Zoledronic acid, Acetophenazine, Albuterol, Almotriptan, Amitriptyline, Amphetamine, Atracurium, Beclomethasone, Benztropine, Biperiden, Bosentan, Bromodiphenhydramine, Brompheniramine carbinoxamine, Caffeine, Capecitabine, Carbergoline, Cetirizine, Chlocylizine, Chlorpheniramine, Chlorphenoxamine, Chlorpromazine, Citalopram, Clavunate potassium, Ciprofloxacin, Clemastine, Clomiphene, Clonidine, Clopidogrel, Codeine, Cyclizine, Cyclobenzaprine, Cyproheptadine, Delavirdine, Diethylpropion, Divalproex, Desipramine, Dexmethylphenidate, Dexbrompheniramine, Dexchlopheniramine, Dexchlor, Dextroamphetamine, Dexedrine, Dextromethorphan, Fiflunisal, Diphemanil methylsulphate, Diphenhydramine, Dolasetron, Doxylamine, Enoxaparin, Ergotamine, Ertepenem, Eprosartan, Escitalopram, Esomeprazole, Fenoldopam, Fentanyl, Fexofenadine, Flufenamic acid, Fluvastatin, Fluphenazine, Fluticasone, Fosinopril, Frovatriptan, Gabapentin, Galatamine, Gatifloxacin, Gemcitabine, Haloperidol, Hyalurondate, Hydrocodone, Hydroxychloroquine, Hyoscyamine, Imatinib, Imipenem, Ipatropin, Lisinopril, Leuprolide, Levopropoxyphene, Losartan, Meclofenamic acid, Mefanamic acid, Mesalamine, Mepenzolate, Meperidine, Mephentermine, Mesalimine, Mesoridazine, Metaproteranol, Metformin, Methdialazine, Methscopolamine, Methysergide, Metoprolol, Metronidazole, Mibefradil, Montelukast, Morphine, Mometasone, Naratriptan, Nelfinavir, Nortriptylene, Noscapine, Nylindrin, Omeprazole, Orphenadrine, Oseltamivir, Oxybutynin, Papaverine, Pentazocine, Phendimetrazine, Phentermine, Pioglitazone, Pilocarpine, Prochloroperazine, Pyrilamine, Quetapine, Ranitidine, Rivastigmine, Rosiglitazone, Salmetrol, Sertaline, Sotalol, Sumatriptan, Tazobactam, Tacrolimus, Tamoxifen, Ticlopidine, Topiramate, Tolterodine,

Triptorelin, Triplennamine, Triprolidine, Tramadol, Trovofloxacin, Ursodiol, Promazine, Propoxyphene, Propanolol, Pseudoephedrine, Pyrilamine, Quinidine, Oxybate sodium, Sermorelin, Tacrolimus, Tegaseroid, Teriparatide, Tolterodine, Triptorelin pamoate, Scoplolamine, Venlafaxine, Zamivir, Aminocaproic acid, Aminosalicylic acid, Hydromorphone, Isosuprine, Levorphanol, Melhalan, Nalidixic acid, and Para-aminosalicylic acid.

2. Deionizing Agent

The deionizing agent functions by causing partial deionization (neutralization) of the salt of one or more pharmaceutically active agents. When the active agent is the salt of a weak acid and a strong base, the deionizing agent is preferably a hydrogen ion species. When the active agent is the salt of a weak base and a strong acid, the deionizing agent is preferably a hydroxide ion species. The deionizing agent is preferably present in an amount between 0.2 to 1.0 mole equivalents per mole of the pharmaceutically active agent.

Exemplary hydrogen ion species useful as de-ionizing agents described herein, include, but are not limited to, hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, fumaric acid, maleic acid, tartaric acid, methane-, ethane-, and benzene sulfonates, citric acid, malic acid, acetic acid, proprionic acid, pyruvic acid, butanoic acid, and lactic acid.

Exemplary hydroxide ion species useful as de-ionizing agents described herein, include, but are not limited to, metal hydroxides such as sodium hydroxide, potassium hydroxide, ammonium hydroxide, calcium hydroxide, aluminum hydroxide, and magnesium hydroxide.

Additional acid or base can be added to adjust the pH of the fill composition. In a preferred embodiment, the pH of the fill composition is from about 2.5 to about 7.5.

3. Excipients

Formulations may be prepared using a pharmaceutically acceptable carrier composed of materials that are considered safe and effective and may be administered to an individual without causing undesirable biological side

effects or unwanted interactions. The carrier is all components present in the pharmaceutical formulation other than the active ingredient or ingredients. As generally used herein "carrier" includes, but is not limited to, plasticizers, crystallization inhibitors, wetting agents, bulk filling agents, solubilizers, bioavailability enhancers, solvents, pH-adjusting agents and combinations thereof.

In a preferred embodiment, a mixture of polyethylene glycol and water is used as a solvent for the salt of the active agent and the de-ionizing agent. Polyethylene glycol is present in an amount from about 10% to about 80% by weight. Water is present in an amount from about 1% to 18% by weight. The molecular weight of polyethylene glycol is between 300 and 1500. Other suitable solvents include surfactants and copolymers of polyethylene glycol. Optionally, glycerin, polyvinyl pyrrolidone (PVP) or propylene glycol (PPG) can be added to enhance the solubility of the drug agent.

B. Shell Composition

1. Gelatin

Gelatin is the product of the partial hydrolysis of collagen. Gelatin is classified as either Type A or Type B gelatin. Type A gelatin is derived from the acid hydrolysis of collagen while Type B gelatin is derived from alkaline hydrolysis of collagen. Traditionally, bovine bones and skins have been used as raw materials for manufacturing Type A and Type B gelatin while porcine skins have been used extensively for manufacturing Type A gelatin. In general acid-processed gelatins form stronger gels than lime-processed gelatins of the same average molecular weight.

2. Other Shell Additives

Other suitable shell additives include plasticizers, opacifiers, colorants, humectants, preservatives, flavorings, and buffering salts and acids.

Plasticizers are chemical agents added to gelatin to make the material softer and more flexible. Suitable plasticizers include glycerin, sorbitol

solutions which are mixtures of sorbitol and sorbitan, and other polyhydric alcohols such as propylene glycol and maltitol or combinations thereof.

Opacifiers are used to opacify the capsule shell when the encapsulated active agents are light sensitive. Suitable opacifiers include titanium dioxide, zinc oxide, calcium carbonate and combinations thereof.

Colorants can be used to for marketing and product identification/differentiation purposes. Suitable colorants include synthetic and natural dyes and combinations thereof.

Humectants can be used to suppress the water activity of the softgel. Suitable humectants include glycerin and sorbitol, which are often components of the plasticizer composition. Due to the low water activity of dried, properly stored softgels, the greatest risk from microorganisms comes from molds and yeasts. For this reason, preservatives can be incorporated into the capsule shell. Suitable preservatives include alkyl esters of p-hydroxy benzoic acid such as methyl, ethyl, propyl, butyl and heptyl (collectively known as "parabens") or combinations thereof.

Flavorings can be used to mask unpleasant odors and tastes of fill formulations. Suitable flavorings include synthetic and natural flavorings. The use of flavorings can be problematic due to the presence of aldehydes which can cross-link gelatin. As a result, buffering salts and acids can be used in conjunction with flavorings that contain aldehydes in order to inhibit cross-linking of the gelatin.

II. Method of Making

A. Fill Material

The fill material is prepared by mixing the agent (such as a salt of the drug), the deionizing agent, water, and polyethylene glycol at a temperature of 50°C to 70°C. The resulting solution is encapsulated using the appropriate gel mass. The pharmaceutical agent is present in an amount from about 10% to about 50% by weight. The deionizing agent is present in an amount from about 0.2 to 1.0 mole per mole of the pharmaceutical agent. Water is present in an amount from about 1% to about 20% by weight and polyethylene glycol is present in amount from about 10% to about 80% by weight.

Optionally, propylene glycol and/or polyvinyl pyrrolidone are present in an amount from about 1% to about 10%.

B. Gel Mass

The main ingredients of the softgel capsule shell are gelatin, plasticizer, and purified water. Typical gel formulations contain (w/w) 40-50% gelatin, 20-30% plasticizer, and 30-40% purified water. Most of the water is subsequently lost during capsule drying. The ingredients are combined to form a molten gelatin mass using either a cold melt or a hot melt process. The prepared gel masses are transferred to preheated, temperature-controlled, jacketed holding tanks where the gel mass is aged at 50-60°C until used for encapsulation.

1. Cold Melt Process

The cold melt process involves mixing gelatin with plasticizer and chilled water and then transferring the mixture to a jacket-heated tank. Typically, gelatin is added to the plasticizer at ambient temperature (18-22°C). The mixture is cooked (57-95°C) under vacuum for 15-30 minutes to a homogeneous, deaerated gel mass. Additional shell additives can be added to the gel mass at any point during the gel manufacturing process or they may be incorporated into the finished gel mass using a high torque mixer.

2. Hot Melt Process

The hot melt process involves adding, under mild agitation, the gelatin to a preheated (60-80°C) mixture of plasticizer and water and stirring the blend until complete melting is achieved. While the hot melt process is faster than the cold melt process, it is less accurately controlled and more susceptible to foaming and dusting.

C. Softgel Capsule

Softgel capsules are typically produced using a rotary die encapsulation process. The gel mass is fed either by gravity or through positive displacement pumping to two heated (48-65°C) metering devices. The metering devices control the flow of gel into cooled (10-18°C), rotating casting drums. Ribbons are formed as the cast gel masses set on contact with the surface of the drums.

The ribbons are fed through a series of guide rolls and between injection wedges and the capsule-forming dies. A food-grade lubricant oil is applied onto the ribbons to reduce their tackiness and facilitate their transfer. Suitable lubricants include mineral oil, medium chain triglycerides, and soybean oil. Fill formulations are fed into the encapsulation machine by gravity. In the preferred embodiment, the softgels contain printing on the surface, optionally identifying the encapsulated agent and/or dosage.

III. Method of Use

The softgels may be used to encapsulate a wide range of pharmaceutically active agents, nutritional agents and personal care products. Softgel capsules may be administered orally to a patient to deliver a pharmaceutically active agent.

Examples

In the following examples, the fill material can be prepared by mixing the salt of one or more pharmaceutically active agents, the deionizing agent, water and polyethylene glycol at a temperature of 50°C to 70°C. The resulting solution can be encapsulated in a softgel capsule using the appropriate gel mass.

Example 1. Naproxen Sodium with Acetic Acid as the Deionizing Agent

Fill Material:

Ingredients	**% (by weight)**
Naproxen Sodium	25.50
Acetic Acid	3.00
PVP	1.85
PEG 400	62.30
Water	7.40

Example 2. Naproxen Sodium with Citric Acid as the Deionizing Agent

Fill Material:

Ingredients	% (by weight)
Naproxen Sodium	25.50
Citric Acid	4.75
PVP	1.85
PEG 400	60.50
Water	7.40

Example 3. Naproxen Sodium with Hydrochloric Acid as the Deionizing Agent

Fill Material:

Ingredients	% (by weight)
Naproxen Sodium	25.50
Hydrochloric Acid	4.72
PVP	1.85
PEG 400	63.52
Water	7.40

Example 4. Naproxen Sodium with Acetic Acid as the Deionizing Agent

Fill Material:

Ingredients	% (by weight)
Naproxen Sodium	25.50
Acetic Acid	3.00
PVP	1.85
PEG 400	31.15
Water	7.40
PEG 600	31.15

Example 5. Naproxen Sodium with Citric Acid as the Deionizing Agent

Fill Material:

Ingredients	% (by weight)
Naproxen Sodium	25.50
Citric Acid	4075
PVP	1.85
PEG 400	30.25
Water	7.40
PEG 600	30.25

Example 6. Naproxen Sodium with Hydrochloric Acid as the Deionizing Agent

Fill Material:

Ingredients	% (by weight)
Naproxen Sodium	25.50
Hydrochloric Acid	4072
PVP	1.85
PEG 400	30.25
Water	7.40
PEG 600	30.25

Example 7. Naproxen Sodium with Lactic Acid as the Deionizing Agent

Fill Material:

Ingredients	% (by weight)
Naproxen Sodium	27.50
Lactic Acid	5.27
Propylene Glycol	2.00
PEG 400	64.64
Water	0.60

Example 8. Naproxen Sodium with Lactic Acid as the Deionizing Agent

Fill Material:

Ingredients	% (by weight)
Naproxen Sodium	25.00
Lactic Acid	0.24-0.35 M
Propylene glycol	2.00
PEG 600.	q.s.

Example 9. Naproxen Sodium with Lactic Acid as the Deionizing Agent

Fill Material:

Ingredients	% (by weight)
Naproxen Sodium	25.00
Lactic Acid	5.00
Propylene glycol	2.00
PEG 600	61.2
PEG 1000	6.80

Example 10. Naproxen Sodium with Lactic Acid as the Deionizing Agent

Fill Material:

Ingredients	% (by weight)
Naproxen Sodium	25.00
Lactic acid	5.00
Propylene glycol	2.00
PEG 600	51.00
PEG 1000	17.00

Example 11. Naproxen Sodium with Lactic Acid as the Deionizing Agent

Fill Material:

Ingredients	% (by weight)
Naproxen Sodium	25.00
Lactic Acid	5.00
Propylene glycol	2.00
PEG 600	34.00
PEG 1000	34.00

Example 12. Naproxen Sodium with Lactic Acid as the Deionizing Agent

Fill Material:

Ingredients	% (by weight)
Naproxen Sodium	25.00
Lactic acid	5.00
Propylene glycol	2.00
PEG 600	17.00
PEG 1000	51.00

It is understood that the disclosed invention is not limited to the particular methodology, protocols, and reagents described as these may vary. It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments only, and is not intended to limit the scope of the present invention which will be limited only by the appended claims.

Unless defined otherwise, all technical and scientific terms used herein have the same meanings as commonly understood by one of skill in the art to which the disclosed invention belongs. Although any methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present invention, the preferred methods, devices, and materials are as described. Publications cited herein and the materials

for which they are cited are specifically incorporated by reference. Nothing herein is to be construed as an admission that the invention is not entitled to antedate such disclosure by virtue of prior invention.

We claim:

1. A pharmaceutical composition comprising

(a) a salt of one or more pharmaceutically active agents; and

(b) a deionizing agent.

2. The composition of claim 1 wherein the pharmaceutically active agent is selected from the group consisting of therapeutically active agents, diagnostic agents, and prophylactic agents.

3. The composition of claim 1 wherein the deionizing agent is present in an
amount from about 0.2 to 1.0 mole equivalents per mole of the pharmaceutically active agent(s).

4. The composition of claim 1 wherein the deionizing agent is selected from the group consisting of hydrogen ion and hydroxide ion.

5. The composition of claim 1 further comprising polyethylene glycol.

6. The composition of claim 5 wherein polyethylene glycol is present in an amount from about 10% to about 80% by weight

7. The composition of claim 5 wherein polyethylene glycol is one or more polyethylene glycols with a molecular weight between 300 and 1500.

8. The composition of claim 1 further comprising water.

9. The composition of claim 8 wherein water is present in an amount from about 1% to about 18% by weight.

10. The composition of claim 1 further comprising one or more excipients.

11. The composition of claim 7 wherein the excipients are selected from the group consisting of plasticizers, crystallization inhibitors, wetting agents, bulk filling agents, solubilizers, bioavailability enhancers, solvents, pH-adjusting agents, dyes, preservatives, solvents, surfactants, and combinations thereof.

12. The composition of claim 11 wherein the solubilizer is selected from the group consisting of glycerin, polyvinylpyrrolidone, propylene glycol and combinations thereof.

13. The composition of claim 12 wherein the solubilizer is present in amount from about 1% to about 10% by weight.

14. A method of making the composition of any of claims 1-13 comprising

(a) mixing the salt of one or more pharmaceutically active agents, and the deionizing agent at an appropriate temperature; and

(b) encapsulating the mixture in a softgel capsule.

15. The method of claim 14 further comprising polyethylene glycol.

16. The method of claim 14 further comprising water.

17. The method of claim 14 wherein the appropriate temperature is from about 50°C to about 70°C.

18. A method of using the composition of any of claims 1-13 comprising

administering to a patient in need thereof the salt of one or more pharmaceutically active agents.

19. A softgel capsule comprising a fill material wherein the fill material comprises

(a) a salt of one or more pharmaceutically active agents; and

(b) a deionizing agent.

20. The capsule of claim 19 wherein the pharmaceutically active agent is selected from the group consisting of therapeutically active agents, diagnostic agents, and prophylactic agents.

21. The capsule of claim 19 wherein the deionizing agent is present in an

amount from about 0.2 to 1.0 mole equivalents per mole of the pharmaceutically active agent(s).

22. The capsule of claim 19 wherein the deionizing agent is selected from the group consisting of hydrogen ion and hydroxide ion.

23. The capsule of claim 19 further comprising polyethylene glycol.

24. The capsule of claim 23 wherein polyethylene glycol is present in an amount from about 10% to about 80% by weight

25. The capsule of claim 23 wherein polyethylene glycol is one or more polyethylene glycols with a molecular weight between 300 and 1500.

26. The capsule of claim 19 further comprising water.

27. The capsule of claim 26 wherein water is present in an amount from about 1% to about 18% by weight.

28. The capsule of claim 19 further comprising one or more excipients.

29. The capsule of claim 28 wherein the excipients are selected from the group consisting of plasticizers, crystallization inhibitors, wetting agents, bulk filling agents, solubilizers, bioavailability enhancers, solvents, pH-adjusting agents, dyes, preservatives, solvents, surfactants, and combinations thereof.

30. The capsule of claim 29 wherein the solubilizer is selected from the group consisting of glycerin, polyvinylpyrrolidone, propylene glycol and combinations thereof.

31. The capsule of claim 29 wherein the solubilizer is present in amount from about 1% to about 10% by weight.

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2006/007788

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K9/48

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, EMBASE, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5 360 615 A (YU ET AL) 1 November 1994 (1994-11-01) cited in the application example 8	1-31
X	WO 95/31979 A (R.P. SCHERER INTERNATIONAL CORPORATION; SHELLEY, RICKEY, S; WEI, YOUCH) 30 November 1995 (1995-11-30) page 4, line 1 - line 10 example 8	1-31
X	US 2001/007668 A1 (SAWYER MARYJEAN ET AL) 12 July 2001 (2001-07-12) paragraph [0061]; tables 1-17	1-31
X	US 5 484 606 A (DHABHAR ET AL) 16 January 1996 (1996-01-16) examples	1-31

-/--

[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
28 June 2006	06/07/2006

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Büttner, U

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INTERNATIONAL SEARCH REPORT

International application No
PCT/US2006/007788

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5 912 011 A (MAKINO ET AL) 15 June 1999 (1999-06-15) tables 2,3 -----	1-31
A	US 2004/157928 A1 (KIM JAE-HWAN ET AL) 12 August 2004 (2004-08-12) tables 5c,5d paragraph [0005] -----	1-31

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2006/007788

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 5360615 A	01-11-1994	NONE	
WO 9531979 A	30-11-1995	AU 2517095 A	18-12-1995
US 2001007668 A1	12-07-2001	US 2002187195 A1	12-12-2002
US 5484606 A	16-01-1996	WO 9519792 A1	27-07-1995
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		DE 69222031 D1	09-10-1997
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		EP 1605916 A1	21-12-2005
		WO 2004071490 A1	26-08-2004

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International application number: PCT/US2006/007788

International filing date: 06 March 2006 (06.03.2006)

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Number: 60/659,679
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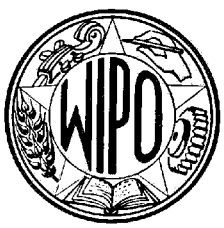
Remark: Priority document submitted or transmitted to the International Bureau in compliance with Rule 17.1(a) or (b)



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April 19, 2006

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APPLICATION NUMBER: *60/659,679*
FILING DATE: *March 08, 2005*
RELATED PCT APPLICATION NUMBER: *PCT/US06/07788*

THE COUNTRY CODE AND NUMBER OF YOUR PRIORITY APPLICATION, TO BE USED FOR FILING ABROAD UNDER THE PARIS CONVENTION, IS *US60/659,679*

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PROVISIONAL APPLICATION FOR PATENT COVER SHEET

This is a request for filing a PROVISIONAL APPLICATION FOR PATENT under 37 CFR 1.53(c).

Express Mail Label No. EV 487328654 US

INVENTOR(S)		
Given Name (first and middle [if any])	Family Name or Surname	Residence (City and either State or Foreign Country)
Nachiappan	Chidambaram	High Point, North Carolina

Additional inventors are being named on the 1 *separately numbered sheets attached hereto*

TITLE OF THE INVENTION (500 characters max):

SOLVENT SYSTEM FOR ENHANCING THE SOLUBILITY OF PHARMACEUTICAL AGENTS

Direct all correspondence to: **CORRESPONDENCE ADDRESS**

☑ The address corresponding to Customer Number: 23579

OR

☐ Firm or Individual Name

Address

City	State	Zip
Country	Telephone	Fax

ENCLOSED APPLICATION PARTS ***(check all that apply)***

☑ Application Data Sheet. See 37 CFR 1.76
☐ CD(s), Number of CDs
☑ Specification *Number of Pages* 19
☑ Other (specify) Return Postcard
☐ Drawing(s) *Number of Sheets* 0

Application Size Fee: If the specification and drawings exceed 100 sheets of paper, the application size fee due is $250 ($125 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).

METHOD OF PAYMENT OF FILING FEES AND APPLICATION SIZE FEE FOR THIS PROVISIONAL APPLICATION FOR PATENT

☐ Applicant claims small entity status. See 37 CFR 1.27.
☐ A check or money order is enclosed to cover the filing fee and application size fee (if applicable).
☐ Payment by credit card. Form PTO-2038 is attached
☑ The Director is hereby authorized to charge the filing fee and application size fee (if applicable) or credit any overpayment to Deposit Account Number: 50-3129. A duplicative copy of this form is enclosed for fee processing.

TOTAL FEE AMOUNT ($) $200.00

The invention was made by an agency of the United States Government or under a contract with an agency of the United States Government.
☑ No.
☐ Yes, the name of the U.S. Government agency and the Government contract number are: _____

SIGNATURE Rivka D. Monheit Date March 8, 2005

TYPED or PRINTED NAME Rivka D. Monheit REGISTRATION NO. 48,731 *(if appropriate)*

TELEPHONE 404-879-2152 Docket Number: BAN 102

USE ONLY FOR FILING A PROVISIONAL APPLICATION FOR PATENT

This collection of information is required by 37 CFR 1.51. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 8 hours to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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First Named Inventor	Nachiappan Chidambaram	Docket Number	BAN 102

INVENTOR(S)/APPLICANT(S)

Given Name (first and middle [if any])	Family or Surname	Residence (City and either State or Foreign Country)
Aqeel	Fatmi	Greensboro, North Carolina

Number 2 of 2

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Title: *"SOLVENT SYSTEM FOR ENHANCING THE SOLUBILITY OF PHARMACEUTICAL AGENTS"*
By: Nachiappan Chidambaram and Aqeel Fatmi
Filed: March 8, 2005

CERTIFICATE OF MAILING UNDER 37 CFR §1.10

I hereby certify that this **PROVISIONAL APPLICATION**, and any documents referred to as attached therein, are being deposited with the United States Postal Service on this date, March 8, 2005, in an envelope as "Express Mail Post Office to Addressee" service under 37 CFR 1.10, Mailing Label Number EV 487328654 US, addressed to Commissioner for Patents, P. O. Box 1450, Alexandria, VA 22313-1450.

Ronna Berman

Date: March 8, 2005

UNITED STATES

PROVISIONAL PATENT APPLICATION

BY

NACHIAPPAN CHIDAMBARAM

AND

AQEEL FATMI

FOR

SOLVENT SYSTEM FOR ENHANCING THE SOLUBILITY OF PHARMACEUTICAL AGENTS

SOLVENT SYSTEM FOR ENHANCING THE SOLUBILITY OF PHARMACEUTICAL AGENTS

FIELD OF THE INVENTION

This invention is in the field of fill materialsencapsulated in soft gelatin capsules.

BACKGROUND OF THE INVENTION

Filled one-piece soft gelatin capsules ("softgels") have been widely used for years to encapsulate consumable materials such as vitamins and pharmaceuticals in a liquid vehicle or carrier. Because softgels have properties which are quite different from two-piece hardshell capsules, softgels are more capable of retaining a liquid fill material.

Not all liquids may be enclosed in a softgel capsule. Liquids containing more than about 20% water by weight are generally not enclosed in softgels, because the water tends to dissolve the gelatin shell. Other solvents such as propylene glycol, glycerin, low molecular weight alcohols, ketones, acids, amines, and esters all tend to degrade or dissolve the gelatin shell to some extent.

Softgels are also somewhat sensitive to pH, and generally require a pH in the encapsulated liquid from about 2.5 to about 7.5. Highly acidic liquids may hydrolyze the gelatin, resulting in leaks, while basic liquids may tan the gelatin, resulting in decreased solubility of the gelatin shell.

Pharmaceutical liquids are usually enclosed in softgels as either viscous solutions or suspensions. Suspensions are pharmaceutically less desirable because they can settle during manufacture, which leads to a less uniform product. In contrast, solutions provide the best liquid form for obtaining optimal "content uniformity" in a batch. Further, solutions typically provide a faster and more uniform absorption of an active agent than do suspensions.

Suitable softgel solutions, however, can be difficult to achieve. One constraint is size. Many pharmaceutical agents require volumes of solvent too large to produce a softgel capsule small enough to be taken by patients. The

solvent must also have sufficient solvating power to dissolve a large amount of the pharmaceutical agent to produce a concentrated solution and yet not dissolve, hydrolyze or tan the gelatin shell.

Concentrated solutions of pharmaceutical agents for use in softgel capsules have been described. Most of these systems involve ionizing the free pharmaceutical agent *in situ* to the corresponding salt. For example, U.S. Patent No. 5,360,615 to Yu *et al.* discloses a solvent system for enhancing the solubility of acidic, basic, or amphoteric pharmaceutical agents. The solvent system comprises polyethylene glycol, an ionizing agent, and water. The ionizing agent functions by causing the partial ionization of the free pharmaceutical agent. U.S. Patent No. 6,383,515, U.S. Patent Application Publication No. 2002/0187195, and U.S. Patent Application Publication No. 2001/0007668 to Sawyer *et al.* discloses pharmaceutically acceptable solutions containing a medicament suitable for filling softgel capsules comprising a polymer such as polyethylene glycol and an acid salt of a compound having 3 or more carbon atoms, such as sodium propionate. The salt helps to ionize the medicament without relying on the use of strong acids or bases. U.S. Patent No. 6,689,382 to Berthel *et al.* describes a pharmaceutical formulation suitable for filling softgel capsules comprising (a) a therapeutically effective amount of a non-steroidal anti-inflammatory drug (NSAID); and (b) a solvent system comprising 40% to 60% by weight a polyoxyethylene ether, 15% to 35% by weight of glycerin and 15% to 35% by weight water. In cases where the NSAID has a carboxyl or an acidic functional group, the solvent system also includes hydroxide ions. U.S. Patent No. 5,505,961 to Shelley *et al.* describes a method for increasing the solubility of acetaminophen alone or in combination with other pharmaceutically active agents to form a clear solution for encapsulation into a softgel capsule. The method comprises solubilizing acetaminophen in a mixture of propylene glycol, polyethylene glycol, water, polyvinylpyrrolidone and sodium or potassium acetate.

The previously described methods all involve the conversion of the free pharmaceutical agent to the corresponding salt. In cases where the free pharmaceutical agent is acidic, the resulting anion can react with the polyethylene glycol in the fill to produce polyethylene glycol esters, thus reducing the amount of available pharmaceutical agent.

There exists a need for a solvent system containing a medicament, which can be encapsulated in a softgel capsule, wherein the formation of PEG esters is minimized.

Therefore it is an object of the invention to provide a stable solvent system for pharmaceutical agents, which is suitable for encapsulation in a softgel capsule, wherein the formation of PEG esters is minimized.

BRIEF SUMMARY OF THE INVENTION

Liquid and semi-solid pharmaceutical compositions, which can be administered in liquid form or can be used for preparing capsules, are described herein. The composition comprises the salt of one or more active agents, and 0.2-1.0 mole equivalents of a de-ionizing agent per mole of active agent. The pH of the composition is adjusted within the range of 2.5 – 7.5. The de-ionizing agent causes partial de-ionization (neutralization) of the salt of the active agent resulting in enhanced bioavailability of salts of weakly acidic, basic or amphoteric active agents as well as decreased amounts of polyethylene glycol (PEG) esters.

DETAILED DESCRIPTION OF THE INVENTION

I. Composition

a. Fill Materials

i. Drugs to be Formulated

Exemplary drug agents useful for forming the composition described herein include, but are not limited to, analeptic agents; analgesic agents; anesthetic agents; antiasthmatic agents; antiarthritic agents; anticancer agents; anticholinergic agents; anticonvulsant agents; antidepressant agents; antidiabetic agents; antidiarrheal agents; antiemetic agents; antihelminthic agents;

antihistamines; antihyperlipidemic agents; antihypertensive agents; anti-infective agents; anti-inflammatory agents; antimigraine agents; antineoplastic agents; antiparkinson drugs; antipruritic agents; antipsychotic agents; antipyretic agents; antispasmodic agents; antitubercular agents; antiulcer agents; antiviral agents; anxiolytic agents; appetite suppressants (anorexic agents); attention deficit disorder and attention deficit hyperactivity disorder drugs; cardiovascular agents including calcium channel blockers, antianginal agents, central nervous system ("CNS") agents, beta-blockers and antiarrhythmic agents; central nervous system stimulants; diuretics; genetic materials; hormonolytics; hypnotics; hypoglycemic agents; immunosuppressive agents; muscle relaxants; narcotic antagonists; nicotine; nutritional agents; parasympatholytics; peptide drugs; psychostimulants; sedatives; sialagogues, steroids; smoking cessation agents; sympathomimetics; tranquilizers; vasodilators; beta-agonist; and tocolytic agents.

A first class of drugs is selected based on inclusion in the molecule of a weakly acidic, basic or amphoteric group that can form a salt. Any drug that bears an acidic or a basic functional group, for example, an amine, imine, imidazoyl, guanidine, piperidinyl, pyridinyl, quaternary ammonium, or other basic group, or a carboxylic, phosphoric, phenolic, sulfuric, sulfonic or other acidic group, can react with the de-ionizing agent.

Some specific drugs that bear acidic or basic functional groups and thus may be converted to the corresponding salt for use in the described formulations include, but are not limited to, Acetaminophen, Acetylsalicylic acid, Alendronic acid, Alosetron, Amantadine, Amlopidine, Anagrelide, Argatroban, Atomoxetine, Atrovastatin, Azithromycin dehydrate, Balsalazide, Bromocriptan, Bupropion, Candesartan, Carboplatin, Ceftriaxone, Clavulonic acid, Clindamycin, Cimetadine, Dehydrocholic (acid), Dexmethylphenidate, Diclofenac, Dicyclomine, Diflunisal, Diltiazem, Donepezil, Doxorubicin, Doxepin, Epirubicin, Etodolic acid, Ethacrynic acid, Fenoprofen, Fluoxetine, Flurbiprofen, Furosemide, Gemfibrozil, Hydroxyzine, Ibuprofen, Imipramine,

Indomethacin, Ketoprofen, Levothyroxine, Maprolitline, Meclizine, Methadone, Methylphenidate, Minocycline, Mitoxantone, Moxifloxacin, Mycophenolic acid, Naproxen, Niflumic acid, Ofloxacin, Ondansetron, Pantoprazole, Paroxetine, Pergolide, Pramipexole, Phenytoin, Pravastain, Probenecid, Rabeprazole, Risedronic acid, Retinoic acid, Ropinirole, Selegiline, Sulindac, Tamsulosin, Telmisertan, Terbinafine, Theophyline, Tiludronic Acid, Tinzaparin, Ticarcillin, Tometin, Valproic acid, Salicylic acid, Sevelamer, Ziprasidone, Zoledronic acid, Acetophenazine, Albuterol, Almotriptan, Amitriptyline, Amphetamine, Atracurium, Beclomethasone, Benztropine, Biperiden, Bosentan, Bromodiphenhydramine, Brompheniramine carbinoxamine, Caffeine, Capecitabine, Carbergoline, Cetirizine, Chlocylizine, Chlorpheniramine, Chlorphenoxamine, Chlorpromazine, Citalopram, Clavunate potassium, Ciprofloxacin, Clemastine, Clomiphene, Clonidine, Clopidogrel, Codeine, Cyclizine, Cyclobenzaprine, Cyproheptadine, Delavirdine, Diethylpropion, Divalproex, Desipramine, Dexmethylphenidate, Dexbrompheniramine, Dexchlopheniramine, Dexchlor, Dextroamphetamine, Dexedrine, Dextromethorphan, Fiflunisal, Diphemanil methylsulphate, Diphenhydramine, Dolasetron, Doxylamine, Enoxaparin, Ergotamine, Ertepenem, Eprosartan, Escitalopram, Esomeprazole, Fenoldopam, Fentanyl, Fexofenadine, Flufenamic acid, Fluvastatin, Fluphenazine, Fluticasone, Fosinopril, Frovatriptan, Gabapentin, Galatamine, Gatifloxacin, Gemcitabine, Haloperidol, Hyalurondate, Hydrocodone, Hydroxychloroquine, Hyoscyamine, Imatinib, Imipenem, Ipatropin, Lisinopril, Leuprolide, Levopropoxyphene, Losartan, Meclofenamic acid, Mefanamic acid, Mesalamine, Mepenzolate, Meperidine, Mephentermine, Mesalimine, Mesoridazine, Metaproteranol, Metformin, Methdialazine, Methscopolamine, Methysergide, Metoprolol, Metronidazole, Mibefradil, Montelukast, Morphine, Mometasone, Naratriptan, Nelfinavir, Nortriptylene, Noscapine, Nylindrin, Omeprazole, Orphenadrine, Oseltamivir, Oxybutynin, Papaverine, Pentazocine, Phendimetrazine, Phentermine, Pioglitazone, Pilocarpine, Prochloroperazine, Pyrilamine, Quetapine, Ranitidine,

Rivastigmine, Rosiglitazone, Salmetrol, Sertaline, Sotalol, Sumatriptan, Tazobactam, Tacrolimus, Tamoxifen, Ticlopidine, Topiramate, Tolterodine, Triptorelin, Triplennamine, Triprolidine, Tramadol, Trovofloxacin, Ursodiol, Promazine, Propoxyphene, Propanolol, Pseudoephedrine, Pyrilamine, Quinidine, Oxybate sodium, Sermorelin, Tacrolimus, Tegaseroid, Teriparatide, Tolterodine, Triptorelin pamoate, Scoplolamine, Venlafaxine, Zamivir, Aminocaproic acid, Aminosalicylic acid, Hydromorphone, Isosuprine, Levorphanol, Melhalan, Nalidixic acid, and Para-aminosalicylic acid.

ii. Deionizing Agent

The deionizing agent functions by causing partial deionization (neutralization) of the salt of one or more pharmaceutically active agents. When the active agent is the salt of a weak acid and a strong base, the deionizing agent is preferably a hydrogen ion species. When the active agent is the salt of a weak base and a strong acid, the deionizing agent is preferably a hydroxide ion species. The deionizing agent is preferably present in an amount between 0.2 to 1.0 mole equivalents per mole of the pharmaceutically active agent.

Exemplary hydrogen ion species useful as de-ionizing agents described herein, include, but are not limited to, hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, fumaric acid, maleic acid, tartaric acid, methane-, ethane-, and benzene sulfonates, citric acid, malic acid, acetic acid, proprionic acid, pyruvic acid, butanoic acid, and lactic acid.

Exemplary hydroxide ion species useful as de-ionizing agents described herein, include, but are not limited to, metal hydroxides such as sodium hydroxide, potassium hydroxide, ammonium hydroxide, calcium hydroxide, aluminum hydroxide, and magnesium hydroxide.

Additional acid or base can be added to adjust the pH of the fill composition. In a preferred embodiment, the pH of the fill composition is from about 2.5 to about 7.5.

iii. Excipients

Formulations may be prepared using a pharmaceutically acceptable carrier composed of materials that are considered safe and effective and may be administered to an individual without causing undesirable biological side effects or unwanted interactions. The carrier is all components present in the pharmaceutical formulation other than the active ingredient or ingredients. As generally used herein "carrier" includes, but is not limited to plasticizers, crystallization inhibitors, wetting agents, bulk filling agents, solubilizers, bioavailability enhancers, solvents, pH-adjusting agents and combinations thereof.

In a preferred embodiment, a mixture of polyethylene glycol and water is used as a solvent for the salt of the active agent and the de-ionizing agent. Polyethylene glycol is present in an amount from about 10% to about 80% by weight. Water is present in an amount from about 1% to 18% by weight. The molecular weight of polyethylene glycol is between 300 and 1500. Other suitable solvents include surfactants and copolymers of polyethylene glycol. Optionally, glycerin, polyvinyl pyrrolidone (PVP) or propylene glycol (PPG) can be added to enhance the solubility of the drug agent.

b. Shell Composition

i. Gelatin

Gelatin is the product of the partial hydrolysis of collagen. Gelatin is classified as either Type A or Type B gelatin. Type A gelatin is derived from the acid hydrolysis of collagen while Type B gelatin is derived from alkaline hydrolysis of collagen. Traditionally, bovine bones and skins have been used as raw materials for manufacturing Type A and Type B gelatin while porcine skins have been used extensively for manufacturing Type A gelatin. In general acid-processed gelatins form stronger gels than lime-processed gelatins of the same average molecular weight.

ii. Other Shell Additives

Other suitable shell additives include plasticizers, opacifiers, colorants, humectants, preservatives, flavorings, and buffering salts and acids.

Plasticizers are chemical agents added to gelatin to make the material softer and more flexible. Suitable plasticizers include glycerin, sorbitol solutions which are mixtures of sorbitol and sorbitan, and other polyhydric alcohols such as propylene glycol and maltitol or combinations thereof.

Opacifiers are used to opacify the capsule shell when the encapsulated active agents are light sensitive. Suitable opacifiers include titanium dioxide, zinc oxide, calcium carbonate and combinations thereof.

Colorants can be used to for marketing and product identification/differentiation purposes. Suitable colorants include synthetic and natural dyes and combinations thereof.

Humectants can be used to suppress the water activity of the softgel. Suitable humectants include glycerin and sorbitol, which are often components of the plasticizer composition. Due to the low water activity of dried, properly stored softgels, the greatest risk from microorganisms comes from molds and yeasts. For this reason, preservatives can be incorporated into the capsule shell. Suitable preservatives include alkyl esters of p-hydroxy benzoic acid such as methyl, ethyl, propyl, butyl and heptyl (collectively known as "parabens") or combinations thereof.

Flavorings can be used to mask unpleasant odors and tastes of fill formulations. Suitable flavorings include synthetic and natural flavorings. The use of flavorings can be problematic due to the presence of aldehydes which can cross-link gelatin. As a result, buffering salts and acids can be used in conjunction with flavorings that contain aldehydes in order to inhibit cross-linking of the gelatin.

II. Method of Making

a. Fill Material

The fill material is prepared by mixing the drug agent (salt), the deionizing agent, water, and polyethylene glycol at a temperature of 50°C to 70°C. The resulting solution is used for encapsulation using the appropriate gel mass. The pharmaceutical agent is present in an amount from about 10% to about 50% by weight. The deionizing agent is present in an amount from about 0.2 to 1.0 mole per mole of the pharmaceutical agent. Water is present in an amount from about 1% to about 20% by weight and polyethylene glycol is present in amount from about 10% to about 80% by weight. Optionally, propylene glycol and/or polyvinyl pyrrolidone are present in an amount from about 1% to about 10%.

b. Gel Mass

The main ingredients of the softgel capsule shell are gelatin, plasticizer, and purified water. Typical gel formulations contain (w/w) 40-50% gelatin, 20-30% plasticizer, and 30-40% purified water. Most of the water is subsequently lost during capsule drying. The ingredients are combined to form a molten gelatin mass using either a cold melt or a hot melt process. The prepared gel masses are transferred to preheated, temperature-controlled, jacketed holding tanks where the gel mass is aged at 50-60°C until used for encapsulation.

i. Cold Melt Process

The cold melt process involves mixing gelatin with plasticizer and chilled water and then transferring the mixture to a jacket-heated tank. Typically, gelatin is added to the plasticizer at ambient temperature (18-22°C). The mixture is cooked (57-95°C) under vacuum for 15-30 minutes to a homogeneous, deaerated gel mass. Additional shell additives can be added to the gel mass at any point during the gel manufacturing process or they may be incorporated into the finished gel mass using a high torque mixer.

ii. Hot Melt Process

The hot melt process involves adding, under mild agitation, the gelatin to a preheated (60-80°C) mixture of plasticizer and water and stirring the blend until complete melting is achieved. While the hot melt process is faster than the cold melt process, it is less accurately controlled and more susceptible to foaming and dusting.

c. Softgel Capsule

Softgel capsules are typically produced using a rotary die encapsulation process. The gel mass is fed either by gravity or through positive displacement pumping to two heated (48-65°C) metering devices. The metering devices control the flow of gel into cooled (10-18°C), rotating casting drums. Ribbons are formed as the cast gel masses set on contact with the surface of the drums.

The ribbons are fed through a series of guide rolls and between injection wedges and the capsule-forming dies. A food-grade lubricant oil is applied onto the ribbons to reduce their tackiness and facilitate their transfer. Suitable lubricants include mineral oil, medium chain triglycerides, and soybean oil. Fill formulations are fed into the encapsulation machine by gravity. In the preferred embodiment, the softgels contain printing on the surface, optionally identifying the encapsulated agent and/or dosage.

III. Method of Use

The softgels may be used to encapsulate a wide range of pharmaceutically active agents, nutritional agents and personal care products. Softgel capsules may be administered orally to a patient to deliver a pharmaceutically active agent.

Examples

In the following examples, the fill material can be prepared by mixing the salt of one or more pharmaceutically active agents, the deionizing agent, water and polyethylene glycol at a temperature of 50°C to 70°C. The resulting solution can be encapsulated in a softgel capsule using the appropriate gel mass.

Example 1. Naproxen Sodium with Acetic Acid as the Deionizing Agent

Fill Material:

Ingredients	% (by weight)
Naproxen Sodium	25.50
Acetic Acid	3.00
PVP	1.85
PEG 400	62.30
Water	7.40

Example 2. Naproxen Sodium with Citric Acid as the Deionizing Agent

Fill Material:

Ingredients	% (by weight)
Naproxen Sodium	25.50
Citric Acid	4.75
PVP	1.85
PEG 400	60.50
Water	7.40

Example 3. Naproxen Sodium with Hydrochloric Acid as the Deionizing Agent

Fill Material:

Ingredients	% (by weight)
Naproxen Sodium	25.50
Hydrochloric Acid	4.72
PVP	1.85
PEG 400	63.52
Water	7.40

Example 4. Naproxen Sodium with Acetic Acid as the Deionizing Agent

Fill Material:

Ingredients	% (by weight)
Naproxen Sodium	25.50
Acetic Acid	3.00
PVP	1.85
PEG 400	31.15
Water	7.40
PEG 600	31.15

Example 5. Naproxen Sodium with Citric Acid as the Deionizing Agent

Fill Material:

Ingredients	% (by weight)
Naproxen Sodium	25.50
Citric Acid	4075
PVP	1.85
PEG 400	30.25
Water	7.40
PEG 600	30.25

Example 6. Naproxen Sodium with Hydrochloric Acid as the Deionizing Agent

Fill Material:

Ingredients	% (by weight)
Naproxen Sodium	25.50
Hydrochloric Acid	4072
PVP	1.85
PEG 400	30.25
Water	7.40
PEG 600	30.25

Example 7. Naproxen Sodium with Lactic Acid as the Deionizing Agent

Fill Material:

Ingredients	% (by weight)
Naproxen Sodium	27.50
Lactic Acid	5.27
Propylene Glycol	2.00
PEG 400	64.64
Water	0.60

Example 8. Naproxen Sodium with Lactic Acid as the Deionizing Agent

Fill Material:

Ingredients	% (by weight)
Naproxen Sodium	25.00
Lactic Acid	0.24-0.35 M
Propylene glycol	2.00
PEG 600.	q.s.

Example 9. Naproxen Sodium with Lactic Acid as the Deionizing Agent

Fill Material:

Ingredients	% (by weight)
Naproxen Sodium	25.00
Lactic Acid	5.00
Propylene glycol	2.00
PEG 600	61.2
PEG 1000	6.80

Example 10. Naproxen Sodium with Lactic Acid as the Deionizing Agent

Fill Material:

Ingredients	% (by weight)
Naproxen Sodium	25.00
Lactic acid	5.00
Propylene glycol	2.00
PEG 600	51.00
PEG 1000	17.00

Example 11. Naproxen Sodium with Lactic Acid as the Deionizing Agent

Fill Material:

Ingredients	% (by weight)
Naproxen Sodium	25.00
Lactic Acid	5.00
Propylene glycol	2.00
PEG 600	34.00
PEG 1000	34.00

Example 12. Naproxen Sodium with Lactic Acid as the Deionizing Agent

Fill Material:

Ingredients	% (by weight)
Naproxen Sodium	25.00
Lactic acid	5.00
Propylene glycol	2.00
PEG 600	17.00
PEG 1000	51.00

It is understood that the disclosed invention is not limited to the particular methodology, protocols, and reagents described as these may vary. It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments only, and is not intended to limit the scope of the present invention which will be limited only by the appended claims.

Unless defined otherwise, all technical and scientific terms used herein have the same meanings as commonly understood by one of skill in the art to which the disclosed invention belongs. Although any methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present invention, the preferred methods, devices, and materials are as described. Publications cited herein and the materials for which they are cited are specifically incorporated by reference. Nothing herein is to be construed as an admission that the invention is not entitled to antedate such disclosure by virtue of prior invention.

Those skilled in the art will recognize, or be able to ascertain using no more than routine experimentation, many equivalents to the specific embodiments of the invention described herein. Such equivalents are intended to be encompassed by the following claims.

We claim:

1. A pharmaceutical composition comprising

(a) a salt of one or more pharmaceutically active agents; and

(b) a deionizing agent.

2. The composition of claim 1 wherein the pharmaceutically active agent is selected from the group consisting of bioactive agents, diagnostic agents, and prophylactic agents.

3. The composition of claim 1 wherein the deionizing agent is present in an amount from about 0.2 to 1.0 mole equivalents per mole of the pharmaceutically active agent(s).

4. The composition of claim 1 wherein the deionizing agent is selected from the group consisting of hydrogen ion and hydroxide ion.

5. The composition of claim 1 further comprising polyethylene glycol.

6. The composition of claim 5 wherein polyethylene glycol is present in an amount from about 10% to about 80% by weight

7. The composition of claim 5 wherein polyethylene glycol is one or more polyethylene glycols with a molecular weight between 300 and 1500.

8. The composition of claim 1 further comprising water.

9. The composition of claim 8 wherein water is present in an amount from about 1% to about 18% by weight.

10. The composition of claim 1 further comprising one or more excipients.

11. The composition of claim 7 wherein the excipients are selected from the group consisting of plasticizers, crystallization inhibitors, wetting agents, bulk filling agents, solubilizers, bioavailability enhancers, solvents, pH-adjusting agents, dyes, preservatives, solvents, surfactants, and combinations thereof.

12. The composition of claim 11 wherein the solubilizer is selected from the group consisting of glycerin, polyvinylpyrrolidone, propylene glycol and combinations thereof.

13. The composition of claim 12 wherein the solubilizer is present in amount from about 1% to about 10% by weight.

10. A method of making the composition of claim 1 comprising

(a) mixing the salt of one or more pharmaceutically active agents, and the deionizing agent at an appropriate temperature; and

(b) encapsulating the mixture in a softgel capsule.

11. The method of claim 10 further comprising polyethylene glycol.

12. The method of claim 10 further comprising water.

13. The method of claim 10 wherein the appropriate temperature is from about 50°C to about 70°C.

14. A method of using the composition of claim 1 comprising administering to a patient in need thereof the salt of one or more pharmaceutically active agents.

SOLVENT SYSTEM FOR ENHANCING THE SOLUBILITY OF PHARMACEUTICAL AGENTS

ABSTRACT OF THE DISCLOSURE

Liquid and semi-solid pharmaceutical compositions, which can be administered in liquid form or can be used for preparing capsules, are described herein. The composition comprises the salt of one ore more active agents, polyethylene glycol, 0.2-1.0 mole equivalents of a de-ionizing agent per mole of active agent, and water. The pH of the composition is adjusted within the range of 2.5 – 7.5. The de-ionizing agent causes partial de-ionization (neutralization) of the salt of the active agent resulting in enhanced bioavailability of salts of weakly acidic, basic or amphoteric active agents as well as lesser amounts of polyethylene glycol (PEG) esters.

APPLICATION DATA SHEET

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Country of Residence::	United States
Citizenship Country::	United States

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Application Information:

Title Line One::	SOLVENT SYSTEM FOR ENHANCING THE
Title Line Two::	SOLUBILITY OF PHARMACEUTICAL AGENTS
Title Line Three::	
Total Drawing Sheets::	0
Formal Drawings?::	No
Application Type::	Provisional
Docket Number::	BAN 102
Licensed US Govt. Agency::	
Contract or Grant Numbers One::	
Contract or Grant Numbers Two::	
Secrecy Order in Parent Appl.?::	No

Assignee::	Banner Pharmacaps, Inc.
State of Incorporation::	Delaware

Representative Information

Representative Customer Number:: 23579

We claim:

1. A pharmaceutical composition comprising

(a) a salt of one or more pharmaceutically active agents; and

(b) a deionizing agent.

2. The composition of claim 1 wherein the pharmaceutically active agent is selected from the group consisting of therapeutically active agents, diagnostic agents, and prophylactic agents.

3. The composition of claim 1 wherein the deionizing agent is present in an amount from about 0.2 to 1.0 mole equivalents per mole of the pharmaceutically active agent(s).

4. The composition of claim 1 wherein the deionizing agent is selected from the group consisting of hydrogen ion and hydroxide ion.

5. The composition of claim 1 further comprising polyethylene glycol.

6. The composition of claim 5 wherein polyethylene glycol is present in an amount from about 10% to about 80% by weight.

7. The composition of claim 5 wherein polyethylene glycol is one or more polyethylene glycols with a molecular weight between 300 and 1500.

8. The composition of claim 1 further comprising water.

9. The composition of claim 8 wherein water is present in an amount from about 1% to about 18% by weight.

10. The composition of claim 1 further comprising one or more excipients.

11. The composition of claim 7 wherein the excipients are selected from the group consisting of plasticizers, crystallization inhibitors, wetting agents, bulk filling agents, solubilizers, bioavailability enhancers, solvents, pH-adjusting agents, dyes, preservatives, solvents, surfactants, and combinations thereof.

12. The composition of claim 11 wherein the solubilizer is selected from the group consisting of glycerin, polyvinylpyrrolidone, propylene glycol and combinations thereof.

13. The composition of claim 12 wherein the solubilizer is present in amount from about 1% to about 10% by weight.

14. A method of making the composition of any of claims 1-13 comprising

(a) mixing the salt of one or more pharmaceutically active agents, and the deionizing agent at an appropriate temperature; and

(b) encapsulating the mixture in a softgel capsule.

15. The method of claim 14 further comprising polyethylene glycol.

16. The method of claim 14 further comprising water.

17. The method of claim 14 wherein the appropriate temperature is from about 50°C to about 70°C.

18. A method of using the composition of any of claims 1-13 comprising administering to a patient in need thereof the salt of one or more pharmaceutically active agents.

19. A softgel capsule comprising a fill material wherein the fill material comprises

(a) a salt of one or more pharmaceutically active agents; and

(b) a deionizing agent.

20. The capsule of claim 19 wherein the pharmaceutically active agent is selected from the group consisting of therapeutically active agents, diagnostic agents, and prophylactic agents.

21. The capsule of claim 19 wherein the deionizing agent is present in an amount from about 0.2 to 1.0 mole equivalents per mole of the pharmaceutically active agent(s).

22. The capsule of claim 19 wherein the deionizing agent is selected from the group consisting of hydrogen ion and hydroxide ion.

23. The capsule of claim 19 further comprising polyethylene glycol.

 AMENDED SHEET

24. The capsule of claim 23 wherein polyethylene glycol is present in an amount from about 10% to about 80% by weight.

25. The capsule of claim 23 wherein polyethylene glycol is one or more polyethylene glycols with a molecular weight between 300 and 1500.

26. The capsule of claim 19 further comprising water.

27. The capsule of claim 26 wherein water is present in an amount from about 1% to about 18% by weight.

28. The capsule of claim 19 further comprising one or more excipients.

29. The capsule of claim 28 wherein the excipients are selected from the group consisting of plasticizers, crystallization inhibitors, wetting agents, bulk filling agents, solubilizers, bioavailability enhancers, solvents, pH-adjusting agents, dyes, preservatives, solvents, surfactants, and combinations thereof.

30. The capsule of claim 29 wherein the solubilizer is selected from the group consisting of glycerin, polyvinylpyrrolidone, propylene glycol and combinations thereof.

31. The capsule of claim 29 wherein the solubilizer is present in amount from about 1% to about 10% by weight.

 AMENDED SHEET

CHAPTER II

Zur Kasse

PCT

FEE CALCULATION SHEET

Annex to the Demand

International application No. PCT/US2006/007788	For International Preliminary Examining Authority use only
Applicant's or agent's file reference BAN 102	Date stamp of the IPEA
Applicant: BANNER PHARMACAPS, INC., et al.	

CALCULATION OF PRESCRIBED FEES

1. Preliminary examination fee	1,595.00 EUR P	
2. Handling fee *(Applicants from certain States are entitled to a reduction of 75% of the handling fee. Where the applicant is (or all applicants are) so entitled, the amount to be entered at H is 25% of the handling fee.)*	129.00 EUR H	
3. Total of prescribed fees Add the amounts entered at P and H and enter total in the TOTAL box	1,724.00 EUR TOTAL	

MODE OF PAYMENT
(Not all modes of payment may be available at all IPEAs)

- ☐ authorization to charge deposit account with the IPEA (see below)
- ☐ cheque
- ☐ postal money order
- ☐ bank draft
- ☐ cash
- ☐ revenue stamps
- ☐ coupons
- ☒ other *(specify)*: Check to follow via DHL Worldwide Express

AUTHORIZATION TO CHARGE (OR CREDIT) DEPOSIT ACCOUNT
(This mode of payment may not be available at all IPEAs)

IPEA/ EP

☐ Authorization to charge the total fees indicated above.

☐ *(This check-box may be marked only if the conditions for deposit accounts of the IPEA so permit)* Authorization to charge any deficiency or credit any overpayment in the total fees indicated above.

Deposit Account No.: _____

Date: 08 January 2007

Name: Michael J. Terapane

Signature: Michael J. Terapane

Form PCT/IPEA/401 (Annex) (April 2006) *See Notes to the fee calculation sheet*

CHAPTER II

PCT

FEE CALCULATION SHEET

Annex to the Demand

International application No. PCT/US2006/007788	For International Preliminary Examining Authority use only
Applicant's or agent's file reference BAN 102	Date stamp of the IPEA
Applicant: BANNER PHARMACAPS, INC., et al.	

CALCULATION OF PRESCRIBED FEES

1. Preliminary examination fee	1,595.00 EUR	P	
2. Handling fee *(Applicants from certain States are entitled to a reduction of 75% of the handling fee. Where the applicant is (or all applicants are) so entitled, the amount to be entered at H is 25% of the handling fee.)*	129.00 EUR	H	
3. Total of prescribed fees Add the amounts entered at P and H and enter total in the TOTAL box	1,724.00 EUR TOTAL		

MODE OF PAYMENT

(Not all modes of payment may be available at all IPEAs)

- ☐ authorization to charge deposit account with the IPEA (see below)
- ☐ cheque
- ☐ postal money order
- ☐ bank draft
- ☐ cash
- ☐ revenue stamps
- ☐ coupons
- ☒ other *(specify)*: Check to follow via DHL Worldwide Express

AUTHORIZATION TO CHARGE (OR CREDIT) DEPOSIT ACCOUNT

(This mode of payment may not be available at all IPEAs)

IPEA/ EP

☐ Authorization to charge the total fees indicated above.

☐ *(This check-box may be marked only if the conditions for deposit accounts of the IPEA so permit)* Authorization to charge any deficiency or credit any overpayment in the total fees indicated above.

Deposit Account No.: _____

Date: 08 January 2007

Name: Michael J. Terapane

Signature: Michael J. Terapane

Form PCT/IPEA/401 (Annex) (April 2006) *See Notes to the fee calculation sheet*

The demand must be filed directly with the competent International Preliminary Examining Authority or, if two or more Authorities are competent, with the one chosen by the applicant. The full name or two-letter code of that Authority may be indicated by the applicant on the line below:

IPEA/ EP

PCT

CHAPTER II

DEMAND

under Article 31 of the Patent Cooperation Treaty:
The undersigned requests that the international application specified below be the subject of international preliminary examination according to the Patent Cooperation Treaty.

For International Preliminary Examining Authority use only

Identification of IPEA	Date of receipt of DEMAND
- EP	08-01-2007

Box No. I IDENTIFICATION OF THE INTERNATIONAL APPLICATION

Applicant's or agent's file reference: BAN 102

International application No.	International filing date *(day/month/year)*	(Earliest) Priority date *(day/month/year)*
PCT/US2006/007788	06 March 2006 (06.03.06)	08 March 2005 (08.03.05)

Title of invention
SOLVENT SYSTEM FOR ENHANCING THE SOLUBILITY OF PHARMACEUTICAL AGENTS

Box No. II APPLICANT(S)

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*
BANNER PHARMACAPS, INC.
4125 Premier Drive
High Point, North Carolina 27265
United States of America

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Facsimile No.: (336) 812-7054
Teleprinter No.:
Applicant's registration No. with the Office:

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US	US

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*
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United States of America

State *(that is, country)* of nationality:	State *(that is, country)* of residence:
IN	US

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*
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Greensboro, North Carolina 27410
United States of America

State *(that is, country)* of nationality:	State *(that is, country)* of residence:
US	US

☐ Further applicants are indicated on a continuation sheet.

Sheet No. 2

International application No.
PCT/US2006/007788

Box No. III AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE

The following person is [X] agent [ ] common representative

and [X] has been appointed earlier and represents the applicant(s) also for international preliminary examination

[ ] is hereby appointed and any earlier appointment of (an) agent(s)/common representative is hereby revoked

[ ] is hereby appointed, specifically for the procedure before the International Preliminary Examining Authority, in addition to the agent(s)/common representative appointed earlier

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

PABST, Patrea L., MONHEIT, Rivka D., and TERAPANE, Michael J., all of
Pabst Patent Group LLP
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1201 Peachtree Street
Atlanta, Georgia 30361

Telephone No.
(404) 879-2156

Facsimile No.
(404) 879-2160

Teleprinter No.

Agent's registration No. with the Office
31,284, 48,731, 57,633

[ ] **Address for correspondence:** Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.

Box No. IV BASIS FOR INTERNATIONAL PRELIMINARY EXAMINATION

Statement concerning amendments:*

1. The applicant wishes the international preliminary examination **to start on the basis of:**

[ ] the international application as originally filed

the description
- [X] as originally filed
- [ ] as amended under Article 34

the claims
- [ ] as originally filed
- [ ] as amended under Article 19 (together with any accompanying statement)
- [X] as amended under Article 34

the drawings
- [ ] as originally filed
- [ ] as amended under Article 34

2. [ ] The applicant wishes any amendment to the claims under Article 19 to be considered as reversed.
3. [ ] Where the IPEA wishes to start the international preliminary examination at the same time as the international search in accordance with Rule 69.1(b), the applicant requests the IPEA **to postpone** the start of the international preliminary examination until the expiration of the applicable time limit under Rule 69.1(d).
4. [ ] The applicant expressly wishes the international preliminary examination **to start earlier** than at the expiration of the applicable time limit under Rule 54*bis*.1(a).

* Where no check-box is marked, international preliminary examination will start on the basis of the international application as originally filed or, where a copy of amendments to the claims under Article 19 and/or amendments of the international application under Article 34 are received by the International Preliminary Examining Authority before it has begun to draw up a written opinion or the international preliminary examination report, as so amended.

Language for the purposes of international preliminary examination: English

- [X] which is the language in which the international application was filed
- [ ] which is the language of a translation furnished for the purposes of international search
- [ ] which is the language of publication of the international application
- [ ] which is the language of the translation (to be) furnished for the purposes of international preliminary examination

Box No. V ELECTION OF STATES

The filing of this demand constitutes the election of all Contracting States which are designated and are bound by Chapter II of the PCT.

Sheet No. 3

International application No.
PCT/US2006/007788

Box No. VI CHECK LIST

The demand is accompanied by the following elements, in the language referred to in Box No. IV, for the purposes of international preliminary examination:

				For International Preliminary Examining Authority use only: received	not received
1. translation of international application	:		sheets	☐	☐
2. amendments under Article 34	:	3	sheets	☐	☐
3. copy (or, where required, translation) of amendments under Article 19	:		sheets	☐	☐
4. copy (or, where required, translation) of statement under Article 19	:		sheets	☐	☐
5. letter	:	4	sheets	☐	☐
6. other *(specify)*	:		sheets	☐	☐

The demand is also accompanied by the item(s) marked below:

1. ☒ fee calculation sheet
2. ☐ original separate power of attorney
3. ☐ original general power of attorney
4. ☐ copy of general power of attorney; reference number, if any:
5. ☐ statement explaining lack of signature
6. ☐ sequence listing in electronic form
7. ☐ tables in electronic form related to a sequence listing
8. ☐ other *(specify)*:

Box No. VII SIGNATURE OF APPLICANT, AGENT OR COMMON REPRESENTATIVE

Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the demand).

Michael Terapane

Michael J. Terapane
(Agent for Applicants)

For International Preliminary Examining Authority use only

1. Date of actual receipt of DEMAND: 08-01-2007

2. Adjusted date of receipt of demand due to CORRECTIONS under Rule 60.1(b):

3. ☐ The date of receipt of the demand is AFTER the expiration of 19 months from the priority date and item 4 or 5, below, does not apply.
   ☐ The applicant has been informed accordingly.
4. ☐ The date of receipt of the demand is WITHIN the time limit of 19 months from the priority date as extended by virtue of Rule 80.5.
5. ☐ Although the date of receipt of the demand is after the expiration of 19 months from the priority date, the delay in arrival is EXCUSED pursuant to Rule 82.
6. ☐ The date of receipt of the demand is AFTER the expiration of the time limit under Rule 54*bis*.1(a) and item 7 or 8, below, does not apply.
7. ☐ The date of receipt of the demand is WITHIN the time limit under Rule 54*bis*.1(a) as extended by virtue of Rule 80.5.
8. ☐ Although the date of receipt of the demand is after the expiration of the time limit under Rule 54*bis*.1(a), the delay in arrival is EXCUSED pursuant to Rule 82.

For International Bureau use only

Demand received from IPEA on:

IN THE INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY/EP

Applicant: Banner Pharmacaps, Inc.

International Application No: PCT/US2006/007788

International Filing Date: 06 March 2006

For: *SOLVENT SYSTEM FOR ENHANCING THE SOLUBILITY OF PHARMACEUTICAL AGENTS*

European Patent Office
D-80298 Munich
GERMANY

RESPONSE TO WRITTEN OPINION

Sir:

The following comments are in response to the Written Opinion mailed July 6, 2006. Please substitute pages 16 to 18 for pages 16 to 18, as originally filed.

Amendments to the claims

The claims were amended to correct typographical errors and to delete extraneous spaces. Claim 1 was amended to delete the space between element (a) and (b). Claims 3 and 21 were amended to delete the space between "an" and "amount". Claims 6 and 24 were amended to include a period at the end of the claim. Claim 18 was amended to delete the space between "comprising" and "administering".

Response to the Examiner's Arguments

Claims 1-31 were rejected as lacking novelty or inventive step over U.S. Patent No. 5,360,615 to Yu *et al.* (D1); WO 95/31979 to R.P. Scherer (D2); U.S. Patent Application Publication No. 2001/007668 to Sawyer *et al.* (D3); and U.S. Patent No. 5,484,606 to Dhabhar *et al.* (D4). Applicants respectfully traverse these rejections.

D1

D1 describes a solvent system for solubilizing an acidic, basic, or amphoteric pharmaceutical agent (abstract). The solvent system contains polyethylene glycol, 0.2-1.0 mole equivalents of an ionizing agent per mole equivalent pharmaceutical agent and 1-20% water. The ionizing agent functions by causing partial ionization of the free pharmaceutical agent (abstract). For example, when the pharmaceutical agent is acidic, the ionizing agent is a hydroxide ion species. D1 does not disclose a pharmaceutical composition containing the salt of one or more pharmaceutically active agents and a deionizing agent. The agents described in D1 are the free acid or free base, not salts. Moreover, the agents described in D1 are combined with an agent, which ionizes the active agent. In contrast, the claimed compositions require an agent that neutralizes the active agent.

Example VIII describes a formulation containing diclofenac sodium and hydrochloric acid. The Examiner alleges that this formulation is an example of a salt of an active agent and a deionizing agent. D1 discloses the use of an ionizing agent which functions by causing the partial ionization of the free pharmaceutical agent. In Example VIII, D1 suggests that the hydrochloric acid reacts with the secondary amine in diclofenac to form an ammonium ion. HCl in this context is an ionizing agent, not a deionizing agent.

D1 is concerned with ionizing the pharmaceutically active agent in order to prepare highly concentrated solutions. In contrast, the problem to be solved in the present application is reducing the formation of active agent-polyethylene glycol esters. One of ordinary skill in the art would not be motivated to modify D1 to arrive at the claimed compositions. Accordingly, claim 1-31 are novel and inventive over D1.

D2

D2 describes methods and compositions for preparing liquid mixtures of aryl or heteroaryl alkanoic acids suitable for encapsulation in softgel capsules (abstract). Example 8 describes a formulation containing ketoprofen and potassium hydroxide. Ketoprofen is neutral and sodium hydroxide is an ionizing agent. D2 does not disclose or suggest a

composition containing a salt of a pharmaceutically active agent and a deionizing agent. One of ordinary skill in the art would not be motivated to modify D2 to arrive at the claimed compositions. Accordingly, claims 1-31 are novel and inventive over D2.

D3

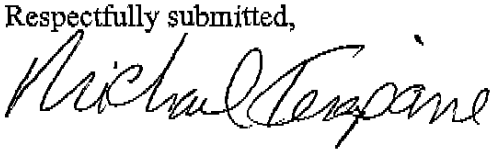
D3 describes pharmaceutically acceptable solutions containing a medicament suitable for filling a soft gelatin capsule. The solvent contains a polymer, such as polyethylene glycol, an acid salt of a compound having three or more carbon atoms, and a salt such as sodium propionate (abstract). The acid salt aids in ionizing the medicament (page 2, paragraph 0028). D3 does not disclose or suggest a composition containing the salt of a pharmaceutically active agent and a deionizing agent. Example 17 describes a formulation containing naproxen sodium and potassium hydroxide. However, this formulation does not describe a deionizing agent. In order to deionize sodium naproxen, a hydrogen ion source must be added. The examples disclose no such source. One of ordinary skill in the art would not be motivated to modify D2 to arrive at the claimed compositions. Accordingly, claims 1-31 are novel and inventive over D3.

D4

D4 describes a process for reducing precipitation of insoluble pharmaceutically active agents in a mixture of polyethylene glycol, polyvinylpyrrolidone, and propylene glycol (abstract). D4 does not disclose or suggest a composition containing the salt of a pharmaceutically active agent and a deionizing agent. The examples describe formulations containing acetaminophen combined with other active agents such as pseudoephedrine HCl, dextromethorphan HBr, and chlorpheniramine maleate. Contrary to the Examiner's assertion, acetaminophen does not release hydrogen ions. Acetaminophen does not contain a carboxylic acid group. The OH group of the phenol group in acetaminophen can be deprotonated using a strong base; however, it will not dissociate on its own in water. The formulations described in D4 do not contain a strong base such as sodium hydroxide.

One of ordinary skill in the art would not be motivated to modify D4 to arrive at the claimed compositions. Accordingly, claims 1-31 are novel and inventive over D4.

Respectfully submitted,



Michael J. Terapane, Ph.D.
Reg. No. 57,633

Date: January 8, 2007

Pabst Patent Group LLP
400 Colony Square, Suite 1200
1201 Peachtree Street
Atlanta, GA 30309
(404) 879-2151
(404) 879-2160 (Fax)

IN THE INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY
FOR THE PATENT COOPERATION TREATY

Applicants: BANNER PHARMACAPS, INC.

International Application No.: PCT/US2006/007788

International Filing Date: 06 March 2006

For: *SOLVENT SYSTEM FOR ENHANCING THE SOLUBILITY OF PHARMACEUTICAL AGENTS*

European Patent Office
D-80298 Munich
GERMANY

TRANSMITTAL OF FILING FEE FOR DEMAND FOR PRELIMINARY EXAMINATION UNDER PCT ARTICLE 31

Sir:

Enclosed are a PCT Fee Calculation Sheet and check in the amount of 1,724.-- EUR in payment of the filing fee for the Demand for Preliminary Examination under PCT Article 31 filed in the European Patent Office in the above-identified application by facsimile transmission on 08 January 2007.

Respectfully submitted,

Patrea L. Pabst
Reg. No. 31,284
Attorney for Applicant

Date: 22 January 2007

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095161-00019
BAN 102 PCT

PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

PCT

To:
PABST, Patrea L.
PABST Patent Group LLP
400 Colony Square, Suite 1200
1201 Peachtree Street
Atlanta, Georgia 30361
ETATS-UNIS D'AMERIQUE

NOTIFICATION OF RECEIPT OF DEMAND BY COMPETENT INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

(PCT Rules 59.3(e) and 61.1(b), first sentence and Administrative Instructions, Section 601(a))

Date of mailing *(day/month/year)*	09-02-2007
Applicant's or agent's file reference: BAN 102	**IMPORTANT NOTIFICATION**

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US2006/007788	06/03/2006	08/03/2005

Applicant

BANNER PHARMACAPS, INC. et al.

1. The applicant is hereby **notified** that this International Preliminary Examining Authority considers the following date as the date of receipt of the demand for international preliminary examination of the international application:

08/01/2007 .

2. This date of receipt is:

- [X] the actual date of receipt of the demand by this Authority (Rule 61.1(b)).
- [ ] the actual date of receipt of the demand on behalf of this Authority (Rule 59.3(e)).
- [ ] the date on which this Authority has, in response to the invitation to correct defects in the demand (Form PCT/IPEA/404), received the required corrections.

3. [ ] **ATTENTION:** That date of receipt is **after** the expiration of 19 months from the priority date. Consequently, in respect of some Offices, the demand does not have the effect of postponing the entry into the national phase until 30 months from the priority date (or later in some Offices) (Article 39(1)) and the acts for entry into the national phase must therefore be performed within 20 months from the priority date (or later in some Offices). **However,** in respect of some other Offices, the time limit of 30 months (or later) may nevertheless apply. See the Annex to Form PCT/IB/301 and, for details about the applicable time limits, Office by Office, see the *PCT Applicant's Guide,* Volume II, National Chapters and the WIPO Internet site.

[ ] *(If applicable)* This notification confirms the information given by telephone, facsimile transmission or in person on: _____

4. Only where paragraph 3 applies, a copy of this notification has been sent to the International Bureau.

Name and mailing address of the IPEA/	Authorized officer
European Patent Office D-80298 Munich Tel. (+49-89) 2399-0, Tx: 523656 epmu d Fax: (+49-89) 2399-4465	OBERHAUSER A S Tel. (+49-89) 2399-8139

Form PCT/IPEA/402 (April 2002; reprint January 2004) (06/02/2007)

Europäisches Patentamt • European Patent Office • Office européen des brevets

PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

PCT

To:
The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20
Switzerland

NOTIFICATION CONCERNING
DOCUMENTS TRANSMITTED

Date of mailing
(day/month/year) 09-02-2007

International application No: PCT/US2006/007788

This International Preliminary Examination Authority transmits herewith the following documents:

1. [X] demand (Rule 61.1(a)).
2. [ ] copy of the international preliminary examination report and its annexes (Rule 71.1).
3. [ ] ____ other documents *(specify)*:

Name and mailing address of the IPEA/

European Patent Office
D-80298 Munich
Tel. (+49-89) 2399-0, Tx: 523656 epmu d
Fax: (+49-89) 2399-4465

Authorized officer

OBERHAUSER A S

Tel. (+49-89) 2399-8139

Form PCT/IPEA/415 (January 1995) P20594

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Article 31(7) and Rule 61.2)

To:

European Patent Office
Postbus 5818
Patentlaan 2
NL-2280 HV RIJSWIJK
PAYS-BAS

in its capacity as elected Office

Date of mailing *(day/month/year)* 08 March 2007 (08.03.2007)	
International application No. PCT/US2006/007788	Applicant's or agent's file reference BAN 102
International filing date *(day/month/year)* 06 March 2006 (06.03.2006)	Priority date *(day/month/year)* 08 March 2005 (08.03.2005)
Applicant BANNER PHARMACAPS, INC. et al	

1. The designated Office is hereby notified of its election made in the demand filed with the International Preliminary Examining Authority on:

   08 January 2007 (08.01.2007)

2. The election ☐ was

   ☑ was not

   made before the expiration of 19 months from the priority date (PCT Article 39(1)(a)).

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Authorized officer Athina Nickitas-Etienne
Facsimile No. +41 22 338 82 70	Facsimile No. +41 22 338 82 70

Form PCT/IB/331 (January 2004)

European Patent Office
80298 MUNICH
GERMANY
Tel.: +49 89 2399 - 0
Fax: +49 89 2399 - 4465

Europäisches Patentamt | **European Patent Office** | **Office européen des brevets**

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EPO Customer Services

Tel.: +31 (0)70 340 45 00

Date
18.07.07

Reference	Application No./Patent No.
	06737018.9 - 2123 PCT/US2006007788
Applicant/Proprietor	
Banner Pharmacaps Inc.	

Entry into the European phase before the European Patent Office

These notes describe the procedural steps required for entry into the European phase before the European Patent Office (EPO). You are advised to read them carefully: failure to take the necessary action in time can lead to your application being deemed withdrawn.

1. The above-mentioned international patent application has been given European application No. **06737018.9**.

2. Applicants **without** a residence or their principal place of business in an EPC contracting state may themselves initiate European processing of their international applications, provided they do so before expiry of the 31st month from the priority date (see also point 6 below).

   During the European phase before the EPO as designated or elected Office, however, such applicants must be represented by a professional representative (Arts. 133(2) and 134(1), (7) EPC).

   Procedural acts performed after expiry of the 31st month by a professional representative who acted during the international phase but is not authorised to act before the EPO have no legal effect and therefore lead to loss of rights.

   Please note that a professional representative authorised to act before the EPO and who acted for the applicant during the international phase does not automatically become the representative for the European phase. Applicants are therefore strongly advised to appoint in good time any representative they wish to initiate the European phase for them; otherwise, the EPO has to send all communications direct to the applicant.

3. Applicants **with** a residence or their principal place of business in an EPC contracting state are not obliged to appoint, for the European phase before the EPO as designated or elected Office, a professional representative authorised to act before the EPO.
   However, in view of the complexity of the procedure it is recommended that they do so.

4. Applicants and professional representatives are also strongly advised to initiate the European phase using EPO Form 1200 (available free of charge from the EPO). This however is not compulsory.

5. **To enter the European phase before the EPO**, the following acts must be performed.
(N.B.: Failure validly to do so will entail loss of rights or other adverse legal consequences.)

5.1 If the EPO is acting as **designated** or **elected** Office (Arts. 22(1)(3) and 39(1) PCT respectively), applicants must, within 31 months from the date of filing or (where applicable) the earliest priority date:

a) Supply a translation of the international application into an EPO official language, if the International Bureau did not publish the application in such a language (Art. 22(1) PCT and R. 107(1)(a) EPC).
If the translation is not filed in time, the international application is deemed withdrawn before the EPO (R. 108(1) EPC).
This loss of rights is deemed not to have occurred if the translation is then filed within a two-month grace period as from notification of an EPO communication, provided a surcharge is paid at the same time (R. 108(3) EPC).

b) Pay the national basic fee and, where a supplementary European search report has to be drawn up, the search fee ; R. 107(1)(c) and (e) EPC).

c) If the time limit under Article 79(2) EPC expires before the 31-month time limit, pay the designation fee for each contracting state designated (R. 107(1)(d) EPC).

d) If the time limit under Article 94(2) EPC expires before the 31-month time limit, file the written request for examination **and** pay the examination fee; R. 107(1)(f) EPC).

e) Pay the third-year renewal fee if it falls due before expiry of the 31-month time limit (R. 107(1)-(g) EPC).

If the fees under (b) to (d) above are not paid in time, or the written request for examination is not filed in time, the international application is deemed withdrawn before the EPO, or the contracting-state designation(s) in question is (are) deemed withdrawn (R. 108(1) and (2) EPC). However, the fees may still be validly paid within a two-month grace period as from notification of an EPO communication, provided the necessary surcharges are paid at the same time (R. 108(3) EPC). For the renewal fee under (e) above, the grace period is **six** months from the fee's due date (Art. 86(2) EPC).

For an overview of search and examination fees, see the Notice from the European Patent Office dated 1 March 2006, OJ EPO 2006, 192.

5.2 If the application documents on which the European grant procedure is to be based comprise more then ten claims, a claims fee is payable within the 31-month time limit under Rule 107(1) EPC for the eleventh and each subsequent claim (R. 110(1) EPC). The fee can however still be paid within a one-month grace period as from notification of an EPO communication pointing out the failure to pay (R. 110(2) EPC).

6. If the applicant had a representative during the application's international phase, the present notes will be sent to the representative, asking him to inform the applicant accordingly.

All subsequent communications will be sent to the applicant, or - if the EPO is informed of his appointment in time - to the applicant's European representative.

7. For more details about time limits and procedural acts before the EPO as designated and elected Office, see the EPO brochure

   How to get a European patent
   Guide for applicants - Part 2
   PCT procedure before the EPO - "Euro-PCT"

   This brochure, the list of professional representatives before the EPO, Form 1200 and details of the latest fees are now all available on the Internet under

   http://www.european-patent-office.org

Receiving Section

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference BAN 102	**FOR FURTHER ACTION**	See Form PCT/IPEA/416
International application No. PCT/US2006/007788	International filing date *(day/month/year)* 06.03.2006	Priority date *(day/month/year)* 08.03.2005
International Patent Classification (IPC) or national classification and IPC INV. A61K9/48		
Applicant Banner Pharmacaps, Inc.		

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 5 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☒ *sent to the applicant and to the International Bureau)* a total of 3 sheets, as follows:
      ☒ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in electronic form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

   ☒ Box No. I Basis of the report
   ☐ Box No. II Priority
   ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   ☐ Box No. IV Lack of unity of invention
   ☒ Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   ☐ Box No. VI Certain documents cited
   ☐ Box No. VII Certain defects in the international application
   ☐ Box No. VIII Certain observations on the international application

Date of submission of the demand	Date of completion of this report
2007-01-08	20.07.2007
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Büttner, Ulf Telephone No. +49 89 2399-7841

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference BAN 102	**FOR FURTHER ACTION**	See Form PCT/IPEA/416
International application No. PCT/US2006/007788	International filing date *(day/month/year)* 06.03.2006	Priority date *(day/month/year)* 08.03.2005
International Patent Classification (IPC) or national classification and IPC INV. A61K9/48		
Applicant Banner Pharmacaps, Inc.		

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 5 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☒ *sent to the applicant and to the International Bureau)* a total of 3 sheets, as follows:
      ☒ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in electronic form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

   ☒ Box No. I Basis of the report
   ☐ Box No. II Priority
   ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   ☐ Box No. IV Lack of unity of invention
   ☒ Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   ☐ Box No. VI Certain documents cited
   ☐ Box No. VII Certain defects in the international application
   ☐ Box No. VIII Certain observations on the international application

Date of submission of the demand	Date of completion of this report
2007-01-08	20.07.2007
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Büttner, Ulf Telephone No. +49 89 2399-7841

Box No. I Basis of the report

1. With regard to the **language**, this report is based on

   ☒ the international application in the language in which it was filed

   ☐ a translation of the international application into , which is the language of a translation furnished for the purposes of:
   - ☐ international search (under Rules 12.3(a) and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4(a))
   - ☐ international preliminary examination (under Rules 55.2(a) and/or 55.3(a))

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

   Description, Pages

   1-15 as originally filed

   Claims, Numbers

   1-31 filed with telefax on 08.01.2007

   ☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	
	No:	Claims	1-31
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-31
Industrial applicability (IA)	Yes:	Claims	1-31
	No:	Claims	

2. Citations and explanations (Rule 70.7):

see separate sheet

Box No. I Basis of the report

1. With regard to the **language**, this report is based on

   ☒ the international application in the language in which it was filed

   ☐ a translation of the international application into , which is the language of a translation furnished for the purposes of:
   - ☐ international search (under Rules 12.3(a) and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4(a))
   - ☐ international preliminary examination (under Rules 55.2(a) and/or 55.3(a))

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

   Description, Pages

   1-15 as originally filed

   Claims, Numbers

   1-31 filed with telefax on 08.01.2007

   ☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	
	No:	Claims	1-31
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-31
Industrial applicability (IA)	Yes:	Claims	1-31
	No:	Claims	

2. Citations and explanations (Rule 70.7):

see separate sheet

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1.) Reference is made to the following documents:

D1: US-A-5 360 615 (YU ET AL) 1 November 1994 (1994-11-01) cited in the application
D2: WO 95/31979 A (R.P. SCHERER INTERNATIONAL CORPORATION; SHELLEY, RICKEY, S; WEI, YOUCH) 30 November 1995 (1995-11-30)
D3: US 2001/007668 A1 (SAWYER MARYJEAN ET AL) 12 July 2001 (2001-07-12)
D4: US-A-5 484 606 (DHABHAR ET AL) 16 January 1996 (1996-01-16)
D5: US-A-5 912 011 (MAKINO ET AL) 15 June 1999 (1999-06-15)
D6: US 2004/157928 A1 (KIM JAE-HWAN ET AL) 12 August 2004 (2004-08-12)

2.) The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claims 1-31 is not new in the sense of Article 33(2) PCT.

Claim 1 relates to a composition comprising:
- a salt of one or more active agents and
- a deionizing agent

According to the description (p. 3, l. 13-21), to the examples and claim 8 the pharmaceutical composition should be an aqueous liquid. In a solution it cannot be distinguished whether the ionized active agent and the corresponding counter-ion have been used during preparation or have been formed during the solution.
The term deionizing agent relates to any agent which is capable to deionize any other agent. No limitation or conditions under which deionization should take place are indicated.
Thus claim 1 relates to any composition comprising an ionized active agent and a counter-ion and at least one additional compound capable to ionize any other compound.

D1 discloses a composition comprising diclofenac sodium, 0.2 mole equivalent hydrogen ions, PEG 600 and 7 % water.
D2 discloses Ketoprofen potassium 0.1 mole equivalent hydroxide ions, PEG 400, propylenglycol and 5 % water.
D3 discloses Naproxen sodium, 0.7 mole equivalent hydroxide ions, PEG 300.
D4 discloses a composition comprising pseudoephedrine HCl and Acetaminophen which releases hydrogen ions, PEG propylenglycol and water.

2.) Even if novelty could be established the subject-matter of claims 1-31 does not involve an inventive step in the sense of Article 33(3) PCT.

According to the description (p. 3, l. 11) the underlying problem may be seen in the minimization of the formation of PEG esters. Claims 1-4 do not require the presence of PEG. Therefore the underlying problem does not exist for the subject matter of those claims.
In addition the application does not contain data showing an effect at all. Thus, the underlying problem has not been plausibly solved.

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1.) Reference is made to the following documents:

D1: US-A-5 360 615 (YU ET AL) 1 November 1994 (1994-11-01) cited in the application
D2: WO 95/31979 A (R.P. SCHERER INTERNATIONAL CORPORATION; SHELLEY, RICKEY, S; WEI, YOUCH) 30 November 1995 (1995-11-30)
D3: US 2001/007668 A1 (SAWYER MARYJEAN ET AL) 12 July 2001 (2001-07-12)
D4: US-A-5 484 606 (DHABHAR ET AL) 16 January 1996 (1996-01-16)
D5: US-A-5 912 011 (MAKINO ET AL) 15 June 1999 (1999-06-15)
D6: US 2004/157928 A1 (KIM JAE-HWAN ET AL) 12 August 2004 (2004-08-12)

2.) The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claims 1-31 is not new in the sense of Article 33(2) PCT.

Claim 1 relates to a composition comprising:
- a salt of one or more active agents and
- a deionizing agent

According to the description (p. 3, l. 13-21), to the examples and claim 8 the pharmaceutical composition should be an aqueous liquid. In a solution it cannot be distinguished whether the ionized active agent and the corresponding counter-ion have been used during preparation or have been formed during the solution.
The term deionizing agent relates to any agent which is capable to deionize any other agent. No limitation or conditions under which deionization should take place are indicated.
Thus claim 1 relates to any composition comprising an ionized active agent and a counter-ion and at least one additional compound capable to ionize any other compound.

D1 discloses a composition comprising diclofenac sodium, 0.2 mole equivalent hydrogen ions, PEG 600 and 7 % water.
D2 discloses Ketoprofen potassium 0.1 mole equivalent hydroxide ions, PEG 400, propylenglycol and 5 % water.
D3 discloses Naproxen sodium, 0.7 mole equivalent hydroxide ions, PEG 300.
D4 discloses a composition comprising pseudoephedrine HCl and Acetaminophen which releases hydrogen ions, PEG propylenglycol and water.

2.) Even if novelty could be established the subject-matter of claims 1-31 does not involve an inventive step in the sense of Article 33(3) PCT.

According to the description (p. 3, l. 11) the underlying problem may be seen in the minimization of the formation of PEG esters. Claims 1-4 do not require the presence of PEG. Therefore the underlying problem does not exist for the subject matter of those claims.
In addition the application does not contain data showing an effect at all. Thus, the underlying problem has not been plausibly solved.

We claim:

1. A pharmaceutical composition comprising

(a) a salt of one or more pharmaceutically active agents; and

(b) a deionizing agent.

2. The composition of claim 1 wherein the pharmaceutically active agent is selected from the group consisting of therapeutically active agents, diagnostic agents, and prophylactic agents.

3. The composition of claim 1 wherein the deionizing agent is present in an amount from about 0.2 to 1.0 mole equivalents per mole of the pharmaceutically active agent(s).

4. The composition of claim 1 wherein the deionizing agent is selected from the group consisting of hydrogen ion and hydroxide ion.

5. The composition of claim 1 further comprising polyethylene glycol.

6. The composition of claim 5 wherein polyethylene glycol is present in an amount from about 10% to about 80% by weight.

7. The composition of claim 5 wherein polyethylene glycol is one or more polyethylene glycols with a molecular weight between 300 and 1500.

8. The composition of claim 1 further comprising water.

9. The composition of claim 8 wherein water is present in an amount from about 1% to about 18% by weight.

10. The composition of claim 1 further comprising one or more excipients.

11. The composition of claim 7 wherein the excipients are selected from the group consisting of plasticizers, crystallization inhibitors, wetting agents, bulk filling agents, solubilizers, bioavailability enhancers, solvents, pH-adjusting agents, dyes, preservatives, solvents, surfactants, and combinations thereof.

 AMENDED SHEET

12. The composition of claim 11 wherein the solubilizer is selected from the group consisting of glycerin, polyvinylpyrrolidone, propylene glycol and combinations thereof.

13. The composition of claim 12 wherein the solubilizer is present in amount from about 1% to about 10% by weight.

14. A method of making the composition of any of claims 1-13 comprising

(a) mixing the salt of one or more pharmaceutically active agents, and the deionizing agent at an appropriate temperature; and

(b) encapsulating the mixture in a softgel capsule.

15. The method of claim 14 further comprising polyethylene glycol.

16. The method of claim 14 further comprising water.

17. The method of claim 14 wherein the appropriate temperature is from about 50°C to about 70°C.

18. A method of using the composition of any of claims 1-13 comprising administering to a patient in need thereof the salt of one or more pharmaceutically active agents.

19. A softgel capsule comprising a fill material wherein the fill material comprises

(a) a salt of one or more pharmaceutically active agents; and

(b) a deionizing agent.

20. The capsule of claim 19 wherein the pharmaceutically active agent is selected from the group consisting of therapeutically active agents, diagnostic agents, and prophylactic agents.

21. The capsule of claim 19 wherein the deionizing agent is present in an amount from about 0.2 to 1.0 mole equivalents per mole of the pharmaceutically active agent(s).

22. The capsule of claim 19 wherein the deionizing agent is selected from the group consisting of hydrogen ion and hydroxide ion.

23. The capsule of claim 19 further comprising polyethylene glycol.

24. The capsule of claim 23 wherein polyethylene glycol is present in an amount from about 10% to about 80% by weight.

25. The capsule of claim 23 wherein polyethylene glycol is one or more polyethylene glycols with a molecular weight between 300 and 1500.

26. The capsule of claim 19 further comprising water.

27. The capsule of claim 26 wherein water is present in an amount from about 1% to about 18% by weight.

28. The capsule of claim 19 further comprising one or more excipients.

29. The capsule of claim 28 wherein the excipients are selected from the group consisting of plasticizers, crystallization inhibitors, wetting agents, bulk filling agents, solubilizers, bioavailability enhancers, solvents, pH-adjusting agents, dyes, preservatives, solvents, surfactants, and combinations thereof.

30. The capsule of claim 29 wherein the solubilizer is selected from the group consisting of glycerin, polyvinylpyrrolidone, propylene glycol and combinations thereof.

31. The capsule of claim 29 wherein the solubilizer is present in amount from about 1% to about 10% by weight.

PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

The International Bureau of WIPO
34, chemin des Colombettes
CH - 1211 Geneva 20
Switzerland

PCT

NOTIFICATION CONCERNING
DOCUMENTS TRANSMITTED

Date of mailing
(day/month/year) 20.07.2007

International application No: PCT/US2006/007788

This International Preliminary Examining Authority transmits herewith the following documents:

1. ☐ demand (Rule 61.1(a)).

2. ☒ copy of the international preliminary examination report and its annexes (Rule 71.1).

3. ☐ _____ other documents *(specify)*:

Name and mailing address of the international preliminary examining authority:

European Patent Office
D-80298 Munich
Tel. +49 89 2399 - 0 Tx: 523656 epmu d
Fax: +49 89 2399 - 4465

Authorized Officer

Sleex, Catherine

Tel. +49 89 2399-8044

PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

PABST PATENT GROUP LLP
400 Colony Square, Suite 1200
1201 Peachtree Street
Atlanta, Georgia 30361
ETATS-UNIS D'AMERIQUE

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(PCT Rule 71.1)

Date of mailing *(day/month/year)*	20.07.2007
Applicant's or agent's file reference: BAN 102	**IMPORTANT NOTIFICATION**

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US2006/007788	06.03.2006	08.03.2005

Applicant: Banner Pharmacaps, Inc.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary report on patentability and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary report on patentability. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

The applicant's attention is drawn to Article 33(5), which provides that the criteria of novelty, inventive step and industrial applicability described in Article 33(2) to (4) merely serve the purposes of international preliminary examination and that "any Contracting State may apply additional or different criteria for the purposes of deciding whether, in that State, the claimed inventions is patentable or not" (see also Article 27(5)). Such additional criteria may relate, for example, to exemptions from patentability, requirements for enabling disclosure, clarity and support for the claims.

Name and mailing address of the international preliminary examining authority:

European Patent Office
D-80298 Munich
Tel. +49 89 2399 - 0 Tx: 523656 epmu d
Fax: +49 89 2399 - 4465

Authorized Officer

Sleex, Catherine

Tel. +49 89 2399-8044

We claim:

1. A pharmaceutical composition comprising

(a) a salt of one or more pharmaceutically active agents; and

(b) a deionizing agent.

2. The composition of claim 1 wherein the pharmaceutically active agent is selected from the group consisting of therapeutically active agents, diagnostic agents, and prophylactic agents.

3. The composition of claim 1 wherein the deionizing agent is present in an amount from about 0.2 to 1.0 mole equivalents per mole of the pharmaceutically active agent(s).

4. The composition of claim 1 wherein the deionizing agent is selected from the group consisting of hydrogen ion and hydroxide ion.

5. The composition of claim 1 further comprising polyethylene glycol.

6. The composition of claim 5 wherein polyethylene glycol is present in an amount from about 10% to about 80% by weight.

7. The composition of claim 5 wherein polyethylene glycol is one or more polyethylene glycols with a molecular weight between 300 and 1500.

8. The composition of claim 1 further comprising water.

9. The composition of claim 8 wherein water is present in an amount from about 1% to about 18% by weight.

10. The composition of claim 1 further comprising one or more excipients.

11. The composition of claim 7 wherein the excipients are selected from the group consisting of plasticizers, crystallization inhibitors, wetting agents, bulk filling agents, solubilizers, bioavailability enhancers, solvents, pH-adjusting agents, dyes, preservatives, solvents, surfactants, and combinations thereof.

We claim:

1. A pharmaceutical composition comprising

(a) a salt of one or more pharmaceutically active agents; and

(b) a deionizing agent.

2. The composition of claim 1 wherein the pharmaceutically active agent is selected from the group consisting of therapeutically active agents, diagnostic agents, and prophylactic agents.

3. The composition of claim 1 wherein the deionizing agent is present in an amount from about 0.2 to 1.0 mole equivalents per mole of the pharmaceutically active agent(s).

4. The composition of claim 1 wherein the deionizing agent is selected from the group consisting of hydrogen ion and hydroxide ion.

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12. The composition of claim 11 wherein the solubilizer is selected from the group consisting of glycerin, polyvinylpyrrolidone, propylene glycol and combinations thereof.

13. The composition of claim 12 wherein the solubilizer is present in amount from about 1% to about 10% by weight.

14. A method of making the composition of any of claims 1-13 comprising

(a) mixing the salt of one or more pharmaceutically active agents, and the deionizing agent at an appropriate temperature; and

(b) encapsulating the mixture in a softgel capsule.

15. The method of claim 14 further comprising polyethylene glycol.

16. The method of claim 14 further comprising water.

17. The method of claim 14 wherein the appropriate temperature is from about 50°C to about 70°C.

18. A method of using the composition of any of claims 1-13 comprising administering to a patient in need thereof the salt of one or more pharmaceutically active agents.

19. A softgel capsule comprising a fill material wherein the fill material comprises

(a) a salt of one or more pharmaceutically active agents; and

(b) a deionizing agent.

20. The capsule of claim 19 wherein the pharmaceutically active agent is selected from the group consisting of therapeutically active agents, diagnostic agents, and prophylactic agents.

21. The capsule of claim 19 wherein the deionizing agent is present in an amount from about 0.2 to 1.0 mole equivalents per mole of the pharmaceutically active agent(s).

22. The capsule of claim 19 wherein the deionizing agent is selected from the group consisting of hydrogen ion and hydroxide ion.

23. The capsule of claim 19 further comprising polyethylene glycol.

24. The capsule of claim 23 wherein polyethylene glycol is present in an amount from about 10% to about 80% by weight.

25. The capsule of claim 23 wherein polyethylene glycol is one or more polyethylene glycols with a molecular weight between 300 and 1500.

26. The capsule of claim 19 further comprising water.

27. The capsule of claim 26 wherein water is present in an amount from about 1% to about 18% by weight.

28. The capsule of claim 19 further comprising one or more excipients.

29. The capsule of claim 28 wherein the excipients are selected from the group consisting of plasticizers, crystallization inhibitors, wetting agents, bulk filling agents, solubilizers, bioavailability enhancers, solvents, pH-adjusting agents, dyes, preservatives, solvents, surfactants, and combinations thereof.

30. The capsule of claim 29 wherein the solubilizer is selected from the group consisting of glycerin, polyvinylpyrrolidone, propylene glycol and combinations thereof.

31. The capsule of claim 29 wherein the solubilizer is present in amount from about 1% to about 10% by weight.

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference BAN 102	**FOR FURTHER ACTION**	See Form PCT/IPEA/416
International application No. PCT/US2006/007788	International filing date *(day/month/year)* 06.03.2006	Priority date *(day/month/year)* 08.03.2005
International Patent Classification (IPC) or national classification and IPC INV. A61K9/48		
Applicant Banner Pharmacaps, Inc.		

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 5 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☒ *sent to the applicant and to the International Bureau)* a total of 3 sheets, as follows:
      ☒ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in electronic form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

☒	Box No. I	Basis of the report
☐	Box No. II	Priority
☐	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☐	Box No. VIII	Certain observations on the international application

Date of submission of the demand	Date of completion of this report
2007-01-08	20.07.2007
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Büttner, Ulf Telephone No. +49 89 2399-7841

Box No. I Basis of the report

1. With regard to the **language**, this report is based on

   ☒ the international application in the language in which it was filed

   ☐ a translation of the international application into , which is the language of a translation furnished for the purposes of:
   - ☐ international search (under Rules 12.3(a) and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4(a))
   - ☐ international preliminary examination (under Rules 55.2(a) and/or 55.3(a))

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

   Description, Pages

   1-15 as originally filed

   Claims, Numbers

   1-31 filed with telefax on 08.01.2007

   ☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	
	No:	Claims	1-31
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-31
Industrial applicability (IA)	Yes:	Claims	1-31
	No:	Claims	

2. Citations and explanations (Rule 70.7):

see separate sheet

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1.) Reference is made to the following documents:

D1: US-A-5 360 615 (YU ET AL) 1 November 1994 (1994-11-01) cited in the application
D2: WO 95/31979 A (R.P. SCHERER INTERNATIONAL CORPORATION; SHELLEY, RICKEY, S; WEI, YOUCH) 30 November 1995 (1995-11-30)
D3: US 2001/007668 A1 (SAWYER MARYJEAN ET AL) 12 July 2001 (2001-07-12)
D4: US-A-5 484 606 (DHABHAR ET AL) 16 January 1996 (1996-01-16)
D5: US-A-5 912 011 (MAKINO ET AL) 15 June 1999 (1999-06-15)
D6: US 2004/157928 A1 (KIM JAE-HWAN ET AL) 12 August 2004 (2004-08-12)

2.) The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claims 1-31 is not new in the sense of Article 33(2) PCT.

Claim 1 relates to a composition comprising:
- a salt of one or more active agents and
- a deionizing agent
According to the description (p. 3, l. 13-21), to the examples and claim 8 the pharmaceutical composition should be an aqueous liquid. In a solution it cannot be distinguished whether the ionized active agent and the corresponding counter-ion have been used during preparation or have been formed during the solution.
The term deionizing agent relates to any agent which is capable to deionize any other agent. No limitation or conditions under which deionization should take place are indicated.
Thus claim 1 relates to any composition comprising an ionized active agent and a counter-ion and at least one additional compound capable to ionize any other compound.

D1 discloses a composition comprising diclofenac sodium, 0.2 mole equivalent hydrogen ions, PEG 600 and 7 % water.
D2 discloses Ketoprofen potassium 0.1 mole equivalent hydroxide ions, PEG 400, propylenglycol and 5 % water.
D3 discloses Naproxen sodium, 0.7 mole equivalent hydroxide ions, PEG 300.
D4 discloses a composition comprising pseudoephedrine HCl and Acetaminophen which releases hydrogen ions, PEG propylenglycol and water.

2.) Even if novelty could be established the subject-matter of claims 1-31 does not involve an inventive step in the sense of Article 33(3) PCT.

According to the description (p. 3, l. 11) the underlying problem may be seen in the minimization of the formation of PEG esters. Claims 1-4 do not require the presence of PEG. Therefore the underlying problem does not exist for the subject matter of those claims.
In addition the application does not contain data showing an effect at all. Thus, the underlying problem has not been plausibly solved.

ERIC POTTER CLARKSON
PATENTS · TRADEMARKS · DESIGNS · COPYRIGHT

To: **The European Patent Office**

Your Fax No: 0031 70 3403016

From: Charlotte Crowhurst

Date: 25 September 2007

Our Ref: PABCA / P38814EP

Your Ref:

Sheet 1 of 1 **Original by Post: No**

MESSAGE:

PCT Application No: PCT/US2006/007788
Applicant(s): Banner Pharmacaps, Inc.

I have been appointed as representative to prosecute this application before the European Patent Office.

Eric Potter Clarkson LLP is a limited liability partnership, registered in England as No. OC315197, having its registered office at the address shown.
A list of the members' names is available for inspection at the registered office.
All instructions are accepted subject to our current terms of engagement.
NOTTINGHAM • MUNICH

Park View House
58 The Ropewalk
Nottingham NG1 5DD
United Kingdom

T. +44 (0) 115 955 2211
F. +44 (0) 115 955 2201
E. epc@eric-potter.com
W. www.eric-potter.com

Eintritt in die europäische Phase (EPA als Bestimmungsamt oder ausgewähltes Amt)

Entry into the European phase (EPO as designated or elected Office)

Entrée dans la phase européenne (l'OEB agissant en qualité d'office désigné ou élu)

Europäische Anmeldenummer oder, falls nicht bekannt, PCT-Aktenzeichen oder PCT-Veröffentlichungsnummer	European application number, or, if not known, PCT application or publication number	Numéro de dépôt de la demande de brevet européen ou, à défaut, numéro de dépôt PCT ou de publication PCT
	06737018.9 PCT/US2006/007788	
Zeichen des Anmelders oder Vertreters (max. 15 Positionen)	**Applicant's or representative's reference** (max. 15 spaces)	**Référence du demandeur ou du mandataire** (15 caractères ou espaces au maximum)
	PABCA / P38814EP	

☒ **1. Anmelder**
Die Angaben über den (die) Anmelder sind in der internationalen Veröffentlichung enthalten oder vom Internatio-nalen Büro nach der internationalen Veröffentlichung vermerkt worden.

☐ Änderungen, die das Internationale Büro noch nicht vermerkt hat, sind auf einem Zusatzblatt angegeben.

Zustellanschrift
(siehe Merkblatt II, 1)

1. Applicant
Indications concerning the applicant(s) are contained in the international publication or recorded by the International Bureau after the international publication.

Changes, which have not yet been recorded by the International Bureau, are set out on an additional sheet.

Address for correspondence
(see *Notes II, 1)*

1. Demandeur
Les indications concernant le(s) de-mandeur(s) figurent dans la publication internationale ou ont été enregistrées par le Bureau international après la publication internationale.

Les changements qui n'ont pas encore été enregistrés par le Bureau international sont indiqués sur une feuille additionelle.

Adresse pour la correspondance
(voir notice II,1)

2. Vertreter

Name (Nur einen Vertreter angeben, der in das europäische Patentregister eingetragen und an den zugestellt wird)

Geschäftsanschrift

Telefon

Telefax **Telex**

☐ Weitere(r) Vertreter auf Zusatzblatt

2. Representative

Name (Name **only one** representative who will be listed in the Register of European Patents and to whom notification will be made)

Charlotte Crowhurst

Address of place of business
ERIC POTTER CLARKSON LLP
PARK VIEW HOUSE, 58 THE ROPEWALK
NOTTINGHAM NG1 5DD UNITED KINGDOM

Telephone
0115 9552211

Fax **Telex**
0115 9552201

Additional representative(s) on additional sheet

2. Mandataire

Nom (N'indiquer **qu' un seul** mandataire, qui sera inscrit au Registre européen des brevets et auquel signification sera faite)

Adresse professionnelle

Téléphone

Téléfax **Télex**

Autre(s) mandataire(s) sur une feuille additionnelle

3. Vollmacht

☐ Einzelvollmacht ist beigefügt.

☒ Allgemeine Vollmacht ist registriert unter Nummer:

☐ Allgemeine Vollmacht ist eingereicht, aber noch nicht registriert.

☐ Die beim EPA als PCT-Anmeldeamt eingereichte Vollmacht schließt ausdrücklich die europäische Phase ein.

3. Authorisation

Individual authorisation is attached.

General authorisation has been registered under No:
47568

A general authorisation has been filed, but not yet registered.

The authorisation filed with the EPO as PCT receiving Office expressly includes the European phase.

3. Pouvoir

Un pouvoir spécial est joint.

Un pouvoir général a été enregistré sous le no :

Un pouvoir général a été déposé mais n'est pas encore enregistré.

Le pouvoir général déposé à l'OEB agissant en qualité d'office récepteur au titre du PCT s'applique expressément à la phase européene.

☒ **3. Prüfungsantrag**
Hiermit wird die Prüfung der Anmel-dung gemäß Art. 94 EPÜ beantragt. Die Prüfungsgebühr wird (wurde) entrichtet.

Prüfungsantrag in einer zugelassenen Nichtamtssprache (siehe Merkblatt III, 5.2):

4. Request for examination
Examination of the application under Art. 94 EPC is hereby requested. The examination fee is being (has been, will be) paid.

Request for examination in an admissible non-EPO language (see Notes III, 5.2):

4. Requête en examen
Il est demandé que soit examinée la demande de brevet, conformément à l'art. 94 CBE. Il est (a été, sera) procédé au paiement de la taxe d'examen.

Requête en examen dans une langue non officielle autorisée (voir notice III, 5.2):

☐ **5. Abschriften**
Zusätzliche Abschrift(en) der im ergänzenden europäischen Recherchenbericht angeführten Schriftstücke wird (werden) beantragt.

Anzahl der **zusätzlichen** Sätze von Abschriften

5. Copies
Additional copy (copies) of the documents cited in the supplementary European search report is (are) requested.

Number of **additional** sets of copies

5. Copies
Prière de fournir une ou plusieurs copies supplémentaires des documents cités dans le rapport complémentaire de recherche européenne.

Nombre de jeux **supplémentaires** de copies

6. Für das Verfahren vor dem EPA bestimmte Unterlagen

6.1 Dem Verfahren vor dem EPA als **Bestimmungsamt** (PCT I) sind folgende Unterlagen zugrunde zu legen:

☒ die vom Internationalen Büro **veröffentlichten Anmeldungsunter-lagen** (mit **allen** Ansprüchen, Beschreibung und Zeichnungen), gegebenenfalls mit den geänderten Ansprüchen nach Art. 19 PCT

☐ soweit sie nicht ersetzt werden durch die beigefügten **Änderungen.**

Falls nötig, sind Klarstellungen auf einem Zusatzblatt einzureichen !

6.2 Dem Verfahren vor dem EPA als **ausgewähltem Amt** PCT II) sind folgende Unterlagen zugrunde zu legen:

☒ die dem **internationalen vorläufigen Prüfungsbericht zugrunde gelegten Unterlagen** einschließlich seiner eventuellen **Anlagen**
(Solche Anlagen müssen immer beigefügt werden)

☒ soweit sie nicht ersetzt werden durch die beige-fügten **Änderungen.**

Falls nötig, sind Klarstellungen auf einem Zusatzblatt einzureichen!

☒ Sind dem EPA als mit der internationalen vorläufigen Prüfung beauftragten Behörde **Versuchsberichte** zugegangen, dürfen diese dem Verfahren vor dem EPA zugrunde gelegt werden.

6. Documents intended for pro-ceedings before the EPO

6.1 Proceedings before the EPO as **designated Office** (PCT I) are to be based on the following documents:

the **application documents pub-lished** by the International Bureau (with **all** claims, description and drawings), where applicable with amended claims under Art. 19 PCT

unless replaced by the **amend-ments** enclosed.

Where necessary, clarifications must be submitted on a separate sheet!

6.2 Proceedings before the EPO as **elected Office** (PCT II) are to be based on the following documents:

the **documents on which the international preliminary examination report is based,** including its possible **annexes**
(Such annexes must always be filed)

unless replaced by the **amendments** enclosed.

Where necessary, clarifications must be submitted on a separate sheet!

If the EPO as International Preliminary Examining Authority has received **test reports,** these may be used as the basis of proceedings before the EPO.

6. Pièces destinées à la procédure devant l'OEB

6.1 La procédure devant l'OEB agissant en qualité **d'office désigné** (PCT I) doit se fonder sur les pièces suivantes :

les **pièces de la demande publiée** par le Bureau international (avec **toutes** les revendications, la description et les dessins), éventuellement avec les revendications modifiées conformé-ment à l'article 19 du PCT

dans la mesure où elles ne sont pas remplacées par les **modifications** jointes.

Le cas échéant, des explications doivent être jointes sur une feuille additionnelle!

6.2 La procédure devant l'OEB **agissant en qualité d'office élu** (PCT II) doit se fonder sur les pièces suivantes :

les **pièces sur lesquelles se fonde le rapport d'examen préliminaire international,** y compris ses **annexes** éventuelles
(De telles annexes sont toujours à joindre)

dans la mesure où elles ne sont pas remplacées par les **modifications** jointes.

Le cas échéant, des explications doivent être jointes sur une feuille additionnelle!

Si l'OEB, agissant en qualité d'administration chargée de l'examen préliminaire international, a reçu des **rapports d'essais,** ceux-ci peuvent constituer la base de la procédure devant l'OEB.

7. Übersetzungen
Beigefügt sind die nachfolgend angekreuzten Übersetzungen in einer der Amtssprachen des EPA (Deutsch, Englisch, Französisch):

- *Im Verfahren vor dem EPA als* ***Bestimmungsamt oder ausgewähltem Amt*** *(PCT I + II):*

☐ Übersetzung der **ursprünglich eingereichten internationalen Anmeldung** (Beschreibung, Ansprüche, etwaige Textbestandteile in den Zeichnungen), der veröffentlichten Zusammenfassung, und etwaiger Angaben über biologisches material nach Regel 13bis.3 und 13bis.4 PCT

☐ Übersetzung der **prioritätsbegründenden Anmeldung(en)**

☐ Es wird hiermit erklärt, daß die internationale Anmeldung in ihrer ursprünglich eingereichten Fassung eine vollständige Übersetzung der früheren An-meldung ist (Regel 38(5) EPÜ)

- ***Zusätzlich*** *im Verfahren vor dem EPA als* ***Bestimmungsamt*** *(PCT I):*

☐ Übersetzung der nach Art. 19 PCT **geänderten Ansprüche** nebst Erklärung, falls diese dem Verfahren vor dem EPA zugrunde gelegt werden sollen (siehe Feld 6)

- ***Zusätzlich*** *im Verfahren vor dem EPA als* ***ausgewähltem Amt*** *(PCT II):*

☐ Übersetzung der **Anlagen zum internationalen vorläufigen Prüfungsbericht**

7. Translations
Translations in one of the official languages of the EPO (English, French, German) are enclosed as crossed below:

- *In proceedings before the EPO as* ***designated or elected Office*** *(PCT I + II):*

Translation of the **international application** (description, claims, any text in the drawings) **as originally filed,** of the abstract as published and of any indication under Rule 13bis.3 and 13bis.4 PCT regarding biological material

Translation of **the priority application (s)**

It is hereby declared that the international application as originally filed is a complete translation of the previous application (Rule 38(5) EPC)

- ***In addition,*** *in proceedings before the EPO as* ***designated Office*** *(PCT I):*

Translation of **amended claims** and any statement under Art. 19 PCT, if the claims as amended are to form the basis for the proceedings before the EPO (see Section 6)

- ***In addition,*** *in proceedings before the EPO as* ***elected office*** *(PCT II):*

Translation of any **annexes to the international preliminary examination report**

7. Traductions
Vous trouverez ci-joint les traductions cochées ci-après dans l'une des langues officielles de l'OEB (allemand, anglais, français):

- *Dans la procédure devant l'OEB agissant en qualité* ***d'office désigné ou élu*** *(PCT I + II):*

Traduction de la **demande internationale telle que déposée initialement** (description, revendications, textes figurant éventuelle-ment dans les dessins), de l'abrégé publié, et de toutes indications visées aux règles 13bis 3 et 13bis.4 du PCT concernant le matériel biologique

Traduction de la (des) **demande(s) ouvrant le droit de priorité**

Il est déclaré par la présente que la demande internationale telle que déposée initialement est une traduction intégrale de la demande anterieure (règle 38(5) CBE)

- ***De plus,*** *dans la procédure devant l'OEB agissant en qualité* ***d'office désigné*** *(PCT I):*

Traduction des **revendications modifiées** et de la déclaration faite conformément à l'article 19 du PCT, si la procédure devant l'OEB doit être fondée sur les revendications modifiées (voir la rubrique 6)

- ***De plus,*** *dans la procédure devant l'OEB agissant en qualité* ***d'office élu*** *(PCT II):*

Traduction des **annexes du rapport d'examen préliminaire international**

☐ **8. Biologisches Material**
Die Erfindung bezieht sich auf bzw. verwendet biologisches Material, das nach Regel 28 EPÜ hinterlegt worden ist.

☐ Die **Angaben nach Regel 28(1)c) EPÜ** (falls noch nicht bekannt, die Hinterlegungsstelle und das (die) Bezugszeichen [Nummer, Symbole usw.] des Hinterlegers) sind in der internationalen Veröffentlichung oder in der gemäß Feld 7 eingereichten Übersetzung enthalten auf:

Seite(n) / Zeile(n)

Die **Empfangsbescheinigung(en)** der Hinterlegungsstelle

☐ ist (sind) beigefügt

☐ wird (werden) nachgereicht

☐ Verzicht auf die Verpflichtung des Antragstellers nach Regel 28(3) EPÜ auf gesondertem Schriftstück

8. Biological material
The invention relates to and/or uses biological material deposited under Rule 28 EPC.

The **particulars referred to in Rule 28(1)(c) EPC** (if not yet known, the depository institution and the identification reference(s) [number, symbols etc.] of the depositor) are given in the international publication or in the translation submitted under Section 7 on:

page(s) / line(s)

The **receipt(s) of deposit** issued by the depositary institution

is (are) enclosed

will be filed at a later date

Waiver of the right to an undertaking from the requester pursuant to Rule 28(3) EPC attached.

8. Matière biologique
L'invention concerne et/ou utilise de la matière biologique, déposée conformément à la règle 28 CBE.

Les **indications visées à la règle 28(1)c) CBE** (si pas encore connues, l'autorité de dépôt et la (les) référence(s) d'identification [numéro ou symboles etc.] du déposant) figurent dans la publication internationale ou dans une traduction produite conformément à la rubrique 7 à la / aux:

page(s) / ligne(s)

Le(s) **récépissé(s) de dépôt** délivré(s) par l'autorité de dépôt

est (sont) joint(s)

sera (seront) produit(s) ultérieurement

Renonciation, sur document distinct, à l'engagement du requérant au titre de la règle 28(3) CBE.

9. Nucleotid- und Aminosäure-sequenzen

☐ Die nach Regeln 5.2 und 13ter PCT sowie Regel 111 (3) EPÜ erforderli-chen Unterlagen liegen dem EPA bereits vor.

☐ Das schriftliche Sequenzprotokoll wird anliegend nachgereicht.

☐ Das Sequenzprotokoll geht nicht über den Inhalt der Anmeldung in der ursprünglich eingereichten Fassung hinaus.

Der vorgeschriebene Datenträger ist beigefügt.

☐ Die auf dem Datenträger gespeicherte Information stimmt mit dem schriftlichen Sequenzprotokoll überein.

9. Nucleotide and amino acid sequences

The items necessary in accordance with Rules 5.2 and 13ter PCT and Rule 111 (3) EPC have already been furnished to the EPO.

The written sequence listing is furnished herewith.

The sequence listing does not include matter which goes beyond the content of the application as filed.

The prescribed data carrier is enclosed.

The information recorded on the data carrier is identical to the written sequence listing.

9. Séquences de nucléotides et d'acides aminés

Les pièces requises selon les règles 5.2 et 13ter PCT et la règle 111(3) CBE ont déjà été déposées auprès de l'OEB.

La liste de séquences écrite est produite ci-joint.

La liste de séquences ne contient pas d'éléments s'étendant au-delà du contenu de la demande telle qu'elle a été déposée.

Le support de données prescrit, est joint.

L'information figurant sur le support de données est identique à celle que contient la liste de séquences écrite.

10. Benennungsgebühren

☒ 10.1 Es ist derzeit beabsichtigt, den **siebenfachen** Betrag einer Benennungsgebühr zu entrichten. Damit gelten die Benennungsgebühren für **alle Vertragsstaaten des EPÜ**[1] als entrichtet. (Art. 2 Nr. 3 GebO), sowelt sie **in der internationalen Anmldung** bestimmt sind[2].

☐ 10.2 Abweichend von der Erklärung in Nr. 10.1 ist derzeit beabsichtigt, **weniger als sieben** Benennungsgebühren für folgende **in der intetnationalen Anmeldung bestimmte Vertragsstaaten des EPÜ**[2] zu entrichten:

(1) ☐ ☐ _____
(2) ☐ ☐ _____
(3) ☐ ☐ _____

Soweit unter Nr. 10.2 Vertragsstaaten aufgeführt sind, wird beantragt, fur die dort nicht aufgeführten Vertragsstaaten von der Zustellung einer Mitteilung nach Regel 108(3) EPÜ abzusehen.

☒ 10.3 Wird **ein automatischer Abbuchungsauftrag** erteilt (Feld 12), so wird das EPA beauftragt, bei Ablauf der Grundfrist nach Regel 107 (1)(d) EPÜ den siebenfachen Betrag einer Bennungsgebühr abzubuchen. Ist eine Erklärung nach Nr. 10.2 abgegeben worden, so sollen die Benennungsgebühren nur für die dort angegebenen Vertragsstaaten abgebucht werden, sofern dem EPA nicht bis zum Ablauf der Grundfrist ein anderslautender Auftrag zugeht.

10. Designation fees

10.1 It is currently intended to pay **seven times** the amount of the designation fee. The designation fees for **all the EPC contracting states**[1] **designated in the international application**[2] are thereby deemed to have been paid (Art. 2 No. 3 Rfees).

10.2 The declaration in No. 10.1 does not apply. Instead, it is currently intended to pay **fewer that seven** designation fees for the following **EPC contracting states**[2] **designated in the international application**:

(4) ☐ ☐ _____
(5) ☐ ☐ _____
(6) ☐ ☐ _____

If contracting states are indicated under No. 10.2, it is requested that no communication under Rule 108(3) EPC be issued for contracting states not thus indicated.

10.3 If an **automatic debit order** has been issued (Section 12), the EPO is authorised, on expiry of the basic period under Rule 107(1)(d) EPC, to debit seven times the amount of the designation fee. If states are indicated under No. 10.2, the EPO will debit designation fees only for those states, unless instructed otherwise before the basic period expires.

10. Taxes de désignation

10.1 Il est actuellement envisagé de payer un montant correspondant à **sept fois** la taxe de désignation. Les taxes de désignation sont ainsi réputées payées pour **tous les Etats contractants de la CBE**[1] **désignés dans la demande internationale**[2] (art. 2, point 3 du RRT).

10.2 Contrairement à ce qui est indiqué au n° 10.1, il est actuellement envisagé de payer **moins de sept** taxes de désignation pour les **Etats contractants de la CBE**[2] suivants **désignés dans la demande internationale** :

(4) ☐ ☐ _____
(5) ☐ ☐ _____
(6) ☐ ☐ _____

Si des Etats contractants sont mentionnés au n° 10.2, prière de ne Pas procéder à la signification d'une Notification prévue par la règle 108(3) CBE pour les Etats contractants n'ayant pas été y mentionnés.

10.3 Si un **ordre de prélèvement automatique** est donné (rubrique 12), il est demandé à l'OEB de prélever, à l'expiration du délai normal visé à la règle 107(1)(d) CBE, un montant correspondant à sept fois la taxe de désignation. Si une déclaration a été faite au n° 10.2, les taxes de désignation ne sont à prélever que pour les Etats contractants qui y sont indiqués,sauf instruction contraire reçue par l'OEB avant l'expiration du délai normal.

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1 Stand bei Drucklegung: 27 Vertragsstaaten, und zwar: / Status when this form was printed: 27 contracting states, namely / Situation à la date d'impression : 27 Etats contractants, à savoir : AT Österreich / Austria / Autriche, BE Belgien / Belgium / Belgique, BG Bulgarien / Bulgaria / Bulgarie, CH/LI Schweiz und Liechtenstein / Switzerland and Liechtenstein / Suisse et Liechtenstein, CY Zypern / Cyprus / Chypre, CZ Tschechische Republik / Czech Republic / République tchèque, DE Deutschland / Germany / Allemagne, DK Dänemark / Denmark / Danemark, EE Estland / Estonia / Estonie, ES Spanien / Spain / Espagne, FI Finnland / Finland / Finlande, FR Frankreich / France / France, GB Vereinigtes Königreich / United Kingdom / Royaume-Uni, GR Griechenland / Greece / Grèce, HU Ungarn / Hungary / Hongrie, IE Irland / Ireland / Irlande, IT Italien / Italy / Italie, LU Luxemburg / Luxembourg / Luxembourg, MC Monaco / Monaco / Monaco, NL Niederlande / Netherlands / Pays-Bas, PT Portugal / Portugal / Portugal, RO Rumänien / Romania / Roumanie, SE Schweden / Sweden / Suède, SK Slowakische Republik / Slovak Republic / République slovaque, SI Slowenien / Slovenia / Slovénie, TR Türkei / Turkey / Turquie

2.Für folgende Staaten nur möglich, falls in der internationalen Anmeldung am oder nach folgendem Tag bestimmt: Slowakische Republik, Bulgarien, Tschechische Republik und Estland: 1. Juli 2002, Slowenien: 1. Dezember 2002, Ungarn: 1. Januar 2003 und Rumänien: 1. März 2003. / For the following states this is possible only if they are designated in the international application on or after the stated date: Slovak Republic, Bulgaria, Czech Republic and Estonia: 1 July 2002, Slovenia: 1 December 2002, Hungary: 1 January 2003 and Romania: 1 March 2003. / En ce qui concerne les Etats suivants seulement si la désignation a été effectuée dans la demande internationale à la date suivante ou à une date ultérieure: République slovaque, Bulgarie, République tchèque et Estonie: 1er juillet 2002, Slovénie: 1er décembre 2002, Hongrie: 1er janvier 2003 et Roumanie: 1er mars 2003:

☒ **11. Erstreckung des europäischen Patents**

Bei Zahlung der Erstreckungsgebühr(en) gilt diese Anmeldung auch als wirksamer Erstreckungsantrag für die in der internationalen Anmeldung bestimmten »Erstreckungsstaaten«.Es ist beabsichtigt, diese Gebühr(en)für folgende Staaten zu entrichten:

11. Extension of the European patent

On payment of the extension fee(s) this application is also deemed to be a request for extension to all the "extension states" designated in the international application. It is intended to pay the fee(s) for the following states:

11. Extension des effets du brevet européen

La taxe (Les taxes) d'extension payée(s), la présente demande est également réputée être une demande d'extension à tous les «Etats autorisant l'extension» désignés dans la demande internationale. Il est envisagé de payer la taxe (les taxes) d'extension pour les Etats suivants:

☐	SI	Slowenien [1]	Slovenia [1]	Slovénie [1]
☐	LT	Litauen	Lithuania	Lituanie
☐	LV	Lettland	Latvia	Lettonie
☐	AL	Albanien	Albania	Albanie
☐	RO	Rumänien [1]	Romania [1]	Roumanie [1]
☐	MK	Ehmalige jugoslawische Republik	Former Yugoslav Republic of	Ex-République yougoslave de Macédoine
☐	BA	Bosnien und Herzegowina	Bosnia and Herzegovina	Bosnie-Herzégovine
☐	HR	Kroatien [2]	Croatia [2]	Croatie [2]
☐	YU	Serbien und Montenegro	Serbia and Montenegro	Serbie-et-Monténégro

1) Für Slowenien und Rumänien nur möglich, falls in der internationalen Anmeldung bis 30. November 2002 (Slowenien) oder bis 28. Februar 2003 (Rumänien) bestimmt. / For Slovenia and Romania this is possible only if they are designated in the international application up to 30 November 2002 (Slovenia) or 28 February 2003 (Romania). / En ce qui concerne la Slovénie et la Roumanie, seulement si la désignation a été effectuée dans la demande internationale jusqu'au 30 novembre 2002 (Slovénie) ou jusqu'au 28 février 2003 (Roumanie).

2) Platz für Staaten, mit denen »Erstreckungsabkommen« nach Drucklegung dieses Formblatts in Kraft treten und die in der internationalen Anmeldung bestimmt waren. / Space for States with which "extension agreements" enter into force after this form has been printed and which were designated in the international application. / Prévu pour des Etats à l'égard desquels des «accords d'extension» entreront en vigueur après l'impression du présent formulaire et qui ont été désignés dans la demande internationale.

☐ ***11. Automatischer Abbuchungsauftrag (Nur möglich für Inhaber von beim EPA geführten laufenden Konten)***

Das EPA wird beauftragt, nach Maßgabe der Vorschriften über das automatische Abbuchungsverfahren fällige Gebühren und Auslagen vom Untenstehenden laufenden Konto abzubuchen. In Bezug auf die **Benennungsgebühren** wird auf Feld 10.3 verwiesen. Das EPA wird ferner beauftragt, die **Erstreckungsgebühren** für jeden in Feld 11 angekreuzten »Erstreckungsstaat« bei Ablauf der Grundfrist zu ihrer Zahlung abzubuchen, sofern ihm nicht bis dahin ein anderslautender Auftrag zugeht.

Nummer und Kontoinhaber

12. Automatic debit order *(for EPO deposit account holders only)*

The EPO is hereby authorised, under the Arrangements for the automatic debiting procedure, to debit from the deposit account below any fees and costs falling due. For **designation fees**, see Section 10.3. The EPO is also authorised, on expiry of the basic period for paying the extension fees, to debit those fees for each of the "extension states" marked with a cross in Section 11, unless instructed otherwise before the said period expires.

Number and account holder

12. Ordre de prélèvement automatique *(uniquement possible pour les titulaires de comptes courants ouverts auprès de l'OEB)*

Par la présente, il est demandé à l'OEB de prélever du compte courant ci-dessous les taxes et frais venant à échéance, conformément à la réglementation relative au prélèvement automatique. Pour les **taxes de désignation,** se reporter à la rubrique 10.3. Il est en outre demandé à l'OEB de prélever, à l'expiration du délai normal prévu pour leur paiement, les **taxes d'extension** pour chaque «Etat autorisant l'extension» coché à la rubrique 11, sauf instruction contraire reçue avant l'expiration de ce délai.

Numéro et titulaire du compte

☒ **13.** Eventuelle **Rückzahlungen** auf das beim EPA geführte laufende Konto

Nummer und Kontoinhaber

13. Any **reimbursement** to EPO deposit account

Number and account holder

28050040 Eric Potter Clarkson LLP

13. Remboursements éventuels à effectuer sur le compte courant ouvert auprès de l'OEB

Nom du titulaire du compte

14. Unterschrift(en) des (der) Anmelder(s) oder Vertreters

14. Signature(s) of applicant(s) or representative

14. Signature(s) du (des) demandeur(s) ou du mandataire

Charlotte Crowhurst
For and on behalf of Eric Potter Clarkson LLP

Ort / Datum

Place / Date
NOTTINGHAM, ENGLAND
25 September 2007

Lieu / Date

Für Angestellte (Art. 133(3) EPÜ) mit allgemeiner Vollmacht:

Nr. _____

Name(n) des (der) Unterzeichneten bitte in Druckschrift wiederholen. Bei juristischen Personen bitte auch die Stellung des (der) Unterzeichneten innerhalb der Gesellschaft in Druckschrift angeben.

For employees (Art. 133(3) EPC) having a general authorisation

No. _____

Please print name(s) under signature(s). In the case of legal persons, the position of the signatory within the company should also be printed.

Pour les employés (art. 133(3) CBE) disposant d'un pouvoir général:

N° _____

Le ou les noms des signataires doivent être indiqués en caractères d'imprimerie. S'il s'agit d'une personne morale, la position occupée au sein de celle-ci par le ou les signataires doit également être indiquée en caractères d'imprimerie.

ERIC POTTER CLARKSON
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European Patent Office
PB 5818
Patentlaan 2
2280 HV Rijswijk (ZH)
The Netherlands

25 September 2007

Dear Sirs

European Application No	:	**06737018.9**
PCT Application No	:	**PCT/US2006/007788**
Applicant(s)	:	**Banner Pharmacaps, Inc.**
Our Ref	:	**PABCA / P38814EP**

We are enclosing documentation for European processing of this PCT application.

We intend that any application, designation, examination and search fees due (together with any surcharges if applicable) should be paid and we are instructing your Cash & Accounts Department to take the fees from our deposit account.

Please note that, if claim amendments have been made, these should not be construed as abandonment of subject matter. If the application contains claims for which excess claims fees are not paid, this is not to be construed as abandonment of subject matter for the purposes of filing any future divisional application.

We shall assume that the requirements of article 20(1) PCT have been met unless you advise us to the contrary.

We request oral proceedings before the application is refused.

Yours faithfully

ES BASSETT

Charlotte Crowhurst
For and on behalf of Eric Potter Clarkson LLP

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W. www.eric-potter.com

CLAIMS

~~We claim~~

1. A pharmaceutical composition comprising

(a) a salt of one or more pharmaceutically active agents; and

(b) a deionizing agent.

~~2. The composition of claim 1 wherein the pharmaceutically active~~ agent is selected from the group consisting of therapeutically active agents, diagnostic agents, and prophylactic agents.

3. The composition of claim 1 wherein the deionizing agent is present in an amount from about 0.2 to 1.0 mole equivalents per mole of the pharmaceutically active agent(s).

4. The composition of claim 1 wherein the deionizing agent is selected from the group consisting of hydrogen ion and hydroxide ion.

5. The composition of claim 1 further comprising polyethylene glycol.

6. The composition of claim 5 wherein polyethylene glycol is present in an amount from about 10% to about 80% by weight.

7. The composition of claim 5 wherein polyethylene glycol is one or more polyethylene glycols with a molecular weight between 300 and 1500.

8. The composition of claim 1 further comprising water.

9. The composition of claim 8 wherein water is present in an amount from about 1% to about 18% by weight.

10. The composition of claim 1 further comprising one or more excipients.

11. The composition of claim 7 wherein the excipients are selected from the group consisting of plasticizers, crystallization inhibitors, wetting agents, bulk filling agents, solubilizers, bioavailability enhancers, solvents, pH-adjusting agents, dyes, preservatives, solvents, surfactants, and ~~combinations thereof.~~

~~12. The composition of claim 11 wherein the solubilizer is selected~~ from the group consisting of glycerin, polyvinylpyrrolidone, propylene glycol and combinations thereof.

13. The composition of claim 12 wherein the solubilizer is present in ~~amount from about 1% to about 10% by weight.~~ or capsule

14. A method of making the composition of any of claims 1-13 comprising

(a) mixing the salt of one or more pharmaceutically active agents, and the deionizing agent at an appropriate temperature; and

(b) encapsulating the mixture in a softgel capsule.

~~15. The method of claim 14 further comprising polyethylene glycol.~~

~~16. The method of claim 14 further comprising water.~~

15 ~~17~~. The method of claim 14 wherein the appropriate temperature is from about 50°C to about 70°C.

~~18. A method of using the composition of any of claims 1-13~~ comprising administering to a ~~patient in need~~ thereof the salt of one or more ~~pharmaceutically active agents.~~

2 ~~19~~. A softgel capsule comprising a fill material wherein the fill material comprises

(a) a salt of one or more pharmaceutically active agents; and

(b) a deionizing agent.

composition or

3 ~~20~~. The capsule of claim ~~19~~ 1 or 2 wherein the pharmaceutically active agent is selected from the group consisting of therapeutically active agents, diagnostic agents, and prophylactic agents.

4 ~~21~~. The capsule of claim ~~19~~ 1 or 2 wherein the deionizing agent is present in an amount from about 0.2 to 1.0 mole equivalents per mole of the pharmaceutically active agent(s).

5 ~~22~~. The capsule of claim ~~19~~ 1 or 2 wherein the deionizing agent is selected from the group consisting of hydrogen ion and hydroxide ion.

6 ~~23~~. The capsule of claim ~~19~~ 1 or 2 further comprising polyethylene glycol.

Composition or

7 ~~24~~. The capsule of claim ~~23~~ 6 wherein polyethylene glycol is present in an amount from about 10% to about 80% by weight.

8 ~~25~~. The capsule of claim ~~23~~ 6 wherein polyethylene glycol is one or more polyethylene glycols with a molecular weight between 300 and 1500.

9 ~~26~~. The capsule of claim ~~19~~ 1 or 2 further comprising water.

10 ~~27~~. The capsule of claim ~~26~~ 9 wherein water is present in an amount from about 1% to about 18% by weight.

11 ~~28~~. The capsule of claim ~~19~~ 1 or 2 further comprising one or more excipients.

~~29. The capsule of claim 28 wherein the excipients are~~ selected from the group consisting of plasticizers, crystallization inhibitors, wetting agents, bulk filling agents, solubilizers, bioavailability enhancers, solvents, pH-adjusting agents, dyes, preservatives, solvents, surfactants, and combinations thereof.

12 ~~30~~. The capsule of claim ~~29~~ 11 wherein the solubilizer is selected from the group consisting of glycerin, polyvinylpyrrolidone, propylene glycol and combinations thereof.

13 ~~31~~. The capsule of claim ~~29~~ 11 wherein the solubilizer is present in amount from about 1% to about 10% by weight.

16. A composition or capsule of any of claims 1 to 13 for use as a medicament.

European Patent Office
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Tel.: +31 (0)70 340 45 00

Date
22-10-2007

Reference	Application No./Patent No.
PABCA/P38814EP	06737018.9 - 2123 PCT/US2006007788

Applicant/Proprietor
Banner Pharmacaps Inc.

Communication pursuant to Rules 109 and 110 EPC

(1) Amendment of application documents, especially the claims (R. 109 EPC)

The above mentioned international (Euro-PCT) application has entered the European phase, or can do so, once the necessary conditions are fulfilled.

Under Articles 28, 41 PCT, Rules 52, 78 PCT and Rule 86(2) to (4) EPC, the applicant may amend the application documents after receiving the international search report.

Whether or not he has already done so, he now has a further opportunity to file amended claims or other application documents within a non-extendable time limit of one month after notification of the present communication (R. 109 EPC).

The claims applicable on expiry of the above time limit, i.e. those filed on entry into the European phase or in response to the present communication, will form the basis for the calculation of any claims fee to be paid (see page 2) and for any supplementary search to be carried out under Article 157(2) EPC (R. 109 EPC).

--2/

(2) Claims fees under Rule 110 EPC

If the application documents on which the European grant procedure is to be based comprise more than ten claims, a claims fee shall be payable for the eleventh and each subsequent claim within the period provided for in Rule 107(1) EPC.

☑ Based on the application documents currently on file, all necessary claims fees have already been paid (or the documents do not comprise more than 10 claims).

☐ All necessary fees will be/have been debited automatically according to the automatic debit order.

☐ The claims fee due for the claims ..... to ..... were not paid within the above-mentioned period.

Any non-paid claims fee, either based on the current set of claims or on any amended claims to be filed pursuant to Rule 109 EPC (see page 1), may still be validly paid within a non-extendable period of grace of **one month** after notification of this communication.

If a payment is made for only some of the claims, it must be indicated for which claims it is intended. If a claims fee is not paid in due time, the claim concerned is deemed to be abandoned (R. 110(4) EPC).

If claims fees have already been paid, but on expiry of the above-mentioned time limit there is a new set of claims containing fewer fee-incurring claims than previously, the claims fees in excess of those due under Rule 110(2), 2nd sentence, EPC will be refunded (R. 110(3) EPC).

You are reminded that any supplementary search under Article 157(2) EPC will relate only to the last set of claims applicable on expiry of the above time limit AND will be confined to those fee-incurring claims for which fees have been paid in due time.

The fee for the eleventh and each subsequent claim is EUR 45,00.

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Date
14.11.07

Reference	Application No./Patent No.
PABCA/P38814EP	06737018.9 - 2123 PCT/US2006007788

Applicant/Proprietor
Banner Pharmacaps Inc.

Notification of European publication number and information on the application of Article 67(3) EPC

The provisional protection under Article 67(1) and (2) EPC in the individual contracting states becomes effective only when the conditions referred to in Article 67(3) EPC have been fulfilled (for further details, see information brochure of the European Patent Office "National Law relating to the EPC" and additional information in the Official Journal of the European Patent Office).

Pursuant to Article 158(1) EPC the publication under Article 21 PCT of an international application for which the European Patent Office is a designated Office takes the place of the publication of a European patent application.

The bibliographic data of the above-mentioned Euro-PCT application will be published on 12.12.07 in Section I.1 of the European Patent Bulletin. The European publication number is 1863458.

In all future communications to the European Patent Office, please quote the application number plus Directorate number.

Receiving Section

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Original bei Liste 5.2.4)

EPO - Munich
79
04. Jan. 2008

The European Patent Office
Erhardstraße 27
D-8000 München 2
Germany

03 January 2008

Europäisches Patentamt
München
08. Jan. 2008
Dir. 5.2.4

Dear Sirs

Change of Name
Our ref: GEN/MB

We advise that as from 7 January 2008 Eric Potter Clarkson LLP, will become Potter Clarkson LLP.

We would be grateful if you could please amend your records of applications to reflect the fact that the address for service will be care of Potter Clarkson LLP rather than care of Eric Potter Clarkson LLP. Our email address will also change to info@potterclarkson.com.

We look forward to hearing from you.

Yours faithfully

FREP

Margaret Beeden
Office Manager

For and on behalf of Eric Potter Clarkson LLP

E. Bike/USA

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POTTER CLARKSON

All Change for Eric Potter Clarkson LLP

As from 7 January 2008 our name will change to POTTER CLARKSON LLP and we will be adopting a new corporate identity.

In the ever changing environment within which we work, we need to ensure that our core values are reflected in our identity.

Research established that our old identity created an inaccurate perception of these values and of our business generally.

We are still the same people, and obviously we aim to retain the successful culture and relationships that have brought us to this point in our 100+ year history. At the same time we want to project a contemporary identity which more closely reflects who we are.

Our new identity signifies this movement forward, while not abandoning all that has been built up in the past. We hope you like it.

If you would like to learn more about our new identity, please go to **www.potterclarkson.com.**

If undelivered please return to:
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1889 - 2007

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2008

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Tel: +49 89 2399 - 7841

Application No.	Ref.	Date
06 737 018.9 - 2123	PABCA/P38814EP	20.11.2008
Applicant: Banner Pharmacaps Inc.		

Communication pursuant to Article 94(3) EPC

The examination of the above-identified application has revealed that it does not meet the requirements of the European Patent Convention for the reasons enclosed herewith. If the deficiencies indicated are not rectified the application may be refused pursuant to Article 97(2) EPC.

You are invited to file your observations and insofar as the deficiencies are such as to be rectifiable, to correct the indicated deficiencies within a period

of 4 months

from the notification of this communication, this period being computed in accordance with Rules 126(2) and 131(2) and (4) EPC. One set of amendments to the description, claims and drawings is to be filed within the said period on separate sheets (R. 50(1) EPC).

Failure to comply with this invitation in due time will result in the application being deemed to be withdrawn (Art. 94(4) EPC).

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Büttner, Ulf
Primary Examiner
For the Examining Division

Enclosure(s): 2 page/s reasons (Form 2906)

The examination is being carried out on the **following application documents**:

Description, Pages

1-15 as published

Claims, Numbers

1-16 filed with entry into the regional phase before the EPO

1.) Reference is made to the following documents:

D1: US-A-5 360 615 (YU ET AL) 1 November 1994 (1994-11-01) cited in the application
D2: WO 95/31979 A (R.P. SCHERER INTERNATIONAL CORPORATION; SHELLEY, RICKEY, S; WEI, YOUCH) 30 November 1995 (1995-11-30)
D3: US 2001/007668 A1 (SAWYER MARYJEAN ET AL) 12 July 2001 (2001-07-12)
D4: US-A-5 484 606 (DHABHAR ET AL) 16 January 1996 (1996-01-16)
D5: US-A-5 912 011 (MAKINO ET AL) 15 June 1999 (1999-06-15)
D6: US 2004/157928 A1 (KIM JAE-HWAN ET AL) 12 August 2004 (2004-08-12)

2.) The present application does not meet the requirements of Article 52(1) EPC because the subject-matter of claims 1-16is not new within the meaning of Article 54(1) and (2) EPC.

Claim 1 relates to a composition comprising:

- a salt of one or more active agents and
- a deionizing agent

According to the description (p. 3, l. 13-21), to the examples and claims 9 the pharmaceutical composition should be an aqueous liquid. In a solution it cannot be distinguished whether the ionized active agent and the corresponding counter-ion have been used during preparation or have been formed during the solution.
The term deionizing agent relates to any agent which is capable to deionize any other agent. No limitation or conditions under which deionization should take place are indicated.
Thus claim 1 relates to any composition comprising an ionized active agent and a counter-ion and at least one additional compound capable to ionize any other compound.

D1 discloses a composition comprising diclofenac sodium, 0.2 mole equivalent hydrogen ions, PEG 600 and 7 % water.
D2 discloses Ketoprofen potassium 0.1 mole equivalent hydroxide ions, PEG 400, propylenglycol and 5 % water.
D3 discloses Naproxen sodium, 0.7 mole equivalent hydroxide ions, PEG 300.
D4 discloses a composition comprising pseudoephedrine HCl and Acetaminophen which releases hydrogen ions, PEG propylenglycol and water.

3.) Even if novelty could be established the subject-matter of claims 1-16 would not involve an inventive step within the meaning of Article 56 EPC.

According to the description (p. 3, l. 11) the underlying problem may be seen in the minimization of the formation of PEG esters. Claims 1-5 do not require the presence of PEG. Therefore the underlying problem does not exist for the subject matter of those claims.
In addition the application does not contain data showing an effect at all. Thus, the underlying problem has not been plausibly solved.

POTTER CLARKSON

European Patent Office
Directorate General 2
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GERMANY

18 March 2009

Sent by fax

Dear Sirs

European Patent Application No. 06737018.9-2123
BANNER PHARMACAPS, INC.
Our ref: PABCA/P38814EP

This is a response to the communication under Article 94(3) EPC dated 20 November 2008.

Amendments

We enclose a new retyped set of claims to replace the claims currently on file. To assist the examiner, we also enclose a copy of the current claims showing in manuscript the amendments that have been made.

Claims 1 and 2 have been amended by including the subject matter of claim 6, which specifies the presence of polyethylene glycol.

Claims 1 and 2 have also been amended to specify that when the active agent is the salt of a weak acid and a strong base, the deionizing agent is a hydrogen ion species, and when the active agent is the salt of a weak base and a strong acid, the deionizing agent is a hydroxide ion species. Basis for this may be found, for example, at page 6, lines 11 to 14 of the application as filed.

Previous claim 6 has been deleted and a new claim 6 has been added which specifies that the composition or fill material has a pH of from about 2.5 to about 7.5. Basis for this may be found, for example, at page 6, lines 26 to 28 of the application as filed.

A new claim 14 has been introduced specifying that the active agent is naproxen sodium and the deionizing agent is a hydrogen ion species. Basis for this may be found, for instance, in the Examples.

cont/....

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A new claim 15 has been added specifying that the hydrogen ion species is selected from the list of species set out on page 6, lines 18 to 21 of the application as filed.

Previous claims 14 and 15 have been renumbered as claims 17 and 18 accordingly.

Any amendment is not to be construed as an abandonment of subject matter.

Novelty and Inventive Step

The examiner appeared to consider that the previous claims lacked novelty over D1 to D4.

There is no disclosure in any of D1 to D4 of a composition or capsule having the components defined in new claims 1 and 2. In particular, these prior art documents do not disclose a composition or capsule comprising a hydrogen ion species deionizing agent when the active agent is the salt of a weak acid and a strong base, or a hydroxide ion species deionizing agent when the active agent is the salt of a weak base and a strong acid.

New claims 1 and 2 are novel over D1 to D4 for at least this reason. The remaining claims are also novel over D1 to D4 at least by virtue of their dependency on new claims 1 and 2.

As to inventive step, there is no teaching or suggestion in any of D1 to D4 to provide the claimed compositions and capsules. In particular, there is nothing in D1 to D4 that would have motivated the skilled person to modify the compositions described in those documents so as to include a hydrogen ion species deionizing agent when the active agent is the salt of a weak acid and a strong base, or a hydroxide ion species deionizing agent when the active agent is the salt of a weak base and a strong acid. The claimed subject matter is inventive for this reason alone.

Moreover, the claimed compositions and capsules have very real advantages in use. For instance, the claimed deionzing agent minimizes the formation of PEG esters and causes partial deionization (neutralization) of the salt of the active agent, thereby enhancing bioavailability of the active agent (see, for example, page 3, lines 18 to 21). Neither of these unexpected advantages could have been predicted from the cited prior art.

In summary, therefore, new claims 1 and 2 are inventive over D1 to D4, alone or in combination. The remaining claims are also inventive over D1 to D4 at least by virtue of their dependency on new claims 1 and 2.

cont/....

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European Patent Office
18 March 2009

Should the examiner be inclined to refuse this application, we request, in order of preference, a telephone interview or a personal interview first. In any event, we request oral proceedings before the application is refused.

Yours faithfully

Robert I Pugh PhD
For and on behalf of Potter Clarkson LLP

jt

Enc: Retyped claims
Manuscript amended claims

POTTER CLARKSON

To:	**European Patent Office**
Your Fax No:	00 49 89 2399 4465
From:	Robert I Pugh PhD
Date:	18 March 2009
Our Ref:	PABCA/P38814EP
Your Ref:	European Patent Application No. 06737018.9-2123

Sheet 1 of 9 **Original by Post:** ✓

MESSAGE:

Potter Clarkson LLP is a limited liability partnership, registered in England as No. OC315197, having its registered office at the address shown. A list of the members' names is available for inspection at the registered office. All instructions are accepted subject to our current terms of engagement.

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CLAIMS

1. A pharmaceutical composition comprising

(a) a salt of one or more pharmaceutically active agents;

(b) a deionizing agent; and

(c) polyethylene glycol;

wherein when the active agent is a salt of a weak acid and a strong base, the deionizing agent is a hydrogen ion species, and when the active agent is the salt of a weak base and a strong acid, the deionizing agent is a hydroxide ion species.

2. A softgel capsule comprising a fill material wherein the fill material comprises

(a) a salt of one or more pharmaceutically active agents;

(b) a deionizing agent; and

(c) polyethylene glycol;

wherein when the active agent is a salt of a weak acid and strong base, the deionizing agent is a hydrogen ion species, and when the active agent is the salt of a weak base and a strong acid, the deionizing agent is a hydroxide ion species.

3. The composition or capsule of claim 1 or 2 wherein the pharmaceutically active agent is selected from the group consisting of therapeutically active agents, diagnostic agents, and prophylactic agents.

4. The composition or capsule of claim 1 or 2 wherein the deionizing agent is present in an amount from about 0.2 to 1.0 mole equivalents per mole of the pharmaceutically active agent(s).

5. The composition or capsule of claim 1 or 2 wherein the deionizing agent is selected from the group consisting of hydrogen ion and hydroxide ion.

6. The composition or capsule of claim 1 or 2, wherein the composition or fill material has a pH of from about 2.5 to about 7.5.

7. The composition or capsule of claim 1 or 2 wherein polyethylene glycol is present in an amount from about 10% to about 80% by weight.

8. The composition or capsule of claim 1 or 2 wherein polyethylene glycol is one or more polyethylene glycols with a molecular weight between 300 and 1500.

9. The composition or capsule of claim 1 or 2 further comprising water.

10. The composition or capsule of claim 9 wherein water is present in an amount from about 1% to about 18% by weight.

11. The composition or capsule of claim 1 or 2 further comprising one or more excipients selected from the group consisting of plasticizers, crystallization inhibitors, wetting agents, bulk filling agents, solubilizers, bioavailability enhancers, solvents, pH-adjusting agents, dyes, preservatives, solvents, surfactants, and combinations thereof.

12. The composition or capsule of claim 11 wherein the solubilizer is selected from the group consisting of glycerin, polyvinylpyrrolidone, propylene glycol and combinations thereof.

13. The composition or capsule of claim 11 wherein the solubilizer is present in amount from about 1% to about 10% by weight.

14. The composition or capsule of claim 1 or 2 wherein the active agent is naproxen sodium and the deionizing agent is a hydrogen ion species.

15. The composition or capsule of claim 14 wherein the hydrogen ion species is selected from hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, fumaric acid, maleic acid, tartaric acid, methane-, ethane-, and benzene sulfonates, citric acid, malic acid, acetic acid, proprionic acid, pyruvic acid, butanoic acid, and lactic acid.

16. A composition or capsule or any of claims 1 to 15 for use as a medicament.

17. A method of making the composition or capsule of any of claims 1 to 15 comprising

(a) mixing the salt of one or more pharmaceutically active agents, and the deionizing agent at an appropriate temperature; and

(b) encapsulating the mixture in a softgel capsule.

18. The method of claim 17 wherein the appropriate temperature is from about 50°C to about 70°C.

CLAIMS

~~We claim~~

1. A pharmaceutical composition comprising

(a) a salt of one or more pharmaceutically active agents; ~~and~~

(b) a deionizing agent; and

~~2. The composition of claim 1 wherein the pharmaceutically active~~ agent is selected from the group consisting of therapeutically active agents, diagnostic agents, and prophylactic agents.

3. The composition of claim 1 wherein the deionizing agent is present in an amount from about 0.2 to 1.0 mole equivalents per mole of the pharmaceutically active agent(s).

4. The composition of claim 1 wherein the deionizing agent is selected from the group consisting of hydrogen ion and hydroxide ion.

5. The composition of claim 1 further comprising polyethylene glycol.

6. The composition of claim 5 wherein polyethylene glycol is present in an amount from about 10% to about 80% by weight.

7. The composition of claim 5 wherein polyethylene glycol is one or more polyethylene glycols with a molecular weight between 300 and 1500.

8. The composition of claim 1 further comprising water.

9. The composition of claim 8 wherein water is present in an amount from about 1% to about 18% by weight.

10. The composition of claim 1 further comprising one or more excipients.

11. The composition of claim 7 wherein the excipients are selected from the group consisting of plasticizers, crystallization inhibitors, wetting agents, bulk filling agents, solubilizers, bioavailability enhancers, solvents, pH-adjusting agents, dyes, preservatives, solvents, surfactants, and ~~combinations thereof.~~

(c) polyethylene glycol;
wherein when the active agent is a salt of a weak acid and a strong base, the deionizing agent is a hydrogen ion species, and when the active agent is the salt of a weak base and a strong acid, the deionizing agent is a hydroxide ion species.

~~12. The composition of claim 11 wherein the solubilizer is selected~~ from the group consisting of glycerin, polyvinylpyrrolidone, propylene glycol and combinations thereof.

13. The composition of claim 12 wherein the solubilizer is present in ~~amount from about 1% to about 10% by weight.~~ or capsule

17 ~~14~~. A method of making the composition of any of claims 1-~~13~~ 15 comprising

(a) mixing the salt of one or more pharmaceutically active agents, and the deionizing agent at an appropriate temperature; and

(b) encapsulating the mixture in a softgel capsule.

~~15. The method of claim 14 further comprising polyethylene glycol.~~

18 ~~16. The method of claim 14 further comprising water.~~

~~15~~ 17. The method of claim ~~14~~ 17 wherein the appropriate temperature is from about 50°C to about 70°C.

~~18. A method of using the composition of any of claims 1-13~~ comprising administering to a patient in need thereof the salt of one or more ~~pharmaceutically active agents.~~

2 ~~19~~. A softgel capsule comprising a fill material wherein the fill material comprises

(a) a salt of one or more pharmaceutically active agents; ~~and~~

(b) a deionizing agent; ~~and~~

composition or 3 ~~20~~. The capsule of claim ~~19~~ 1 or 2 wherein the pharmaceutically active agent is selected from the group consisting of therapeutically active agents, diagnostic agents, and prophylactic agents.

4 ~~21~~. The capsule of claim ~~19~~ 1 or 2 wherein the deionizing agent is present in an amount from about 0.2 to 1.0 mole equivalents per mole of the pharmaceutically active agent(s).

5 ~~22~~. The capsule of claim ~~19~~ 1 or 2 wherein the deionizing agent is selected from the group consisting of hydrogen ion and hydroxide ion.

6 ~~23~~. The capsule of claim ~~19~~ 1 or 2, ~~further comprising polyethylene glycol.~~ wherein the composition or fill material has a pH of from about 2.5 to about 7.5.

Composition or

24. The capsule of claim 23 wherein polyethylene glycol is present in an amount from about 10% to about 80% by weight.

25. The capsule of claim 23 wherein polyethylene glycol is one or more polyethylene glycols with a molecular weight between 300 and 1500.

26. The capsule of claim 18 further comprising water.

27. The capsule of claim 26 wherein water is present in an amount from about 1% to about 18% by weight.

28. The capsule of claim 18 further comprising one or more excipients.

~~29. The capsule of claim 28 wherein the excipients are~~ selected from the group consisting of plasticizers, crystallization inhibitors, wetting agents, bulk filling agents, solubilizers, bioavailability enhancers, solvents, pH-adjusting agents, dyes, preservatives, solvents, surfactants, and combinations thereof.

30. The capsule of claim 29 wherein the solubilizer is selected from the group consisting of glycerin, polyvinylpyrrolidone, propylene glycol and combinations thereof.

31. The capsule of claim 29 wherein the solubilizer is present in amount from about 1% to about 10% by weight.

16. A composition or capsule of any of claims 1 to 15 for use as a medicament.

14. The composition or capsule of claim 1 or 2 wherein the active agent is naproxen sodium and the deionizing agent is a hydrogen ion species.

15. The composition or capsule of claim 14 wherein the hydrogen ion species is selected from hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, fumaric acid, maleic acid, tartaric acid, methane-, ethane-, and benzene sulfonates, citric acid, malic acid, acetic acid, proprionic acid, pyruvic acid, butanoic acid, and lactic acid.

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18 March 2009

Sent by fax

Dear Sirs

European Patent Application No. 06737018.9-2123
BANNER PHARMACAPS, INC.
Our ref: PABCA/P38814EP

This is a response to the communication under Article 94(3) EPC dated 20 November 2008.

Amendments

We enclose a new retyped set of claims to replace the claims currently on file. To assist the examiner, we also enclose a copy of the current claims showing in manuscript the amendments that have been made.

Claims 1 and 2 have been amended by including the subject matter of claim 6, which specifies the presence of polyethylene glycol.

Claims 1 and 2 have also been amended to specify that when the active agent is the salt of a weak acid and a strong base, the deionizing agent is a hydrogen ion species, and when the active agent is the salt of a weak base and a strong acid, the deionizing agent is a hydroxide ion species. Basis for this may be found, for example, at page 6, lines 11 to 14 of the application as filed.

Previous claim 6 has been deleted and a new claim 6 has been added which specifies that the composition or fill material has a pH of from about 2.5 to about 7.5. Basis for this may be found, for example, at page 6, lines 26 to 28 of the application as filed.

A new claim 14 has been introduced specifying that the active agent is naproxen sodium and the deionizing agent is a hydrogen ion species. Basis for this may be found, for instance, in the Examples.

cont/....

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A new claim 15 has been added specifying that the hydrogen ion species is selected from the list of species set out on page 6, lines 18 to 21 of the application as filed.

Previous claims 14 and 15 have been renumbered as claims 17 and 18 accordingly.

Any amendment is not to be construed as an abandonment of subject matter.

Novelty and Inventive Step

The examiner appeared to consider that the previous claims lacked novelty over D1 to D4.

There is no disclosure in any of D1 to D4 of a composition or capsule having the components defined in new claims 1 and 2. In particular, these prior art documents do not disclose a composition or capsule comprising a hydrogen ion species deionizing agent when the active agent is the salt of a weak acid and a strong base, or a hydroxide ion species deionizing agent when the active agent is the salt of a weak base and a strong acid.

New claims 1 and 2 are novel over D1 to D4 for at least this reason. The remaining claims are also novel over D1 to D4 at least by virtue of their dependency on new claims 1 and 2.

As to inventive step, there is no teaching or suggestion in any of D1 to D4 to provide the claimed compositions and capsules. In particular, there is nothing in D1 to D4 that would have motivated the skilled person to modify the compositions described in those documents so as to include a hydrogen ion species deionizing agent when the active agent is the salt of a weak acid and a strong base, or a hydroxide ion species deionizing agent when the active agent is the salt of a weak base and a strong acid. The claimed subject matter is inventive for this reason alone.

Moreover, the claimed compositions and capsules have very real advantages in use. For instance, the claimed deionzing agent minimizes the formation of PEG esters and causes partial deionization (neutralization) of the salt of the active agent, thereby enhancing bioavailability of the active agent (see, for example, page 3, lines 18 to 21). Neither of these unexpected advantages could have been predicted from the cited prior art.

In summary, therefore, new claims 1 and 2 are inventive over D1 to D4, alone or in combination. The remaining claims are also inventive over D1 to D4 at least by virtue of their dependency on new claims 1 and 2.

cont/....

Should the examiner be inclined to refuse this application, we request, in order of preference, a telephone interview or a personal interview first. In any event, we request oral proceedings before the application is refused.

Yours faithfully

Robert I Pugh PhD
For and on behalf of Potter Clarkson LLP

jt

Enc: Retyped claims
Manuscript amended claims

CLAIMS

1. A pharmaceutical composition comprising

(a) a salt of one or more pharmaceutically active agents;

(b) a deionizing agent; and

(c) polyethylene glycol;

wherein when the active agent is a salt of a weak acid and a strong base, the deionizing agent is a hydrogen ion species, and when the active agent is the salt of a weak base and a strong acid, the deionizing agent is a hydroxide ion species.

2. A softgel capsule comprising a fill material wherein the fill material comprises

(a) a salt of one or more pharmaceutically active agents;

(b) a deionizing agent; and

(c) polyethylene glycol;

wherein when the active agent is a salt of a weak acid and strong base, the deionizing agent is a hydrogen ion species, and when the active agent is the salt of a weak base and a strong acid, the deionizing agent is a hydroxide ion species.

3. The composition or capsule of claim 1 or 2 wherein the pharmaceutically active agent is selected from the group consisting of therapeutically active agents, diagnostic agents, and prophylactic agents.

4. The composition or capsule of claim 1 or 2 wherein the deionizing agent is present in an amount from about 0.2 to 1.0 mole equivalents per mole of the pharmaceutically active agent(s).

5. The composition or capsule of claim 1 or 2 wherein the deionizing agent is selected from the group consisting of hydrogen ion and hydroxide ion.

6. The composition or capsule of claim 1 or 2, wherein the composition or fill material has a pH of from about 2.5 to about 7.5.

7. The composition or capsule of claim 1 or 2 wherein polyethylene glycol is present in an amount from about 10% to about 80% by weight.

8. The composition or capsule of claim 1 or 2 wherein polyethylene glycol is one or more polyethylene glycols with a molecular weight between 300 and 1500.

9. The composition or capsule of claim 1 or 2 further comprising water.

10. The composition or capsule of claim 9 wherein water is present in an amount from about 1% to about 18% by weight.

11. The composition or capsule of claim 1 or 2 further comprising one or more excipients selected from the group consisting of plasticizers, crystallization inhibitors, wetting agents, bulk filling agents, solubilizers, bioavailability enhancers, solvents, pH-adjusting agents, dyes, preservatives, solvents, surfactants, and combinations thereof.

12. The composition or capsule of claim 11 wherein the solubilizer is selected from the group consisting of glycerin, polyvinylpyrrolidone, propylene glycol and combinations thereof.

13. The composition or capsule of claim 11 wherein the solubilizer is present in amount from about 1% to about 10% by weight.

14. The composition or capsule of claim 1 or 2 wherein the active agent is naproxen sodium and the deionizing agent is a hydrogen ion species.

15. The composition or capsule of claim 14 wherein the hydrogen ion species is selected from hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, fumaric acid, maleic acid, tartaric acid, methane-, ethane-, and benzene sulfonates, citric acid, malic acid, acetic acid, proprionic acid, pyruvic acid, butanoic acid, and lactic acid.

16. A composition or capsule or any of claims 1 to 15 for use as a medicament.

17. A method of making the composition or capsule of any of claims 1 to 15 comprising

(a) mixing the salt of one or more pharmaceutically active agents, and the deionizing agent at an appropriate temperature; and

(b) encapsulating the mixture in a softgel capsule.

18. The method of claim 17 wherein the appropriate temperature is from about 50°C to about 70°C.

CLAIMS

~~We claim~~

1. A pharmaceutical composition comprising

(a) a salt of one or more pharmaceutically active agents; ~~And~~

(b) a deionizing agent; and

~~2. The composition of claim 1 wherein the pharmaceutically active~~ agent is selected from the group consisting of therapeutically active agents, diagnostic agents, and prophylactic agents.

3. The composition of claim 1 wherein the deionizing agent is present in an amount from about 0.2 to 1.0 mole equivalents per mole of the pharmaceutically active agent(s).

4. The composition of claim 1 wherein the deionizing agent is selected from the group consisting of hydrogen ion and hydroxide ion.

5. The composition of claim 1 further comprising polyethylene glycol.

6. The composition of claim 5 wherein polyethylene glycol is present in an amount from about 10% to about 80% by weight.

7. The composition of claim 5 wherein polyethylene glycol is one or more polyethylene glycols with a molecular weight between 300 and 1500.

8. The composition of claim 1 further comprising water.

9. The composition of claim 8 wherein water is present in an amount from about 1% to about 18% by weight.

10. The composition of claim 1 further comprising one or more excipients.

11. The composition of claim 7 wherein the excipients are selected from the group consisting of plasticizers, crystallization inhibitors, wetting agents, bulk filling agents, solubilizers, bioavailability enhancers, solvents, pH-adjusting agents, dyes, preservatives, solvents, surfactants, and ~~combinations thereof.~~

(c) polyethylene glycol;
wherein when the active agent is a salt of a weak acid and a strong base, the deionizing agent is a hydrogen ion species, and when the active agent is the salt of a weak base and a strong acid, the deionizing agent is a hydroxide ion species.

~~12. The composition of claim 11 wherein the solubilizer is selected~~ from the group consisting of glycerin, polyvinylpyrrolidone, propylene glycol and combinations thereof.

13. The composition of claim 12 wherein the solubilizer is present in ~~amount from about 1% to about 10% by weight.~~ or capsule

17 ~~14~~. A method of making the composition of any of claims 1-~~13~~15 comprising

(a) mixing the salt of one or more pharmaceutically active agents, and the deionizing agent at an appropriate temperature; and

(b) encapsulating the mixture in a softgel capsule.

~~15. The method of claim 14 further comprising polyethylene glycol.~~

18 ~~16. The method of claim 14 further comprising water.~~

15 ~~17~~. The method of claim ~~14~~ 17 wherein the appropriate temperature is from about 50°C to about 70°C.

~~18. A method of using the composition of any of claims 1-13~~ comprising administering to a ~~patient in need~~ thereof the salt of one or more ~~pharmaceutically active agents.~~

2 ~~19~~. A softgel capsule comprising a fill material wherein the fill material comprises

(a) a salt of one or more pharmaceutically active agents; ~~and~~

composition or (b) a deionizing agent; ~~and~~ 1 or 2

3 ~~20~~. The capsule of claim ~~19~~ wherein the pharmaceutically active agent is selected from the group consisting of therapeutically active agents, diagnostic agents, and prophylactic agents.

4 ~~21~~. The capsule of claim ~~19~~ 1 or 2 wherein the deionizing agent is present in an amount from about 0.2 to 1.0 mole equivalents per mole of the pharmaceutically active agent(s).

5 ~~22~~. The capsule of claim ~~19~~ 1 or 2 wherein the deionizing agent is selected from the group consisting of hydrogen ion and hydroxide ion.

6 ~~23~~. The capsule of claim ~~19~~ 1 or 2, ~~further comprising polyethylene glycol.~~ wherein the composition or fill material has a pH of from about 2.5 to about 7.5.

Composition or

7 24. The capsule of claim 6 1 or 2 wherein polyethylene glycol is present in an amount from about 10% to about 80% by weight.

8 25. The capsule of claim 6 1 or 2 wherein polyethylene glycol is one or more polyethylene glycols with a molecular weight between 300 and 1500.

9 26. The capsule of claim 1 or 2 further comprising water.

10 27. The capsule of claim 26 9 wherein water is present in an amount from about 1% to about 18% by weight.

11 28. The capsule of claim 1 or 2 further comprising one or more excipients

~~29. The capsule of claim 28 wherein the excipients are~~ selected from the group consisting of plasticizers, crystallization inhibitors, wetting agents, bulk filling agents, solubilizers, bioavailability enhancers, solvents, pH-adjusting agents, dyes, preservatives, solvents, surfactants, and combinations thereof.

12 30. The capsule of claim 29 11 wherein the solubilizer is selected from the group consisting of glycerin, polyvinylpyrrolidone, propylene glycol and combinations thereof.

13 31. The capsule of claim 29 11 wherein the solubilizer is present in amount from about 1% to about 10% by weight.

16. A composition or capsule of any of claims 1 to ~~13~~ 15 for use as a medicament.

14. The composition or capsule of claim 1 or 2 wherein the active agent is naproxen sodium and the deionizing agent is a hydrogen ion species.

15. The composition or capsule of claim 14 wherein the hydrogen ion species is selected from hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, fumaric acid, maleic acid, tartaric acid, methane-, ethane-, and benzene sulfonates, citric acid, malic acid, acetic acid, proprionic acid, pyruvic acid, butanoic acid, and lactic acid.

POTTER CLARKSON

To: **European Patent Office**

Your Fax No: 00 49 89 2399 4465

From: Dr Robert I Pugh

Date: 16 November 2010

Our Ref: PABCA/P38814EP

Your Ref: European Patent Application No. 06737018.9-2123

Sheet 1 of 2 **Original by Post:** ✓

MESSAGE:

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GERMANY

16 November 2010

Sent by fax

Dear Sirs

European Patent Application No. 06737018.9-2123
BANNER PHARMACAPS, INC.
Our ref: PABCA/P38814EP

We responded to a communication pursuant to Article 94(3) EPC on 18 March 2009. Please let us know when we can expect to receive the next communication from the Examining Division.

Yours faithfully

Dr Robert I Pugh
For and on behalf of Potter Clarkson LLP

js

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18. Nov. 2010

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For any questions about this communication:
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Crowhurst, Charlotte Waveney
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GRANDE BRETAGNE

Date
21-01-2011

Reference	Application No./Patent No.
PABCA/P38814EP	06737018.9 - 2123 / 1863458

Applicant/Proprietor
Banner Pharmacaps Inc.

Summons to attend oral proceedings pursuant to Rule 115(1) EPC

You are hereby summoned to attend oral proceedings arranged in connection with the above-mentioned European patent application.

The matters to be discussed are set out in the communication accompanying this summons (EPO Form 2906).

The oral proceedings, which will not be public, will take place before the Examining Division.

on 07.10.11 at 09.00 hrs at the EPO,
PschorrHöfe, Bayerstr. 34, D-80335 München

No changes to the date of the oral proceedings can be made, except on serious grounds (see OJ EPO 1/2009, 68). If you do not appear as summoned, the oral proceedings may continue without you (R. 115(2) EPC, see also OJ EPO 10/2008, 471).

Your attention is drawn to Rule 4 EPC, regarding the language of the oral proceedings, and to the Special edition No. 3 OJ EPO 2007, L.1., concerning the filing of authorisations for company employees and lawyers acting as representatives before the EPO.

The final date for making written submissions and/or amendments (R. 116 EPC) is 07.09.11.

The actual room number as well as the waiting room numbers will be given to you by the porter in the foyer at the above EPO address.

Parking is available free of charge in the underground car park. However, this applies only in the case of accessing the car park via the entrance "Zollstrasse".

1st Examiner:
Büttner U

2nd Examiner:
Paúl Soto R

Chairman:
Borst M

For the Examining Division

Annexes:
Confirmation of receipt (Form 2936)
Communication (EPO Form 2906)

Registered letter with advice of delivery

to EPO postal service: 18.01.11

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4. Request language service to provide simultaneous interpretation facilities as necessary

....
Date Initials

5. Return the dossier to primary examiner with Form 2041 (15 days before the oral proceedings)

....
Date Initials

6. Check that summons has been received (Form 2936 / advice of delivery)

7. 15 days before the oral proceedings:
- dispatch the dossier to the primary examiner.

10.04.11
Date

Borst, Markus	Paul Soto, Raquel	Büttner, Ulf	
Chairman	2nd examiner	1st examiner	Legal member

Enclosure(s):

The examination is being carried out on the **following application documents**

Description, Pages

1-15 as published

Claims, Numbers

1-18 filed with telefax on 18-03-2009

1 The amendment filed with the letter dated 18.03.2009 introduces subject-matter which extends beyond the content of the application as filed, contrary to Article 123(2) EPC. The amendment concerned is the following:

A basis for the process as defined in claim 17 may be found on page 8 of the application. This process however does not relate to compositions in general and in addition requires that PEG is mixed at 50 to 70 degree. These features however are not part of the claims.

2 The application does not meet the requirements of Article 84 EPC, because claim 1 and 4 are not clear.

Claim 1 requires that the deionizing agent is either a hydrogen ion species or a hydroxide ion species.

Claim 4 requires that the deionizing agent is present in defined amounts. However, the amount of hydrogen ions or hydroxide ions is characterized by the pH-value of a solution. The pH-value of a solution however is not only dependent on the molar amount of the deionizing agent such as an alkaline or acidic compounds but also on their acid strength or basicity. Thus it is not clear whether the defined molar amount should relate to the counter-ion of the deionizing agent or the final concentration of the hydrogen/hydroxide ions (the pH value).

This is decisive for the manufacture of the claimed formulation as exemplified in the following

An active agent may be used in a molar amount of 0.1 to 1 mol/liter. 1 equivalent hydrogen ions (0,1 molar to 1 molar) relate to a pH of 0 to 1. This however, would cause a number of technical and physiological problems, and thus does not appear to make sense.

In view of this it might be concluded that the amount of claim 4 apparently should relate to the molar amount of the counter ion of the used ionizing agent. Although this information is not expressed within the claims it will be used for interpreting the claims.

However, it is still not clear to what extent the molar amount of the counter ion in claim 4 is limiting. In a composition where one anion is present in an amount of 0.6 mole equivalents and a second anion such as a second weak acid is present in an amount of 0.6 mole equivalents it is not clear whether such formulations fall within the scope of the claim or not.

It is further noted that hydrogen ions or hydroxide ions are always present in aqueous solutions. As a consequence, every aqueous solution of a salt of an active agent that comprises PEG anticipates the subject matter of claim 1 (see D1-D4).

As a consequence, in favour of the application claim 1 is interpreted in a way that there must be the weak acid salt of an active agent and an anion or vice versa.

3 The present application does not meet the requirements of Article 52(1) EPC because the subject-matter of claims 1-14, (17-18) is not new within the meaning of Article 54(1) and (2) EPC. [insert reasoning]

As already stated in the previous communication, in a solution it cannot be distinguished whether the ionized active agent and the corresponding counter-ion have been used during preparation or have been formed during the solution. As explained above it is not possible to use the term hydrogen ion species or hydroxide ion species as technical features of the claim.

Thus claim 1 simply requires the presence of the following features:

- an active agent, which might form a salt
- a counter ion in an at least equimolar amount and an additional cation in case the pharmaceutical agent is a base or an additional anions in case the pharmaceutical agent is an acid
- polyethylene glycol

D1 discloses a composition comprising:

- diclofenac sodium (a salt of weak acid and strong base)
- hydrochloric acid: a hydrogen ion species (0.2 mole equivalent)

- polyethylenglycol 600 : 71 %
- water: 8 %

D3 discloses the following compositions

examples 1-16

- acetaminophen (a weak acid that can form a salt)
- sodium propionate and propionic acid
- polyethylenglycol 600
- the pH is 6.8
- water in amount about 10-14%

example 17

- Naproxen sodium
- propionate: 0.7 mole equivalent
- PEG 300
- D4 discloses the following composition:
- acetaminophen (a weak acid that can form a salt)
- pseudoephedrine HCl
- chlorpheniramine maleate

4 The present application does not meet the requirements of Article 52(1) EPC because the subject-matter of claim 14 does not involve an inventive step within the meaning of Article 56 EPC.

4.1 D1 as closest prior art

The present application relates to the filling of soft gelatin capsules. It appears that the idea behind the application lies in the use of an additional acid if the active agent is the salt of a weak as acid and vice versa to cause partial neutralisation. This should decrease the formation of PEG esters. As it has been discussed under clarity and novelty this has not been reflected by the claims.

Nevertheless, it will be considered for the assessment of inventive step.

D1 relates to the filling of soft gel capsules and to the use of agent that causes partial neutralisation. In practice this means if the active agent is the salt of a weak as acid and acid should be added (see e.g. example VIII). D1 discloses also compositions comprising naproxen (see e.g example X).

Therefore, D1 might represent the closest prior art.

If the focus is put on naproxen than example X might represent the closest prior art.

Example X in D1 discloses a composition comprising naproxen and potassium hydroxide.

The subject matter of claim 14 differs from example X in D1 to the extent that there is an additional amount of an "salt" (anions and cations) formed by the counterion of naproxen and the anion of the acid. No effect has been attributed to this difference.

Therefore, the underlying technical problem must be seen in the provision of a further composition. In order to solve the technical problem of providing an alternative composition the addition of any salt such as defined in claim 14 must be considered to be arbitrary.

If the use of a **salt** is the critical feature than example VIII is considered to represent the closest example.

Example VIII discloses a composition of the sodium salt of diclofenac, PEG and hydrochloric acid.

The subject matter of claim 14 differs from example VIII in that a different analgetic agent is used. No effect has been attributed to this difference.

Therefore, the underlying technical problem must be seen in the provision of a further composition. In order to solve the technical problem of providing an alternative composition the use of naproxen must be considered obvious.

With respect to the problem formulated by the applicant the following applies.

There is no relation of the distinguishing feature and the alleged problem to be solved. Thus, the avoidance of PEG esters must be considered as bonus effect.

More importantly, the application does not contain any data which show or make plausible that the intended formulations avoid the formation of PEG esters. Thus, the problem as formualted by the applicant has not been solved any way, and therefore may not be taken into account for the assesment of inventive step.

4.2 D3 as closest prior art

Specific documents identified in the application are family members of D3 (US2001007668). D3 relates to the filling of a soft gelating capsule preferably such as naproxen. D3 describes formulations comprising naproxen sodium and sodium propionate. It is one aspect of D3 that the solvent system enhances the solubility of the medicaments.

Claim 14 differs from D3 to the extent that different anions are present.

The applicant formulates the problem as to avoid the formation of PEG esters. As explained above said problem has not been solved.

Therefore, the underlying technical problem must be seen in the provision of a further composition. In order to solve the technical problem of providing an alternative composition the addition of any salt such as defined in claim 14 must be considered to be arbitrary.

Even if the idea of adding an acid (which is not reflected in the wording of the claims) is taken into account the problem of avoiding of PEG esters has not been solved.

5 No submissions should be made later than one month prior to the date set for the oral proceedings.

The Division will exert its discretion in allowing further amendments according to Rule 137(3) EPC. (Any new set of claims should comply with all the formal and substantial requirements of the EPC.)

It should also be noted that the application will be refused under Article 113(2) EPC if no admissible requests remain on file.

6 According to the request of the Applicant, oral proceedings will be held. The summons are enclosed.

The forthcoming oral proceedings will focus on items 1 to 3 and if appropriate item 4 as discussed above.

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Date: 21-01-2011

Reference	Application No./Patent No.
PABCA/P38814EP	06737018.9 - 2123 / 1863458

Applicant/Proprietor: Banner Pharmacaps Inc.

EPA/EPO/OEB Formblatt/Form/Formulaire : 2008 - 2906

Empfangsbescheinigung über den Zugang des vorstehend bezeichneten Schriftstücks
Acknowledgement of receipt of the document specified above
Récépissé du document spécifié ci-dessus

Unter Bezugnahme auf die Mitteilung im ABl EPA 7/2010, 377 wird gebeten, die Empfangsbescheinigung mit Empfangsdatum und Unterschrift zu versehen und **umgehend** an das EPA zurückzusenden:

With reference to the Notice in OJ EPO 7/2010, 377, you are requested to date and sign the acknowledgement of receipt and return it to the EPO **immediately**:

Conformément au communiqué paru au JO OEB 7/2010, 377, vous êtes prié d'indiquer sur le récépissé la date de réception du document, de signer le récépissé et de le renvoyer **sans délai** à l' OEB:

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26. Jan. 2011

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Applicant/Proprietor: Banner Pharmacaps Inc.	

EPA/EPO/OEB Formblatt/Form/Formulaire : 2008 – 2906

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- **per Fax / by fax / par téléfax (+49 (0) 89 2399-4465 or +31 (0) 70 340-3016)**
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GERMANY

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05. Aug. 2011

4 August 2011

Dear Sirs

European Patent Application No. 06737018.9-2123
BANNER PHARMACAPS, INC.
Our ref: PABCX/P38814EP

This is a response to the Summons to Oral Proceedings dated 21 January 2011.

This response includes a main request and seven auxiliary requests to be considered in the order presented if the examiner is not prepared to allow the main request. The applicant reserves the right to file further auxiliary requests, should this be necessary. In particular, the applicant reserves the right to make combinations of the claims now presented, including combining claims from within the same request and combining claims from different requests or to delete claims.

Main Request

We enclose a new retyped set of claims to replace the claims currently on file.

Our comments on each of the points raised in the summons with reference to the amended claims are set out below.

The Amendments to the Claims

Claim 1 has been amended by introducing the subject matter of previous claim 4. Basis for this can be found at page 3, lines 15 and 16 and page 6, lines 9 to 16. Claims 1 has also been amended to specify that component (a) is a salt of an acidic or basic pharmaceutically active agent. Basis for this amendment can be found at, for example, page 3, line 20 of the application as filed.

Claim 1 has also been amended to state that the inclusion of water is optional. It is clear from the application as a whole that the inclusion of water is optional. In particular, Example 1 to 7 include water and Examples 8 to 12 does not.

The clarity of the section of claim 1 after "wherein" has been improved by replacing "active agent" with "salt (a)". This makes this section of the claim consistent with part (a) of the claim.

cont/....

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Claim 2 has been amended in the same way as claim 1.

Previous claims 3, 5 and 9 have been deleted as they are not necessary in view of the wording of new claim 1.

Previous claim 17 has been amended to include the subject matter of previous claims 18 as suggested by the examiner.

New claims 15 and 16 are in Swiss style second medical use format. The application as a whole provides basis for these claims.

New claims 17 and 18 are product by process claim. It is clear from, for example, page 8, lines 23 to 32 that the compositions of the invention are made by the specified process.

Article 123(2) EPC

The examiner suggested that previous claim 17 should be amended to state that polyethylene glycol is used in the claimed process and that mixing is conducted at a temperature of from 50°C to 70°C. Previous claim 17 (new claim 14) has been amended as the examiner suggested. Basis for this amendment can be found at page 8 lines 25 to 27. As a result of this amendment, previous claim 18 has been deleted.

Article 84 EPC

The examiner raised an objection of lack of clarity against previous claims 1 and 4. The subject matter of previous claim 4 has been incorporated into claim 1 and claim 2.

Claims 1 and 2 have also been amended to clarify that component (a) is a salt of one or more acidic or basic pharmaceutically active agents. These claims have also been amended to clarify that the deionizing agent is present in an amount to cause partial deionization of the salt. That is, the molar amount defined in claims 1 and 2 relates to the counter ion of the deionizing agent.

Claims 1 and 2 have also been amended to state that the composition/fill may optionally comprise water in addition to the deionizing agent. This makes it clear that the deionizing agent is a separate component to the water.

It is clear from the application as a whole that in the present invention water is not used a deionizing agent. For example, in each of Examples 1 to 7 which comprise water, an acid is included as the deionizing agent. It is also clear from page 7, lines 7 to 9 that a mixture of polyethylene glycol and water is used as a solvent for the salt of the active agent and the deionizing agent; that is water functions as a solvent, not as a deionizing agent.

The claims of the present application are directed to a composition comprising a salt of an active agent and a deionizing agent. The deionizing agent is an acid or a base, depending on the nature of the salt of the active agent. In solution, the deionizing agent ionizes to form

cont/....

a counter ion which reacts with the salt of the active agent to partially neutralise the salt. That is, the amount of the deionizing agent specified in claims 1 and 2 reflects the amount of the counter ion provided by the deionizing agent to react with the salt of the active agent to partially neutralise the active agent. The wording of the claims is now clear.

The examiner has suggested that as hydrogen ions and hydroxide ions are always present in aqueous solution every aqueous solution of a salt of an active agent that contains PEG could be considered to anticipate claim 1. The examiner is kindly asked to reconsider this in view of the amendments made to the claims and on the basis of the following comments.

The amendments to the wording of the claims make it clear that the deionizing agent is a separate component of the composition to the water.

Additionally, the water (if present in a composition of the invention) does not produce H^+ and OH^- ions in sufficient amounts such that these ions would be present in an amount from 0.2 to 1.0 mole equivalents per mole of pharmaceutically active agent. Water contains very miniscule amounts of H^+ and OH^- and as quickly as these ions form they react to reform water due to the high acidity and bacidity of these ions. The dissociation constant of water is $1x10^{-14}$, which correspond to an H^+ concentration of $1x10^{-7}$. In other words, the amount of H^+ generated by water is not within the range specified in claims 1 and 2. Some information taken from http://www.chemguide.co.uk/physical/acidbaseeqia/kw.ht is enclosed. This document explains the principals just described.

These properties of water and the H^+ and OH^- ions present in water mean that simply dissolving the salt of a drug, which is composed of a positively charged ion and a negatively charged ion in water, alone or in combination with PEG, is not sufficient to neutralise the drug. That is water does not act as the deionizing agent. In order to neutralize the drug, a deionizing agent capable of deionizaing the salt of the drug must be added, as specified in the claims.

Article 54(1) and (2) EPC - Novelty

The examiner raised objections of lack of novelty against the claims 1 to 14 in view of the disclosure of US 5,360,615 (D1) and US 2001/007668 (D3).

US 5,360,615 (D1)

The examiner's objection of lack of novelty in view of D1 was based largely on the disclosure of Example VII of D1. This Example describes a composition comprising diclofenac sodium, hydrochloric acid (0.2 mole equivalent), PEG 600 and water.

Diclofenac sodium is an amphoteric molecule. It contains both an acidic functional group and a basic functional group. Thus, the use of diclofenac sodium is outside the scope of the amended claims, which require that the salt is a salt of an acidic or basic active agent. The use of amphoteric active agents is excluded from the scope of the claims.

cont/....

Additionally, it is known in the art that acids such as hydrochloric acid catalyse the intramolecular cyclisation of diclofenac to form an indoline derivative. A copy of a paper that describes the intramolecular cyclisation of diclofenac is enclosed, Palomo *et al*, "Analysis of diclofenac sodium and derivatives", Journal of Pharmaceutical and Biomedical Analysis, 21 (1999), 83-94. As stated in the abstract of Palomo, the intramolecular cyclisation of diclofenac sodium causes the salt to become inactivated.

Thus, Example VII of D1 does not describe a pharmaceutical composition having the essential features of the compositions of the present invention. In particular, the composition of Example VII of D1 is not a composition comprising a salt of an acid or basic active agent and a deionizing agent that causes partial neutralization of the salt of the active agent resulting in enhanced bioavailability of the active agent. In fact, cyclization of the drug will have the opposite effect.

The examiner has also referred to Example X of D1. This Example describes a composition comprising naproxen and potassium hydroxide. Naproxen is in the free acid form in Example X. The sodium hydroxide acts an ionizing agent which deprotonates naproxen to form the base addition salt. In other words, the potassium hydroxide causes the formation of naproxen potassium. This is the complete opposite to the effect achieved by combining the ingredients used in the compositions of the present invention. In the compositions of the present invention in which the active agent is naproxen, the salt of naproxen, sodium naproxen is used in combination with an acid such as acetic acid (see the Examples of the present application). The acid causes at least partial neutralization of the sodium naproxen. That salt is partially neutralised to provide naproxen in the free acid form.

In summary, the properties of the potassium hydroxide used in Example X of D1 are completely different to the properties of the acid used in combination with sodium naproxen compositions of the present invention. Thus, D1 does not disclose a composition comprising the combination of ingredients specified in claim 1 and its dependent claims.

For at least these reasons, the claimed compositions are novel in view of the disclosure of D1.

US 2001/007668 (D3)

The examiner considered that the claimed compositions lack novelty in view of the disclosure of Examples 1 to 17 of D3.

The compositions of each of Examples 1 to 16 of D3 comprise the active agent acetaminophen in the form of the free base and sodium propionate. None of these Examples use a salt of an active agent. If a further active agent in addition to acetaminophen is used, this is also in the form of the free acid or the free base. As the active agents used in the compositions of Examples 1 to 16 of D3 are in the free acid or base form, the compositions do not comprise a deionizing agent. The active agent is not in an ionized form that can under go deionization. On the contrary, the active agent is in the free

cont/....

acid or base form and can be ionized. Thus, the compositions of these Examples do not comprise each of the essential components of the claimed compositions.

For at least these reasons, the subject matter claimed is novel over the disclosure of examples 1 to 16 of D3.

Example 17 of D3 describes a composition comprising naproxen sodium, PEG 300, potassium hydroxide and sodium propionate. Naproxen sodium is a base-addition salt and a potassium hydroxide and sodium propionate are both basic. In order to neutralise naproxen sodium one would need to add a source of H^+ ions (an acid) as a deionizing agent. There is no source of H^+ ions other than water in the composition of Example 17 of D3. As discussed above, under neutral conditions the concentration of H^+ ions in water is $1x10^{-7}$. However, under the basic conditions described in Example 17 of D3 the concentration of H^+ ions will be significantly lower than $1x10^{-7}$ as OH^- is the dominant species. Thus, Example 17 does not disclose a composition comprising a salt of an active agent and a deionizing agent for that salt in an amount as required by claims 1 and 2. For at least this reason, the subject matter claimed is novel in view of the disclosure of Example 17 of D3.

The teaching of D3 as a whole makes it clear that the use of a deionizing agent is not contemplated. It is a clear purpose of the invention of D3 to provide compositions in which the medicament is ionized. In this regard, the examiner's attention is drawn to paragraph [0028] where it is stated "in addition to the polymeric material, the invention also comprises a salt of an organic acid containing at least three carbon atoms. The salt **helps to ionize the medicament** (emphasis added)". The salt of an organic acid that is used in Examples 1 to 17 of D3 is sodium propionate. In other words, D3 teaches the ionization of an active agent to form a salt, not deionization of a salt as required by the present invention.

For at least these reasons, the claimed invention is novel over the teaching of D3.

Article 56 EPC - Inventive Step

The subject matter claimed is also inventive in view of the cited prior art.

The examiner has characterised the problem addressed by the present invention as reducing the formation of PEG esters. This assessment of the technical problem seems to be based on the disclosure at page 3 lines 6 to 11 of the application as filed.

The examiner has proposed two lines of argument in relation to inventive step. One taking D1 as the closest prior art and secondly taking D3 as the closest prior art.

D1 as the closest prior art

The examiner has particularly focused on Example X of D1 in which the active agent is naproxen. Example X of D1 describes a composition containing naproxen free acid and potassium hydroxide. When these two compounds are mixed the naproxen is ionized (that is deprotonated to form a salt).

cont/....

As explained above, this is the complete opposite to the effect that is achieved by combining the ingredients used in the present invention. In the compositions of the invention, the salt (for example, naproxen sodium) is deionized (that is protonated). This causes a reduction in the concentration of the carboxylate anions of naproxen. It is these anions that could react with PEG to form esters. Thus, decreasing the concentration of the carboxylate anions decreases the formation of PEG esters. In contrast, in Example X of D1 the concentration of the carboxylate ions of naproxen will increase, the carboxylate ions will then react with PEG to form PEG esters, which decreases the therapeutic efficacy of the formulation. Thus, the invention as claimed does address the technical problem set out by the examiner.

The examiner has asked us to provide data which show that the claimed formulations have reduced formation of PEG esters. This is not considered necessary in view of the information provided in the cited prior art. In this regard, the examiner is asked to consider the disclosure of WO 95/31979 (D2) which describes at page 4 lines 1 to 6 the formation of PEG esters in the compositions of D1.

More particularly, D2 describes a composition containing PEG 400, potassium hydroxide and ketoprofen. Ketoprofen and naproxen both contain a carboxylic acid group. The mole range of potassium hydroxide to ketoprofen in D2 was from 0.4 to 1. D2 indicates that it was surprisingly found that the resultant formulation was not sufficiently stable for soft gel encapsulation due to undesirable formation of ketoprofen esters. This was due to the increased concentration of the ketoprofen ions as potassium hydroxide reacts with ketoprofen. In contrast, the use of a composition of the invention results in a decreasing concentration of the carboxylate anion and therefore a decreased formation of PEG esters.

In summary, D1 does not teach or suggest that a decrease in the formation of PEG esters could be achieved by using compositions as defined in the claims of the present application, while this effect is indeed achieved by the present invention.

The examiner has also alleged that if the critical feature of the invention is the use of a salt, then Example VIII of D1 is the closest prior art. As discussed above, Example VIII discloses a composition comprising diclofenac sodium, PEG and hydrochloric acid. The examiner has suggested that the only difference between Example VIII of D1 and claim 14 is the difference in the nature of the therapeutic agent. This is an over simplification of the situation.

As discussed above, diclofenac sodium is not a salt within the definition in amended claim 1. Additionally, diclofenac sodium is unsuitable for use in the composition as claimed. This is because diclofenac sodium reacts with acid to form a pharmaceutically inactive indolinone derivative. Thus, Example VIII of D1 does not disclose or suggest a solution to the problem addressed by the present invention.

Still further, the skilled person reading D1 would not have contemplated partial deionization of the active agent as D1 teaches that ionization to form a salt of the active agent is advantageous.

The subject matter claimed is therefore inventive in view of the disclosure of D1.

cont/....

D3 as the closest prior art

The examiner also formulated an argument taking D3 as the closest prior art. As discussed above, the compositions of the present invention are novel in view of the disclosure of D3. There is nothing in D3 that would have encouraged the skilled person to make the changes necessary to provide a composition as now claimed.

In fact, the teaching of D3 would have actively discouraged the skilled person from providing a composition as claimed. It is a stated aim of the teaching of D3 to maintain ionization of the medicament, that is maintain carboxylate anions. The skilled person starting from D3 would not have been motivated by the teaching of that document to attempt to produce a composition in which the presence of carboxylate anions is minimised. Thus the skilled person would not have been motivated to provide a composition as claimed.

Again, the skilled person would have learnt from D3, like D1, that maintaining ionization and formation of a salt of an active ingredient is important. He would not have been encouraged to use a combination of ingredients that would cause partial deionization of a salt of the active ingredient.

The subject matter claimed is therefore inventive over the teaching of D3.

Auxiliary Requests

First Auxiliary Request

The Claims

The claims of this request are based on the claims of the main request. Claim 1 of the main request has been deleted and claim 2 of the main request is claim 1 of this request. All of the claims of this request are directed to a softgel capsule and medical uses and methods of manufacturing such a capsule.

Article 123(2) EPC

The comments above on the main request in relation to Article 123(2) EPC also apply to this request.

Article 84 EPC

The comments above on the main request in relation to Article 84 EPC also apply to this request.

Article 54(1) and (2) and Article 56 EPC

The subject matter of this auxiliary request is novel and inventive for the reasons set out above in relation to the main request.

cont/....

More particular, both D1 and D3 describe the advantages of ionizing an active agent when producing a fill material for encapsulation into a softgel. In order to arrive at the present invention the skilled person would have had to completely ignore the teaching of both of thes documents. As discussed above, in the present invention, a deionizing agent is used in combination with a salt of one or more acidic or basic pharmaceutically active agents. There is nothing in D1 or D3 that would have encouraged the skilled person to work in a way that is contradictory to the teaching of those documents with the expectation of achieving an advantageous filled softgel capsule.

The subject matter of this request is both novel and inventive.

Second Auxiliary Request

The Claims

The claims of the second auxiliary request are in product-by-process format. Claims 1 and 2 of this request are based on claims 17 and 18 of the main request. Claims 3 to 16 of this request are based on claims 3 to 16 of the main request.

Article 123(2) EPC

The comments above on the main request in relation to Article 123(2) EPC also apply to this request.

Article 84 EPC

The comments above on the main request in relation to Article 84 EPC also apply to this request.

Article 54(1) and (2) and Article 56 EPC

The subject matter of this auxiliary request is novel and inventive for the reasons set out above in relation to the main request.

More particularly, the method defined in claims 1 and 2 involves the use of a unique combination of ingredients that is not disclosed or suggested in the prior art. This unique combination of ingredients produces pharmaceutical compositions that have a unique composition that could not have been produced using the methods described in the prior art.

Still further, the use of the method defined in the claims to make the compositions of the invention results in a product comprising fewer PEG esters than composition made according to methods of the prior art. The reduction of the formation of PEG esters achieved by the present invention is discussed above in relation to the main request.

For at least these reasons, the claims of the second auxiliary request are novel and inventive in view of the disclosure of the cited prior art.

cont/....

The Third Auxiliary Request

The Claims

The claims of the third auxiliary request are directed to a method of manufacturing a pharmaceutical composition. Claim 1 is directed to a method of making a pharmaceutical composition and claim 2 is directed to a method of making a softgel capsule. Claims 3 to 12 of this request are based on claims 3 to 12 of the main request.

Article 123(2) EPC

Both claims 1 and 2 of this request include the features of previous claim 18. Thus, these claims satisfy the requirements of Article 123(2) EPC.

Article 84 EPC

In the summons to oral proceedings, the examiner did not raise an objection under Article 84 EPC against the method claims. The claims of this request satisfy the requirements of Article 84 EPC.

Article 54(1) and (2) and Article 56 EPC

The claimed method of manufacturing a pharmaceutical composition is novel and inventive as none of the cited prior art document discloses or suggests a method as claimed. In particular, none of the cited prior art documents disclose or suggest a method in which a salt of an active agent is used in combination with a deionizing agent as used in the present invention. In fact, D1 teaches the complete opposite, the use of a drug in its free form together with an ionizing agent.

From the teaching of the prior art, the skilled person would have had no expectation that the use of the salt of a drug and a deionizing agent could result in a pharmaceutical composition having reduced levels of PEG esters, as is achieved by the present invention. The evidence for the reduced levels of PEG esters in the compositions obtained using the claimed method is discussed above in relation to the main request.

For at least these reasons, the subject matter of the third auxiliary request is novel and inventive in view of the cited prior art.

Fourth Auxiliary Request

The claims are in Swiss style second medical use format and are based on claims 15 and 16 of the main request. Claims 3 to 14 of this request are based on claims 3 to 14 of the main request.

cont/....

The Claims

Article 123(2) EPC

The comments above on the main request in relation to Article 123(2) EPC also apply to this request.

Article 84 EPC

The comments above on the main request in relation to Article 84 EPC also apply to this request.

Article 54(1) and (2) and Article 56 EPC

The subject matter of this auxiliary request is novel and inventive for the reasons set out above in relation to the main request.

More particularly, the skilled person would not have appreciated from the prior art that the combination of ingredients, which according to the present invention are used to manufacture a pharmaceutical composition could produce an effective pharmaceutical composition which has the additional advantage of reduced formation of PEG esters, as discussed above in relation to the main request.

Fifth Auxiliary Request

The Claims

This auxiliary request is based on the main request expect that the nature of the hydrogen ion species has been limited by the inclusion of the subject matter of claim 12 of the main request into claim 1. As a result, claim 12 of the main request has been deleted from this set of claims.

Article 123(2) EPC

The comments above on the main request in relation to Article 123(2) EPC also apply to this request.

Article 84 EPC

The comments above on the main request in relation to Article 84 EPC also apply to this request. Additionally, the examiner's comments about the presence of hydrogen ions is further addressed by the inclusion of a definition of the hydrogen ion species. It is entirely clear from the claims that water is not the deionizing agent.

cont/....

Article 54(1) and (2) and Article 56 EPC

The subject matter of the claims of this request is novel and inventive for the reasons set out above in relation to the main request.

Sixth Auxiliary Request

The Claims

This auxiliary request is based on the fifth auxiliary request except that the nature of the hydroxide ion species has also been limited. Basis for the definition of the hydroxide ion species can be found at page 6, lines 22 to 25 of the application as filed.

Article 123(2) EPC

The comments above on the main request in relation to Article 123(2) EPC also apply to this request.

Article 84 EPC

The comments above on the main request in relation to Article 84 EPC also apply to this request. Additionally, the examiner's comments above the presence of hydrogen ions and hydroxide ions are further addressed by the inclusion of a definition of the hydrogen ion and hydroxide ion species. It is entirely clear from the claims that water is not the deionizing agent.

Article 54(1) and (2) and Article 56 EPC

The subject matter of the claims of this request is novel and inventive for the reasons set out above in relation to the main request.

Seventh Auxiliary Request

The Claims

This request is based on the main auxiliary request but the salt of the active agent has been limited to naproxen sodium. Claim 11 of the main request specified the use of naproxen sodium. This claim has been deleted.

Article 123(2) EPC

The comments above on the main request in relation to Article 123(2) EPC also apply to this request.

cont/....

Article 84 EPC

The comments above on the main request in relation to Article 84 EPC also apply to this request. Additionally, the examiner's comments above the presence of hydrogen ions is further addressed by the inclusion of a definition of the hydrogen ion species. It is entirely clear from the claims that water is not the deionizing agent.

Article 54(1) and (2) and Article 56 EPC

The subject matter of the claims of this request is novel and inventive for the reasons set out above in relation to the main request.

More particularly, as noted above, even though Example X of D1 does describe a composition comprising naproxen, the drug is used in its free form in combination with the ionizing agent, potassium hydroxide, which causes the formation of the salt naproxen potassium. Additionally, Example 17 of D3 describes a composition comprising naproxen sodium and basic materials. Neither of these documents disclose or suggest the use of naproxen sodium with an acidic deionizing agent as used in the present invention. There is certainly no suggestion that such a combination could have the advantages discussed above.

For at least these reasons the subject matter claimed is novel and inventive.

The Description

It is appreciated that it will be necessary to amend the description for conformity with the amended claims. It is proposed that this is done once agreement has been reached as to the wording of the claims.

Telephone Discussion

The writer proposes to telephone the examiner during the week of 22 August 2011 to discuss the any remaining issues the examiner may have with the aim of avoiding the need to hold oral proceedings in October.

Yours faithfully

Charlotte Crowhurst PhD
For and on behalf of Potter Clarkson LLP

ncu/es

Enc: Paloma *et al*
Main request and seven auxiliary requests
Copy of http://www.chemguide.co.uk/phycial/acidbaseeqia.kw.ht

THE IONIC PRODUCT FOR WATER, K_w

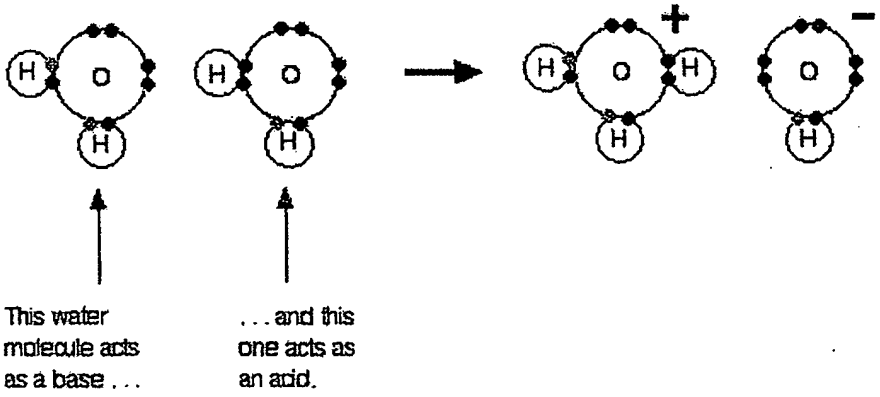
This page explains what is meant by the ionic product for water. It looks at how the ionic product varies with temperature, and how that determines the pH of pure water at different temperatures.

K_w and pK_w

The important equilibrium in water

Water molecules can function as both acids and bases. One water molecule (acting as a base) can accept a hydrogen ion from a second one (acting as an acid). This will be happening anywhere there is even a trace of water - it doesn't have to be pure.

A hydroxonium ion and a hydroxide ion are formed.



However, the hydroxonium ion is a very strong acid, and the hydroxide ion is a very strong base. As fast as they are formed, they react to poduce water again.

The net effect is that an equilibrium is set up.

$$2H_2O_{(l)} \rightleftharpoons H_3O^+_{(aq)} + OH^-_{(aq)}$$

At any one time, there are incredibly small numbers of hydroxonium ions and hydroxide ions present. Further down this page, we shall calculate the concentration of hydroxonium

ions present in pure water. It turns out to be 1.00×10^{-7} mol dm^{-3} at room temperature.

You may well find this equilibrium written in a simplified form:

$$H_2O_{(l)} \rightleftharpoons H^+_{(aq)} + OH^-_{(aq)}$$

This is OK provided you remember that $H^+_{(aq)}$ actually refers to a hydroxonium ion.

Defining the ionic product for water, K_w

K_w is essentially just an equilibrium constant for the reactions shown. You may meet it in two forms:

Based on the fully written equilibrium . . .

$$K_w = [H_3O^+][OH^-]$$

. . . or on the simplified equilibrium:

$$K_w = [H^+][OH^-]$$

You may find them written with or without the state symbols. Whatever version you come across, they all mean exactly the same thing!

You may wonder why the water isn't written on the bottom of these equilibrium constant expressions. So little of the water is ionised at any one time, that its concentration remains virtually unchanged - a constant. K_w is defined to avoid making the expression unnecessarily complicated by including another constant in it.

The value of K_w

Like any other equilibrium constant, the value of K_w varies with temperature. Its value is usually taken to be 1.00×10^{-14} mol^2 dm^{-6} at room temperature. In fact, this is its value at a bit less than 25°C.

The units of K_w: K_w is found by multiplying two concentration terms together. Each of these has the units of

mol dm^{-3}.

Multiplying mol dm^{-3} x mol dm^{-3} gives you the units above.

---

pK_w

The relationship between K_w and pK_w is exactly the same as that between K_a and pK_a, or $[H^+]$ and pH.

$$pK_w = - \log_{10} K_w$$

The K_w value of 1.00×10^{-14} mol^2 dm^{-6} at room temperature gives you a pK_w value of 14. Try it on your calculator! Notice that pK_w doesn't have any units.

The pH of pure water

Why does pure water have a pH of 7?

That question is actually misleading! In fact, pure water only has a pH of 7 at a particular temperature - the temperature at which the K_w value is 1.00×10^{-14} mol^2 dm^{-6}.

This is how it comes about:

To find the pH you need first to find the hydrogen ion concentration (or hydroxonium ion concentration - it's the same thing). Then you convert it to pH.

In pure water at room temperature the K_w value tells you that:

$$[H^+] [OH^-] = 1.00 \times 10^{-14}$$

But in pure water, the hydrogen ion (hydroxonium ion) concentration must be equal to the hydroxide ion concentration. For every hydrogen ion formed, there is a hydroxide ion formed as well.

That means that you can replace the $[OH^-]$ term in the K_w expression by another $[H^+]$.

$$[H^+]^2 = 1.00 \times 10^{-14}$$

Taking the square root of each side gives:

$$[H^+] = 1.00 \times 10^{-7} \text{ mol dm}^{-3}$$

Converting that into pH:

$$pH = - \log_{10} [H^+]$$

$$pH = 7$$

That's where the familiar value of 7 comes from.

The variation of the pH of pure water with temperature

The formation of hydrogen ions (hydroxonium ions) and hydroxide ions from water is an endothermic process. Using the simpler version of the equilibrium:

$$H_2O_{(l)} \rightleftharpoons H^+_{(aq)} + OH^-_{(aq)}$$

The forward reaction absorbs heat.

According to Le Chatelier's Principle, if you make a change to the conditions of a reaction in dynamic equilibrium, the position of equilibrium moves to counter the change you have made.

Note: If you don't understand Le Chatelier's Principle, you should follow this link before you go on. Make sure that you understand the effect of temperature on position of equilibrium.

Use the BACK button on your browser when you are ready to return to this page.

According to Le Chatelier, if you increase the temperature of the water, the equilibrium will move to lower the temperature again. It will do that by absorbing the extra heat.

That means that the forward reaction will be favoured, and more hydrogen ions and hydroxide ions will be formed. The effect of

that is to increase the value of K_w as temperature increases.

The table below shows the effect of temperature on K_w. For each value of K_w, a new pH has been calculated using the same method as above. It might be useful if you were to check these pH values yourself.

T (°C)	K_w ($mol^2\ dm^{-6}$)	pH
0	0.114×10^{-14}	7.47
10	0.293×10^{-14}	7.27
20	0.681×10^{-14}	7.08
25	1.008×10^{-14}	7.00
30	1.471×10^{-14}	6.92
40	2.916×10^{-14}	6.77
50	5.476×10^{-14}	6.63
100	51.3×10^{-14}	6.14

You can see that the pH of pure water falls as the temperature increases.

A word of warning!

If the pH falls as temperature increases, does this mean that water becomes more acidic at higher temperatures? **NO!**

A solution is acidic if there is an excess of hydrogen ions over hydroxide ions. In the case of pure water, there are always the same number of hydrogen ions and hydroxide ions. That means that the water remains neutral - even if its pH changes.

The problem is that we are all so familiar with 7 being the pH of pure water, that anything else feels really strange. Remember that you calculate the neutral value of pH from K_w. If that changes, then the neutral value for pH changes as well.

At 100°C, the pH of pure water is 6.14. That is the neutral point on the pH scale at this higher temperature. A solution with a pH of 7 at this temperature is slightly alkaline because its pH is a bit higher than the neutral value of 6.14.

Similarly, you can argue that a solution with a pH of 7 at 0°C is slightly acidic, because its pH is a bit lower than the neutral value of 7.47 at this temperature.

Where would you like to go now?

To the acid-base equilibria menu . . .

To the Physical Chemistry menu . . .

To Main Menu . . .

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JOURNAL OF
PHARMACEUTICAL
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ANALYSIS

Analysis of diclofenac sodium and derivatives

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Abstract

There are two reasons explaining why several researchers have carried out the in vitro release studies of diclofenac sodium (DFNa) using pH media of above 6.5. Firstly the pH dependence of solubility, and secondly the intramolecular cyclization suffered under acidic conditions which causes the salt to become inactivated. Nevertheless, many commercially available pharmaceutical dosage forms have no protective coat to avoid the inactivation in the gastric juices. A possible explanation may be found if reconstitution of the cyclated form takes place. It is therefore necessary to study the behaviour of diclofenac sodium when it is submitted to the action of different solutions in a wide pH range. To perform this study five analytical methods have been employed: UV-vis spectrophotometry, differential scanning calorimetry (DSC), infrared analysis (IR), X-ray diffractometry (DRX) and energy dispersive X-ray analysis (EDS). © 1999 Elsevier Science B.V. All rights reserved.

Keywords: Diclofenac; Cyclization; DSC; DRX; EDS; IR

1. Introduction

There are many stages involved in drug development: for example, the technological stage, where the research focuses on getting a dosage form of the active substance. This involves different techniques being used to look for the most appropriate substance. However, some of these can damage the active substance, which can loose its effectiveness totally or partially. Therefore, once a dosage form is obtained it has to be analyzed.

The great variety of analytical techniques available provides valuable information which makes it easier to intérpret the behaviour of a drug.

Some years ago, one or two analytical techniques were enough to study an active substance, nowadays more than two are required. Of all of these, the most popular is UV-vis spectrophotometry. This technique is based on the absorbance capability of a substance at a specific wavelength. Interference with another substance that absorbs at the same wavelength limits the use of this technique.

In recent years DSC (differential scanning calorimetry) has gained popularity since it is easy and quick. It is based on the detection of endothermic and exothermic peaks that appear as a

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consequence of small changes in temperatures. The number, location and shape of these peaks are used to identify a substance [1].

Other analytical techniques include infrared and X-ray analysis. The first is used commonly to detect the presence of functional groups, whilst the second depends on the crystalline properties of the sample.

SEM (scanning electron microscopy) gives information about the shape of the compound due to the interactions of electrons on the sample, which creates a map of the surface. As a consequence of this interaction the atoms that constitute the compound can loose an electron. Another electron, from a more energetic stage, migrates to the free place generating an X-ray whose energy is characteristic for every atom. Hence it is possible to perform a qualitative analysis (EDS).

If all analytical techniques were employed in the study of an active substance then a great deal of information about its chemical structure would be obtained. Thus the aim of this work is to study what happens to an active substance (diclofenac sodium) when it is treated with acidic solutions and then treated with neutral and basic solutions.

Diclofenac is a non-steroidal anti-inflammatory drug that it is specially indicated in rheumatoid arthritis [2]. Due to its low solubility it is commercially available as diclofenac sodium [3]. This substance, sodium(*O*-((2,6-dichlorophenyl)-amino)-phenyl)-acetate is a weak acid with a pK_a of 4 and a partition coefficient (*n*-octanol/aqueous buffer, pH 7.4) of 13.4.

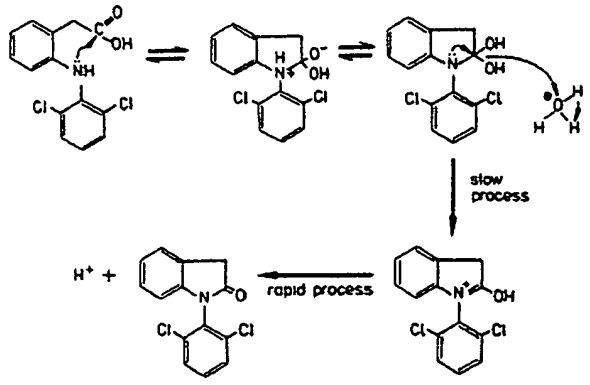


Fig. 1. Cyclization reaction of diclofenac sodium in acidic conditions [4].

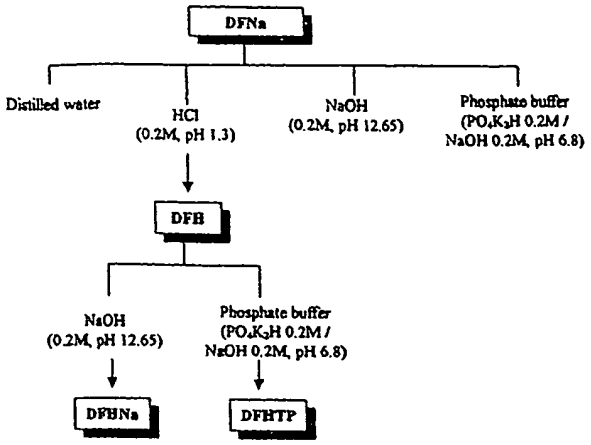


Fig. 2. Schematic representation of diclofenac sodium treatment procedure.

Two important characteristics are linked to this substance. Firstly, its solubility, which depends on the pH of the surrounding solution; in acidic solutions the solubility is lower than 1 mg ml^{-1} [4]. Nevertheless, the solubility increases with pHs of above 6.5 [5–7]. This fact explains why 'in vitro' dissolution tests have to be performed using buffered solutions with those pHs [8]. Secondly, diclofenac sodium undergoes an intramolecular cyclization under the acidic conditions (Fig. 1) found in gastric juices, which can cause its inactivation, so it is recommended to take it after meals [9]. As a consequence of the intramolecular cyclization Na^+ is lost hence the solubility of the compound decreases.

If cyclization under acidic conditions is be reversible when the surrounding solution changes into basic or neutral solutions with a high proportion of Na^+ then a reconstitution of the original structure would take place. Therefore, it would not be necessary to protect it from the action of gastric juices. In fact, some authors [10] suggest that the acid–base reaction takes place only on the external surface of the monolithic form, the low solubility of the acidic form prevents further dissolution and release at low pH; once the pH increases, the thin layer enables release to start again.

Considering that the structure of the cyclated form proposed by Racz [9] is the same structure

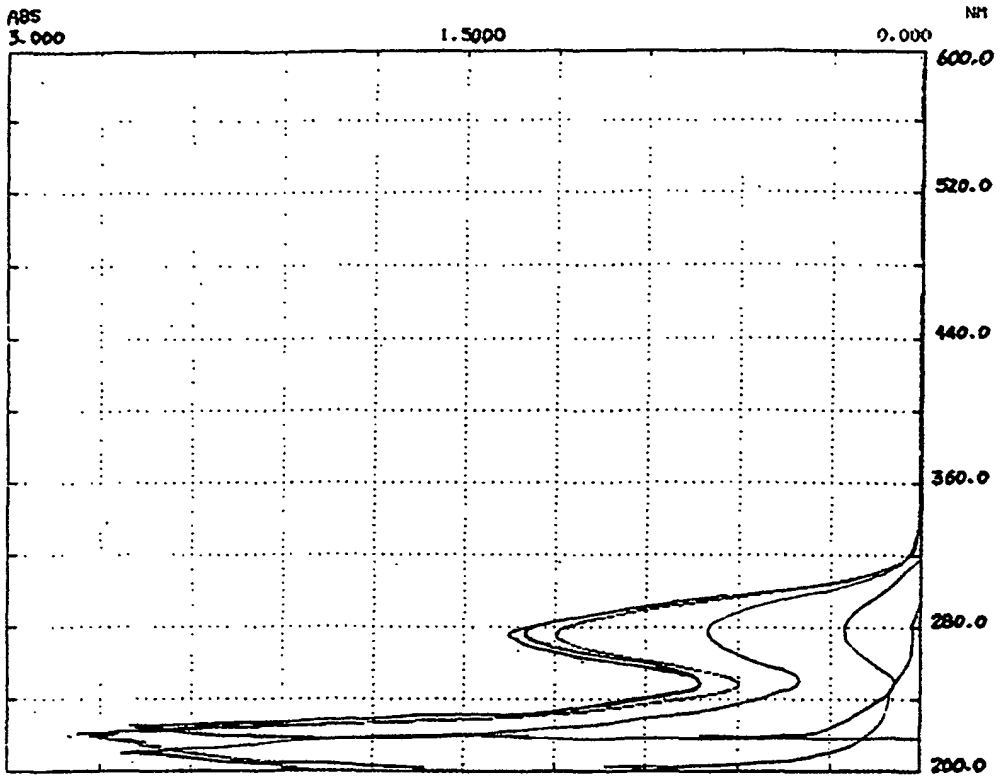


Fig. 3. UV-vis spectrophotometry scans. From left to right: DFNa in buffer solution; DFNa in NaOH solution; DFNa in distilled water; DFHTP (previous crystallization); DFHNa (previous crystallization); DFH (previous filtration).

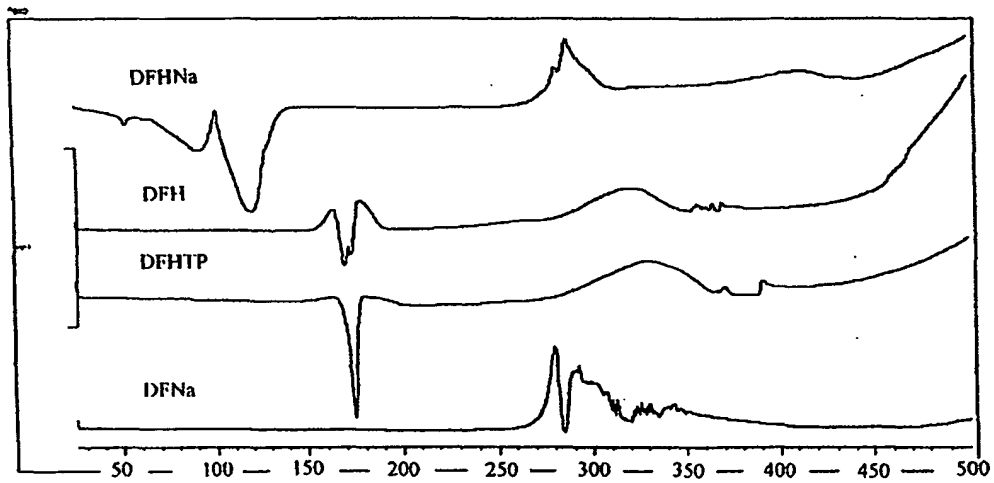


Fig. 4. Results of DSC analysis.

used by Tamura [11] to synthesize diclofenac sodium by reaction with NaOH, then it can be assumed that the reconstitution of the active substance takes place.

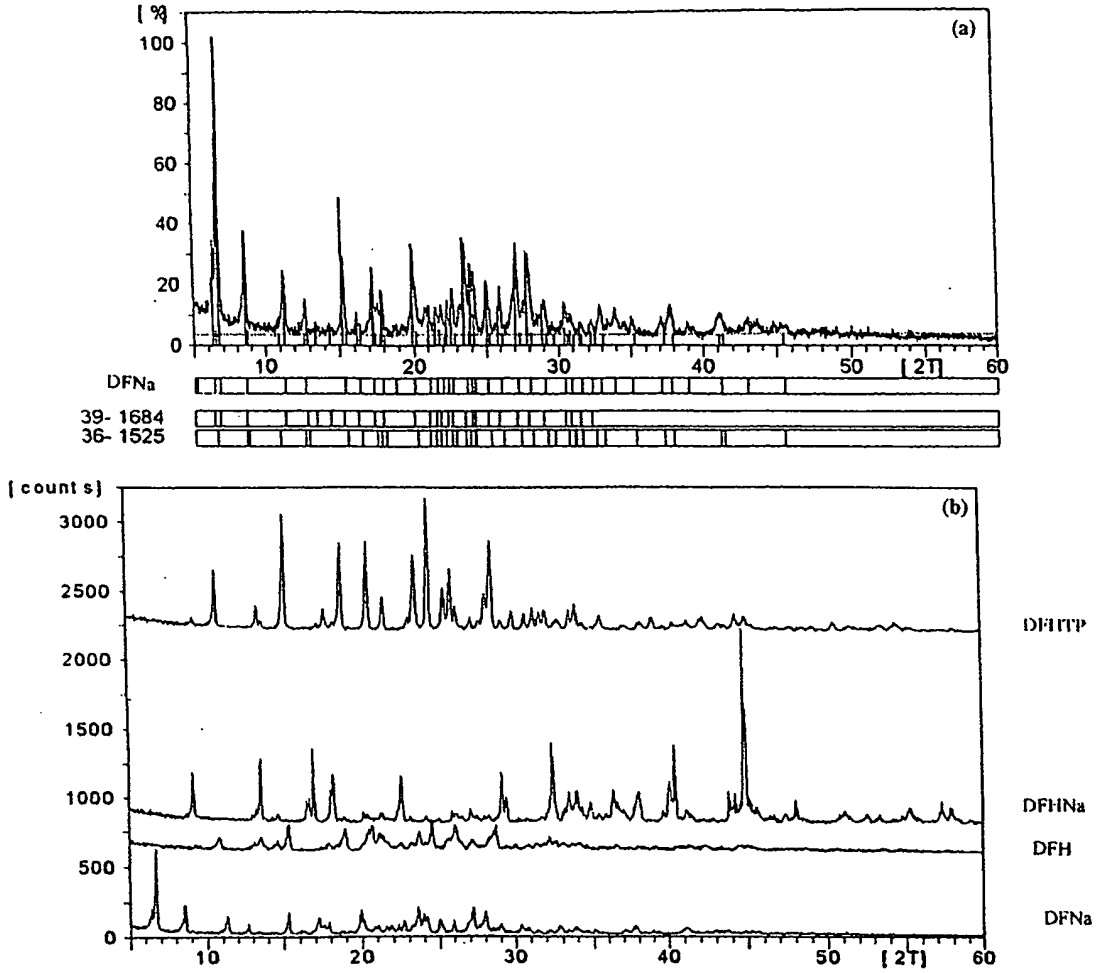


Fig. 5. (a) DRX of DFNa compared to main peaks of two technical files. (b) Results of DRX of all substances assayed.

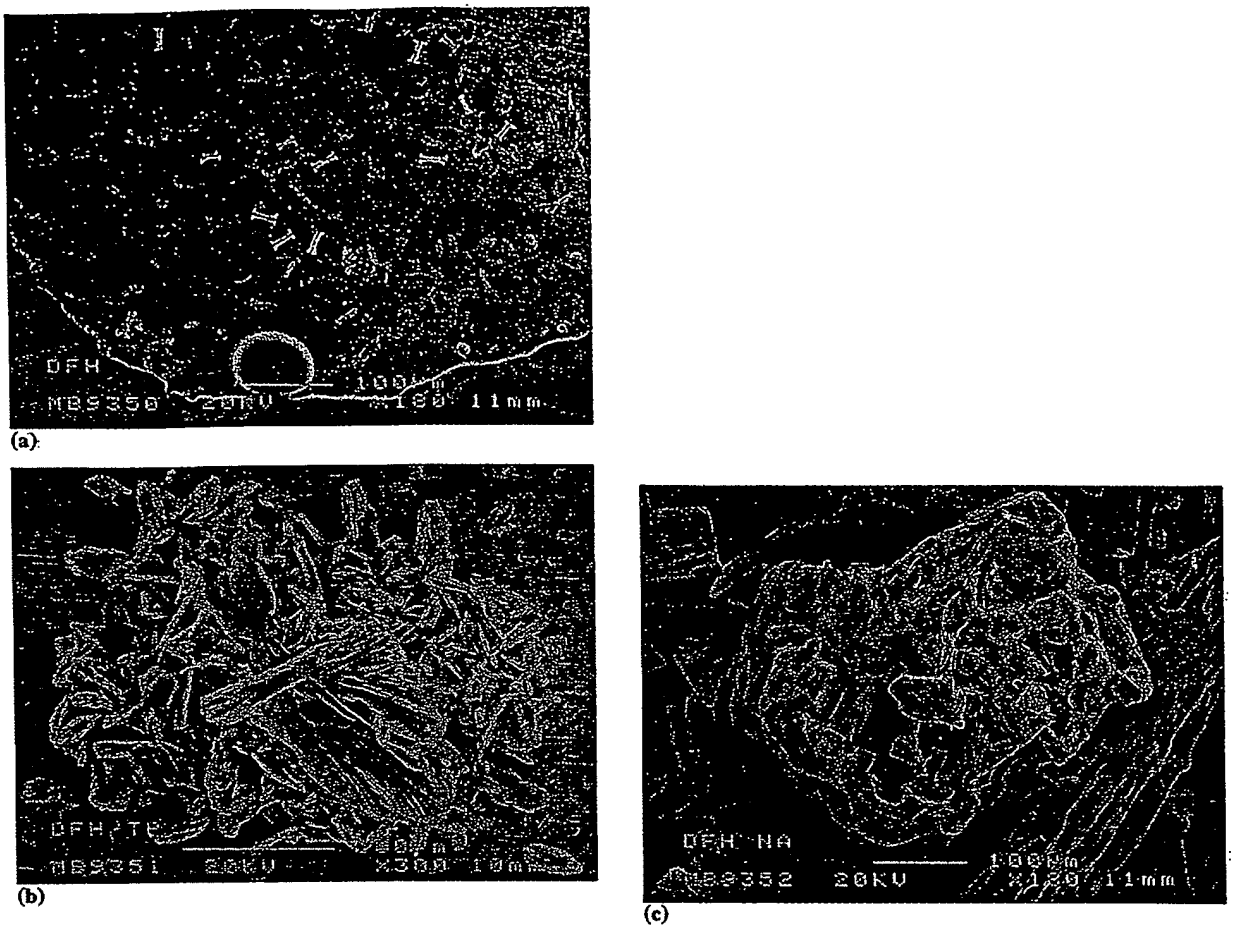
Nevertheless, there is no evidence to confirm this fact. It is therefore necessary to study the behaviour of this substance and it is helpful to establish the best conditions to avoid its inactivation in order to obtain an appropriate and effective dosage form from a therapeutical point of view.

To perform this study the active substance (diclofenac sodium) will undergo to the action of different solutions in a complex procedure. The resultant compounds will be analyzed using the analytical techniques described above which were selected because of the results obtained in a previous study with diclofenac sodium and in accordance with the literature [4].

2. Materials and methods

The active substance diclofenac sodium (DFNa) was purchased from Impex Química. Equal amounts of diclofenac sodium were treated independently with the next solutions: NaOH 0.2M, pH 12.65; HCl 0.2 M, pH 1.3; distilled water; phosphate buffered solution (PO_4K_2H 0.2 M; NaOH 0.2M; pH 6.8).

As expected, diclofenac sodium was freely soluble in all solutions mentioned above except in HCl. With this last solution and after 24 h at a constant stirring rate (100 rpm), a precipitate (DFH) was obtained. This precipitate was filtered and equal parts of it were submitted to a second



(a) (b) (c)

Fig. 6. SEM photographs: (a) DFH; (b) DFHTP; (c) DFHNa.

treatment with the first solution (NaOH 0.2 M, pH 12,65) and another part of the precipitate (DFH) was treated with the last solution (PO_4K_2H 0.2 M; NaOH 0.2 M; pH 6.8) used previously.

In both cases the precipitate (DFH) was dissolved and crystallized in a crystallizer until evaporation at room temperature without stirring; the two solids products were obtained: DFHNa (after the second treatment with NaOH) and DFHTP (after the second treatment with phosphate buffer). Fig. 2 shows the whole procedure.

In order to perform a qualitative study, the analytical techniques mentioned previously were employed:

1. UV-vis spectrophotometry: a Beckman DU-6 was used. The scans were carried out from 210–600 nm at a rate of 60 nm min^{-1}.
2. Differential scanning calorimetry (DSC): Mettler Toledo TA8000 equipment with a DSC-820 furnace was used. Samples of 3–10 mg were weighed directly into aluminium samples pans. The thermal analyses were conducted in a flow of air at atmospheric pressure. Scans were carried out from 30–500°C at a heating rate of 10°C min^{-1}.
3. X-ray diffractometry (DRX): Philips X-Pert MPD equipment was used with Cu–K_α radiation from 5–40°2θ, with a wide angle of 0.04° at a rate of 1 s.

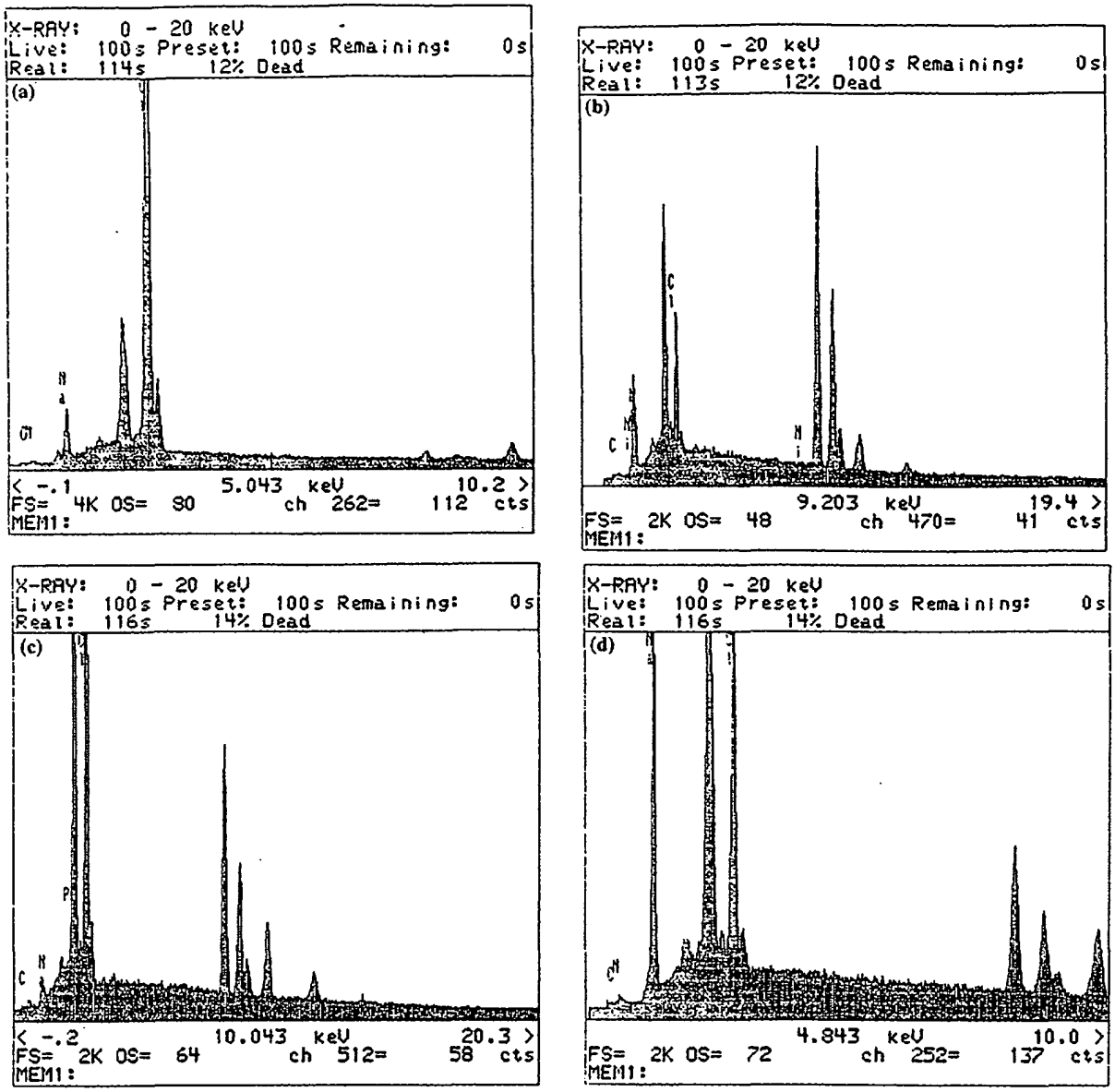


Fig. 7. EDS results: (a) DFNa; (b) DFH; (c) DFHTP; (d) DFHNa, elongated crystals; (e) DFHNa, agglomerates.

4. Energy disperse X-ray analysis (EDS): a LINK eXL coupled to a scanning electron microscope (SEM) JSM-6400 was used for a qualitative analysis of Na and Cl in all compounds.
5. Infrared analysis: tablets of a mixture of the compounds and KBr at a concentration of 4% were analysed with a Perkin Elmer Paragon 100. Each IR was the result of four rounds.

3. Results and discussion

3.1. UV-vis spectrophotometry analysis

In the spectrophotometry analysis (Fig. 3) all solutions showed absorbances between 270–276 nm. No significant differences were found between them except that the reduction of the intensity of absorbance, which is due to the fact that

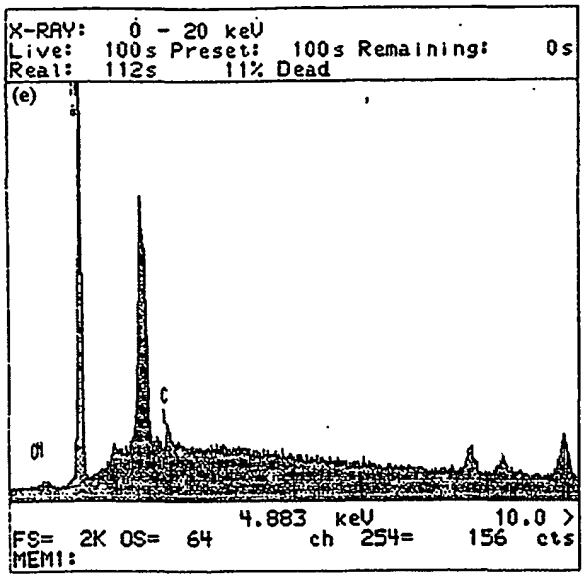


Fig. 7. (*Continued*)

just only the salt (diclofenac sodium), can dissolve in all the solutions. Meanwhile the acidic compound cannot dissolve. These results were confirmed in the literature [4–7,12].

3.2. DSC analysis

The results are shown in Fig. 4. The DSC curve of DFNa (active substance) showed an exothermic peak of melting at 280°C followed by an endothermic peak of decomposition as mentioned in the literature [4]. An accurate measurement was performed and the exothermic peaks were found in the interval from 280.45 to 349.96°C.

The DSC curve of DFH showed two exothermic peaks and an endothermic one from 160–190°C, these peaks corresponded to the melting point (156–158°C) of the acidic compound [13]. In comparison to the DSC curve of DFNa, the peaks were shifted to lower temperatures, and when a temperature of 270°C was reached the decomposition of the product started. Again, an accurate measurement of the thermogram was performed and the main exothermic peak was found at 321.87°C. Meanwhile the secondary exothermic peaks were found in the range of temperatures from 356.85 to 366.55°C.

The DSC curve of DFHNa showed endothermic peaks below 130°C due to the evaporation of the water of crystallisation. This fact was confirmed later when the sample was heated from 25 to 140°C, cooled to 30°C and finally heated again to 400°C. In the new thermogram the endothermic peaks that were located below 130°C disappeared. After heating, two exothermic peaks appeared at 281.98 and 288.48°. A soft exothermic peak was also located at 411.34°C. The thermogram of DFHNa was compared with the those of solid NaOH and a 0.2 M NaOH solution (previously crystallized in a crystalliser at room temperature). Neither of these last two thermograms showed exothermic peaks at 280°C. Hence, the exothermic peaks exhibit between 281–288° by DFHNa substance probably correspond to the presence of DFNa.

The thermogram of DFHTP is quite similar to that of DFH and in an accurate measurement the main exothermic peak was found at 329.631°C, while two secondary exothermic peaks were found at 370.59 and 390.64°C.

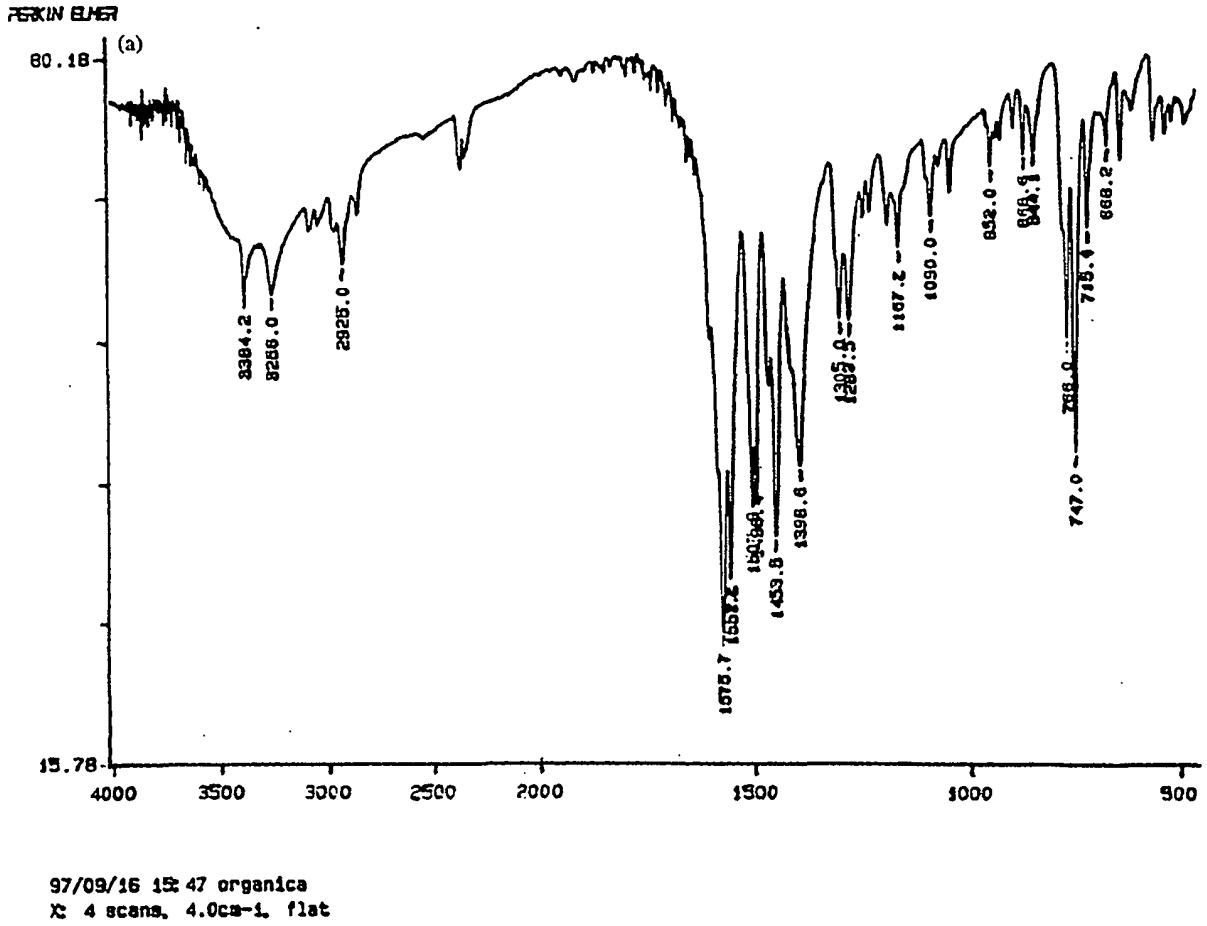


Fig. 8. IR results: (a) DFNa; (b) DFH; (c) DFHTP; (d) DFHNa.

3.3. DRX analysis

The diffractogram of DFNa was compared with two technical files (39-1684) and (36-1525). A high degree of similarity was found between them (Fig. 5(a)). The diffractogram of DFH was quite different (Fig. 5(b)) in comparison to DFNa.

The diffractogram of DFHNa (Fig. 5(c)) showed the presence of DFNa, although the peaks showed lower intensity, nevertheless, other peaks appeared. In comparison with the technical files, it could be observed that the peaks had moved to the right. Thus hypotheses thus arise.

1. The crystals show a preferential disposition. The peaks in the diffractogram of DFNa that appeared with lower intensity are now exalted and vice versa.
2. Some ions have been replaced by other ions so that a variation of distance occurred which corresponds to a displacement of the peaks. The displacement towards the right means the distances were reduced, hence large atoms (Na^+) were substituted by atoms (H^+) of smaller size.

Finally, in the diffractogram of DFHTP (Fig. 5(d)) there were some peaks that corresponded to DFNa, however, more peaks appeared. In comparison with the technical file a displacement of the peaks towards the right can be observed. The peaks on the left have disappeared, which meant that a reduction of the distances took place due to the substitution of some atoms by others of smaller size.

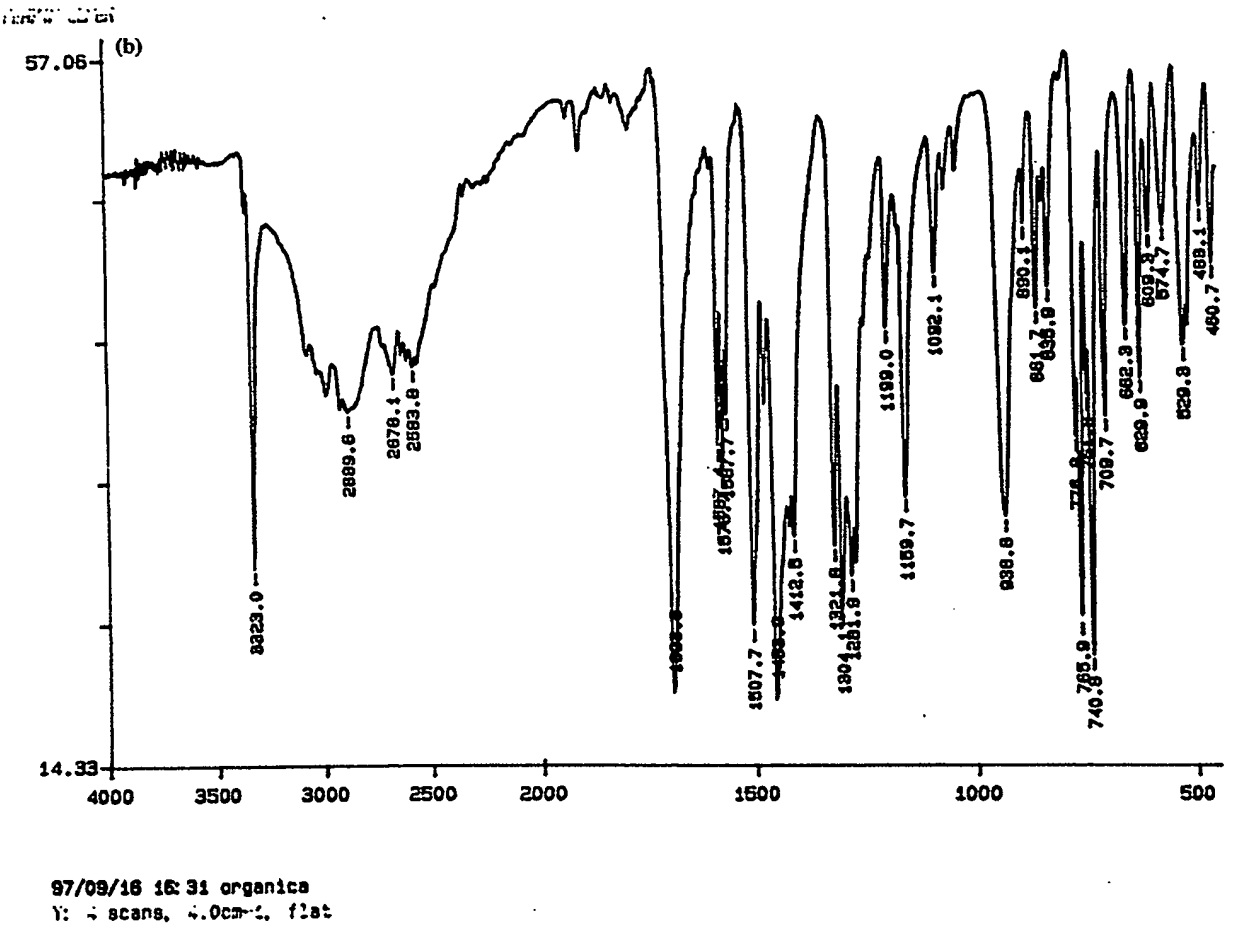


Fig. 8. (*Continued*)

3.4. EDS analysis and SEM photographs

All SEM photographs and EDS results are shown in Figs. 6 and 7, respectively. Fig. 7(a) corresponds to EDS of DFNa. A high proportion of Cl in relation to Na can be observed. In the EDS analysis of DFH, two different structures were observed, one of them has an X shape (Fig. 6(a)) and its EDS (Fig. 7(b)) reveals a lower proportion of Cl and a higher proportion of Na compared to the EDS of DFNa. This probably means that Cl was lost. The second structure has a round shape and its EDS shows also a low proportion of Cl.

With respect to the results obtained with the second treatment, it can be observed that the EDS of DFHTP (Fig. 7(c)) showed increased levels of Cl and P while the proportion of Na decreased.

Finally, in the analysis of DFHNa (Fig. 6(d)) two types of crystals were observed. The elongated one revealed the presence of Cl (Fig. 7(d)). The other structure (Fig. 7(e)), which was an agglomeration of the previous one, revealed a high proportion of Na compared to Cl, which was probably due to the presence of NaOH.

3.5. IR analysis

Fig. 8(a) shows the IR of DFNa, at 1600 a signal of a carbonyl group appeared. Fig. 8(b) corresponds to DFH. In this IR three types of signals were obtained: at 3323 the signal of the

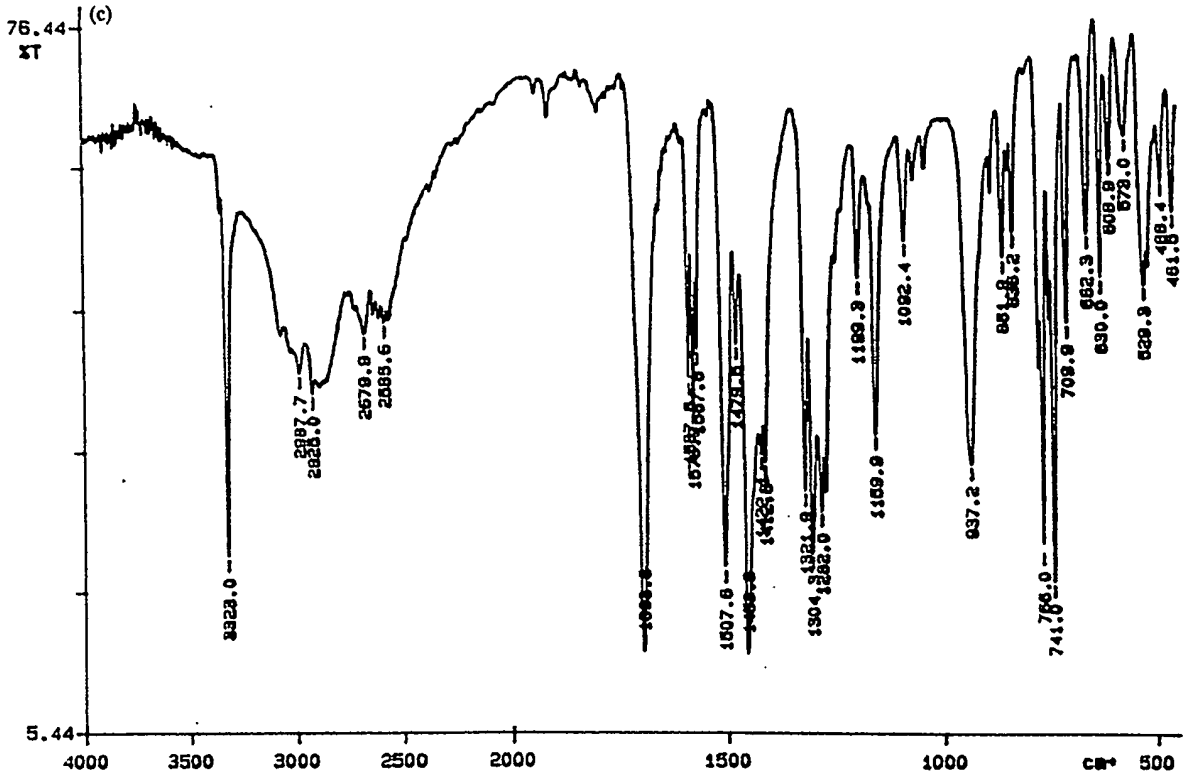


Fig. 8. (*Continued*)

–NH– group appeared, the signals between 2580–2900 corresponded to acidic compounds and finally the signal of the carbonyl group appeared at 1693. All these results suggested that this compound did not have a lactamic structure, hence this compound was not cyclated.

When DFH was treated with phosphate buffer, the structure of the acidic compound remained. The IR (Fig. 8(c)) was quite similar to the IR of DFH. This suggested that the treatment with phosphate solution was not enough to recover the salt.

On the other hand the treatment of DFH with NaOH produced a compound (DFHNa) whose IR (Fig. 8(d)) showed evidence of a NaOH residual in a high proportion. In consequence the spectrum of NaOH overlapped the spectrum of DFHNa, nevertheless a significant difference regarding IR of acidic compound was observed. The signal at 1693 of carbonyl group disappeared and there were signals of DFNa, hence it was possible to assume that the salt was recovered.

4. Conclusions

From the analytical study of Diclofenac sodium and its derivatives, the following conclusions can be drawn.

(1) UV-vis spectrophotometry: no significant differences were observed.

(2) DSC: in the second treatment with phosphate buffer no reconstitution of the DFNa was appreciated. Nevertheless, the treatment with NaOH showed a possible reconstitution of DFNa.

(3) DRX: the treatment of the acidic compound with phosphate buffer or NaOH promoted the exchange of large atoms with smaller ones, hence the distances between planes of crystallization were reduced.

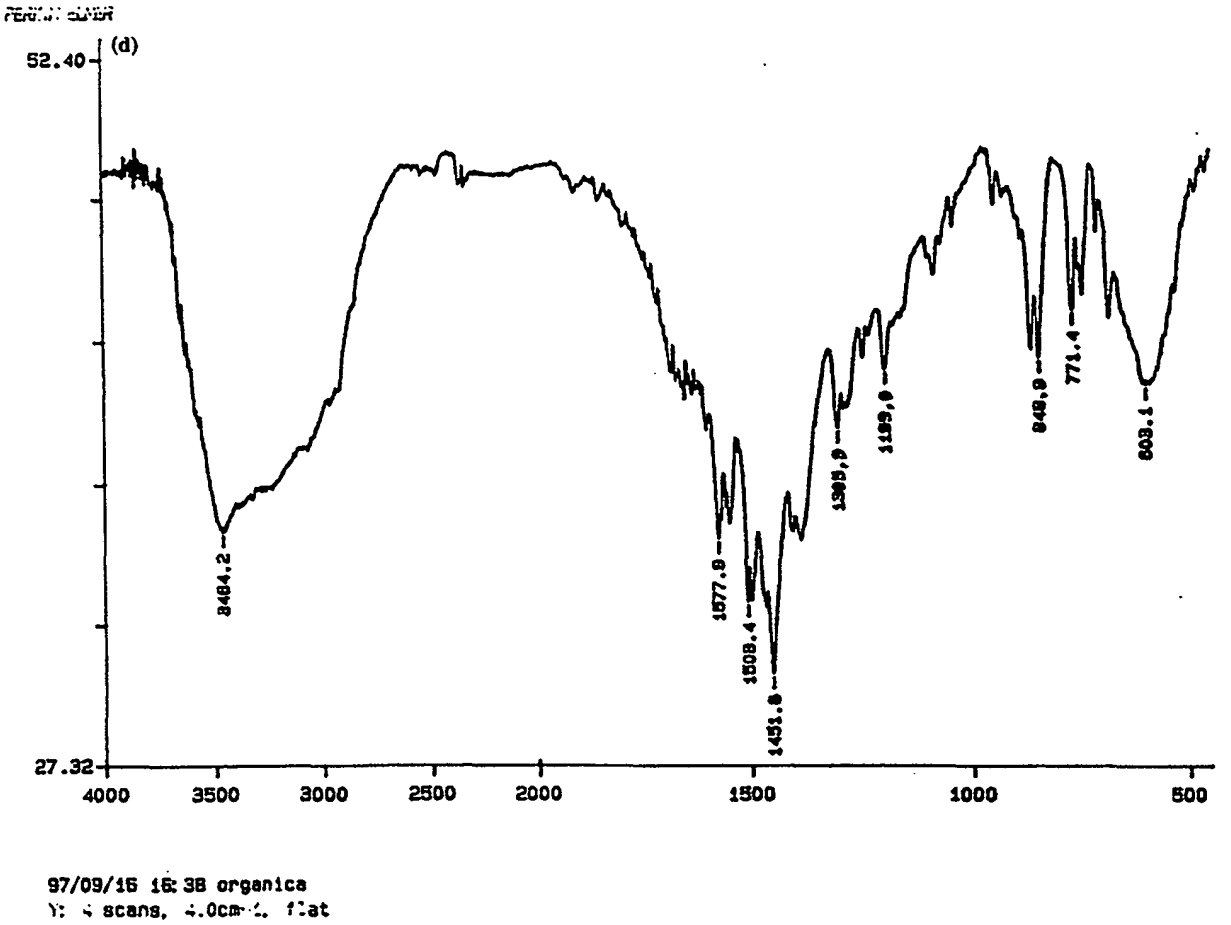


Fig. 8. (*Continued*)

(4) EDS and SEM: the SEM photographs of DFH revealed strange shapes. Its EDS gave a low level of Cl, and the same result was obtained in the analysis of DFHTP. Conversely, the EDS of DFHNa showed high levels of Cl and very high levels of Na, due to saturation with NaOH.

(5) IR analysis: the results obtained in the analysis of acidic compound (DFH) revealed that it was not a lactamic structure, hence it was not cyclated. The treatment with phosphate buffer did not modify the structure. However treatment with NaOH could recover DFNa, although the spectrum was overlapped by NaOH residuals.

Contrary to the literature [9], diclofenac sodium did not undergo intramolecular cyclization in acidic conditions; in fact this substance loose Na^+ in acidic solutions decreasing its solubility. The analytical techniques employed (DSC, DRX, EDS, IR) give evidence for the chemical structure modification of diclofenac sodium (DFNa) once it has been treated with an acidic solution.

When the new compound (DFH) is analysed by IR the spectrum obtained (Fig. 8(b)) does not correspond to a cyclated structure in opposition to what was expected [9]. The acidic solution only takes away the NA ion from the DFNa structure giving rise to a compound (DFH) with a rather low water solubility but not cyclated.

Moreover the original salt (DFNa) can be recovered with an appropriate solution and this means again that the DFH is not a cyclated structure (a lactamic structure does not react as

easily because it has a rather high chemical stability).

Acknowledgements

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MAIN REQUEST

CLAIMS

1. A pharmaceutical composition comprising

(a) a salt of one or more acidic or basic pharmaceutically active agents;

(b) a deionizing agent in an amount to cause partial deionization of the salt of from about 0.2 to 1.0 mole equivalents per mole of the pharmaceutically active agent(s);

(c) polyethylene glycol; and optionally

(d) water;

wherein when the salt (a) is a salt of a weak acid and a strong base, the deionizing agent is a hydrogen ion species, and when the salt (a) is the salt of a weak base and a strong acid, the deionizing agent is a hydroxide ion species.

2. A softgel capsule comprising a fill material wherein the fill material comprises

(a) a salt of one or more acidic or basic pharmaceutically active agents;

(b) a deionizing agent in an amount to cause partial deionization of the salt of from about 0.2 to 1.0 mole equivalents per mole of the pharmaceutically active agent(s);

(c) polyethylene glycol; and optionally

(d) water

wherein when the salt (a) is a salt of a weak acid and a strong base, the deionizing agent is a hydrogen ion species, and when the salt (a) is the salt of a weak base and a strong acid, the deionizing agent is a hydroxide ion species.

3. The composition or capsule of claim 1 or 2 wherein the pharmaceutically active agent is selected from the group consisting of therapeutically active agents, diagnostic agents, and prophylactic agents.

4. The composition or capsule of any one of the preceding claims wherein the composition or fill material has a pH of from about 2.5 to about 7.5.

5. The composition or capsule of any one of the preceding claims wherein polyethylene glycol is present in an amount from about 10% to about 80% by weight.

6. The composition or capsule of any one of the preceding claims wherein the polyethylene glycol is one or more polyethylene glycols with a molecular weight between 300 and 1500.

7. The composition or the capsule of any one of the preceding claims wherein water is present in an amount from about 1% to about 18% by weight.

8. The composition or capsule of any one of the preceding claims further comprising one or more excipients selected from the group consisting of plasticizers, crystallization inhibitors, wetting agents, bulk filling agents, solubilizers, bioavailability enhancers, solvents, pH-adjusting agents, dyes, preservatives, solvents, surfactants, and combinations thereof.

9. The composition or capsule of claim 8 wherein the solubilizer is selected from the group consisting of glycerin, polyvinylpyrrolidone, propylene glycol and combinations thereof.

10. The composition or capsule of claim 8 wherein the solubilizer is present in amount from about 1% to about 10% by weight.

11. The composition or capsule of any one of the preceding claims wherein the salt (a) is naproxen sodium and the deionizing agent is a hydrogen ion species.

12. The composition or capsule of any one of the preceding claims wherein the hydrogen ion species is selected from hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, fumaric acid, maleic acid, tartaric acid, methane-, ethane-, and benzene sulfonates, citric acid, malic acid, acetic acid, proprionic acid, pyruvic acid, butanoic acid, and lactic acid.

13. A composition or capsule of any of claims 1 to 12 for use as a medicament.

14. A method of making the composition or capsule of any of claims 1 to 13 comprising

(a) mixing the salt of one or more acidic or basic pharmaceutically active agents, the polyethylene glycol and the deionizing agent and optionally water at a temperature of from 50°C to 70°C; and

(b) encapsulating the mixture in a softgel capsule.

15. The use of

(a) a salt of one or more acidic or basic pharmaceutically active agents;

(b) a deionizing agent in an amount to cause partial deionization of the salt of from about 0.2 to 1.0 mole equivalents per mole of the pharmaceutically active agent(s);

(c) polyethylene glycol; and optionally

(d) water

in the manufacture of a medicament for administration of the pharmaceutically active agent to a patient in need thereof;

wherein when the salt (a) is a salt of a weak acid and a strong base, the deionizing agent is a hydrogen ion species, and when the salt (a) is the salt of a weak base and a strong acid, the deionizing agent is a hydroxide ion species.

16. The use of claim 15 wherein the medicament is in the form of a softgel capsule.

17. A pharmaceutical composition obtainable by a method which comprises

(I) mixing

(a) a salt of one or more acidic or basic pharmaceutically active agents;

(b) a deionizing agent in an amount to cause partial deionization of the salt of from about 0.2 to 1.0 mole equivalents per mole of the pharmaceutically active agent(s);

(c) polyethylene glycol; and optionally

(d) water

at a temperature of from 50°C to 70°C;

wherein when the salt (a) is a salt of a weak acid and a strong base, the deionizing agent is a hydrogen ion species, and when the salt (a) is the salt of a weak base and a strong acid, the deionizing agent is a hydroxide ion species.

18. A softgel capsule obtainable by a method which comprises

(I) producing a fill material by mixing

(a) a salt of one or more acidic or basic pharmaceutically active agents;

(b) a deionizing agent in an amount to cause partial deionization of the salt of from about 0.2 to 1.0 mole equivalents per mole of the pharmaceutically active agent(s);

(c) polyethylene glycol; and optionally

(d) water

at a temperature of from 50°C to 70°C; and

(II) encapsulating the mixture in a softgel capsule;

wherein when the salt (a) is a salt of a weak acid and a strong base, the deionizing agent is a hydrogen ion species, and when the salt (a) is the salt of a weak base and a strong acid, the deionizing agent is a hydroxide ion species.

FIRST AUXILIARY REQUEST

CLAIMS

1. A softgel capsule comprising a fill material wherein the fill material comprises
   (a) a salt of one or more acidic or basic pharmaceutically active agents;
   (b) a deionizing agent in an amount to cause partial deionization of the salt of from about 0.2 to 1.0 mole equivalents per mole of the pharmaceutically active agent(s);
   (c) polyethylene glycol; and optionally
   (d) water

   wherein when the salt (a) is a salt of a weak acid and a strong base, the deionizing agent is a hydrogen ion species, and when the salt (a) is the salt of a weak base and a strong acid, the deionizing agent is a hydroxide ion species.

2. The capsule of claim 1 wherein the pharmaceutically active agent is selected from the group consisting of therapeutically active agents, diagnostic agents, and prophylactic agents.

3. The capsule of claim 1 or 2 wherein the fill material has a pH of from about 2.5 to about 7.5.

4. The capsule of any one of the preceding claims wherein polyethylene glycol is present in an amount from about 10% to about 80% by weight.

5. The capsule of any one of the preceding claims wherein the polyethylene glycol is one or more polyethylene glycols with a molecular weight between 300 and 1500.

6. The capsule of any one of the preceding claims wherein water is present in an amount from about 1% to about 18% by weight.

7. The capsule of any one of the preceding claims further comprising one or more excipients selected from the group consisting of plasticizers, crystallization inhibitors, wetting agents, bulk filling agents, solubilizers, bioavailability enhancers, solvents, pH-adjusting agents, dyes, preservatives, solvents, surfactants, and combinations thereof.

8. The capsule of claim 7 wherein the solubilizer is selected from the group consisting of glycerin, polyvinylpyrrolidone, propylene glycol and combinations thereof.

9. The capsule of claim 7 wherein the solubilizer is present in amount from about 1% to about 10% by weight.

10. The capsule of any one of the preceding claims wherein the salt (a) is naproxen sodium and the deionizing agent is a hydrogen ion species.

11. The capsule of any one of the preceding claims wherein the hydrogen ion species is selected from hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, fumaric acid, maleic acid, tartaric acid, methane-, ethane-, and benzene sulfonates, citric acid, malic acid, acetic acid, proprionic acid, pyruvic acid, butanoic acid, and lactic acid.

12. A capsule of any of claims 1 to 12 for use as a medicament.

13. A method of making the capsule of any of claims 1 to 12 comprising

(a) mixing the salt of one or more acidic or basic pharmaceutically active agents, the polyethylene glycol and the deionizing agent and optionally water at a temperature of from 50°C to 70°C; and

(b) encapsulating the mixture in a softgel capsule.

14. The use of

(a) a salt of one or more acidic or basic pharmaceutically active agents;

(b) a deionizing agent in an amount to cause partial deionization of the salt of from about 0.2 to 1.0 mole equivalents per mole of the pharmaceutically active agent(s);

(c) polyethylene glycol; and optionally

(d) water

in the manufacture of a medicament in the form of a softgel capsule for administration of the pharmaceutically active agent to a patient in need thereof; wherein when the salt (a) is a salt of a weak acid and a strong base, the deionizing agent is a hydrogen ion species, and when the salt (a) is the salt of a weak base and a strong acid, the deionizing agent is a hydroxide ion species.

15. A softgel capsule obtainable by a method which comprises

(I) producing a fill material by mixing

(a) a salt of one or more acidic or basic pharmaceutically active agents;

(b) a deionizing agent in an amount to cause partial deionization of the salt of from about 0.2 to 1.0 mole equivalents per mole of the pharmaceutically active agent(s);

(c) polyethylene glycol; and optionally

(d) water

at a temperature of from 50°C to 70°C; and

(II) encapsulating the mixture in a softgel capsule;

wherein when the salt (a) is a salt of a weak acid and a strong base, the deionizing agent is a hydrogen ion species, and when the salt (a) is the salt of a weak base and a strong acid, the deionizing agent is a hydroxide ion species.

SECOND AUXILIARY REQUEST

CLAIMS

1. A pharmaceutical composition obtainable by a method which comprises

(I) mixing

(a) a salt of one or more acidic or basic pharmaceutically active agents;

(b) a deionizing agent in an amount to cause partial deionization of the salt of from about 0.2 to 1.0 mole equivalents per mole of the pharmaceutically active agent(s);

(c) polyethylene glycol; and optionally

(d) water

at a temperature of from 50°C to 70°C;

wherein when the salt (a) is a salt of a weak acid and a strong base, the deionizing agent is a hydrogen ion species, and when the salt (a) is the salt of a weak base and a strong acid, the deionizing agent is a hydroxide ion species.

2. A softgel capsule obtainable by a method which comprises

(I) producing a fill material by mixing

(a) a salt of one or more acidic or basic pharmaceutically active agents;

(b) a deionizing agent in an amount to cause partial deionization of the salt of from about 0.2 to 1.0 mole equivalents per mole of the pharmaceutically active agent(s);

(c) polyethylene glycol; and optionally

(d) water

at a temperature of from 50°C to 70°C; and

(II) encapsulating the mixture in a softgel capsule;

wherein when the salt (a) is a salt of a weak acid and a strong base, the deionizing agent is a hydrogen ion species, and when the salt (a) is the salt of a weak base and a strong acid, the deionizing agent is a hydroxide ion species.

3. The composition or capsule of claim 1 or 2 wherein the pharmaceutically active agent is selected from the group consisting of therapeutically active agents, diagnostic agents, and prophylactic agents.

4. The composition or capsule of any one of the preceding claims wherein the composition or fill material of the softgel capsule has a pH of from about 2.5 to about 7.5.

5. The composition or capsule of any one of the preceding claims wherein polyethylene glycol is present in an amount from about 10% to about 80% by weight.

6. The composition or capsule of any one of the preceding claims wherein the polyethylene glycol is one or more polyethylene glycols with a molecular weight between 300 and 1500.

7. The composition or the capsule of any one of the preceding claims wherein water is present in an amount from about 1% to about 18% by weight.

8. The composition or capsule of any one of the preceding claims further comprising one or more excipients selected from the group consisting of plasticizers, crystallization inhibitors, wetting agents, bulk filling agents, solubilizers, bioavailability enhancers, solvents, pH-adjusting agents, dyes, preservatives, solvents, surfactants, and combinations thereof.

9. The composition or capsule of claim 8 wherein the solubilizer is selected from the group consisting of glycerin, polyvinylpyrrolidone, propylene glycol and combinations thereof.

10. The composition or capsule of claim 8 wherein the solubilizer is present in amount from about 1% to about 10% by weight.

11. The composition or capsule of any one of the preceding claims wherein the salt (a) is naproxen sodium and the deionizing agent is a hydrogen ion species.

12. The composition or capsule of any on eof the preceding claims wherein the hydrogen ion species is selected from hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, fumaric acid, maleic acid, tartaric acid, methane-, ethane-, and benzene sulfonates, citric acid, malic acid, acetic acid, proprionic acid, pyruvic acid, butanoic acid, and lactic acid.

13. A composition or capsule of any of claims 1 to 12 for use as a medicament.

14. A method of making the composition or capsule of any of claims 1 to 13 comprising

(a) mixing the salt of one or more acidic or basic pharmaceutically active agents, the polyethylene glycol and the deionizing agent and optionally water at a temperature of from 50°C to 70°C; and

(b) encapsulating the mixture in a softgel capsule.

15. The use of

(a) a salt of one or more acidic or basic pharmaceutically active agents;

(b) a deionizing agent in an amount to cause partial deionization of the salt of from about 0.2 to 1.0 mole equivalents per mole of the pharmaceutically active agent(s);

(c) polyethylene glycol; and optionally

(d) water

in the manufacture of a medicament for administration of the pharmaceutically active agent to a patient in need thereof;

wherein when the salt (a) is a salt of a weak acid and a strong base, the deionizing agent is a hydrogen ion species, and when the salt (a) is the salt of a weak base and a strong acid, the deionizing agent is a hydroxide ion species.

16. The use of claim 15 wherein the medicament is in the form of a softgel capsule.

THIRD AUXILIARY REQUEST

CLAIMS

1. A method of making a pharmaceutical composition comprising

(a) mixing a salt of one or more acidic or basic pharmaceutically active agents, a polyethylene glycol and a deionizing agent and optionally water at a temperature of from 50°C to 70°C;

wherein the deionizing agent is used in an amount to cause partial ionization of the salt of from about 0.2 to 1.0 mole equivalents per mole of the pharmaceutically active agent(s) and wherein when the salt (a) is a salt of a weak acid and a strong base, the deionizing agent is a hydrogen ion species, and when the salt (a) is a salt of a weak base and a strong acid, the deionizing agent is a hydroxide ions species.

2. A method of making a softgel capsule comprising making a fill mixture by the method of claim 1 and

(b) encapsulating the mixture in a softgel capsule.

3. The method of claim 1 or 2 wherein the pharmaceutically active agent is selected from the group consisting of therapeutically active agents, diagnostic agents, and prophylactic agents.

4. The method of any one of the preceding claims wherein the composition or fill material has a pH of from about 2.5 to about 7.5.

5. The method of any one of the preceding claims wherein polyethylene glycol is present in an amount from about 10% to about 80% by weight.

6. The method of any one of the preceding claims wherein the polyethylene glycol is one or more polyethylene glycols with a molecular weight between 300 and 1500.

7. The method of any one of the preceding claims wherein water is present in an amount from about 1% to about 18% by weight.

8. The method of any one of the preceding claims further comprising one or more excipients selected from the group consisting of plasticizers, crystallization inhibitors,

wetting agents, bulk filling agents, solubilizers, bioavailability enhancers, solvents, pH-adjusting agents, dyes, preservatives, solvents, surfactants, and combinations thereof.

9. The method of claim 8 wherein the solubilizer is selected from the group consisting of glycerin, polyvinylpyrrolidone, propylene glycol and combinations thereof.

10. The method of claim 8 wherein the solubilizer is present in amount from about 1% to about 10% by weight.

11. The method of any one of the preceding claims wherein the salt (a) is naproxen sodium and the deionizing agent is a hydrogen ion species.

12. The method of any one of the preceding claims wherein the hydrogen ion species is selected from hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, fumaric acid, maleic acid, tartaric acid, methane-, ethane-, and benzene sulfonates, citric acid, malic acid, acetic acid, proprionic acid, pyruvic acid, butanoic acid, and lactic acid.

13. A method of making a pharmaceutical composition or softgel capsule comprising

(a) mixing the salt of one or more acidic or basic pharmaceutically active agents, the polyethylene glycol and the deionizing agent and optionally water at a temperature of from 50°C to 70°C; and

(b) encapsulating the mixture in a softgel capsule.

FOURTH AUXILIARY REQUEST

CLAIMS

1. The use of
   (a) a salt of one or more acidic or basic pharmaceutically active agents;
   (b) a deionizing agent in an amount to cause partial deionization of the salt of from about 0.2 to 1.0 mole equivalents per mole of the pharmaceutically active agent(s);
   (c) polyethylene glycol; and optionally
   (d) water
   in the manufacture of a medicament for administration of the pharmaceutically active agent to a patient in need thereof;
   wherein when the salt (a) is a salt of a weak acid and a strong base, the deionizing agent is a hydrogen ion species, and when the salt (a) is the salt of a weak base and a strong acid, the deionizing agent is a hydroxide ion species.

2. The use of claim 1 wherein the medicament is in the form of a softgel capsule.

3. The use of claim 1 or 2 wherein the pharmaceutically active agent is selected from the group consisting of therapeutically active agents, diagnostic agents, and prophylactic agents.

4. The use of any one of the preceding claims wherein the composition or fill material of the soft gel capsule has a pH of from about 2.5 to about 7.5.

5. The use of any one of the preceding claims wherein polyethylene glycol is present in an amount from about 10% to about 80% by weight.

6. The use of any one of the preceding claims wherein the polyethylene glycol is one or more polyethylene glycols with a molecular weight between 300 and 1500.

7. The use any one of the preceding claims wherein water is present in an amount from about 1% to about 18% by weight.

8. The use of any one of the preceding claims further comprising one or more excipients selected from the group consisting of plasticizers, crystallization inhibitors,

wetting agents, bulk filling agents, solubilizers, bioavailability enhancers, solvents, pH-adjusting agents, dyes, preservatives, solvents, surfactants, and combinations thereof.

9. The use of claim 8 wherein the solubilizer is selected from the group consisting of glycerin, polyvinylpyrrolidone, propylene glycol and combinations thereof.

10. The use of claim 8 wherein the solubilizer is present in amount from about 1% to about 10% by weight.

11. The use of any one of the preceding claims wherein the salt (a) is naproxen sodium and the deionizing agent is a hydrogen ion species.

12. The use of any one of the preceding claims wherein the hydrogen ion species is selected from hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, fumaric acid, maleic acid, tartaric acid, methane-, ethane-, and benzene sulfonates, citric acid, malic acid, acetic acid, proprionic acid, pyruvic acid, butanoic acid, and lactic acid.

13. A method of making a pharmaceutical composition or softgel capsule comprising

(a) mixing the salt of one or more acidic or basic pharmaceutically active agents, the polyethylene glycol and the deionizing agent and optionally water at a temperature of from 50°C to 70°C; and

(b) encapsulating the mixture in a softgel capsule.

FIFTH AUXILIARY REQUEST

CLAIMS

1. A pharmaceutical composition comprising
   (a) a salt of one or more acidic or basic pharmaceutically active agents;
   (b) a deionizing agent in an amount to cause partial deionization of the salt of from about 0.2 to 1.0 mole equivalents per mole of the pharmaceutically active agent(s);
   (c) polyethylene glycol; and optionally
   (d) water;

wherein when the salt (a) is a salt of a weak acid and a strong base, the deionizing agent is a hydrogen ion species selected from hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, fumaric acid, maleic acid, tartaric acid, methane-, ethane-, and benzene sulfonates, citric acid, malic acid, acetic acid, proprionic acid, pyruvic acid, butanoic acid, and lactic acid, and when the salt (a) is the salt of a weak base and a strong acid, the deionizing agent is a hydroxide ion species.

2. A softgel capsule comprising a fill material wherein the fill material comprises
   (a) a salt of one or more acidic or basic pharmaceutically active agents;
   (b) a deionizing agent in an amount to cause partial deionization of the salt of from about 0.2 to 1.0 mole equivalents per mole of the pharmaceutically active agent(s);
   (c) polyethylene glycol; and optionally
   (d) water

wherein when the salt (a) is a salt of a weak acid and a strong base, the deionizing agent is a hydrogen ion species selected from hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, fumaric acid, maleic acid, tartaric acid, methane-, ethane-, and benzene sulfonates, citric acid, malic acid, acetic acid, proprionic acid, pyruvic acid, butanoic acid, and lactic acid, and when the salt (a) is the salt of a weak base and a strong acid, the deionizing agent is a hydroxide ion species.

3. The composition or capsule of claim 1 or 2 wherein the pharmaceutically active agent is selected from the group consisting of therapeutically active agents, diagnostic agents, and prophylactic agents.

4. The composition or capsule of any one of the preceding claims wherein the composition or fill material has a pH of from about 2.5 to about 7.5.

5. The composition or capsule of any one of the preceding claims wherein polyethylene glycol is present in an amount from about 10% to about 80% by weight.

6. The composition or capsule of any one of the preceding claims wherein the polyethylene glycol is one or more polyethylene glycols with a molecular weight between 300 and 1500.

7. The composition or the capsule any one of the preceding claims wherein water is present in an amount from about 1% to about 18% by weight.

8. The composition or capsule of any one of the preceding claims comprising one or more excipients selected from the group consisting of plasticizers, crystallization inhibitors, wetting agents, bulk filling agents, solubilizers, bioavailability enhancers, solvents, pH-adjusting agents, dyes, preservatives, solvents, surfactants, and combinations thereof.

9. The composition or capsule of claim 8 wherein the solubilizer is selected from the group consisting of glycerin, polyvinylpyrrolidone, propylene glycol and combinations thereof.

10. The composition or capsule of claim 8 wherein the solubilizer is present in amount from about 1% to about 10% by weight.

11. The composition or capsule of any one of the preceding claims wherein the salt (a) is naproxen sodium and the deionizing agent is a hydrogen ion species.

12. A composition or capsule of any of claims 1 to 11 for use as a medicament.

13. A method of making the composition or capsule of any of claims 1 to 12 comprising

(a) mixing the salt of one or more acidic or basic pharmaceutically active agents, the polyethylene glycol and the deionizing agent and optionally water at a temperature of from 50°C to 70°C; and

(b) encapsulating the mixture in a softgel capsule.

14. The use of

(a) a salt of one or more acidic or basic pharmaceutically active agents;

(b) a deionizing agent in an amount to cause partial deionization of the salt of from about 0.2 to 1.0 mole equivalents per mole of the pharmaceutically active agent(s);

(c) polyethylene glycol; and optionally

(d) water

in the manufacture of a medicament for administration of the pharmaceutically active agent to a patient in need thereof;

wherein when the salt (a) is a salt of a weak acid and a strong base, the deionizing agent is a hydrogen ion species selected from hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, fumaric acid, maleic acid, tartaric acid, methane-, ethane-, and benzene sulfonates, citric acid, malic acid, acetic acid, proprionic acid, pyruvic acid, butanoic acid, and lactic acid, and when the salt (a) is the salt of a weak base and a strong acid, the deionizing agent is a hydroxide ion species.

15. The use of claim 14 wherein the medicament is in the form of a softgel capsule.

16. A pharmaceutical composition obtainable by a method which comprises

(I) mixing

(a) a salt of one or more acidic or basic pharmaceutically active agents;

(b) a deionizing agent in an amount to cause partial deionization of the salt of from about 0.2 to 1.0 mole equivalents per mole of the pharmaceutically active agent(s);

(c) polyethylene glycol; and optionally

(d) water

at a temperature of from 50°C to 70°C;

wherein when the salt (a) is a salt of a weak acid and a strong base, the deionizing agent is a hydrogen ion species selected from hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, fumaric acid, maleic acid, tartaric acid, methane-, ethane-, and benzene sulfonates, citric acid, malic acid, acetic acid, proprionic acid, pyruvic acid, butanoic acid, and lactic acid, and when the salt (a) is the salt of a weak base and a strong acid, the deionizing agent is a hydroxide ion species.

17. A softgel capsule obtainable by a method which comprises

(I) producing a fill material by mixing

(a) a salt of one or more acidic or basic pharmaceutically active agents;

(b) a deionizing agent in an amount to cause partial deionization of the salt of from about 0.2 to 1.0 mole equivalents per mole of the pharmaceutically active agent(s);

(c) polyethylene glycol; and optionally

(d) water

at a temperature of from 50°C to 70°C; and

(II) encapsulating the mixture in a softgel capsule;

wherein when the salt (a) is a salt of a weak acid and a strong base, the deionizing agent is a hydrogen ion species selected from hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, fumaric acid, maleic acid, tartaric acid, methane-, ethane-, and benzene sulfonates, citric acid, malic acid, acetic acid, proprionic acid, pyruvic acid, butanoic acid, and lactic acid, and when the salt (a) is the salt of a weak base and a strong acid, the deionizing agent is a hydroxide ion species.

SIXTH AUXILIARY REQUEST

CLAIMS

1. A pharmaceutical composition comprising

(a) a salt of one or more acidic or basic pharmaceutically active agents;

(b) a deionizing agent in an amount to cause partial deionization of the salt of from about 0.2 to 1.0 mole equivalents per mole of the pharmaceutically active agent(s);

(c) polyethylene glycol; and optionally

(d) water;

wherein when the salt (a) is a salt of a weak acid and a strong base, the deionizing agent is a hydrogen ion species selected from hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, fumaric acid, maleic acid, tartaric acid, methane-, ethane-, and benzene sulfonates, citric acid, malic acid, acetic acid, proprionic acid, pyruvic acid, butanoic acid, and lactic acid, and when the salt (a) is the salt of a weak base and a strong acid, the deionizing agent is a hydroxide ion species selected from sodium hydroxide, potassium hydroxide, ammonium hydroxide, calcium hydroxide, aluminum hydroxide and magnesium hydroxide.

2. A softgel capsule comprising a fill material wherein the fill material comprises

(a) a salt of one or more acidic or basic pharmaceutically active agents;

(b) a deionizing agent in an amount to cause partial deionization of the salt of from about 0.2 to 1.0 mole equivalents per mole of the pharmaceutically active agent(s);

(c) polyethylene glycol; and optionally

(d) water

wherein when the salt (a) is a salt of a weak acid and a strong base, the deionizing agent is a hydrogen ion species selected from hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, fumaric acid, maleic acid, tartaric acid, methane-, ethane-, and benzene sulfonates, citric acid, malic acid, acetic acid, proprionic acid, pyruvic acid, butanoic acid, and lactic acid, and when the salt (a) is the salt of a weak base and a strong acid, the deionizing agent is a hydroxide ion species selected from soldium hydroxide, potassium hydroxide, ammonium hydroxide, calcium hydroxide, aluminum hydroxide and magnesium hydroxide.

3. The composition or capsule of claim 1 or 2 wherein the pharmaceutically active agent is selected from the group consisting of therapeutically active agents, diagnostic agents, and prophylactic agents.

4. The composition or capsule of any one of the preceding claims wherein the composition or fill material has a pH of from about 2.5 to about 7.5.

5. The composition or capsule of any one of the preceding claims wherein polyethylene glycol is present in an amount from about 10% to about 80% by weight.

6. The composition or capsule of any one of the preceding claims wherein the polyethylene glycol is one or more polyethylene glycols with a molecular weight between 300 and 1500.

7. The composition of any one of the preceding claims wherein water is present in an amount from about 1% to about 18% by weight.

8. The composition or capsule of any one of the preceding claims further comprising one or more excipients selected from the group consisting of plasticizers, crystallization inhibitors, wetting agents, bulk filling agents, solubilizers, bioavailability enhancers, solvents, pH-adjusting agents, dyes, preservatives, solvents, surfactants, and combinations thereof.

9. The composition or capsule of claim 8 wherein the solubilizer is selected from the group consisting of glycerin, polyvinylpyrrolidone, propylene glycol and combinations thereof.

10. The composition or capsule of claim 8 wherein the solubilizer is present in amount from about 1% to about 10% by weight.

11. The composition or capsule of any one of the preceding claims wherein the salt (a) is naproxen sodium and the deionizing agent is a hydrogen ion species.

12. A composition or capsule of any of claims 1 to 11 for use as a medicament.

13. A method of making the composition or capsule of any of claims 1 to 12 comprising

(a) mixing the salt of one or more acidic or basic pharmaceutically active agents, the polyethylene glycol and the deionizing agent and optionally water at a temperature of from 50°C to 70°C; and

(b) encapsulating the mixture in a softgel capsule.

14. The use of

(a) a salt of one or more acidic or basic pharmaceutically active agents;

(b) a deionizing agent in an amount to cause partial deionization of the salt of from about 0.2 to 1.0 mole equivalents per mole of the pharmaceutically active agent(s);

(c) polyethylene glycol; and optionally

(d) water

in the manufacture of a medicament for administration of the pharmaceutically active agent to a patient in need thereof;

wherein when the salt (a) is a salt of a weak acid and a strong base, the deionizing agent is a hydrogen ion species selected from hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, fumaric acid, maleic acid, tartaric acid, methane-, ethane-, and benzene sulfonates, citric acid, malic acid, acetic acid, proprionic acid, pyruvic acid, butanoic acid, and lactic acid, and when the salt (a) is the salt of a weak base and a strong acid, the deionizing agent is a hydroxide ion species selected from sodium hydroxide, potassium hydroxide, ammonium hydroxide, calcium hydroxide, aluminum hydroxide and magnesium hydroxide.

15. The use of claim 14 wherein the medicament is in the form of a softgel capsule.

16. A pharmaceutical composition obtainable by a method which comprises

(I) mixing

(a) a salt of one or more acidic or basic pharmaceutically active agents;

(b) a deionizing agent in an amount to cause partial deionization of the salt of from about 0.2 to 1.0 mole equivalents per mole of the pharmaceutically active agent(s);

(c) polyethylene glycol; and optionally

(d) water

at a temperature of from 50°C to 70°C;

wherein when the salt (a) is a salt of a weak acid and a strong base, the deionizing agent is a hydrogen ion species selected from hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, fumaric acid, maleic acid, tartaric acid, methane-,

ethane-, and benzene sulfonates, citric acid, malic acid, acetic acid, proprionic acid, pyruvic acid, butanoic acid, and lactic acid, and when the salt (a) is the salt of a weak base and a strong acid, the deionizing agent is a hydroxide ion species selected from sodium hydroxide, potassium hydroxide, ammonium hydroxide, calcium hydroxide, aluminum hydroxide and magnesium hydroxide.

17. A softgel capsule obtainable by a method which comprises

(I) producing a fill material by mixing

(a) a salt of one or more acidic or basic pharmaceutically active agents;

(b) a deionizing agent in an amount to cause partial deionization of the salt of from about 0.2 to 1.0 mole equivalents per mole of the pharmaceutically active agent(s);

(c) polyethylene glycol: and optionally

(d) water

at a temperature of from 50°C to 70°C; and

(II) encapsulating the mixture in a softgel capsule;

wherein when the salt (a) is a salt of a weak acid and a strong base, the deionizing agent is a hydrogen ion species selected from hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, fumaric acid, maleic acid, tartaric acid, methane-, ethane-, and benzene sulfonates, citric acid, malic acid, acetic acid, proprionic acid, pyruvic acid, butanoic acid, and lactic acid, and when the salt (a) is the salt of a weak base and a strong acid, the deionizing agent is a hydroxide ion species selected from sodium hydroxide, potassium hydroxide, ammonium hydroxide, calcium hydroxide, aluminum hydroxide and magnesium hydroxide.

SEVENTH AUXILIARY REQUEST

CLAIMS

1. A pharmaceutical composition comprising
   (a) naproxen sodium;
   (b) a deionizing agent in an amount to cause partial deionization of the salt of from about 0.2 to 1.0 mole equivalents per mole of the naproxen sodium;
   (c) polyethylene glycol; and optionally
   (d) water.

2. A softgel capsule comprising a fill material wherein the fill material comprises
   (a) naproxen sodium;
   (b) a deionizing agent selected from hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, fumaric acid, maleic acid, tartaric acid, methane-, ethane-, and benzene sulfonates, citric acid, malic acid, acetic acid, proprionic acid, pyruvic acid, butanoic acid, and lactic acid in an amount to cause partial deionization of the salt of from about 0.2 to 1.0 mole equivalents per mole of the naproxen sodium;
   (c) polyethylene glycol; and optionally
   (d) water.

3. The composition or capsule of claim 1 or 2 wherein the deionizing agent is selected from hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, fumaric acid, maleic acid, tartaric acid, methane-, ethane-, and benzene sulfonates, citric acid, malic acid, acetic acid, proprionic acid, pyruvic acid, butanoic acid, and lactic acid.

4. The composition or capsule of any one of the preceding claims wherein the composition or fill material has a pH of from about 2.5 to about 7.5.

5. The composition or capsule of any one of the preceding claims wherein polyethylene glycol is present in an amount from about 10% to about 80% by weight.

6. The composition or capsule of any one of the preceding claims wherein the polyethylene glycol is one or more polyethylene glycols with a molecular weight between 300 and 1500.

7. The composition or the capsule of any one of the preceding claims wherein water is present in an amount from about 1% to about 18% by weight.

8. The composition or capsule of any one of the preceding claims further comprising one or more excipients selected from the group consisting of plasticizers, crystallization inhibitors, wetting agents, bulk filling agents, solubilizers, bioavailability enhancers, solvents, pH-adjusting agents, dyes, preservatives, solvents, surfactants, and combinations thereof.

9. The composition or capsule of claim 8 wherein the solubilizer is selected from the group consisting of glycerin, polyvinylpyrrolidone, propylene glycol and combinations thereof.

10. The composition or capsule of claim 8 wherein the solubilizer is present in amount from about 1% to about 10% by weight.

11. A composition or capsule of any of claims 1 to 10 for use as a medicament.

12. A method of making the composition or capsule of any of claims 1 to 11 comprising

(a) mixing the naproxen sodium, the polyethylene glycol and the deionizing agent and optionally water at a temperature of from 50°C to 70°C; and

(b) encapsulating the mixture in a softgel capsule.

13. The use of

(a) naproxen sodium;

(b) a deionizing agent selected from hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, fumaric acid, maleic acid, tartaric acid, methane-, ethane-, and benzene sulfonates, citric acid, malic acid, acetic acid, proprionic acid, pyruvic acid, butanoic acid, and lactic acid in an amount to cause partial deionization of the salt of from about 0.2 to 1.0 mole equivalents per mole of the pharmaceutically active agent(s);

(c) polyethylene glycol: and optionally

(d) water

in the manufacture of a medicament for administration of naproxen sodium to a patient in need thereof.

14. The use of claim 13 wherein the medicament is in the form of a softgel capsule.

15. A pharmaceutical composition obtainable by a method which comprises

(I) mixing

(a) naproxen sodium;

(b) a deionizing agent selected from hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, fumaric acid, maleic acid, tartaric acid, methane-, ethane-, and benzene sulfonates, citric acid, malic acid, acetic acid, proprionic acid, pyruvic acid, butanoic acid, and lactic acid in an amount to cause partial deionization of the salt of from about 0.2 to 1.0 mole equivalents per mole of the naproxen sodium;

(c) polyethylene glycol; and optionally

(d) water

at a temperature of from 50°C to 70°C.

16. A softgel capsule obtainable by a method which comprises

(I) producing a fill material by mixing

(a) naproxen sodium;

(b) a deionizing agent selected from hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, fumaric acid, maleic acid, tartaric acid, methane-, ethane-, and benzene sulfonates, citric acid, malic acid, acetic acid, proprionic acid, pyruvic acid, butanoic acid, and lactic acid in an amount to cause partial deionization of the salt of from about 0.2 to 1.0 mole equivalents per mole of the pharmaceutically active agent(s);

(c) polyethylene glycol; and optionally

(d) water

at a temperature of from 50°C to 70°C; and

(II) encapsulating the mixture in a softgel capsules.

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European Patent Office
Office européen des brevets

European patent application No. 06737018.9

URGENT !
To be completed (under II.) and returned to the formalities officer immediately

Maintenance / Change of date / Cancellation of oral proceedings arranged for: day 07.10.11 at 09.00 hrs

I. To the Examining / Opposition division

1. ☐ The proprietor has requested the revocation (or the like) of his patent (date: .....).

2. ☒ The party / witness ..... has indicated (date: ....04.08.2011...) that he / she

   ☐ requests the date / time of oral proceedings to be changed.

   ☐ withdraws the request for oral proceedings.

   ☐ will not be attending.

   ☐ wishes to be heard by a national court.

   ☒ has filed amendments (in examination proceedings).

   ☐ has requested that the oral proceedings be held as a videoconference (in examination proceedings).

3. ☐ Two months before the oral proceedings the application is deemed to be withdrawn (in examination proceedings). The oral proceedings have to be cancelled.

09-08-2011
Date

Stark, Saskia
Formalities Officer

European patent application No. 06737018.9

II. To the Formalities Officer

1. ☒ The date / time fixed for oral proceedings is maintained.

   ☐ (if necessary) The reasons are indicated on enclosed EPO Form 2906/2906O, which is to be dispatched to the party with EPO Form 2008A/2310A.

2. ☐ At the instigation of the division the oral proceedings cannot take place on the arranged date for the reasons indicated on enclosed EPO Form 2906, which is to be dispatched to the party with EPO Form 2008A/2310A.

Date _____ Director (see Internal Instructions IE-III, 1.2) _____

3. ☐ The summons to attend oral proceedings on 07.10.11 should be cancelled.

   3.1 ☐ The proceedings will be continued in writing.

   3.2 ☐ A new date will be set later.

   3.3 ☐ A new date/time is set as follows:

   date ..... at ..... hrs.
   Parties' written submissions and amendments in preparation for the oral proceedings, if any, should be made not later than

   ..... month(s) before the date of the oral proceedings.

4. ☐ The request for the oral proceedings to be held as a videoconference

   4.1 ☐ is allowed.

   4.2 ☐ is rejected for the reasons indicated on enclosed EPO Form 2906, which is to be dispatched to the party with EPO Form 2008A.

5. ☐ The application is deemed to be withdrawn. The oral proceedings are cancelled.

Date 16.08.11

Chairman _____ Second member _____ Primary Examiner _____ Legal member _____

III. Action taken by the formalities officer

☐ EPO Form 2008A/2310A has been dispatched, if applicable (see point II above) together with EPO Form 2906/2906O.

☐ A new summons has been dispatched.

☐ .....

Date _____ Formalities Officer _____

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or call:
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Date: 18-08-2011

Reference	Application No./Patent No.
PABCA/P38814EP	06737018.9 - 2123 / 1863458

Applicant/Proprietor: Banner Pharmacaps Inc.

BRIEF COMMUNICATION

Oral Proceedings on 07.10.11

Subject: [X] Your letter of 04.08.2011

Communication:

- [ ] The summons to attend oral proceedings on 07.10.11 has been cancelled.
- [ ] The procedure will be continued in writing.
- [X] The date fixed for oral proceedings is maintained.
- [ ] A new date will be set later.
- [ ]

Please take note.

For the Examining Division

Europäisches Patentamt • European Patent Office • Office européen des brevets

Registered letter
EPO Form 2008A 12.07 (12/08/11)

POTTER CLARKSON

URGENT

PLEASE PASS DIRECTLY TO THE EXAMINER MR BUTTNER
ORAL PROCEEDINGS IMMINENT

To:	**European Patent Office**
Your Fax No:	00 49 89 2399 4465
From:	Charlotte Crowhurst PhD
Date:	16 September 2011
Our Ref:	PABCX/P38814EP
Your Ref:	European Patent Application No. 06737018.9-2123

Sheet 1 of 32 **Original by Post:** ✓

MESSAGE:

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16 September 2011

URGENT

PLEASE PASS DIRECTLY TO THE EXAMINER MR BUTTNER
ORAL PROCEEDINGS IMMINENT

Sent by fax

Dear Sirs

European Patent Application No. 06737018.9-2123
BANNER PHARMACAPS, INC.
Our ref: PABCX/P38814EP

We refer to the written submissions filed on 4 August 2011 and are now providing supplemental written submissions, which include experimental data and seek to address the issues discussed during a telephone conversation between the examiner, Mr Buttner and the representative, Dr Crowhurst on 5 September 2011.

The Requests

We enclose a new main request and six auxiliary requests to replace the requests filed on 4 August 2011. The applicant reserves the right to file further auxiliary requests, should this be necessary. In particular, the applicant reserves the right to make combinations of the claims now presented, including combining claims from within the same request and combining claims from different requests or to delete claims.

The Main Request

The Amendments to the Claims

The new main request is based on the main request filed on 4 August 2011, except that the definition of the salt of the pharmaceutically active agent has been amended and consequential amendments have been made to the wording of the claims.

cont/....

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It is now an essential feature of the claimed composition that component (a) is a salt of an acidic pharmaceutically active agent and that the deionizing agent is a hydrogen ion species.

Article 54(1) and (2) EPC – Novelty

US 5,360,615 (D1)

As discussed in our letter of 4 August 2011, the examiner raised an objection of lack of novelty in view of the disclosure in D1 of a composition comprising a salt of an amphoteric active agent, diclofenac sodium.

The amendments made to the claims make it clear that compositions comprising diclofenac sodium are outside the scope of the invention as now claimed.

Diclofenac contains both an acidic functional group and a basic functional group and is therefore an amphoteric molecule. In the application as originally filed a very clear distinction is made between acidic active agents, basic active agents and amphoteric active agents. See, for example, page 3, lines 18-21, where each of these types of active agent are referred to individually. It would be entirely clear to the skilled person reading the application as a whole in the light of their general knowledge that amphoteric active agents such as diclofenac are not acidic active agents and that the language now used in claim 1 excludes the use of salts of amphoteric active agents such as diclofenac.

The claimed compositions are therefore novel over the disclosure of D1.

Additionally, the examiner is also asked to consider the comments on page 4 of our letter of 4 August 2011, in which the problems caused by the intramolecular cyclisation of diclofenac to form a pharmaceutically inactive indole derivative in the presence of an acid such as hydrochloric acid were discussed. Mixing diclofenac sodium and an acid such a hydrochloric acid does not result in the formation of a pharmaceutical composition as it inactivates the diclofenac.

US 2001/007668 (D3)

The comments set out in our letter of 4 August 2011 also apply to the claims of the main request as now amended.

Article 56 EPC – Inventive Step

The following comments supplement the comments in our letter of 4 August 2011.

cont/....

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The examiner has characterised the problem addressed by the invention as reducing the formation of PEG esters.

During the telephone conversation on 5 September he noted that this problem does not occur with basic pharmaceutically active agents and that therefore this problem could not be solved if the pharmaceutically active agent in the claimed composition is basic. This objection has been addressed by the amendments made to the claims. It is now essential that the claimed composition contains a salt of an acidic pharmaceutically active agent.

Reducing the formation of PEG-esters, as achieved by the present invention, improves the stability of the pharmaceutical composition. The examiner asked that we provide evidence that this effect is indeed achieved by the present invention.

It seems that the examiner may be of the view that the teaching of D2 (WO95/31979) suggests that the present invention would not solve the problem. The examiner is kindly asked to reconsider the combined teaching of D1 and D2 in the light of the following comments.

D2 was published after D1 and provides a detailed discussion of the problems associated with the compositions described in D1. Specifically, on pages 3 and 4, D2 discusses the fact that a composition as described in D1, which comprises ketoprofen and potassium hydroxide with a mole ratio of potassium hydroxide to ketoprofen of 0.4 to 1.0 and PEG was unstable due to the undesirable formation of PEG esters (see particularly page 4, lines 1 to 6). The formation of PEG esters inactivates the active compound and thus results in the need to use a larger amount of the active agent to provide a desired therapeutic effect.

At page 4, lines 7 to 17 D2 discusses a potential solution to this problem, attempting to completely ionize the drug (ketoprofen) by using a molar ratio of potassium hydroxide to ketoprofen of from 1.1 to 1. However, this potential solution caused its own stability issues, for example as a result of the high pH caused by the excess of potassium hydroxide.

The present inventors have developed an alternative solution, which surprisingly effectively addresses the problem of PEG ester formation. The compositions of the invention do not suffer from problems associated with PEG ester formation.

We enclose, as Annex A, a summary of some experiments conducted by the applicant company which show that even on long term storage the compositions of the invention do not degrade by the formation of PEG esters.

As described in Annex A, the applicant made soft gel capsules comprising naproxen sodium, lactic acid (the deionising agent), and PEG 600 using a method as described in the Examples of the present application. The amount of PEG esters in the initial capsules was measured as a percentage of the active agent (naproxen) and none were detected. The capsules were then

cont/....

POTTER CLARKSON

subjected to a variety of storage conditions and the amount of PEG esters in the capsules (again as a percentage of the amount of active agent) was measured at three monthly intervals.

The capsules were considered not to suffer problems associated with PEG ester formation if no more than 1% of the drug had formed PEG esters. As can be seen from the results in Annex A, under all of the storage conditions tested, all of the capsules of the invention contained less than 1% PEG esters even after storage for 12 months. Extrapolating these results, it is predicted that even after storage for 3 years, the capsules of the invention would contain less than 1 % PEG esters.

This low level of PEG ester formation is very surprising and is advantageous. In particular, the compositions of the invention do not suffer from a reduction in potency as a result of inactivation of the drug caused by PEG ester formation. Since the composition is very stable, one does not have to increase the dose of drug in the capsule to account for drug degradation. As a result, less drug is needed and less drug is ingested by the patient.

It could not have been predicted from any of the cited prior art that, even after prolonged storage, compositions of the invention would contain such low levels of PEG esters. These results show very clearly that the compositions of the invention do unexpectedly solve the problem of reducing the formation of PEG ester in pharmaceutical compositions comprising PEG and an acidic drug.

The claimed invention is therefore inventive over the cited prior art.

Auxiliary Requests

First Auxiliary Request

This request is based on the first auxiliary request field on 4 August 2011, except that the definition of the salt of the pharmaceutically active agent has been amended and consequential amendments have been made to the wording of the claims.

It is now an essential feature of the claimed composition that component (a) is a salt of an acidic pharmaceutically active agent and that the deionizing agent is a hydrogen ion species.

The subject matter of this request is patentable for the reasons set out above and in our letter of 4 August 2011.

cont/....

POTTER CLARKSON

Second Auxiliary Request

This request is based on the second auxiliary request field on 4 August 2011, except that the definition of the salt of the pharmaceutically active agent has been amended and consequential amendments have been made to the wording of the claims.

It is now an essential feature of the claimed composition that component (a) is a salt of an acidic pharmaceutically active agent and that the deionizing agent is a hydrogen ion species.

The subject matter of this request is patentable for the reasons set out above and in our letter of 4 August 2011.

Third Auxiliary Request

This request is based on the third auxiliary request field on 4 August 2011, except that the definition of the salt of the pharmaceutically active agent has been amended and consequential amendments have been made to the wording of the claims.

It is now an essential feature of the claimed composition that component (a) is a salt of an acidic pharmaceutically active agent and that the deionizing agent is a hydrogen ion species.

The subject matter of this request is patentable for the reasons set out above and in our letter of 4 August 2011.

Fourth Auxiliary Request

This request is based on the fourth auxiliary request field on 4 August 2011, except that the definition of the salt of the pharmaceutically active agent has been amended and consequential amendments have been made to the wording of the claims.

It is now an essential feature of the claimed composition that component (a) is a salt of an acidic pharmaceutically active agent and that the deionizing agent is a hydrogen ion species.

The subject matter of this request is patentable for the reasons set out above and in our letter of 4 August 2011.

Fifth Auxiliary Request

This request is based on the fifth auxiliary request field on 4 August 2011, except that the definition of the salt of the pharmaceutically active agent has been amended and consequential amendments have been made to the wording of the claims.

cont/....

POTTER CLARKSON

It is now an essential feature of the claimed composition that component (a) is a salt of an acidic pharmaceutically active agent and that the deionizing agent is a hydrogen ion species.

The subject matter of this request is patentable for the reasons set out above and in our letter of 4 August 2011.

Sixth Auxiliary Request

This request is identical to the seventh auxiliary request filed on 4 August 2011. The subject matter of this request is patentable for the reasons set out above and in our letter of 4 August 2011.

The Description

It is appreciated that it will be necessary to amend the description for conformity with the amended claims. It is proposed that this is done one agreement has been reached as to the wording of the claims.

Telephone Discussion

The writer proposes to telephone the examiner on 23 September 2011 to discuss any remaining issues the examiner may have with the aim of avoiding the need to hold oral proceedings.

Yours faithfully

Charlotte Crowhurst PhD
For and on behalf of Potter Clarkson LLP

js

Enc: Main Request
Auxiliary Requests 1 to 6
Annex A

MAIN REQUEST

CLAIMS

1. A pharmaceutical composition comprising
   (a) a salt of an acidic pharmaceutically active agent;
   (b) a deionizing agent which is a hydrogen ion species in an amount to cause partial deionization of the salt of from about 0.2 to 1.0 mole equivalents per mole of the pharmaceutically active agent;
   (c) polyethylene glycol; and optionally
   (d) water.

2. A softgel capsule comprising a fill material wherein the fill material comprises
   (a) a salt of an acidic pharmaceutically active agent;
   (b) a deionizing agent which is a hydrogen ion species in an amount to cause partial deionization of the salt of from about 0.2 to 1.0 mole equivalents per mole of the pharmaceutically active agent;
   (c) polyethylene glycol; and optionally
   (d) water.

3. The composition or capsule of claim 1 or 2 wherein the pharmaceutically active agent is selected from the group consisting of therapeutically active agents, diagnostic agents, and prophylactic agents.

4. The composition or capsule of any one of the preceding claims wherein the composition or fill material has a pH of from about 2.5 to about 7.5.

5. The composition or capsule of any one of the preceding claims wherein polyethylene glycol is present in an amount from about 10% to about 80% by weight.

6. The composition or capsule of any one of the preceding claims wherein the polyethylene glycol is one or more polyethylene glycols with a molecular weight between 300 and 1500.

7. The composition or the capsule of any one of the preceding claims wherein water is present in an amount from about 1% to about 18% by weight.

8. The composition or capsule of any one of the preceding claims further comprising one or more excipients selected from the group consisting of plasticizers, crystallization inhibitors, wetting agents, bulk filling agents, solubilizers, bioavailability enhancers, solvents, pH-adjusting agents, dyes, preservatives, solvents, surfactants, and combinations thereof.

9. The composition or capsule of claim 8 wherein the solubilizer is selected from the group consisting of glycerin, polyvinylpyrrolidone, propylene glycol and combinations thereof.

10. The composition or capsule of claim 8 wherein the solubilizer is present in amount from about 1% to about 10% by weight.

11. The composition or capsule of any one of the preceding claims wherein the salt (a) is naproxen sodium.

12. The composition or capsule of any one of the preceding claims wherein the hydrogen ion species is selected from hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, fumaric acid, maleic acid, tartaric acid, methane-, ethane-, and benzene sulfonates, citric acid, malic acid, acetic acid, proprionic acid, pyruvic acid, butanoic acid, and lactic acid.

13. A composition or capsule of any of claims 1 to 12 for use as a medicament.

14. A method of making the composition or capsule of any of claims 1 to 13 comprising

(a) mixing the salt of an acidic pharmaceutically active agent, the polyethylene glycol and the deionizing agent and optionally water at a temperature of from 50°C to 70°C; and

(b) encapsulating the mixture in a softgel capsule.

15. The use of

(a) a salt of an acidic pharmaceutically active agent;

(b) a deionizing agent which is a hydrogen ion species in an amount to cause partial deionization of the salt of from about 0.2 to 1.0 mole equivalents per mole of the pharmaceutically active agent;

(c) polyethylene glycol; and optionally

(d) water

in the manufacture of a medicament for administration of the pharmaceutically active agent to a patient in need thereof.

16. The use of claim 15 wherein the medicament is in the form of a softgel capsule.

17. A pharmaceutical composition obtainable by a method which comprises

(I) mixing

(a) a salt of an acidic pharmaceutically active agent;

(b) a deionizing agent which is a hydrogen ion species in an amount to cause partial deionization of the salt of from about 0.2 to 1.0 mole equivalents per mole of the pharmaceutically active agent(s);

(c) polyethylene glycol; and optionally

(d) water

at a temperature of from 50°C to 70°C.

18. A softgel capsule obtainable by a method which comprises

(I) producing a fill material by mixing

(a) a salt of an acidic pharmaceutically active agent;

(b) a deionizing agent which is a hydrogen ion species in an amount to cause partial deionization of the salt of from about 0.2 to 1.0 mole equivalents per mole of the pharmaceutically active agent;

(c) polyethylene glycol; and optionally

(d) water

at a temperature of from 50°C to 70°C; and

(II) encapsulating the mixture in a softgel capsules.

FIRST AUXILIARY REQUEST

CLAIMS

1. A softgel capsule comprising a fill material wherein the fill material comprises
   (a) a salt of an acidic pharmaceutically active agent;
   (b) a deionizing agent which is a hydrogen ion species in an amount to cause partial deionization of the salt of from about 0.2 to 1.0 mole equivalents per mole of the pharmaceutically active agent;
   (c) polyethylene glycol; and optionally
   (d) water.

2. The capsule of claim 1 wherein the pharmaceutically active agent is selected from the group consisting of therapeutically active agents, diagnostic agents, and prophylactic agents.

3. The capsule of claim 1 or 2 wherein the fill material has a pH of from about 2.5 to about 7.5.

4. The capsule of any one of the preceding claims wherein polyethylene glycol is present in an amount from about 10% to about 80% by weight.

5. The capsule of any one of the preceding claims wherein the polyethylene glycol is one or more polyethylene glycols with a molecular weight between 300 and 1500.

6. The capsule of any one of the preceding claims wherein water is present in an amount from about 1% to about 18% by weight.

7. The capsule of any one of the preceding claims further comprising one or more excipients selected from the group consisting of plasticizers, crystallization inhibitors, wetting agents, bulk filling agents, solubilizers, bioavailability enhancers, solvents, pH-adjusting agents, dyes, preservatives, solvents, surfactants, and combinations thereof.

8. The capsule of claim 7 wherein the solubilizer is selected from the group consisting of glycerin, polyvinylpyrrolidone, propylene glycol and combinations thereof.

9. The capsule of claim 7 wherein the solubilizer is present in amount from about 1% to about 10% by weight.

10. The capsule of any one of the preceding claims wherein the salt (a) is naproxen sodium.

11. The capsule of any one of the preceding claims wherein the hydrogen ion species is selected from hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, fumaric acid, maleic acid, tartaric acid, methane-, ethane-, and benzene sulfonates, citric acid, malic acid, acetic acid, proprionic acid, pyruvic acid, butanoic acid, and lactic acid.

12. A capsule of any of claims 1 to 12 for use as a medicament.

13. A method of making the capsule of any of claims 1 to 12 comprising
(a) mixing the salt of an acidic pharmaceutically active agent, the polyethylene glycol and the deionizing agent and optionally water at a temperature of from 50°C to 70°C; and
(b) encapsulating the mixture in a softgel capsule.

14. The use of
(a) a salt of an acidic pharmaceutically active agent;
(b) a deionizing agent which is a hydrogen ion species in an amount to cause partial deionization of the salt of from about 0.2 to 1.0 mole equivalents per mole of the pharmaceutically active agent(s);
(c) polyethylene glycol; and optionally
(d) water
in the manufacture of a medicament in the form of a softgel capsule for administration of the pharmaceutically active agent to a patient in need thereof.

15. A softgel capsule obtainable by a method which comprises

(I) producing a fill material by mixing

(a) a salt of an acidic pharmaceutically active agent;

(b) a deionizing agent in an amount to cause partial deionization of the salt of from about 0.2 to 1.0 mole equivalents per mole of the pharmaceutically active agent;

(c) polyethylene glycol; and optionally

(d) water

at a temperature of from 50°C to 70°C; and

(II) encapsulating the mixture in a softgel capsule.

SECOND AUXILIARY REQUEST

CLAIMS

1. A pharmaceutical composition obtainable by a method which comprises
   (I) mixing
   (a) a salt of an acidic pharmaceutically active agent;
   (b) a deionizing agent which is a hydrogen ion species in an amount to cause partial deionization of the salt of from about 0.2 to 1.0 mole equivalents per mole of the pharmaceutically active agent;
   (c) polyethylene glycol; and optionally
   (d) water
   at a temperature of from 50°C to 70°C.

2. A softgel capsule obtainable by a method which comprises
   (I) producing a fill material by mixing
   (a) a salt of an acidic pharmaceutically active agent;
   (b) a deionizing agent which is a hydrogen ion species in an amount to cause partial deionization of the salt of from about 0.2 to 1.0 mole equivalents per mole of the pharmaceutically active agent;
   (c) polyethylene glycol; and optionally
   (d) water
   at a temperature of from 50°C to 70°C; and
   (II)encapsulating the mixture in a softgel capsule.

3. The composition or capsule of claim 1 or 2 wherein the pharmaceutically active agent is selected from the group consisting of therapeutically active agents, diagnostic agents, and prophylactic agents.

4. The composition or capsule of any one of the preceding claims wherein the composition or fill material of the softgel capsule has a pH of from about 2.5 to about 7.5.

5. The composition or capsule of any one of the preceding claims wherein polyethylene glycol is present in an amount from about 10% to about 80% by weight.

6. The composition or capsule of any one of the preceding claims wherein the polyethylene glycol is one or more polyethylene glycols with a molecular weight between 300 and 1500.

7. The composition or the capsule of any one of the preceding claims wherein water is present in an amount from about 1% to about 18% by weight.

8. The composition or capsule of any one of the preceding claims further comprising one or more excipients selected from the group consisting of plasticizers, crystallization inhibitors, wetting agents, bulk filling agents, solubilizers, bioavailability enhancers, solvents, pH-adjusting agents, dyes, preservatives, solvents, surfactants, and combinations thereof.

9. The composition or capsule of claim 8 wherein the solubilizer is selected from the group consisting of glycerin, polyvinylpyrrolidone, propylene glycol and combinations thereof.

10. The composition or capsule of claim 8 wherein the solubilizer is present in amount from about 1% to about 10% by weight.

11. The composition or capsule of any one of the preceding claims wherein the salt (a) is naproxen sodium.

12. The composition or capsule of any one of the preceding claims wherein the hydrogen ion species is selected from hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, fumaric acid, maleic acid, tartaric acid, methane-, ethane-, and benzene sulfonates, citric acid, malic acid, acetic acid, proprionic acid, pyruvic acid, butanoic acid, and lactic acid.

13. A composition or capsule of any of claims 1 to 12 for use as a medicament.

14. A method of making the composition or capsule of any of claims 1 to 13 comprising

(a) mixing the salt of an acidic pharmaceutically active agent, the polyethylene glycol and the deionizing agent and optionally water at a temperature of from 50°C to 70°C; and

(b) encapsulating the mixture in a softgel capsule.

15. The use of

(a) a salt of an acidic pharmaceutically active agent;

(b) a deionizing agent which is a hydrogen ion species in an amount to cause partial deionization of the salt of from about 0.2 to 1.0 mole equivalents per mole of the pharmaceutically active agent;

(c) polyethylene glycol; and optionally

(d) water

in the manufacture of a medicament for administration of the pharmaceutically active agent to a patient in need thereof.

16. The use of claim 15 wherein the medicament is in the form of a softgel capsule.

THIRD AUXILIARY REQUEST

CLAIMS

1. A method of making a pharmaceutical composition comprising

(a) mixing a salt of an acidic pharmaceutically active agent, a polyethylene glycol and a deionizing agent which is a hydrogen ion species and optionally water at a temperature of from 50°C to 70°C;

wherein the deionizing agent is used in an amount to cause partial ionization of the salt of from about 0.2 to 1.0 mole equivalents per mole of the pharmaceutically active agent.

2. A method of making a softgel capsule comprising making a fill mixture by the method of claim 1 and

(b) encapsulating the mixture in a softgel capsule.

3. The method of claim 1 or 2 wherein the pharmaceutically active agent is selected from the group consisting of therapeutically active agents, diagnostic agents, and prophylactic agents.

4. The method of any one of the preceding claims wherein the composition or fill material has a pH of from about 2.5 to about 7.5.

5. The method of any one of the preceding claims wherein polyethylene glycol is present in an amount from about 10% to about 80% by weight.

6. The method of any one of the preceding claims wherein the polyethylene glycol is one or more polyethylene glycols with a molecular weight between 300 and 1500.

7. The method of any one of the preceding claims wherein water is present in an amount from about 1% to about 18% by weight.

8. The method of any one of the preceding claims further comprising one or more excipients selected from the group consisting of plasticizers, crystallization inhibitors, wetting agents, bulk filling agents, solubilizers, bioavailability enhancers, solvents, pH-adjusting agents, dyes, preservatives, solvents, surfactants, and combinations thereof.

9. The method of claim 8 wherein the solubilizer is selected from the group consisting of glycerin, polyvinylpyrrolidone, propylene glycol and combinations thereof.

10. The method of claim 8 wherein the solubilizer is present in amount from about 1% to about 10% by weight.

11. The method of any one of the preceding claims wherein the salt (a) is naproxen sodium.

12. The method of any one of the preceding claims wherein the hydrogen ion species is selected from hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, fumaric acid, maleic acid, tartaric acid, methane-, ethane-, and benzene sulfonates, citric acid, malic acid, acetic acid, proprionic acid, pyruvic acid, butanoic acid, and lactic acid.

FOURTH AUXILIARY REQUEST

CLAIMS

1. The use of
   (a) a salt of an acidic pharmaceutically active agent;
   (b) a deionizing agent which is a hydrogen ion species in an amount to cause partial deionization of the salt of from about 0.2 to 1.0 mole equivalents per mole of the pharmaceutically active agent;
   (c) polyethylene glycol; and optionally
   (d) water
   in the manufacture of a medicament for administration of the pharmaceutically active agent to a patient in need thereof.

2. The use of claim 1 wherein the medicament is in the form of a softgel capsule.

3. The use of claim 1 or 2 wherein the pharmaceutically active agent is selected from the group consisting of therapeutically active agents, diagnostic agents, and prophylactic agents.

4. The use of any one of the preceding claims wherein the composition or fill material of the soft gel capsule has a pH of from about 2.5 to about 7.5.

5. The use of any one of the preceding claims wherein polyethylene glycol is present in an amount from about 10% to about 80% by weight.

6. The use of any one of the preceding claims wherein the polyethylene glycol is one or more polyethylene glycols with a molecular weight between 300 and 1500.

7. The use any one of the preceding claims wherein water is present in an amount from about 1% to about 18% by weight.

8. The use of any one of the preceding claims further comprising one or more excipients selected from the group consisting of plasticizers, crystallization inhibitors, wetting agents, bulk filling agents, solubilizers, bioavailability enhancers, solvents, pH-adjusting agents, dyes, preservatives, solvents, surfactants, and combinations thereof.

9. The use of claim 8 wherein the solubilizer is selected from the group consisting of glycerin, polyvinylpyrrolidone, propylene glycol and combinations thereof.

10. The use of claim 8 wherein the solubilizer is present in amount from about 1% to about 10% by weight.

11. The use of any one of the preceding claims wherein the salt (a) is naproxen sodium.

12. The use of any one of the preceding claims wherein the hydrogen ion species is selected from hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, fumaric acid, maleic acid, tartaric acid, methane-, ethane-, and benzene sulfonates, citric acid, malic acid, acetic acid, proprionic acid, pyruvic acid, butanoic acid, and lactic acid.

13. A method of making a pharmaceutical composition or softgel capsule comprising

(a) mixing the salt of an acidic pharmaceutically active agent, polyethylene glycol and a deionizing agent which is a hydrogen ion species and optionally water at a temperature of from 50°C to 70°C; and

(b) encapsulating the mixture in a softgel capsule.

FIFTH AUXILIARY REQUEST

CLAIMS

1. A pharmaceutical composition comprising
   (a) a salt of an acidic pharmaceutically active agent;
   (b) a deionizing agent in an amount to cause partial deionization of the salt of from about 0.2 to 1.0 mole equivalents per mole of the pharmaceutically active agent;
   (c) polyethylene glycol; and optionally
   (d) water;

wherein the deionizing agent is a hydrogen ion species selected from hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, fumaric acid, maleic acid, tartaric acid, methane-, ethane-, and benzene sulfonates, citric acid, malic acid, acetic acid, proprionic acid, pyruvic acid, butanoic acid, and lactic acid.

2. A softgel capsule comprising a fill material wherein the fill material comprises
   (a) a salt of an acidic pharmaceutically active agent;
   (b) a deionizing agent in an amount to cause partial deionization of the salt of from about 0.2 to 1.0 mole equivalents per mole of the pharmaceutically active agent;
   (c) polyethylene glycol; and optionally
   (d) water

wherein the deionizing agent is a hydrogen ion species selected from hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, fumaric acid, maleic acid, tartaric acid, methane-, ethane-, and benzene sulfonates, citric acid, malic acid, acetic acid, proprionic acid, pyruvic acid, butanoic acid, and lactic acid.

3. The composition or capsule of claim 1 or 2 wherein the pharmaceutically active agent is selected from the group consisting of therapeutically active agents, diagnostic agents, and prophylactic agents.

4. The composition or capsule of any one of the preceding claims wherein the composition or fill material has a pH of from about 2.5 to about 7.5.

5. The composition or capsule of any one of the preceding claims wherein polyethylene glycol is present in an amount from about 10% to about 80% by weight.

6. The composition or capsule of any one of the preceding claims wherein the polyethylene glycol is one or more polyethylene glycols with a molecular weight between 300 and 1500.

7. The composition or the capsule any one of the preceding claims wherein water is present in an amount from about 1% to about 18% by weight.

8. The composition or capsule of any one of the preceding claims comprising one or more excipients selected from the group consisting of plasticizers, crystallization inhibitors, wetting agents, bulk filling agents, solubilizers, bioavailability enhancers, solvents, pH-adjusting agents, dyes, preservatives, solvents, surfactants, and combinations thereof.

9. The composition or capsule of claim 8 wherein the solubilizer is selected from the group consisting of glycerin, polyvinylpyrrolidone, propylene glycol and combinations thereof.

10. The composition or capsule of claim 8 wherein the solubilizer is present in amount from about 1% to about 10% by weight.

11. The composition or capsule of any one of the preceding claims wherein the salt (a) is naproxen sodium.

12. A composition or capsule of any of claims 1 to 11 for use as a medicament.

13. A method of making the composition or capsule of any of claims 1 to 12 comprising

(a) mixing the salt of an acidic pharmaceutically active agent, the polyethylene glycol and the deionizing agent and optionally water at a temperature of from 50°C to 70°C; and

(b) encapsulating the mixture in a softgel capsule.

14. The use of

(a) a salt of an acidic pharmaceutically active agent;

(b) a deionizing agent in an amount to cause partial deionization of the salt of from about 0.2 to 1.0 mole equivalents per mole of the pharmaceutically active agent;

(c) polyethylene glycol; and optionally

(d) water

in the manufacture of a medicament for administration of the pharmaceutically active agent to a patient in need thereof;

wherein the deionizing agent is a hydrogen ion species selected from hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, fumaric acid, maleic acid, tartaric acid, methane-, ethane-, and benzene sulfonates, citric acid, malic acid, acetic acid, proprionic acid, pyruvic acid, butanoic acid, and lactic acid.

15. The use of claim 14 wherein the medicament is in the form of a softgel capsule.

16. A pharmaceutical composition obtainable by a method which comprises

(I) mixing

(a) a salt of an acidic pharmaceutically active agent;

(b) a deionizing agent in an amount to cause partial deionization of the salt of from about 0.2 to 1.0 mole equivalents per mole of the pharmaceutically active agent;

(c) polyethylene glycol; and optionally

(d) water

at a temperature of from 50°C to 70°C;

wherein the deionizing agent is a hydrogen ion species selected from hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, fumaric acid, maleic acid, tartaric acid, methane-, ethane-, and benzene sulfonates, citric acid, malic acid, acetic acid, proprionic acid, pyruvic acid, butanoic acid, and lactic acid.

17. A softgel capsule obtainable by a method which comprises

(I) producing a fill material by mixing

(a) a salt of an acidic pharmaceutically active agent;

(b) a deionizing agent in an amount to cause partial deionization of the salt of from about 0.2 to 1.0 mole equivalents per mole of the pharmaceutically active agent;

(c) polyethylene glycol; and optionally

(d) water

at a temperature of from 50°C to 70°C; and

(II) encapsulating the mixture in a softgel capsule;

wherein the deionizing agent is a hydrogen ion species selected from hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, fumaric acid, maleic acid, tartaric acid, methane-, ethane-, and benzene sulfonates, citric acid, malic acid, acetic acid, proprionic acid, pyruvic acid, butanoic acid, and lactic acid.

SIXTH AUXILIARY REQUEST

CLAIMS

1. A pharmaceutical composition comprising
   (a) naproxen sodium;
   (b) a deionizing agent in an amount to cause partial deionization of the salt of from about 0.2 to 1.0 mole equivalents per mole of the naproxen sodium;
   (c) polyethylene glycol; and optionally
   (d) water.

2. A softgel capsule comprising a fill material wherein the fill material comprises
   (a) naproxen sodium;
   (b) a deionizing agent in an amount to cause partial deionization of the salt of from about 0.2 to 1.0 mole equivalents per mole of the naproxen sodium;
   (c) polyethylene glycol; and optionally
   (d) water.

3. The composition or capsule of claim 1 or 2 wherein the deionizing agent is selected from hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, fumaric acid, maleic acid, tartaric acid, methane-, ethane-, and benzene sulfonates, citric acid, malic acid, acetic acid, proprionic acid, pyruvic acid, butanoic acid, and lactic acid.

4. The composition or capsule of any one of the preceding claims wherein the composition or fill material has a pH of from about 2.5 to about 7.5.

5. The composition or capsule of any one of the preceding claims wherein polyethylene glycol is present in an amount from about 10% to about 80% by weight.

6. The composition or capsule of any one of the preceding claims wherein the polyethylene glycol is one or more polyethylene glycols with a molecular weight between 300 and 1500.

7. The composition or the capsule of any one of the preceding claims wherein water is present in an amount from about 1% to about 18% by weight.

8. The composition or capsule of any one of the preceding claims further comprising one or more excipients selected from the group consisting of plasticizers, crystallization inhibitors, wetting agents, bulk filling agents, solubilizers, bioavailability enhancers, solvents, pH-adjusting agents, dyes, preservatives, solvents, surfactants, and combinations thereof.

9. The composition or capsule of claim 8 wherein the solubilizer is selected from the group consisting of glycerin, polyvinylpyrrolidone, propylene glycol and combinations thereof.

10. The composition or capsule of claim 8 wherein the solubilizer is present in amount from about 1% to about 10% by weight.

11. A composition or capsule of any of claims 1 to 10 for use as a medicament.

12. A method of making the composition or capsule of any of claims 1 to 11 comprising

(a) mixing the naproxen sodium, the polyethylene glycol and the deionizing agent and optionally water at a temperature of from 50°C to 70°C; and

(b) encapsulating the mixture in a softgel capsule.

13. The use of

(a) naproxen sodium;

(b) a deionizing agent selected from hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, fumaric acid, maleic acid, tartaric acid, methane-, ethane-, and benzene sulfonates, citric acid, malic acid, acetic acid, proprionic acid, pyruvic acid, butanoic acid, and lactic acid in an amount to cause partial deionization of the salt of from about 0.2 to 1.0 mole equivalents per mole of the pharmaceutically active agent(s);

(c) polyethylene glycol: and optionally

(d) water

in the manufacture of a medicament for administration of naproxen sodium to a patient in need thereof.

14. The use of claim 13 wherein the medicament is in the form of a softgel capsule.

15. A pharmaceutical composition obtainable by a method which comprises

(I) mixing

(a) naproxen sodium;

(b) a deionizing agent selected from hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, fumaric acid, maleic acid, tartaric acid, methane-, ethane-, and benzene sulfonates, citric acid, malic acid, acetic acid, proprionic acid, pyruvic acid, butanoic acid, and lactic acid in an amount to cause partial deionization of the salt of from about 0.2 to 1.0 mole equivalents per mole of the naproxen sodium;

(c) polyethylene glycol; and optionally

(d) water

at a temperature of from 50°C to 70°C.

16. A softgel capsule obtainable by a method which comprises

(I) producing a fill material by mixing

(a) naproxen sodium;

(b) a deionizing agent selected from hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, fumaric acid, maleic acid, tartaric acid, methane-, ethane-, and benzene sulfonates, citric acid, malic acid, acetic acid, proprionic acid, pyruvic acid, butanoic acid, and lactic acid in an amount to cause partial deionization of the salt of from about 0.2 to 1.0 mole equivalents per mole of the pharmaceutically active agent(s);

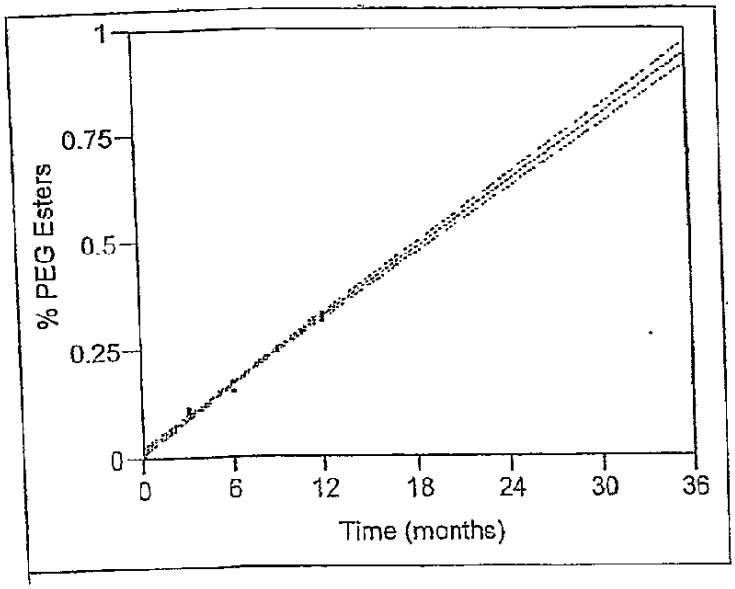
(c) polyethylene glycol; and optionally

(d) water

at a temperature of from 50°C to 70°C; and

(II) encapsulating the mixture in a softgel capsules.

Naproxen Sodium 220 mg SGC 25°C/60% RH
(% PEG esters vs. Time)



ANNEX A

Experiments to Test the Stability of Compositions of the Invention Against Formation of PEG Esters

PRODUCTION OF CAPSULES IN ACCORDANCE WITH THE INVENTION

Active Ingredients

Ingredient	Amount per Capsule
naproxen sodium	220mg

Fill Excipients

Ingredient	Amount (mg) per Capsule
Lactic Acid	44.0
Propylene Glycol	17.7
Povidone K-30	17.7
Polyethylene Glycol 600	580.6

Gelain Shell Excipients

Ingredient
Gelatin
Glycerin
Sorbital Special
Purified Water
ED&C Yellow # 6
FD&C Blue # 1

Using these ingredients capsules were produced using a method as described in the Examples of European Patent Application No. 06737018.9.

PACKAGING OF THE CAPSULES

The capsules were either packaged 15 to a bottle or 200 to a bottle or in a bulk carton. The bottles containing 15 capsules were 45 cc, round, opaque white HDPE bottles with child resistant caps.

The bottles containing 200 capsules were 400 cc, round, opaque, white, HDPE bottles with child resistant caps.

STUDY DESIGN

Bottles containing 15 capsules and bottles containing 200 capsules were stored at 25°C and a relative humidity of 60% and at 30°C and a relative humidity of 65%. A carton containing the capsules stored in bulk was stored at 25°C and 60% relative humidity.

The percentage of PEG esters in the capsules, as a percentage of the drug (naproxen sodium), was determined using HPLC, before storage and after storage for 3 months, 6 months, 9 months and 12 months.

THE RESULTS

TEST WITH BOTTLES CONTAINING 15 CAPSULES

Storage at 25°C/60% Relative Humidity

	No. Of Months				
	0	3	6	9	12
% PEG-esters	None	0.10%	0.17%	0.25%	0.32%
	None	0.10%	0.17%	0.25%	0.33%
	None	0.10%	0.15%	0.25%	0.32%

European Patent Application No. 06737018.9
BANNER PHARMACAPS, INC.
PABCX/P36814EP

Storage at 30°C/65% Relative Humidity

	No. Of Months				
	0	3	6	9	12
% PEG-esters	None	0.15%	0.28%	0.30%	0.57%
	None	0.15%	0.29%	0.44%	0.58%
	None	0.15%	0.29%	0.44%	0.59%

TEST WITH BOTTLES CONTAINING 200 CAPSULES

Storage at 25°C/60% Relative Humidity

	No. Of Months				
	0	3	6	9	12
% PEG-esters	None	0.10%	0.17%	0.25%	0.31%
	None	0.11%	0.17%	0.25%	0.32%
	None	0.10%	0.17%	0.24%	0.32%

Storage at 30°C/65% Relative Humidity

	No. Of Months				
	0	3	6	9	12
% PEG-esters	None	0.16%	0.29%	0.41%	0.57%
	None	0.15%	0.29%	0.45%	0.59%
	None	0.15%	0.28%	0.44%	0.58%

TEST OF BULK PACK CAPSULES

Storage at 25°c/60% Relative Humidity

	No. Of Months				
	0	3	6	9	12
% PEG-esters	None	0.10%	0.17%	0.25%	0.32%
	None	0.10%	0.16%	0.26%	0.32%
	None	0.09%	0.17%	0.22%	0.32%

These results show that initially the capsules of the invention contained no PEG esters and that even after storage for up to one year under a variety of storage conditions the capsules of the invention contained very low levels of PEG esters. In every case, significantly less than 1% of the drug had formed PEG esters even after storage for a year. Less than 1% PEG ester formation was considered to represent a low level of PEG ester formation which did not cause significant loss of activity and therefore compositions with less than 1% PEG ester were considered to be stable. All of the capsules tested passed this test.

EVALUATION OF PEG ESTER RESULTS

The percent PEG esters was plotted versus time (see graph on page 5). In addition, the 95% confidence bounds were added to the plot. Both the fitted least-squares line and the 95% upper confidence bound were extrapolated through 36 months to examine product expiration. According to the extrapolated data points for the upper 95% confidence bound, the percent PEG esters at 24 months should be 0.65 and according to the fitted least-squares line, the percent PEG esters should be 0.63. This means that even after three years the predicted values from both the upper 95% confidence and the least-squares line did not exceed the upper acceptable specification limit of not more than 1.0% PEG esters. In other words, compositions of the invention are not predicted to lose activity through PEG ester formation after 3 years and to therefore have a shelf life of at least three years.

EPO - Munich
68
20. Sep. 2011

POTTER CLARKSON

European Patent Office
Directorate General 2
Erhardtstraße 27
D-80298 München
GERMANY

16 September 2011

URGENT

PLEASE PASS DIRECTLY TO THE EXAMINER MR BUTTNER
ORAL PROCEEDINGS IMMINENT

Sent by fax

Dear Sirs

European Patent Application No. 06737018.9-2123
BANNER PHARMACAPS, INC.
Our ref: PABCX/P38814EP

We refer to the written submissions filed on 4 August 2011 and are now providing supplemental written submissions, which include experimental data and seek to address the issues discussed during a telephone conversation between the examiner, Mr Buttner and the representative, Dr Crowhurst on 5 September 2011.

The Requests

We enclose a new main request and six auxiliary requests to replace the requests filed on 4 August 2011. The applicant reserves the right to file further auxiliary requests, should this be necessary. In particular, the applicant reserves the right to make combinations of the claims now presented, including combining claims from within the same request and combining claims from different requests or to delete claims.

The Main Request

The Amendments to the Claims

The new main request is based on the main request filed on 4 August 2011, except that the definition of the salt of the pharmaceutically active agent has been amended and consequential amendments have been made to the wording of the claims.

cont/....

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It is now an essential feature of the claimed composition that component (a) is a salt of an acidic pharmaceutically active agent and that the deionizing agent is a hydrogen ion species.

Article 54(1) and (2) EPC – Novelty

US 5,360,615 (D1)

As discussed in our letter of 4 August 2011, the examiner raised an objection of lack of novelty in view of the disclosure in D1 of a composition comprising a salt of an amphoteric active agent, diclofenac sodium.

The amendments made to the claims make it clear that compositions comprising diclofenac sodium are outside the scope of the invention as now claimed.

Diclofenac contains both an acidic functional group and a basic functional group and is therefore an amphoteric molecule. In the application as originally filed a very clear distinction is made between acidic active agents, basic active agents and amphoteric active agents. See, for example, page 3, lines 18-21, where each of these types of active agent are referred to individually. It would be entirely clear to the skilled person reading the application as a whole in the light of their general knowledge that amphoteric active agents such as diclofenac are not acidic active agents and that the language now used in claim 1 excludes the use of salts of amphoteric active agents such as diclofenac.

The claimed compositions are therefore novel over the disclosure of D1.

Additionally, the examiner is also asked to consider the comments on page 4 of our letter of 4 August 2011, in which the problems caused by the intramolecular cyclisation of diclofenac to form a pharmaceutically inactive indole derivative in the presence of an acid such as hydrochloric acid were discussed. Mixing diclofenac sodium and an acid such a hydrochloric acid does not result in the formation of a pharmaceutical composition as it inactivates the diclofenac.

US 2001/007668 (D3)

The comments set out in our letter of 4 August 2011 also apply to the claims of the main request as now amended.

Article 56 EPC – Inventive Step

The following comments supplement the comments in our letter of 4 August 2011.

cont/....

The examiner has characterised the problem addressed by the invention as reducing the formation of PEG esters.

During the telephone conversation on 5 September he noted that this problem does not occur with basic pharmaceutically active agents and that therefore this problem could not be solved if the pharmaceutically active agent in the claimed composition is basic. This objection has been addressed by the amendments made to the claims. It is now essential that the claimed composition contains a salt of an acidic pharmaceutically active agent.

Reducing the formation of PEG-esters, as achieved by the present invention, improves the stability of the pharmaceutical composition. The examiner asked that we provide evidence that this effect is indeed achieved by the present invention.

It seems that the examiner may be of the view that the teaching of D2 (WO95/31979) suggests that the present invention would not solve the problem. The examiner is kindly asked to reconsider the combined teaching of D1 and D2 in the light of the following comments.

D2 was published after D1 and provides a detailed discussion of the problems associated with the compositions described in D1. Specifically, on pages 3 and 4, D2 discusses the fact that a composition as described in D1, which comprises ketoprofen and potassium hydroxide with a mole ratio of potassium hydroxide to ketoprofen of 0.4 to 1.0 and PEG was unstable due to the undesirable formation of PEG esters (see particularly page 4, lines 1 to 6). The formation of PEG esters inactivates the active compound and thus results in the need to use a larger amount of the active agent to provide a desired therapeutic effect.

At page 4, lines 7 to 17 D2 discusses a potential solution to this problem, attempting to completely ionize the drug (ketoprofen) by using a molar ratio of potassium hydroxide to ketoprofen of from 1.1 to 1. However, this potential solution caused its own stability issues, for example as a result of the high pH caused by the excess of potassium hydroxide.

The present inventors have developed an alternative solution, which surprisingly effectively addresses the problem of PEG ester formation. The compositions of the invention do not suffer from problems associated with PEG ester formation.

We enclose, as Annex A, a summary of some experiments conducted by the applicant company which show that even on long term storage the compositions of the invention do not degrade by the formation of PEG esters.

As described in Annex A, the applicant made soft gel capsules comprising naproxen sodium, lactic acid (the deionising agent), and PEG 600 using a method as described in the Examples of the present application. The amount of PEG esters in the initial capsules was measured as a percentage of the active agent (naproxen) and none were detected. The capsules were then

cont/....

subjected to a variety of storage conditions and the amount of PEG esters in the capsules (again as a percentage of the amount of active agent) was measured at three monthly intervals.

The capsules were considered not to suffer problems associated with PEG ester formation if no more than 1% of the drug had formed PEG esters. As can be seen from the results in Annex A, under all of the storage conditions tested, all of the capsules of the invention contained less than 1% PEG esters even after storage for 12 months. Extrapolating these results, it is predicted that even after storage for 3 years, the capsules of the invention would contain less than 1 % PEG esters.

This low level of PEG ester formation is very surprising and is advantageous. In particular, the compositions of the invention do not suffer from a reduction in potency as a result of inactivation of the drug caused by PEG ester formation. Since the composition is very stable, one does not have to increase the dose of drug in the capsule to account for drug degradation. As a result, less drug is needed and less drug is ingested by the patient.

It could not have been predicted from any of the cited prior art that, even after prolonged storage, compositions of the invention would contain such low levels of PEG esters. These results show very clearly that the compositions of the invention do unexpectedly solve the problem of reducing the formation of PEG ester in pharmaceutical compositions comprising PEG and an acidic drug.

The claimed invention is therefore inventive over the cited prior art.

Auxiliary Requests

First Auxiliary Request

This request is based on the first auxiliary request field on 4 August 2011, except that the definition of the salt of the pharmaceutically active agent has been amended and consequential amendments have been made to the wording of the claims.

It is now an essential feature of the claimed composition that component (a) is a salt of an acidic pharmaceutically active agent and that the deionizing agent is a hydrogen ion species.

The subject matter of this request is patentable for the reasons set out above and in our letter of 4 August 2011.

cont/....

Second Auxiliary Request

This request is based on the second auxiliary request field on 4 August 2011, except that the definition of the salt of the pharmaceutically active agent has been amended and consequential amendments have been made to the wording of the claims.

It is now an essential feature of the claimed composition that component (a) is a salt of an acidic pharmaceutically active agent and that the deionizing agent is a hydrogen ion species.

The subject matter of this request is patentable for the reasons set out above and in our letter of 4 August 2011.

Third Auxiliary Request

This request is based on the third auxiliary request field on 4 August 2011, except that the definition of the salt of the pharmaceutically active agent has been amended and consequential amendments have been made to the wording of the claims.

It is now an essential feature of the claimed composition that component (a) is a salt of an acidic pharmaceutically active agent and that the deionizing agent is a hydrogen ion species.

The subject matter of this request is patentable for the reasons set out above and in our letter of 4 August 2011.

Fourth Auxiliary Request

This request is based on the fourth auxiliary request field on 4 August 2011, except that the definition of the salt of the pharmaceutically active agent has been amended and consequential amendments have been made to the wording of the claims.

It is now an essential feature of the claimed composition that component (a) is a salt of an acidic pharmaceutically active agent and that the deionizing agent is a hydrogen ion species.

The subject matter of this request is patentable for the reasons set out above and in our letter of 4 August 2011.

Fifth Auxiliary Request

This request is based on the fifth auxiliary request field on 4 August 2011, except that the definition of the salt of the pharmaceutically active agent has been amended and consequential amendments have been made to the wording of the claims.

cont/....

It is now an essential feature of the claimed composition that component (a) is a salt of an acidic pharmaceutically active agent and that the deionizing agent is a hydrogen ion species.

The subject matter of this request is patentable for the reasons set out above and in our letter of 4 August 2011.

Sixth Auxiliary Request

This request is identical to the seventh auxiliary request filed on 4 August 2011. The subject matter of this request is patentable for the reasons set out above and in our letter of 4 August 2011.

The Description

It is appreciated that it will be necessary to amend the description for conformity with the amended claims. It is proposed that this is done one agreement has been reached as to the wording of the claims.

Telephone Discussion

The writer proposes to telephone the examiner on 23 September 2011 to discuss any remaining issues the examiner may have with the aim of avoiding the need to hold oral proceedings.

Yours faithfully

Charlotte Crowhurst PhD
For and on behalf of Potter Clarkson LLP

js

Enc: Main Request
Auxiliary Requests 1 to 6
Annex A

Europäisches Patentamt
European Patent Office
Office européen des brevets

European patent application No. 06737018.9

URGENT !
To be completed (under II.) and returned to the formalities officer immediately

Maintenance / Change of date / Cancellation of oral proceedings arranged for: day 07.10.11 at 09.00 hrs

I. To the Examining / Opposition division

1. ☐ The proprietor has requested the revocation (or the like) of his patent (date: .....).

2. ☒ The party / witness ..... has indicated (date: ..16.09.11.....) that he / she

   ☐ requests the date / time of oral proceedings to be changed.

   ☐ withdraws the request for oral proceedings.

   ☐ will not be attending.

   ☐ wishes to be heard by a national court.

   ☒ has filed amendments (in examination proceedings).

   ☐ has requested that the oral proceedings be held as a videoconference (in examination proceedings).

3. ☐ Two months before the oral proceedings the application is deemed to be withdrawn (in examination proceedings). The oral proceedings have to be cancelled.

19-09-2011
Date

Morancho Alcaine, Natalia
Formalities Officer

European patent application No. 06737018.9

II. To the Formalities Officer

1. ☒ The date / time fixed for oral proceedings is maintained.

   ☐ (if necessary) The reasons are indicated on enclosed EPO Form 2906/2906O, which is to be dispatched to the party with EPO Form 2008A/2310A.

2. ☐ At the instigation of the division the oral proceedings cannot take place on the arranged date for the reasons indicated on enclosed EPO Form 2906, which is to be dispatched to the party with EPO Form 2008A/2310A.

   Date _____ Director (see Internal Instructions IE-III, 1.2) _____

3. ☐ The summons to attend oral proceedings on 07.10.11 should be cancelled.

   3.1 ☐ The proceedings will be continued in writing.

   3.2 ☐ A new date will be set later.

   3.3 ☐ A new date/time is set as follows:

   date ..... at ..... hrs.
   Parties' written submissions and amendments in preparation for the oral proceedings, if any, should be made not later than

   ..... month(s) before the date of the oral proceedings.

4. ☐ The request for the oral proceedings to be held as a videoconference

   4.1 ☐ is allowed.

   4.2 ☐ is rejected for the reasons indicated on enclosed EPO Form 2906, which is to be dispatched to the party with EPO Form 2008A.

5. ☐ The application is deemed to be withdrawn. The oral proceedings are cancelled.

20.09.11
Date

Chairman | Second member | Primary Examiner | Legal member

III. Action taken by the formalities officer

☒ EPO Form 2008A/2310A has been dispatched, if applicable (see point II above) together with EPO Form 2906/2906O.

☐ A new summons has been dispatched.

☐ .....

19.09.11 SM
Date

Marie Schlemmer
Formalities Officer

ANNEX A

Experiments to Test the Stability of Compositions of the Invention Against Formation of PEG Esters

PRODUCTION OF CAPSULES IN ACCORDANCE WITH THE INVENTION

Active Ingredients

Ingredient	Amount per Capsule
naproxen sodium	220mg

Fill Excipients

Ingredient	Amount (mg) per Capsule
Lactic Acid	44.0
Propylene Glycol	17.7
Povidone K-30	17.7
Polyethylene Glycol 600	580.6

Gelain Shell Excipients

Ingredient
Gelatin
Glycerin
Sorbital Special
Purified Water
ED&C Yellow # 6
FD&C Blue # 1

Using these ingredients capsules were produced using a method as described in the Examples of European Patent Application No. 06737018.9.

PACKAGING OF THE CAPSULES

The capsules were either packaged 15 to a bottle or 200 to a bottle or in a bulk carton. The bottles containing 15 capsules were 45 cc, round, opaque white HDPE bottles with child resistant caps.

The bottles containing 200 capsules were 400 cc, round, opaque, white, HDPE bottles with child resistant caps.

STUDY DESIGN

Bottles containing 15 capsules and bottles containing 200 capsules were stored at 25°C and a relative humidity of 60% and at 30°C and a relative humidity of 65%. A carton containing the capsules stored in bulk was stored at 25°C and 60% relative humidity.

The percentage of PEG esters in the capsules, as a percentage of the drug (naproxen sodium), was determined using HPLC, before storage and after storage for 3 months, 6 months, 9 months and 12 months.

THE RESULTS

TEST WITH BOTTLES CONTAINING 15 CAPSULES

Storage at 25°C/60% Relative Humidity

	No. Of Months				
	0	3	6	9	12
% PEG-esters	None	0.10%	0.17%	0.25%	0.32%
	None	0.10%	0.17%	0.25%	0.33%
	None	0.10%	0.15%	0.25%	0.32%

Storage at 30°C/65% Relative Humidity

	No. Of Months				
	0	3	6	9	12
% PEG-esters	None	0.15%	0.28%	0.30%	0.57%
	None	0.15%	0.29%	0.44%	0.58%
	None	0.15%	0.29%	0.44%	0.59%

TEST WITH BOTTLES CONTAINING 200 CAPSULES

Storage at 25°C/60% Relative Humidity

	No. Of Months				
	0	3	6	9	12
% PEG-esters	None	0.10%	0.17%	0.25%	0.31%
	None	0.11%	0.17%	0.25%	0.32%
	None	0.10%	0.17%	0.24%	0.32%

Storage at 30°C/65% Relative Humidity

	No. Of Months				
	0	3	6	9	12
% PEG-esters	None	0.16%	0.29%	0.41%	0.57%
	None	0.15%	0.29%	0.45%	0.59%
	None	0.15%	0.28%	0.44%	0.58%

TEST OF BULK PACK CAPSULES

Storage at 25°c/60% Relative Humidity

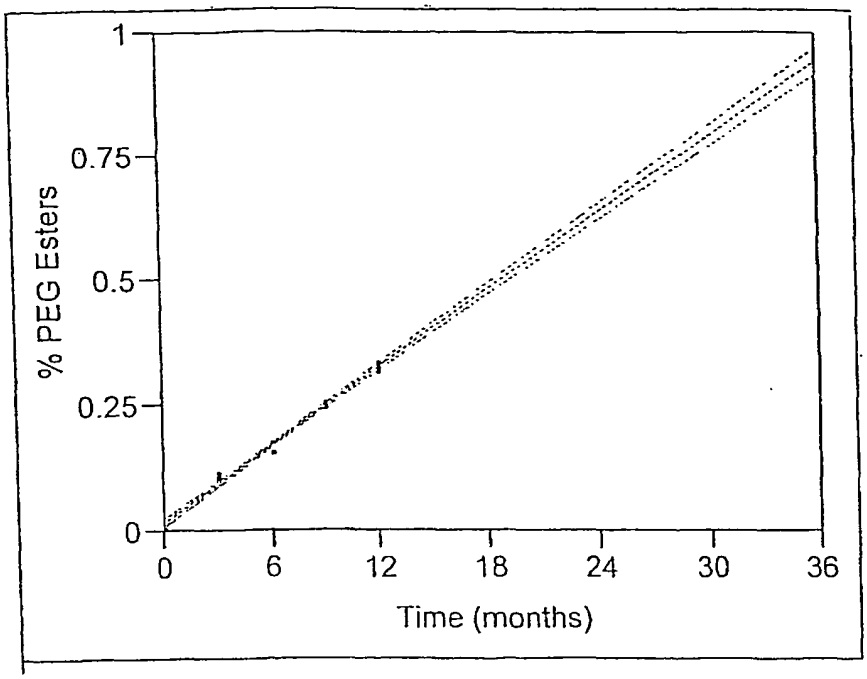
	No. Of Months				
	0	3	6	9	12
% PEG-esters	None	0.10%	0.17%	0.25%	0.32%
	None	0.10%	0.16%	0.26%	0.32%
	None	0.09%	0.17%	0.22%	0.32%

These results show that initially the capsules of the invention contained no PEG esters and that even after storage for up to one year under a variety of storage conditions the capsules of the invention contained very low levels of PEG esters. In every case, significantly less than 1% of the drug had formed PEG esters even after storage for a year. Less than 1% PEG ester formation was considered to represent a low level of PEG ester formation which did not cause significant loss of activity and therefore compositions with less than 1% PEG ester were considered to be stable. All of the capsules tested passed this test.

EVALUATION OF PEG ESTER RESULTS

The percent PEG esters was plotted versus time (see graph on page 5). In addition, the 95% confidence bounds were added to the plot. Both the fitted least-squares line and the 95% upper confidence bound were extrapolated through 36 months to examine product expiration. According to the extrapolated data points for the upper 95% confidence bound, the percent PEG esters at 24 months should be 0.65 and according to the fitted least-squares line, the percent PEG esters should be 0.63. This means that even after three years the predicted values from both the upper 95% confidence and the least-squares line did not exceed the upper acceptable specification limit of not more than 1.0% PEG esters. In other words, compositions of the invention are not predicted to lose activity through PEG ester formation after 3 years and to therefore have a shelf life of at least three years.

Naproxen Sodium 220 mg SGC 25°C/60% RH
(% PEG esters vs. Time)



MAIN REQUEST

CLAIMS

1. A pharmaceutical composition comprising
   (a) a salt of an acidic pharmaceutically active agent;
   (b) a deionizing agent which is a hydrogen ion species in an amount to cause partial deionization of the salt of from about 0.2 to 1.0 mole equivalents per mole of the pharmaceutically active agent;
   (c) polyethylene glycol; and optionally
   (d) water.

2. A softgel capsule comprising a fill material wherein the fill material comprises
   (a) a salt of an acidic pharmaceutically active agent;
   (b) a deionizing agent which is a hydrogen ion species in an amount to cause partial deionization of the salt of from about 0.2 to 1.0 mole equivalents per mole of the pharmaceutically active agent;
   (c) polyethylene glycol; and optionally
   (d) water.

3. The composition or capsule of claim 1 or 2 wherein the pharmaceutically active agent is selected from the group consisting of therapeutically active agents, diagnostic agents, and prophylactic agents.

4. The composition or capsule of any one of the preceding claims wherein the composition or fill material has a pH of from about 2.5 to about 7.5.

5. The composition or capsule of any one of the preceding claims wherein polyethylene glycol is present in an amount from about 10% to about 80% by weight.

6. The composition or capsule of any one of the preceding claims wherein the polyethylene glycol is one or more polyethylene glycols with a molecular weight between 300 and 1500.

7. The composition or the capsule of any one of the preceding claims wherein water is present in an amount from about 1% to about 18% by weight.

8. The composition or capsule of any one of the preceding claims further comprising one or more excipients selected from the group consisting of plasticizers, crystallization inhibitors, wetting agents, bulk filling agents, solubilizers, bioavailability enhancers, solvents, pH-adjusting agents, dyes, preservatives, solvents, surfactants, and combinations thereof.

9. The composition or capsule of claim 8 wherein the solubilizer is selected from the group consisting of glycerin, polyvinylpyrrolidone, propylene glycol and combinations thereof.

10. The composition or capsule of claim 8 wherein the solubilizer is present in amount from about 1% to about 10% by weight.

11. The composition or capsule of any one of the preceding claims wherein the salt (a) is naproxen sodium.

12. The composition or capsule of any one of the preceding claims wherein the hydrogen ion species is selected from hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, fumaric acid, maleic acid, tartaric acid, methane-, ethane-, and benzene sulfonates, citric acid, malic acid, acetic acid, proprionic acid, pyruvic acid, butanoic acid, and lactic acid.

13. A composition or capsule of any of claims 1 to 12 for use as a medicament.

14. A method of making the composition or capsule of any of claims 1 to 13 comprising

(a) mixing the salt of an acidic pharmaceutically active agent, the polyethylene glycol and the deionizing agent and optionally water at a temperature of from 50°C to 70°C; and

(b) encapsulating the mixture in a softgel capsule.

15. The use of

(a) a salt of an acidic pharmaceutically active agent;

(b) a deionizing agent which is a hydrogen ion species in an amount to cause partial deionization of the salt of from about 0.2 to 1.0 mole equivalents per mole of the pharmaceutically active agent;

(c) polyethylene glycol; and optionally

(d) water

in the manufacture of a medicament for administration of the pharmaceutically active agent to a patient in need thereof.

16. The use of claim 15 wherein the medicament is in the form of a softgel capsule.

17. A pharmaceutical composition obtainable by a method which comprises

(I) mixing

(a) a salt of an acidic pharmaceutically active agent;

(b) a deionizing agent which is a hydrogen ion species in an amount to cause partial deionization of the salt of from about 0.2 to 1.0 mole equivalents per mole of the pharmaceutically active agent(s);

(c) polyethylene glycol; and optionally

(d) water

at a temperature of from 50°C to 70°C.

18. A softgel capsule obtainable by a method which comprises

(I) producing a fill material by mixing

(a) a salt of an acidic pharmaceutically active agent;

(b) a deionizing agent which is a hydrogen ion species in an amount to cause partial deionization of the salt of from about 0.2 to 1.0 mole equivalents per mole of the pharmaceutically active agent;

(c) polyethylene glycol; and optionally

(d) water

at a temperature of from 50°C to 70°C; and

(II) encapsulating the mixture in a softgel capsules.

FIRST AUXILIARY REQUEST

CLAIMS

1. A softgel capsule comprising a fill material wherein the fill material comprises
   (a) a salt of an acidic pharmaceutically active agent;
   (b) a deionizing agent which is a hydrogen ion species in an amount to cause partial deionization of the salt of from about 0.2 to 1.0 mole equivalents per mole of the pharmaceutically active agent;
   (c) polyethylene glycol; and optionally
   (d) water.

2. The capsule of claim 1 wherein the pharmaceutically active agent is selected from the group consisting of therapeutically active agents, diagnostic agents, and prophylactic agents.

3. The capsule of claim 1 or 2 wherein the fill material has a pH of from about 2.5 to about 7.5.

4. The capsule of any one of the preceding claims wherein polyethylene glycol is present in an amount from about 10% to about 80% by weight.

5. The capsule of any one of the preceding claims wherein the polyethylene glycol is one or more polyethylene glycols with a molecular weight between 300 and 1500.

6. The capsule of any one of the preceding claims wherein water is present in an amount from about 1% to about 18% by weight.

7. The capsule of any one of the preceding claims further comprising one or more excipients selected from the group consisting of plasticizers, crystallization inhibitors, wetting agents, bulk filling agents, solubilizers, bioavailability enhancers, solvents, pH-adjusting agents, dyes, preservatives, solvents, surfactants, and combinations thereof.

8. The capsule of claim 7 wherein the solubilizer is selected from the group consisting of glycerin, polyvinylpyrrolidone, propylene glycol and combinations thereof.

9. The capsule of claim 7 wherein the solubilizer is present in amount from about 1% to about 10% by weight.

10. The capsule of any one of the preceding claims wherein the salt (a) is naproxen sodium.

11. The capsule of any one of the preceding claims wherein the hydrogen ion species is selected from hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, fumaric acid, maleic acid, tartaric acid, methane-, ethane-, and benzene sulfonates, citric acid, malic acid, acetic acid, proprionic acid, pyruvic acid, butanoic acid, and lactic acid.

12. A capsule of any of claims 1 to 12 for use as a medicament.

13. A method of making the capsule of any of claims 1 to 12 comprising

(a) mixing the salt of an acidic pharmaceutically active agent, the polyethylene glycol and the deionizing agent and optionally water at a temperature of from 50°C to 70°C; and

(b) encapsulating the mixture in a softgel capsule.

14. The use of

(a) a salt of an acidic pharmaceutically active agent;

(b) a deionizing agent which is a hydrogen ion species in an amount to cause partial deionization of the salt of from about 0.2 to 1.0 mole equivalents per mole of the pharmaceutically active agent(s);

(c) polyethylene glycol; and optionally

(d) water

in the manufacture of a medicament in the form of a softgel capsule for administration of the pharmaceutically active agent to a patient in need thereof.

15. A softgel capsule obtainable by a method which comprises

(I) producing a fill material by mixing

(a) a salt of an acidic pharmaceutically active agent;

(b) a deionizing agent in an amount to cause partial deionization of the salt of from about 0.2 to 1.0 mole equivalents per mole of the pharmaceutically active agent;

(c) polyethylene glycol; and optionally

(d) water

at a temperature of from 50°C to 70°C; and

(II) encapsulating the mixture in a softgel capsule.

SECOND AUXILIARY REQUEST

CLAIMS

1. A pharmaceutical composition obtainable by a method which comprises
   (I) mixing
   (a) a salt of an acidic pharmaceutically active agent;
   (b) a deionizing agent which is a hydrogen ion species in an amount to cause partial deionization of the salt of from about 0.2 to 1.0 mole equivalents per mole of the pharmaceutically active agent;
   (c) polyethylene glycol; and optionally
   (d) water
   at a temperature of from 50°C to 70°C.

2. A softgel capsule obtainable by a method which comprises
   (I) producing a fill material by mixing
   (a) a salt of an acidic pharmaceutically active agent;
   (b) a deionizing agent which is a hydrogen ion species in an amount to cause partial deionization of the salt of from about 0.2 to 1.0 mole equivalents per mole of the pharmaceutically active agent;
   (c) polyethylene glycol; and optionally
   (d) water
   at a temperature of from 50°C to 70°C; and
   (II)encapsulating the mixture in a softgel capsule.

3. The composition or capsule of claim 1 or 2 wherein the pharmaceutically active agent is selected from the group consisting of therapeutically active agents, diagnostic agents, and prophylactic agents.

4. The composition or capsule of any one of the preceding claims wherein the composition or fill material of the softgel capsule has a pH of from about 2.5 to about 7.5.

5. The composition or capsule of any one of the preceding claims wherein polyethylene glycol is present in an amount from about 10% to about 80% by weight.

6. The composition or capsule of any one of the preceding claims wherein the polyethylene glycol is one or more polyethylene glycols with a molecular weight between 300 and 1500.

7. The composition or the capsule of any one of the preceding claims wherein water is present in an amount from about 1% to about 18% by weight.

8. The composition or capsule of any one of the preceding claims further comprising one or more excipients selected from the group consisting of plasticizers, crystallization inhibitors, wetting agents, bulk filling agents, solubilizers, bioavailability enhancers, solvents, pH-adjusting agents, dyes, preservatives, solvents, surfactants, and combinations thereof.

9. The composition or capsule of claim 8 wherein the solubilizer is selected from the group consisting of glycerin, polyvinylpyrrolidone, propylene glycol and combinations thereof.

10. The composition or capsule of claim 8 wherein the solubilizer is present in amount from about 1% to about 10% by weight.

11. The composition or capsule of any one of the preceding claims wherein the salt (a) is naproxen sodium.

12. The composition or capsule of any one of the preceding claims wherein the hydrogen ion species is selected from hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, fumaric acid, maleic acid, tartaric acid, methane-, ethane-, and benzene sulfonates, citric acid, malic acid, acetic acid, proprionic acid, pyruvic acid, butanoic acid, and lactic acid.

13. A composition or capsule of any of claims 1 to 12 for use as a medicament.

14. A method of making the composition or capsule of any of claims 1 to 13 comprising

(a) mixing the salt of an acidic pharmaceutically active agent, the polyethylene glycol and the deionizing agent and optionally water at a temperature of from 50°C to 70°C; and

(b) encapsulating the mixture in a softgel capsule.

15. The use of

(a) a salt of an acidic pharmaceutically active agent;

(b) a deionizing agent which is a hydrogen ion species in an amount to cause partial deionization of the salt of from about 0.2 to 1.0 mole equivalents per mole of the pharmaceutically active agent;

(c) polyethylene glycol; and optionally

(d) water

in the manufacture of a medicament for administration of the pharmaceutically active agent to a patient in need thereof.

16. The use of claim 15 wherein the medicament is in the form of a softgel capsule.

THIRD AUXILIARY REQUEST

CLAIMS

1. A method of making a pharmaceutical composition comprising

(a) mixing a salt of an acidic pharmaceutically active agent, a polyethylene glycol and a deionizing agent which is a hydrogen ion species and optionally water at a temperature of from 50°C to 70°C;

wherein the deionizing agent is used in an amount to cause partial ionization of the salt of from about 0.2 to 1.0 mole equivalents per mole of the pharmaceutically active agent.

2. A method of making a softgel capsule comprising making a fill mixture by the method of claim 1 and

(b) encapsulating the mixture in a softgel capsule.

3. The method of claim 1 or 2 wherein the pharmaceutically active agent is selected from the group consisting of therapeutically active agents, diagnostic agents, and prophylactic agents.

4. The method of any one of the preceding claims wherein the composition or fill material has a pH of from about 2.5 to about 7.5.

5. The method of any one of the preceding claims wherein polyethylene glycol is present in an amount from about 10% to about 80% by weight.

6. The method of any one of the preceding claims wherein the polyethylene glycol is one or more polyethylene glycols with a molecular weight between 300 and 1500.

7. The method of any one of the preceding claims wherein water is present in an amount from about 1% to about 18% by weight.

8. The method of any one of the preceding claims further comprising one or more excipients selected from the group consisting of plasticizers, crystallization inhibitors, wetting agents, bulk filling agents, solubilizers, bioavailability enhancers, solvents, pH-adjusting agents, dyes, preservatives, solvents, surfactants, and combinations thereof.

9. The method of claim 8 wherein the solubilizer is selected from the group consisting of glycerin, polyvinylpyrrolidone, propylene glycol and combinations thereof.

10. The method of claim 8 wherein the solubilizer is present in amount from about 1% to about 10% by weight.

11. The method of any one of the preceding claims wherein the salt (a) is naproxen sodium.

12. The method of any one of the preceding claims wherein the hydrogen ion species is selected from hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, fumaric acid, maleic acid, tartaric acid, methane-, ethane-, and benzene sulfonates, citric acid, malic acid, acetic acid, proprionic acid, pyruvic acid, butanoic acid, and lactic acid.

FOURTH AUXILIARY REQUEST

CLAIMS

1. The use of
   (a) a salt of an acidic pharmaceutically active agent;
   (b) a deionizing agent which is a hydrogen ion species in an amount to cause partial deionization of the salt of from about 0.2 to 1.0 mole equivalents per mole of the pharmaceutically active agent;
   (c) polyethylene glycol; and optionally
   (d) water
   in the manufacture of a medicament for administration of the pharmaceutically active agent to a patient in need thereof.

2. The use of claim 1 wherein the medicament is in the form of a softgel capsule.

3. The use of claim 1 or 2 wherein the pharmaceutically active agent is selected from the group consisting of therapeutically active agents, diagnostic agents, and prophylactic agents.

4. The use of any one of the preceding claims wherein the composition or fill material of the soft gel capsule has a pH of from about 2.5 to about 7.5.

5. The use of any one of the preceding claims wherein polyethylene glycol is present in an amount from about 10% to about 80% by weight.

6. The use of any one of the preceding claims wherein the polyethylene glycol is one or more polyethylene glycols with a molecular weight between 300 and 1500.

7. The use any one of the preceding claims wherein water is present in an amount from about 1% to about 18% by weight.

8. The use of any one of the preceding claims further comprising one or more excipients selected from the group consisting of plasticizers, crystallization inhibitors, wetting agents, bulk filling agents, solubilizers, bioavailability enhancers, solvents, pH-adjusting agents, dyes, preservatives, solvents, surfactants, and combinations thereof.

9. The use of claim 8 wherein the solubilizer is selected from the group consisting of glycerin, polyvinylpyrrolidone, propylene glycol and combinations thereof.

10. The use of claim 8 wherein the solubilizer is present in amount from about 1% to about 10% by weight.

11. The use of any one of the preceding claims wherein the salt (a) is naproxen sodium.

12. The use of any one of the preceding claims wherein the hydrogen ion species is selected from hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, fumaric acid, maleic acid, tartaric acid, methane-, ethane-, and benzene sulfonates, citric acid, malic acid, acetic acid, proprionic acid, pyruvic acid, butanoic acid, and lactic acid.

13. A method of making a pharmaceutical composition or softgel capsule comprising

(a) mixing the salt of an acidic pharmaceutically active agent, polyethylene glycol and a deionizing agent which is a hydrogen ion species and optionally water at a temperature of from 50°C to 70°C; and

(b) encapsulating the mixture in a softgel capsule.

FIFTH AUXILIARY REQUEST

CLAIMS

1. A pharmaceutical composition comprising
   (a) a salt of an acidic pharmaceutically active agent;
   (b) a deionizing agent in an amount to cause partial deionization of the salt of from about 0.2 to 1.0 mole equivalents per mole of the pharmaceutically active agent;
   (c) polyethylene glycol; and optionally
   (d) water;

wherein the deionizing agent is a hydrogen ion species selected from hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, fumaric acid, maleic acid, tartaric acid, methane-, ethane-, and benzene sulfonates, citric acid, malic acid, acetic acid, proprionic acid, pyruvic acid, butanoic acid, and lactic acid.

2. A softgel capsule comprising a fill material wherein the fill material comprises
   (a) a salt of an acidic pharmaceutically active agent;
   (b) a deionizing agent in an amount to cause partial deionization of the salt of from about 0.2 to 1.0 mole equivalents per mole of the pharmaceutically active agent;
   (c) polyethylene glycol; and optionally
   (d) water

wherein the deionizing agent is a hydrogen ion species selected from hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, fumaric acid, maleic acid, tartaric acid, methane-, ethane-, and benzene sulfonates, citric acid, malic acid, acetic acid, proprionic acid, pyruvic acid, butanoic acid, and lactic acid.

3. The composition or capsule of claim 1 or 2 wherein the pharmaceutically active agent is selected from the group consisting of therapeutically active agents, diagnostic agents, and prophylactic agents.

4. The composition or capsule of any one of the preceding claims wherein the composition or fill material has a pH of from about 2.5 to about 7.5.

5. The composition or capsule of any one of the preceding claims wherein polyethylene glycol is present in an amount from about 10% to about 80% by weight.

6. The composition or capsule of any one of the preceding claims wherein the polyethylene glycol is one or more polyethylene glycols with a molecular weight between 300 and 1500.

7. The composition or the capsule any one of the preceding claims wherein water is present in an amount from about 1% to about 18% by weight.

8. The composition or capsule of any one of the preceding claims comprising one or more excipients selected from the group consisting of plasticizers, crystallization inhibitors, wetting agents, bulk filling agents, solubilizers, bioavailability enhancers, solvents, pH-adjusting agents, dyes, preservatives, solvents, surfactants, and combinations thereof.

9. The composition or capsule of claim 8 wherein the solubilizer is selected from the group consisting of glycerin, polyvinylpyrrolidone, propylene glycol and combinations thereof.

10. The composition or capsule of claim 8 wherein the solubilizer is present in amount from about 1% to about 10% by weight.

11. The composition or capsule of any one of the preceding claims wherein the salt (a) is naproxen sodium.

12. A composition or capsule of any of claims 1 to 11 for use as a medicament.

13. A method of making the composition or capsule of any of claims 1 to 12 comprising

(a) mixing the salt of an acidic pharmaceutically active agent, the polyethylene glycol and the deionizing agent and optionally water at a temperature of from 50°C to 70°C; and

(b) encapsulating the mixture in a softgel capsule.

14. The use of

(a) a salt of an acidic pharmaceutically active agent;

(b) a deionizing agent in an amount to cause partial deionization of the salt of from about 0.2 to 1.0 mole equivalents per mole of the pharmaceutically active agent;

(c) polyethylene glycol; and optionally

(d) water

in the manufacture of a medicament for administration of the pharmaceutically active agent to a patient in need thereof;

wherein the deionizing agent is a hydrogen ion species selected from hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, fumaric acid, maleic acid, tartaric acid, methane-, ethane-, and benzene sulfonates, citric acid, malic acid, acetic acid, proprionic acid, pyruvic acid, butanoic acid, and lactic acid.

15. The use of claim 14 wherein the medicament is in the form of a softgel capsule.

16. A pharmaceutical composition obtainable by a method which comprises

(I) mixing

(a) a salt of an acidic pharmaceutically active agent;

(b) a deionizing agent in an amount to cause partial deionization of the salt of from about 0.2 to 1.0 mole equivalents per mole of the pharmaceutically active agent;

(c) polyethylene glycol; and optionally

(d) water

at a temperature of from 50°C to 70°C;

wherein the deionizing agent is a hydrogen ion species selected from hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, fumaric acid, maleic acid, tartaric acid, methane-, ethane-, and benzene sulfonates, citric acid, malic acid, acetic acid, proprionic acid, pyruvic acid, butanoic acid, and lactic acid.

17. A softgel capsule obtainable by a method which comprises

(I) producing a fill material by mixing

(a) a salt of an acidic pharmaceutically active agent;

(b) a deionizing agent in an amount to cause partial deionization of the salt of from about 0.2 to 1.0 mole equivalents per mole of the pharmaceutically active agent;

(c) polyethylene glycol; and optionally

(d) water

at a temperature of from 50°C to 70°C; and

(II) encapsulating the mixture in a softgel capsule;

wherein the deionizing agent is a hydrogen ion species selected from hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, fumaric acid, maleic acid, tartaric acid, methane-, ethane-, and benzene sulfonates, citric acid, malic acid, acetic acid, proprionic acid, pyruvic acid, butanoic acid, and lactic acid.

SIXTH AUXILIARY REQUEST

CLAIMS

1. A pharmaceutical composition comprising
   (a) naproxen sodium;
   (b) a deionizing agent in an amount to cause partial deionization of the salt of from about 0.2 to 1.0 mole equivalents per mole of the naproxen sodium;
   (c) polyethylene glycol; and optionally
   (d) water.

2. A softgel capsule comprising a fill material wherein the fill material comprises
   (a) naproxen sodium;
   (b) a deionizing agent in an amount to cause partial deionization of the salt of from about 0.2 to 1.0 mole equivalents per mole of the naproxen sodium;
   (c) polyethylene glycol; and optionally
   (d) water.

3. The composition or capsule of claim 1 or 2 wherein the deionizing agent is selected from hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, fumaric acid, maleic acid, tartaric acid, methane-, ethane-, and benzene sulfonates, citric acid, malic acid, acetic acid, proprionic acid, pyruvic acid, butanoic acid, and lactic acid.

4. The composition or capsule of any one of the preceding claims wherein the composition or fill material has a pH of from about 2.5 to about 7.5.

5. The composition or capsule of any one of the preceding claims wherein polyethylene glycol is present in an amount from about 10% to about 80% by weight.

6. The composition or capsule of any one of the preceding claims wherein the polyethylene glycol is one or more polyethylene glycols with a molecular weight between 300 and 1500.

7. The composition or the capsule of any one of the preceding claims wherein water is present in an amount from about 1% to about 18% by weight.

8. The composition or capsule of any one of the preceding claims further comprising one or more excipients selected from the group consisting of plasticizers, crystallization inhibitors, wetting agents, bulk filling agents, solubilizers, bioavailability enhancers, solvents, pH-adjusting agents, dyes, preservatives, solvents, surfactants, and combinations thereof.

9. The composition or capsule of claim 8 wherein the solubilizer is selected from the group consisting of glycerin, polyvinylpyrrolidone, propylene glycol and combinations thereof.

10. The composition or capsule of claim 8 wherein the solubilizer is present in amount from about 1% to about 10% by weight.

11. A composition or capsule of any of claims 1 to 10 for use as a medicament.

12. A method of making the composition or capsule of any of claims 1 to 11 comprising

(a) mixing the naproxen sodium, the polyethylene glycol and the deionizing agent and optionally water at a temperature of from 50°C to 70°C; and

(b) encapsulating the mixture in a softgel capsule.

13. The use of

(a) naproxen sodium;

(b) a deionizing agent selected from hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, fumaric acid, maleic acid, tartaric acid, methane-, ethane-, and benzene sulfonates, citric acid, malic acid, acetic acid, proprionic acid, pyruvic acid, butanoic acid, and lactic acid in an amount to cause partial deionization of the salt of from about 0.2 to 1.0 mole equivalents per mole of the pharmaceutically active agent(s);

(c) polyethylene glycol: and optionally

(d) water

in the manufacture of a medicament for administration of naproxen sodium to a patient in need thereof.

14. The use of claim 13 wherein the medicament is in the form of a softgel capsule.

15. A pharmaceutical composition obtainable by a method which comprises

(I) mixing

(a) naproxen sodium;

(b) a deionizing agent selected from hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, fumaric acid, maleic acid, tartaric acid, methane-, ethane-, and benzene sulfonates, citric acid, malic acid, acetic acid, proprionic acid, pyruvic acid, butanoic acid, and lactic acid in an amount to cause partial deionization of the salt of from about 0.2 to 1.0 mole equivalents per mole of the naproxen sodium;

(c) polyethylene glycol; and optionally

(d) water

at a temperature of from 50°C to 70°C.

16. A softgel capsule obtainable by a method which comprises

(I) producing a fill material by mixing

(a) naproxen sodium;

(b) a deionizing agent selected from hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, fumaric acid, maleic acid, tartaric acid, methane-, ethane-, and benzene sulfonates, citric acid, malic acid, acetic acid, proprionic acid, pyruvic acid, butanoic acid, and lactic acid in an amount to cause partial deionization of the salt of from about 0.2 to 1.0 mole equivalents per mole of the pharmaceutically active agent(s);

(c) polyethylene glycol; and optionally

(d) water

at a temperature of from 50°C to 70°C; and

(II) encapsulating the mixture in a softgel capsules.

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Formalities Officer
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Date: 27-09-2011

Reference	Application No./Patent No.
PABCA/P38814EP	06737018.9 - 2123 / 1863458

Applicant/Proprietor: Banner Pharmacaps Inc.

BRIEF COMMUNICATION

Oral Proceedings on 07.10.11

Subject: ☒ Your letter of 16.9.2011

Communication:

- ☐ The summons to attend oral proceedings on 07.10.11 has been cancelled.
- ☐ The procedure will be continued in writing.
- ☒ The date fixed for oral proceedings is maintained.
- ☐ A new date will be set later.
- ☐

Please take note.

For the Examining Division

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Registered letter
EPO Form 2008A 12.07 (20/09/11)

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European Patent Office
Office européen des brevets

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Application No. : 06 737 018.9

Consultation by telephone with the applicant / representative

Despatch for information

Participants

Applicant: Banner Pharmacaps Inc.

Representative: Crowhurst, Charlotte Waveney

Member(s) of the Examining Division: Büttner, Ulf

Result of consultation

See Separate Sheet

23.09.2011
. . . . . .
Date

Büttner, Ulf
. . . . . .
Examiner

Enclosure(s):

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Substantive Examiner
Name: Büttner, Ulf
Tel: +49 89 2399 - 7841

Application No.	Ref.	Date
06 737 018.9 - 2123	PABCA/P38814EP	29.09.2011
Applicant Banner Pharmacaps Inc.		

Result of consultation

A copy of the result of consultation of 23.09.2011 is enclosed for your information.

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Büttner, Ulf
For the Examining Division

Enclosure(s): Copy of result of consultation (Form 2036)

The representative was informed about the following objections:

Novelty:

D1 still anticipates the subject matter of claim 1 of the main request. Diclofenac is considered as an acidic pharmaceutical active agent.

Inventive step.

the provided data do not represent a fair comparison with the closest prior art (D1 or D3 if the claims were restricted to naproxen). The tested compositions differ significantly from the compositions of the prior art (e.g. water content and active). Therefore, it was not possible to deduce any unexpected effect related to the possible distinguishing feature namely the presence of an additional deionizing agent. It was further pointed out, that even if a particular effect was shown, there was no justification to extrapolate from one single example to all compositions comprised within the scope of the claims, such as to compositions with a different active agent or a different acid.

Article 123 (2) EPC

The representative was further informed that a possible combination of specific active agents and specific acids might cause problems under the provisions of Article 123(2) EPC.

Postponement of the oral proceedings

The representative asked whether it was possible to postpone the oral proceedings in order to produce comparative data.

The examiner pointed out that the lack of data was already objected in the IPER. Further, the application did not contain any data which made any unexpected effect plausible. However, the point will be discussed with the other members of the examining division.

Hereby, the applicant is informed that after consultation with the other members of the examining division, the examining division came to the conclusion that there is no justification to postpone the oral proceedings.

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European Patent Office
Directorate General 2
Erhardtstraße 27
D-80298 München
GERMANY

4 October 2011

URGENT

ORAL PROCEEDINGS SCHEDULED FOR 7 OCTOBER 2011

PLEASE PASS DIRECTLY TO THE EXAMINER MR BUTTNER

Sent by fax

Dear Sirs

European Patent Application No. 06737018.9-2123
BANNER PHARMACAPS, INC.
Our ref: PABCX/P38814EP

We are now providing some further written submissions prior to the oral proceedings set for 7 October 2011.

The Oral Proceedings

Nobody will attend the oral proceedings on behalf of the applicant. We request a decision on the basis of the current state of the file, taking into account the comments below.

Amended Claims

We enclose a new set of claims to replace the 6th auxiliary request currently on file. We request that the decision of the Examining Division is made on the basis of the main request and auxiliary requests 1 to 5 as filed with our letter of 16 September 2011 and the enclosed 6th auxiliary request.

The enclosed claims are based on the claims of the 6th auxiliary request as filed with our letter of 16 September 2011. The claims of that request have been further amended to limit the claimed pharmaceutical composition and the fill material of the soft gel capsules to liquid compositions and fills. Basis for this amendment can be found at page 3, line 13 of the application as filed.

It is an essential feature of the enclosed claims that the composition/fill contains naproxen sodium. It is clear from the application as filed that that naproxen sodium is the preferred salt of an acid drug. This salt is used in all of the examples in the application as filed.

cont/....

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European Patent Office
4 October 2011

Novelty

The subject matter claimed is novel in view of the cited prior art. In particular, none of the cited prior art documents disclose a liquid pharmaceutical composition comprising the ingredients specified in enclosed claim 1.

Inventive Step

The claimed compositions are also inventive over the disclosure of the cited prior art.

The experimental data filed with our letter of 16 September 2011 clearly show that compositions of the invention do not suffer from problems associated with PEG ester formation, even on prolonged storage. This is entirely unexpected from the prior art.

The examiner has suggested that further, extensive experimental data is needed to show that the invention solves the problem of PEG ester formation. We consider that the examiner's request is unjustified.

The examiner suggested that the molecular weight of the PEG contained in the compositions of the invention may have an effect on PEG ester formation and that experimental data is needed to show that reduced PEG ester formation is achieved using PEGs of different molecular weights. This is not necessary or appropriate. The claims of the sixth auxiliary request have been limited to specify that the pharmaceutical composition or fill material is liquid. This places a limitation on the nature of the PEG.

Increasing the molecular weight of PEG increases its viscosity. Therefore, higher molecular weight PEGs will produce compositions that are semi-solid or solid. Lower molecular weight PEGs such as PEG 400 and PEG 600 will produce liquid compositions. This information about PEGs is readily available and the skilled person would know which PEGs could be used to produce liquid composition. PEG 600 was used in the compositions for which stability testing was reported in the experimental data filed on 16 September 2011.

The examiner has not clearly indicated why he thinks that the molecular weight of the PEG will affect the formation of PEG esters. Regardless of molecular weight, all PEGs contain groups that have the potential to react with acid drugs to form PEG esters.

Thus, it is not considered necessary to conduct experiments using PEGs having a range of molecular weights.

The examiner has also suggested that data relating to compositions comprising different acids at different concentrations is required. We do not agree. The claims are directed to compositions. What is important for the patentability of the composition claims is that the composition comprises 0.2 to 1.0 mol equivalents of a deionising agent. In the case of naproxen sodium this deionising agent is H^+ ions. The source of the H^+ ions is irrelevant, as

cont/....

POTTER CLARKSON

is the concentration of the acid used to provide the required amount of H^+ ions. These are, at most, features of the process used to produce the compositions, and not features of the compositions. However, the examiner has in any case not explained why the concentration of the acid that is used to form the composition (as opposed to the molar ratio of the acid in the composition) should matter.

The examiner indicated, that in his opinion, examples in which lactic acid is used as the source of H^+ ions cannot be considered to be representative of compositions comprising other acids. It seems that he thinks that lactic acid may stabilize the composition in some other way (perhaps by means of chelation), in addition to providing a source of H^+ ions. However, the examiner has not provided any scientific evidence that this could indeed be the case. In fact, there is no reason to suppose that chelation of lactic acid could have any effect on PEG ester formation.

The examiner also suggested that the data provided may not be representative of the compositions of the invention because the compositions tested contained propylene glycol and povidone K-30. However, the examiner has not provided any rationale as to why these components may prevent PEG ester formation. It is clear from page 7, lines 13 to 15 of the application as filed that these materials are used simply to enhance drug solubility. It is unjustified to say that the inclusion of these ingredients means the compositions tested do not provide an appropriate representation of the invention.

In summary, we do not think that the examiner's request for such a large of amount of experimental data is reasonable. The information provided illustrates the advantages of the invention, and shows that it works. We consider that it is at least plausible that the effect will be achieved over the whole scope of the claim.

Yours faithfully

Charlotte Crowhurst PhD
For and on behalf of Potter Clarkson LLP

js

Enc: New auxiliary request 6

POTTER CLARKSON

URGENT

ORAL PROCEEDINGS SCHEDULED FOR 7 OCTOBER 2011

PLEASE PASS DIRECTLY TO THE EXAMINER MR BUTTNER

To:	**European Patent Office**
Your Fax No:	00 49 89 2399 4465
From:	Charlotte Crowhurst PhD
Date:	4 October 2011
Our Ref:	PABCX/P38814EP
Your Ref:	European Patent Application No. 06737018.9-2123

Sheet 1 of 7 **Original by Post:** ✓

MESSAGE:

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Application No. : 06 737 018.9

Consultation by telephone with the applicant / representative

Despatch for information

Participants

Applicant: Banner Pharmacaps Inc.

Representative: Crowhurst, Charlotte Waveney

Member(s) of the Examining Division: Büttner, Ulf

Result of consultation

See Separate Sheet

29.09.2011
. . . . . .
Date

Büttner, Ulf
. . . . . .
Examiner

Enclosure(s):

Europäisches Patentamt
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Application No.	Ref.	Date
06 737 018.9 - 2123	PABCA/P38814EP	04.10.2011
Applicant: Banner Pharmacaps Inc.		

Result of consultation

A copy of the result of consultation of 29.09.2011 is enclosed for your information.

Büttner, Ulf
For the Examining Division

Enclosure(s): Copy of result of consultation (Form 2036)

This is a summary of two telephone calls made on 28.09 and 29.09.2011.

The representative explained that new data might be produced within a two month time period. She therefore, asked whether it would be possible to postpone the oral proceedings or to continue in writing.

The examiner pointed out that the lack of data was already objected in the IPER, in that therefore was enough time to produce data. It was also pointed out that in case of doubt about the nature of the data, there was plenty of time before the oral proceedings to contact the examiner.

The examiner explained that it was necessary that the claims at least met the requirements of Article 54(2) EPC and Article 123(2) EPC before discussing about a postponement of the oral proceedings.

Further, it was pointed out that the application did not contain any data relating to the stability of the claimed compositions. In view the teaching of D2 (p.4) to which the applicant referred to with the submissions of 05.08.2011, it was not plausible that a formulation where the acid was only partially ionized had an improved stability. Therefore, the alleged improved stability is based on pure speculation. Such a lack of plausibility normally cannot be remedied by later evidence.

It was further noted that in order to decide about a postponement of oral proceedings, it was necessary to provide a detailed plan about the scheduled comparative tests. Only in such a case it was possible to evaluate whether the possibly obtained data were suitable to demonstrate an unexpected effect.

The examiner pointed out that at the moment, the examining division did not see how such tests could look like, due to the extreme breath of the claims.

Points to be considered were, the different pka values for the active compounds and for the acids and their mutual interaction. The importance of the pH-value for the formation of esters was highlighted. It was further pointed out that protonation of the acid active compounds would decrease their water solubility, which was related to an increased volume, which the person skilled in the art was trying to avoid in the prior art. It was further pointed out that the molecular weight of the PEG might influence the stability and solubility. Thus, if data were produced they only could show an effect for very specifc conditions. A number of these parameters were not included within the application and therefore could not be introduced as possible limiting features into the claims. Therefore, it was doubted that it was possible to carry out tests which would cover the whole scope of the claims.

It was further pointed out that the latest data were made in compositions were no water was added. Since PEG was highly hygroscopic and always contained traces of water it was doubted that water could be excluded from the claims in view of Decision G 2/10. Compositions comprising water were the preferred embodiments of the inventions.

Summarizing as discussed with all members of the examining division, first there must a request where the only remaining issue was inventive step and second the planned experiments were suitable to demonstrate an effect over the whole breadth claimed, before a possible postponement of oral proceedings could be taken into consideration.

Sixth Auxiliary Request

CLAIMS

1. A liquid pharmaceutical composition comprising
   (a) naproxen sodium;
   (b) a deionizing agent in an amount to cause partial deionization of the naproxen sodium of from about 0.2 to 1.0 mole equivalents per mole of the naproxen sodium;
   (c) polyethylene glycol; and optionally
   (d) water.

2. A softgel capsule comprising a liquid fill material wherein the fill material comprises
   (a) naproxen sodium;
   (b) a deionizing agent in an amount to cause partial deionization of the naproxen sodium of from about 0.2 to 1.0 mole equivalents per mole of the naproxen sodium;
   (c) polyethylene glycol; and optionally
   (d) water.

3. The composition or capsule of claim 1 or 2 wherein the deionizing agent is selected from hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, fumaric acid, maleic acid, tartaric acid, methane-, ethane-, and benzene sulfonates, citric acid, malic acid, acetic acid, proprionic acid, pyruvic acid, butanoic acid, and lactic acid.

4. The composition or capsule of any one of the preceding claims wherein the composition or fill material has a pH of from about 2.5 to about 7.5.

5. The composition or capsule of any one of the preceding claims wherein polyethylene glycol is present in an amount from about 10% to about 80% by weight.

6. The composition or the capsule of any one of the preceding claims wherein water is present in an amount from about 1% to about 18% by weight.

7. The composition or capsule of any one of the preceding claims further comprising one or more excipients selected from the group consisting of plasticizers, crystallization inhibitors, wetting agents, bulk filling agents, solubilizers, bioavailability enhancers, solvents, pH-adjusting agents, dyes, preservatives, solvents, surfactants, and combinations thereof.

8. The composition or capsule of claim 7 wherein the solubilizer is selected from the group consisting of glycerin, polyvinylpyrrolidone, propylene glycol and combinations thereof.

9. The composition or capsule of claim 7 wherein the solubilizer is present in amount from about 1% to about 10% by weight.

10. A composition or capsule of any of claims 1 to 9 for use as a medicament.

11. A method of making the composition or capsule of any of claims 1 to 10 comprising

(a) mixing the naproxen sodium, the polyethylene glycol and the deionizing agent and optionally water at a temperature of from 50°C to 70°C; and

(b) encapsulating the mixture in a softgel capsule.

12. The use of

(a) naproxen sodium;

(b) a deionizing agent selected from hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, fumaric acid, maleic acid, tartaric acid, methane-, ethane-, and benzene sulfonates, citric acid, malic acid, acetic acid, proprionic acid, pyruvic acid, butanoic acid, and lactic acid in an amount to cause partial deionization of the naproxen sodium of from about 0.2 to 1.0 mole equivalents per mole of the pharmaceutically active agent(s);

(c) polyethylene glycol: and optionally

(d) water

in the manufacture of a liquid medicament for administration of naproxen sodium to a patient in need thereof.

13. The use of claim 12 wherein the medicament is in the form of a softgel capsule.

14. A liquid pharmaceutical composition obtainable by a method which comprises

(I) mixing

(a) naproxen sodium;

(b) a deionizing agent selected from hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, fumaric acid, maleic acid, tartaric acid, methane-, ethane-, and benzene sulfonates, citric acid, malic acid, acetic acid, proprionic acid, pyruvic acid, butanoic acid, and lactic acid in an amount to cause partial deionization of the naproxen sodium of from about 0.2 to 1.0 mole equivalents per mole of the naproxen sodium;

(c) polyethylene glycol; and optionally

(d) water

at a temperature of from 50°C to 70°C.

15. A softgel capsule obtainable by a method which comprises

(I) producing a liquid fill material by mixing

(a) naproxen sodium;

(b) a deionizing agent selected from hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, fumaric acid, maleic acid, tartaric acid, methane-, ethane-, and benzene sulfonates, citric acid, malic acid, acetic acid, proprionic acid, pyruvic acid, butanoic acid, and lactic acid in an amount to cause partial deionization of the naproxen sodium of from about 0.2 to 1.0 mole equivalents per mole of the pharmaceutically active agent(s);

(c) polyethylene glycol; and optionally

(d) water

at a temperature of from 50°C to 70°C; and

(II) encapsulating the mixture in a softgel capsules.

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4 October 2011

URGENT

ORAL PROCEEDINGS SCHEDULED FOR 7 OCTOBER 2011

PLEASE PASS DIRECTLY TO THE EXAMINER MR BUTTNER

Sent by fax

Dear Sirs

European Patent Application No. 06737018.9-2123
BANNER PHARMACAPS, INC.
Our ref: PABCX/P38814EP

We are now providing some further written submissions prior to the oral proceedings set for 7 October 2011.

The Oral Proceedings

Nobody will attend the oral proceedings on behalf of the applicant. We request a decision on the basis of the current state of the file, taking into account the comments below.

Amended Claims

We enclose a new set of claims to replace the 6th auxiliary request currently on file. We request that the decision of the Examining Division is made on the basis of the main request and auxiliary requests 1 to 5 as filed with our letter of 16 September 2011 and the enclosed 6th auxiliary request.

The enclosed claims are based on the claims of the 6th auxiliary request as filed with our letter of 16 September 2011. The claims of that request have been further amended to limit the claimed pharmaceutical composition and the fill material of the soft gel capsules to liquid compositions and fills. Basis for this amendment can be found at page 3, line 13 of the application as filed.

It is an essential feature of the enclosed claims that the composition/fill contains naproxen sodium. It is clear from the application as filed that that naproxen sodium is the preferred salt of an acid drug. This salt is used in all of the examples in the application as filed.

cont/....

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Novelty

The subject matter claimed is novel in view of the cited prior art. In particular, none of the cited prior art documents disclose a liquid pharmaceutical composition comprising the ingredients specified in enclosed claim 1.

Inventive Step

The claimed compositions are also inventive over the disclosure of the cited prior art.

The experimental data filed with our letter of 16 September 2011 clearly show that compositions of the invention do not suffer from problems associated with PEG ester formation, even on prolonged storage. This is entirely unexpected from the prior art.

The examiner has suggested that further, extensive experimental data is needed to show that the invention solves the problem of PEG ester formation. We consider that the examiner's request is unjustified.

The examiner suggested that the molecular weight of the PEG contained in the compositions of the invention may have an effect on PEG ester formation and that experimental data is needed to show that reduced PEG ester formation is achieved using PEGs of different molecular weights. This is not necessary or appropriate. The claims of the sixth auxiliary request have been limited to specify that the pharmaceutical composition or fill material is liquid. This places a limitation on the nature of the PEG.

Increasing the molecular weight of PEG increases its viscosity. Therefore, higher molecular weight PEGs will produce compositions that are semi-solid or solid. Lower molecular weight PEGs such as PEG 400 and PEG 600 will produce liquid compositions. This information about PEGs is readily available and the skilled person would know which PEGs could be used to produce liquid composition. PEG 600 was used in the compositions for which stability testing was reported in the experimental data filed on 16 September 2011.

The examiner has not clearly indicated why he thinks that the molecular weight of the PEG will affect the formation of PEG esters. Regardless of molecular weight, all PEGs contain groups that have the potential to react with acid drugs to form PEG esters.

Thus, it is not considered necessary to conduct experiments using PEGs having a range of molecular weights.

The examiner has also suggested that data relating to compositions comprising different acids at different concentrations is required. We do not agree. The claims are directed to compositions. What is important for the patentability of the composition claims is that the composition comprises 0.2 to 1.0 mol equivalents of a deionising agent. In the case of naproxen sodium this deionising agent is H^+ ions. The source of the H^+ ions is irrelevant, as

cont/....

is the concentration of the acid used to provide the required amount of H^+ ions. These are, at most, features of the process used to produce the compositions, and not features of the compositions. However, the examiner has in any case not explained why the concentration of the acid that is used to form the composition (as opposed to the molar ratio of the acid in the composition) should matter.

The examiner indicated, that in his opinion, examples in which lactic acid is used as the source of H^+ ions cannot be considered to be representative of compositions comprising other acids. It seems that he thinks that lactic acid may stabilize the composition in some other way (perhaps by means of chelation), in addition to providing a source of H^+ ions. However, the examiner has not provided any scientific evidence that this could indeed be the case. In fact, there is no reason to suppose that chelation of lactic acid could have any effect on PEG ester formation.

The examiner also suggested that the data provided may not be representative of the compositions of the invention because the compositions tested contained propylene glycol and povidone K-30. However, the examiner has not provided any rationale as to why these components may prevent PEG ester formation. It is clear from page 7, lines 13 to 15 of the application as filed that these materials are used simply to enhance drug solubility. It is unjustified to say that the inclusion of these ingredients means the compositions tested do not provide an appropriate representation of the invention.

In summary, we do not think that the examiner's request for such a large of amount of experimental data is reasonable. The information provided illustrates the advantages of the invention, and shows that it works. We consider that it is at least plausible that the effect will be achieved over the whole scope of the claim.

Yours faithfully

Charlotte Crowhurst PhD
For and on behalf of Potter Clarkson LLP

js

Enc: New auxiliary request 6

Sixth Auxiliary Request

CLAIMS

1. A liquid pharmaceutical composition comprising
   (a) naproxen sodium;
   (b) a deionizing agent in an amount to cause partial deionization of the naproxen sodium of from about 0.2 to 1.0 mole equivalents per mole of the naproxen sodium;
   (c) polyethylene glycol; and optionally
   (d) water.

2. A softgel capsule comprising a liquid fill material wherein the fill material comprises
   (a) naproxen sodium;
   (b) a deionizing agent in an amount to cause partial deionization of the naproxen sodium of from about 0.2 to 1.0 mole equivalents per mole of the naproxen sodium;
   (c) polyethylene glycol; and optionally
   (d) water.

3. The composition or capsule of claim 1 or 2 wherein the deionizing agent is selected from hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, fumaric acid, maleic acid, tartaric acid, methane-, ethane-, and benzene sulfonates, citric acid, malic acid, acetic acid, proprionic acid, pyruvic acid, butanoic acid, and lactic acid.

4. The composition or capsule of any one of the preceding claims wherein the composition or fill material has a pH of from about 2.5 to about 7.5.

5. The composition or capsule of any one of the preceding claims wherein polyethylene glycol is present in an amount from about 10% to about 80% by weight.

6. The composition or the capsule of any one of the preceding claims wherein water is present in an amount from about 1% to about 18% by weight.

7. The composition or capsule of any one of the preceding claims further comprising one or more excipients selected from the group consisting of plasticizers, crystallization inhibitors, wetting agents, bulk filling agents, solubilizers, bioavailability enhancers, solvents, pH-adjusting agents, dyes, preservatives, solvents, surfactants, and combinations thereof.

8. The composition or capsule of claim 7 wherein the solubilizer is selected from the group consisting of glycerin, polyvinylpyrrolidone, propylene glycol and combinations thereof.

9. The composition or capsule of claim 7 wherein the solubilizer is present in amount from about 1% to about 10% by weight.

10. A composition or capsule of any of claims 1 to 9 for use as a medicament.

11. A method of making the composition or capsule of any of claims 1 to 10 comprising

(a) mixing the naproxen sodium, the polyethylene glycol and the deionizing agent and optionally water at a temperature of from 50°C to 70°C; and

(b) encapsulating the mixture in a softgel capsule.

12. The use of

(a) naproxen sodium;

(b) a deionizing agent selected from hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, fumaric acid, maleic acid, tartaric acid, methane-, ethane-, and benzene sulfonates, citric acid, malic acid, acetic acid, proprionic acid, pyruvic acid, butanoic acid, and lactic acid in an amount to cause partial deionization of the naproxen sodium of from about 0.2 to 1.0 mole equivalents per mole of the pharmaceutically active agent(s);

(c) polyethylene glycol: and optionally

(d) water

in the manufacture of a liquid medicament for administration of naproxen sodium to a patient in need thereof.

13. The use of claim 12 wherein the medicament is in the form of a softgel capsule.

14. A liquid pharmaceutical composition obtainable by a method which comprises

(I) mixing

(a) naproxen sodium;

(b) a deionizing agent selected from hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, fumaric acid, maleic acid, tartaric acid, methane-, ethane-, and benzene sulfonates, citric acid, malic acid, acetic acid, proprionic acid, pyruvic acid, butanoic acid, and lactic acid in an amount to cause partial deionization of the naproxen sodium of from about 0.2 to 1.0 mole equivalents per mole of the naproxen sodium;

(c) polyethylene glycol; and optionally

(d) water

at a temperature of from 50°C to 70°C.

15. A softgel capsule obtainable by a method which comprises

(I) producing a liquid fill material by mixing

(a) naproxen sodium;

(b) a deionizing agent selected from hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, fumaric acid, maleic acid, tartaric acid, methane-, ethane-, and benzene sulfonates, citric acid, malic acid, acetic acid, proprionic acid, pyruvic acid, butanoic acid, and lactic acid in an amount to cause partial deionization of the naproxen sodium of from about 0.2 to 1.0 mole equivalents per mole of the pharmaceutically active agent(s);

(c) polyethylene glycol; and optionally

(d) water

at a temperature of from 50°C to 70°C; and

(II) encapsulating the mixture in a softgel capsules.

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Date
18-10-2011

Reference	Application No./Patent No.
PABCA/P38814EP	06737018.9 - 2123 / 1863458

Applicant/Proprietor
Banner Pharmacaps Inc.

Communication pursuant to Rule 2(1) EPC and Article 7 of the Decision of the President of the EPO dated 12.07.2007 on the use of facsimile for filing patent applications and other documents

For the above-mentioned European patent application, on 04.10.2011 .....the following document was filed by facsimile, which is of inferior quality:

claims (faint quality)

You are invited, within a period of **two months** from notification of this communication, to submit a document that reproduces the contents of the above document and complies with the Implementing Regulations to the EPC.

If this is not done in due time, the facsimile shall be deemed not to have been received (R. 2(1) EPC in conjunction with Art. 7 of the above-mentioned Decision (Special edition No. 3, OJ EPO 2007, 7)).

Receiving Section / For the Examining Division

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Registered letter
EPO Form 1072A 12.07

POTTER CLARKSON

European Patent Office
Directorate General 2
Erhardtstraße 27
D-80298 München
GERMANY

4 October 2011

URGENT

ORAL PROCEEDINGS SCHEDULED FOR 7 OCTOBER 2011

PLEASE PASS DIRECTLY TO THE EXAMINER MR BUTTNER

Sent by fax

Dear Sirs

European Patent Application No. 06737018.9-2123
BANNER PHARMACAPS, INC.
Our ref: PABCX/P38814EP

We are now providing some further written submissions prior to the oral proceedings set for 7 October 2011.

The Oral Proceedings

Nobody will attend the oral proceedings on behalf of the applicant. We request a decision on the basis of the current state of the file, taking into account the comments below.

Amended Claims

We enclose a new set of claims to replace the 6th auxiliary request currently on file. We request that the decision of the Examining Division is made on the basis of the main request and auxiliary requests 1 to 5 as filed with our letter of 16 September 2011 and the enclosed 6th auxiliary request.

The enclosed claims are based on the claims of the 6th auxiliary request as filed with our letter of 16 September 2011. The claims of that request have been further amended to limit the claimed pharmaceutical composition and the fill material of the soft gel capsules to liquid compositions and fills. Basis for this amendment can be found at page 3, line 13 of the application as filed.

It is an essential feature of the enclosed claims that the composition/fill contains naproxen sodium. It is clear from the application as filed that that naproxen sodium is the preferred salt of an acid drug. This salt is used in all of the examples in the application as filed.

cont/....

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POTTER CLARKSON

European Patent Office
4 October 2011

Novelty

The subject matter claimed is novel in view of the cited prior art. In particular, none of the cited prior art documents disclose a liquid pharmaceutical composition comprising the ingredients specified in enclosed claim 1.

Inventive Step

The claimed compositions are also inventive over the disclosure of the cited prior art.

The experimental data filed with our letter of 16 September 2011 clearly show that compositions of the invention do not suffer from problems associated with PEG ester formation, even on prolonged storage. This is entirely unexpected from the prior art.

The examiner has suggested that further, extensive experimental data is needed to show that the invention solves the problem of PEG ester formation. We consider that the examiner's request is unjustified.

The examiner suggested that the molecular weight of the PEG contained in the compositions of the invention may have an effect on PEG ester formation and that experimental data is needed to show that reduced PEG ester formation is achieved using PEGs of different molecular weights. This is not necessary or appropriate. The claims of the sixth auxiliary request have been limited to specify that the pharmaceutical composition or fill material is liquid. This places a limitation on the nature of the PEG.

Increasing the molecular weight of PEG increases its viscosity. Therefore, higher molecular weight PEGs will produce compositions that are semi-solid or solid. Lower molecular weight PEGs such as PEG 400 and PEG 600 will produce liquid compositions. This information about PEGs is readily available and the skilled person would know which PEGs could be used to produce liquid composition. PEG 600 was used in the compositions for which stability testing was reported in the experimental data filed on 16 September 2011.

The examiner has not clearly indicated why he thinks that the molecular weight of the PEG will affect the formation of PEG esters. Regardless of molecular weight, all PEGs contain groups that have the potential to react with acid drugs to form PEG esters.

Thus, it is not considered necessary to conduct experiments using PEGs having a range of molecular weights.

The examiner has also suggested that data relating to compositions comprising different acids at different concentrations is required. We do not agree. The claims are directed to compositions. What is important for the patentability of the composition claims is that the composition comprises 0.2 to 1.0 mol equivalents of a deionising agent. In the case of naproxen sodium this deionising agent is H^+ ions. The source of the H^+ ions is irrelevant, as

cont/....

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European Patent Office
4 October 2011

is the concentration of the acid used to provide the required amount of H^+ ions. These are, at most, features of the process used to produce the compositions, and not features of the compositions. However, the examiner has in any case not explained why the concentration of the acid that is used to form the composition (as opposed to the molar ratio of the acid in the composition) should matter.

The examiner indicated, that in his opinion, examples in which lactic acid is used as the source of H^+ ions cannot be considered to be representative of compositions comprising other acids. It seems that he thinks that lactic acid may stabilize the composition in some other way (perhaps by means of chelation), in addition to providing a source of H^+ ions. However, the examiner has not provided any scientific evidence that this could indeed be the case. In fact, there is no reason to suppose that chelation of lactic acid could have any effect on PEG ester formation.

The examiner also suggested that the data provided may not be representative of the compositions of the invention because the compositions tested contained propylene glycol and povidone K-30. However, the examiner has not provided any rationale as to why these components may prevent PEG ester formation. It is clear from page 7, lines 13 to 15 of the application as filed that these materials are used simply to enhance drug solubility. It is unjustified to say that the inclusion of these ingredients means the compositions tested do not provide an appropriate representation of the invention.

In summary, we do not think that the examiner's request for such a large of amount of experimental data is reasonable. The information provided illustrates the advantages of the invention, and shows that it works. We consider that it is at least plausible that the effect will be achieved over the whole scope of the claim.

Yours faithfully

Charlotte Crowhurst PhD
For and on behalf of Potter Clarkson LLP

js

Enc: New auxiliary request 6

POTTER CLARKSON

To:	**European Patent Office**
Your Fax No:	00 49 89 2399 4465
From:	Charlotte Crowhurst PhD
Date:	27 October 2011
Our Ref:	PABCX/P38814EP
Your Ref:	European Patent Application No. 06737018.9-2123

Sheet 1 of 8 **Original by Post:** ✓

MESSAGE:

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27 October 2011

Sent by fax

Dear Sirs

European Patent Application No. 06737018.9-2123
BANNER PHARMACAPS, INC.
Our ref: PABCX/P38814EP

In response to the communication of 18 October 2011 we enclose a copy of the documents filed on 4 October 2011 including the claims of the sixth auxiliary request.

We believe that this should address the issues raised in the communication of 18 October 2011. However, if there are any remaining issues, the Formalities Officer is kindly asked to telephone Dr Charlotte Crowhurst.

Yours faithfully

Charlotte Crowhurst PhD
For and on behalf of Potter Clarkson LLP

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Enc: Documents filed on 4 October 2011

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Sixth Auxiliary Request

CLAIMS

1. A liquid pharmaceutical composition comprising
   (a) naproxen sodium;
   (b) a deionizing agent in an amount to cause partial deionization of the naproxen sodium of from about 0.2 to 1.0 mole equivalents per mole of the naproxen sodium;
   (c) polyethylene glycol; and optionally
   (d) water.

2. A softgel capsule comprising a liquid fill material wherein the fill material comprises
   (a) naproxen sodium;
   (b) a deionizing agent in an amount to cause partial deionization of the naproxen sodium of from about 0.2 to 1.0 mole equivalents per mole of the naproxen sodium;
   (c) polyethylene glycol; and optionally
   (d) water.

3. The composition or capsule of claim 1 or 2 wherein the deionizing agent is selected from hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, fumaric acid, maleic acid, tartaric acid, methane-, ethane-, and benzene sulfonates, citric acid, malic acid, acetic acid, proprionic acid, pyruvic acid, butanoic acid, and lactic acid.

4. The composition or capsule of any one of the preceding claims wherein the composition or fill material has a pH of from about 2.5 to about 7.5.

5. The composition or capsule of any one of the preceding claims wherein polyethylene glycol is present in an amount from about 10% to about 80% by weight.

6. The composition or the capsule of any one of the preceding claims wherein water is present in an amount from about 1% to about 18% by weight.

7. The composition or capsule of any one of the preceding claims further comprising one or more excipients selected from the group consisting of plasticizers, crystallization inhibitors, wetting agents, bulk filling agents, solubilizers, bioavailability enhancers, solvents, pH-adjusting agents, dyes, preservatives, solvents, surfactants, and combinations thereof.

8. The composition or capsule of claim 7 wherein the solubilizer is selected from the group consisting of glycerin, polyvinylpyrrolidone, propylene glycol and combinations thereof.

9. The composition or capsule of claim 7 wherein the solubilizer is present in amount from about 1% to about 10% by weight.

10. A composition or capsule of any of claims 1 to 9 for use as a medicament.

11. A method of making the composition or capsule of any of claims 1 to 10 comprising

(a) mixing the naproxen sodium, the polyethylene glycol and the deionizing agent and optionally water at a temperature of from 50°C to 70°C; and

(b) encapsulating the mixture in a softgel capsule.

12. The use of

(a) naproxen sodium;

(b) a deionizing agent selected from hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, fumaric acid, maleic acid, tartaric acid, methane-, ethane-, and benzene sulfonates, citric acid, malic acid, acetic acid, proprionic acid, pyruvic acid, butanoic acid, and lactic acid in an amount to cause partial deionization of the naproxen sodium of from about 0.2 to 1.0 mole equivalents per mole of the pharmaceutically active agent(s);

(c) polyethylene glycol: and optionally

(d) water

in the manufacture of a liquid medicament for administration of naproxen sodium to a patient in need thereof.

13. The use of claim 12 wherein the medicament is in the form of a softgel capsule.

14. A liquid pharmaceutical composition obtainable by a method which comprises

(I) mixing

(a) naproxen sodium;

(b) a deionizing agent selected from hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, fumaric acid, maleic acid, tartaric acid, methane-, ethane-, and benzene sulfonates, citric acid, malic acid, acetic acid, proprionic acid, pyruvic acid, butanoic acid, and lactic acid in an amount to cause partial deionization of the naproxen sodium of from about 0.2 to 1.0 mole equivalents per mole of the naproxen sodium;

(c) polyethylene glycol; and optionally

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at a temperature of from 50°C to 70°C.

15. A softgel capsule obtainable by a method which comprises

(I) producing a liquid fill material by mixing

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(c) polyethylene glycol; and optionally

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at a temperature of from 50°C to 70°C; and

(II) encapsulating the mixture in a softgel capsules.

POTTER CLARKSON

European Patent Office
Directorate General 2
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27 October 2011

Sent by fax

Dear Sirs

European Patent Application No. 06737018.9-2123
BANNER PHARMACAPS, INC.
Our ref: PABCX/P38814EP

In response to the communication of 18 October 2011 we enclose a copy of the documents filed on 4 October 2011 including the claims of the sixth auxiliary request.

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Yours faithfully

Charlotte Crowhurst PhD
For and on behalf of Potter Clarkson LLP

js

Enc: Documents filed on 4 October 2011

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4 October 2011

URGENT

ORAL PROCEEDINGS SCHEDULED FOR 7 OCTOBER 2011

PLEASE PASS DIRECTLY TO THE EXAMINER MR BUTTNER

Sent by fax

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Our ref: PABCX/P38814EP

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Nobody will attend the oral proceedings on behalf of the applicant. We request a decision on the basis of the current state of the file, taking into account the comments below.

Amended Claims

We enclose a new set of claims to replace the 6th auxiliary request currently on file. We request that the decision of the Examining Division is made on the basis of the main request and auxiliary requests 1 to 5 as filed with our letter of 16 September 2011 and the enclosed 6th auxiliary request.

The enclosed claims are based on the claims of the 6th auxiliary request as filed with our letter of 16 September 2011. The claims of that request have been further amended to limit the claimed pharmaceutical composition and the fill material of the soft gel capsules to liquid compositions and fills. Basis for this amendment can be found at page 3, line 13 of the application as filed.

It is an essential feature of the enclosed claims that the composition/fill contains naproxen sodium. It is clear from the application as filed that that naproxen sodium is the preferred salt of an acid drug. This salt is used in all of the examples in the application as filed.

cont/....

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Novelty

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Inventive Step

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The examiner suggested that the molecular weight of the PEG contained in the compositions of the invention may have an effect on PEG ester formation and that experimental data is needed to show that reduced PEG ester formation is achieved using PEGs of different molecular weights. This is not necessary or appropriate. The claims of the sixth auxiliary request have been limited to specify that the pharmaceutical composition or fill material is liquid. This places a limitation on the nature of the PEG.

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The examiner has not clearly indicated why he thinks that the molecular weight of the PEG will affect the formation of PEG esters. Regardless of molecular weight, all PEGs contain groups that have the potential to react with acid drugs to form PEG esters.

Thus, it is not considered necessary to conduct experiments using PEGs having a range of molecular weights.

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cont/....

is the concentration of the acid used to provide the required amount of H^+ ions. These are, at most, features of the process used to produce the compositions, and not features of the compositions. However, the examiner has in any case not explained why the concentration of the acid that is used to form the composition (as opposed to the molar ratio of the acid in the composition) should matter.

The examiner indicated, that in his opinion, examples in which lactic acid is used as the source of H^+ ions cannot be considered to be representative of compositions comprising other acids. It seems that he thinks that lactic acid may stabilize the composition in some other way (perhaps by means of chelation), in addition to providing a source of H^+ ions. However, the examiner has not provided any scientific evidence that this could indeed be the case. In fact, there is no reason to suppose that chelation of lactic acid could have any effect on PEG ester formation.

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In summary, we do not think that the examiner's request for such a large of amount of experimental data is reasonable. The information provided illustrates the advantages of the invention, and shows that it works. We consider that it is at least plausible that the effect will be achieved over the whole scope of the claim.

Yours faithfully

Charlotte Crowhurst PhD
For and on behalf of Potter Clarkson LLP

js

Enc: New auxiliary request 6

Sixth Auxiliary Request

CLAIMS

1. A liquid pharmaceutical composition comprising
   (a) naproxen sodium;
   (b) a deionizing agent in an amount to cause partial deionization of the naproxen sodium of from about 0.2 to 1.0 mole equivalents per mole of the naproxen sodium;
   (c) polyethylene glycol; and optionally
   (d) water.

2. A softgel capsule comprising a liquid fill material wherein the fill material comprises
   (a) naproxen sodium;
   (b) a deionizing agent in an amount to cause partial deionization of the naproxen sodium of from about 0.2 to 1.0 mole equivalents per mole of the naproxen sodium;
   (c) polyethylene glycol; and optionally
   (d) water.

3. The composition or capsule of claim 1 or 2 wherein the deionizing agent is selected from hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, fumaric acid, maleic acid, tartaric acid, methane-, ethane-, and benzene sulfonates, citric acid, malic acid, acetic acid, proprionic acid, pyruvic acid, butanoic acid, and lactic acid.

4. The composition or capsule of any one of the preceding claims wherein the composition or fill material has a pH of from about 2.5 to about 7.5.

5. The composition or capsule of any one of the preceding claims wherein polyethylene glycol is present in an amount from about 10% to about 80% by weight.

6. The composition or the capsule of any one of the preceding claims wherein water is present in an amount from about 1% to about 18% by weight.

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12. The use of

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(c) polyethylene glycol: and optionally

(d) water

in the manufacture of a liquid medicament for administration of naproxen sodium to a patient in need thereof.

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(a) naproxen sodium;

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(c) polyethylene glycol; and optionally

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at a temperature of from 50°C to 70°C; and

(II) encapsulating the mixture in a softgel capsules.

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Application No.	Ref.	Date
06 737 018.9 - 2123	PABCA/P38814EP	29.11.2011
Applicant: Banner Pharmacaps Inc.		

Provision of a copy of the minutes in accordance with Rule 124(4) EPC

The attached copy of the minutes of the oral proceedings is sent to you in accordance with Rule 124(4) EPC.

Europäisches Patentamt • European Patent Office • Office européen des brevets

Morancho Alcaine, N
For the Examining Division
Tel. No.: +49 89 2399 - 7462

Enclosure(s): Copy of the minutes (Form 2009)

Registered Letter
EPO Form 2042 12.07TRI

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European Patent Office
Office européen des brevets

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Application No.: 06 737 018.9

Decision of the Examining Division

In the oral proceedings held on 07.10.2011, the examining division has decided:

The European patent application is refused on the basis of Article 97(2) EPC. The reasons for the decision are attached (Form(s) 2916).

25.11.11
Date

Borst, Markus
Chairman

Büttner, Ulf
1st examiner

Paul Soto, Raquel
2nd examiner

Enclosure(s): Form 2916

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Substantive Examiner
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Application No.	Ref.	Date
06 737 018.9 - 2123	PABCA/P38814EP	29.11.2011
Applicant: Banner Pharmacaps Inc.		

Decision to refuse a European Patent application

The Examining Division - at the oral proceedings dated 07.10.2011 - has decided:

European Patent application No. 06 737 018.9 is refused.

Applicant/s:
Banner Pharmacaps Inc.
4125 Premier Drive
High Point, NC 27265-8144
US

Title
SOLVENT SYSTEM FOR ENHANCING THE SOLUBILITY OF PHARMACEUTICAL AGENTS

The grounds for the decision are set out on the supplemental sheets annexed hereto.

Means of redress

This decision is open to appeal.
Attention is drawn to the attached text of Articles 106 to 108 EPC and Rules 97 and 98 EPC.

Registered letter with advice of delivery
EPO Form 2007 12.07TRI

Examining Division:

Chairman:	Borst, Markus
2nd Examiner:	Paul Soto, Raquel
1st Examiner:	Büttner, Ulf

Morancho Alcaine, N
Formalities Officer
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Enclosure(s): 15 page/s reasons (Form 2916)
Form 2019

to EPO postal service: 24.11.11

Registered letter with advice of delivery
EPO Form 2007 12.07TRI

I . FACTS AND SUBMISSIONS

The present European patent application (EP06 737 018.9, herein after referred to as "the Application") was filed on 06-03-2006 and claims a priority date of 08-03-2005 (US20050659679). The Application was published as publication number WO2006096580.

The Applicant is Banner Pharmacaps Inc.
4125 Premier Drive
High Point, NC 27265-8144
US.

The title is "SOLVENT SYSTEM FOR ENHANCING THE SOLUBILITY OF PHARMACEUTICAL AGENTS"

1 A written opinion of the ISA was issued on 06.07.2006 in which lack of novelty and inventive step was objected.

2 An request for an international preliminary examination was filed on 08.01.2007 in which arguments with respect to novelty and inventive step were filed.

3 An International Preliminary Report on Patentability was issued 20.07.2007, in which lack of novelty and inventive step were maintained.

4 With entry into the regional phase new claims were submitted.

5 A first communication from the Examining Division was issued on 20.11.2008 where objections were raised in respect of lack of novelty and inventive step

6 The Applicant replied to these objections with the letter of 18.03.2009 and submitted amended pages of description and an amended set of claims.

7 The Examining Division considered, however that the amendments to the claims have had no material effect on the scope thereof and failed to overcome the previously raised objections to lack of novelty and inventive step. A summons to oral proceedings was issued on 18.01.11 scheduled to take place on 07.10.2011.

8 With letter of 04.08.11 the applicant submitted a new main request and seven auxiliary requests.

9 After a telephone conversation the applicant submitted a new main request and six auxiliary request with letter of 16.09.2011. Further, experimental data were submitted.

10 Three telephone conversations followed in which the examining division expressed its opinion that the application did not contain patentable subject matter.

11 With letter of 04.10.2011 the applicant informed the examining division that they will not attend the oral proceedings and submitted a new auxiliary request 6.

12 The following decision is based on the current application documents:

Main Request

Description, Pages

1-15 as published

Claims, Numbers

1-18 filed on 16-09-2011

Auxiliary Request 1

Description, Pages

1-15 as published

Claims, Numbers

1-15 filed on 16-09-2011

Auxiliary Request 2

Description, Pages

1-15 as published

Claims, Numbers

1-16 filed on 16-09-2011

Auxiliary Request 3

Description, Pages

1-15 as published

Claims, Numbers

1-12 filed on 16-09-2011

Auxiliary Request 4

Description, Pages

1-15 as published

Claims, Numbers

1-13 filed on 16-09-2011

Auxiliary Request 5

Description, Pages

1-15	as published	

Claims, Numbers

1-17	filed on	16-09-2011

Auxiliary Request 6

Description, Pages

1-15	as published	

Claims, Numbers

1-15	filed on	04-10-2011

13 Claims

13.1 Claim 1 of the Main request reads as follows:

A pharmaceutical composition comprising

(a) a salt of an acidic pharmaceutically active agent;

(b) a deionizing agent which is a hydrogen ion species in an amount to cause partial deionization of the salt of from about 0.2 to 1.0 mole equivalents per mole of the pharmaceutically active agent;

(c) polyethylene glycol; and optionally

(d) water.

13.2 Claim 1 of the first auxiliary request reads as follows:

A softgel capsule comprising a fill material wherein the fill material comprises

(a) a salt of an acidic pharmaceutically active agent;

(b) a deionizing agent which is a hydrogen ion species in an amount to cause partial deionization of the salt of from about 0.2 to 1.0 mole equivalents per mole of the pharmaceutically active agent;

(c) polyethylene glycol; and optionally

(d) water

13.3 Claim 1 of the second auxiliary request reads as follows:

A pharmaceutical composition obtainable by a method which comprises

(I) mixing

(a) a salt of an acidic pharmaceutically active agent;

(b) a deionizing agent which is a hydrogen ion species in an amount to cause partial deionization of the salt of from about 0.2 to 1.0 mole equivalents per mole of the pharmaceutically active agent;

(c) polyethylene glycol; and optionally

(d) water at a temperature of from 50 °C to 70 °C.

13.4 Claim 1 of the third auxiliary request reads as follows:

A method of making a pharmaceutical composition comprising
(a) mixing a salt of an acidic pharmaceutically active agent, a polyethylene glycol and a deionizing agent which is a hydrogen ion species and optionally water at a temperature of from 50 °C to 70 °C;
wherein the deionizing agent is used in an amount to cause partial ionization of the salt of from about 0.2 to 1.0 mole equivalents per mole of the pharmaceutically active agent.

13.5 Claim 1 of the forth auxiliary request reads as follows:

The use of

(a) a salt of an acidic pharmaceutically active agent;

(b) a deionizing agent which is a hydrogen ion species in an amount to cause partial deionization of the salt of from about 0.2 to 1.0 mole equivalents per mole of the pharmaceutically active agent;

(c) polyethylene glycol; and optionally

(d) water in the manufacture of a medicament for administration of the pharmaceutically active agent to a patient in need thereof.

13.6 Claim 1 of the forth auxiliary request reads as follows:

A pharmaceutical composition comprising

(a) a salt of an acidic pharmaceutically active agent;

(b) a deionizing agent in an amount to cause partial deionization of the salt of from about 0.2 to 1.0 mole equivalents per mole of the pharmaceutically active agent;

(c) polyethylene glycol; and optionally

(d) water;
wherein the deionizing agent is a hydrogen ion species selected from hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, fumaric acid, maleic acid, tartaric acid, methane-, ethane-, and benzene sulfonates, citric acid, malic acid, acetic acid, proprionic acid, pyruvic acid, butanoic acid, and lactic acid.

13.7 Claim 1 of the sixth auxiliary request reads as follows:

A liquid pharmaceutical composition comprising

(a) naproxen sodium;

(b) a deionizing agent in an amount to cause partial deionization of the salt of from about 0.2 to 1.0 mole equivalents per mole of the naproxen sodium;

(c) polyethylene glycol; and optionally

(d) water.

14 Reference is made to the following documents;

D1 US 5 360 615 A (YU ET AL) 1 November 1994 (1994-11-01)

D2 WO 95/31979 A (R.P. SCHERER INTERNATIONAL CORPORATION; SHELLEY, RICKEY, S; WEI, YOUCH) 30 November 1995 (1995-11-30)

D3 US 2001/007668 A1 (SAWYER MARYJEAN ET AL) 12 July 2001 (2001-07-12)

D4 US 5 484 606 A (DHABHAR ET AL) 16 January 1996 (1996-01-16)

D5 US 5 912 011 A (MAKINO ET AL) 15 June 1999 (1999-06-15)

D6 US 2004/157928 A1 (KIM JAE-HWAN ET AL) 12 August 2004 (2004-08-12)

II. REASONS FOR THE DECISION

1 MAIN REQUEST

1.1 The application does not meet the requirements of Article 84 EPC, because claim 1 not clear.

Claim 1 requires that the deionizing agent is a hydrogen ion species which can cause partial deionization. This deionizing agent must be present in a predefined relative amount. However, it is not clear what exactly is meant by the term "deionizing agent". In the specification (p. 6) some deionizing agents are named, such as a number of acids. In a solution, which is the preferred embodiment of the application, the acid will dissociate into an anion and hydrogen ion (H^+). Therefore it cannot be distinguished whether the acid is introduced as acid or salt. Thus, in a solution both the amount of H^+ ions or the amount of anions might be considered.

The amount of hydrogen ions (H^+) is characterized by the pH-value of a solution. The pH-value of a solution however is not only dependent on the molar amount of the deionizing agent acidic compounds but also on their acid strength. Thus, it is not clear whether the defined molar amount should relate to the counter-ion (anion) of the deionizing agent or the final concentration of the hydrogen ions (the pH value).

It might be concluded that the relative amount of claim 1 apparently should relate to the molar amount of the counter ion of the acid introduced into the formulation. However, with the letter of 05.08.2011 (p.5) letter the applicant replied to the novelty objection with respect to D3 that propionate which is introduced in the form of sodium propionate is not a deionizing agent. Further the acid anion is not capable to deionize a salt of an acidic pharmaceutical active agent. Consequently, the hydrogen ion concentration must be decisive for the determination of the scope of claims. This again would be in contrast to claim 4 which defined that the pH may be up 7.5, where concentration of the H^+ ion is not significant (see applicants letter of 05.08.2011 (p. 5)).

Summarizing, claim 1 is not clear because the person skilled in the art does not know what exactly is meant by the term deionizing agent and to what agent the molar equivalents of the deionizing agent should refer to.

For the further examination, it is assumed that the molar equivalence relates to the amount of additional anion present in the solution.

Applicant's arguments:

The applicant argued that the deionizing agent must be present in an amount to cause partial deionization, so that the molar amount relates to the counter ion. Further the optional presence of water makes clear that the deionizing agent is separate to water.

However, the counter ion cannot deionize a salt of an acidic pharmaceutical active agent. Further this is in contrast to applicant's own submission with respect to novelty. The optional presence of water does not exclude the possibility the H^+ ions are considered as deionizing agent. Thus, applicant's arguments are not convincing.

1.2 Novelty

The present application does not meet the requirements of Article 52(1) EPC because the subject-matter of claims 1-8, 11-18 is not new within the meaning of Article 54(1) and (2) EPC.

1.2.1 Reading of claim 1:

Claim 1 relates to a pharmaceutical composition comprising solutions. Solutions are the preferred form of compositions (see e.g. p. 3 l. 10). In a solution it is not possible to distinguish whether the active agent has been added in form of a salt or in form of the acid. The same applies to the addition of the deionizing agent (see clarity).

Thus claim 1 is read as being directed to pharmaceutical composition requiring the presence of the following features:

- an acidic pharmaceutically active agent, which is able to form a salt
- a cation in an at least equimolar amount and an additional anion in an amount of 0.2 to 1.0 mole equivalents per mole of the pharmaceutically active agent.
- polyethylene glycol

1.2.2 Prior art:

- D1 discloses a composition comprising:
  - diclofenac sodium (a salt of weak acid and strong base), wherein the counter ion (Na) is present in an at least equimolar amount
  - Cl^- (hydrochloric acid): a hydrogen ion species (0.2 mole equivalent)
  - polyethyleneglycol 600 : 71 %
  - water: 8 %

- the mixing is carried out at 60 °C (col 10 last paragraph)

Therefore, the subject matter of claims 1, 3-7, 13-18 is not novel.

- D3 (example 17) discloses a composition comprising:
  - Naproxen sodium (a salt of weak acid and strong base)
  - propionate: 0.7 mole equivalent (an anion of the deionizing agent)
  - PEG 300 about 70 %
  - water about 8 %
  - This solution is filled into a gel capsule.

Therefore, the subject matter of claims 1-3, 5-8, 11-13, 15-18 is not novel.

1.2.3 Applicant's arguments:

D1:

The applicant argued that diclofenac is an amphoteric molecule containing both an acidic and basic functional group. Thus, it falls outside the scope of the claims. The examining division cannot accept this argument because the term acidic pharmaceutically agent does not exclude the presence of basic functional groups. The inventors of D1 e.g. considered diclofenac as an acidic pharmaceutical agent (see claim 8). Due to the presence of an acid group diclofenac therefore falls within the scope of the claim acidic pharmaceutically active agent.

The applicant further argued that it was known that acidic agents such as hydrochloric acids catalyse intramolecular cyclisation of diclofenac. This argument only makes sense if the applicant intends to say that all diclofenac has undergone cyclisation and therefore no more diclofenac is present in the composition of D1. However, in this case it is the burden of the applicant to demonstrate that all diclofenac has been converted into the cyclic form.

D3:

The applicant argued that sodium propionate is a basic compound. Under basic conditions such as described in Example 17 the concentration of the H^+ ions will not be significant. Further it was argued that sodium propionate was added to ionize the active agent, which was the opposite aim as in the present application.

As already discussed under 1.1 in a solution it is not possible to distinguish whether the deionizing agent is introduced in the form of a salt or acid. Further, the claim is not limited with respect to the pH value, even alkaline conditions fall within the preferred embodiment of the invention (see e.g. claim 4). Further the presence of pH-adjusting agents is optional. Thus, it is impossible to determine whether sodium propionate has been added in the form of a salt or an acid. The purpose to ionize the active agent cannot be considered as distinguishing feature for assessing novelty.

1.3 Inventive Step

The present application does not meet the requirements of Article 52(1) EPC because the subject-matter of claims 1-18 does not involve an inventive step within the meaning of Article 56 EPC.

1.3.1 closest prior art

The present application relates to the filling of soft gelatin capsules. It appears that the idea behind the application lies in the use of an additional acid that causes partial deionification of the salt of the acidic pharmaceutical agent. This should decrease the formation of PEG esters. As it has been discussed under clarity and novelty this has not been reflected by the claims.

Nevertheless, it will be considered for the assessment of inventive step.

D1 as closest prior art

D1 relates to the filling of soft gel capsules and to the use of an agent that causes partial neutralisation. In practice this means that addition of an alkaline substance causes partial ionisation (neutralisation) of the acidic pharmaceutically active agent. D1 discloses also compositions comprising naproxen (see e.g example X). As a consequence the pharmaceutical active agent may be present both in acidic or in ionized form in one formulation. Such a composition should also be the result when the salt of acidic pharmaceutical agent and an acid in the defined amount are mixed (it is again highlighted that the claims are not limited to such compositions).

Therefore, D1 might represent a valid starting point for the assessment of inventive step.

D3 as closest prior art

On the other hand also D3 might represent a valid starting point for the assessment of inventive step.

Specific documents identified in the application are family members of D3 (US2001007668). D3 relates to the filling of a soft gelating capsule with an analgesic, such as naproxen. D3 describes formulations comprising naproxen sodium and sodium propionate. It is one aspect of D3 that the solvent system enhances the solubility of the medicaments. Further it has been found that the formulations of D3 are stable and robust in a number of tests (paragraph [38]). Thus, D3 addresses the same problem as the present invention and therefore also D3 might represent a valid starting point for the assessment of inventive step.

1.3.1.1 Claims 9, 10

D1 or D3 as closest prior art

The subject matter of claims 9 or 10 differs from D1 or D3 to the extent that one solubilizer must be present. In view of this difference, the underlying problem is seen as to enhance solubility. Although no effect has been shown, it is assumed that a solubilizer also increases the solubility. The person skilled in the art in order to solve the underlying problem of increasing the solubility would search for known methods of increasing solubility.

D1 (col 5, lines 5-10) discloses that enhancement of the solubility of the pharmaceutical agent in polyethylene glycol is accomplished by the addition of 4-12% by weight of glycerin or propylene glycol and/or by the further addition of 1-20% by weight of polyvinylpyrrolidone.

D3 (paragraph [6]) discloses that glycerin or propylene glycol are well known solvents, which however can only be used in small amounts in gel capsules.

Therefore, the addition of the claimed solubilizer in the defined amounts (claim 19) is obvious.

1.3.1.2 General aspects.

The applicant emphasizes that the invention lies in the idea of mixing the salt of the acidic pharmaceutical agent with an deionizing agent to prevent formation of PEG esters. Although so far this idea does not represent a distinguishing feature over the prior art some aspects will discussed.

Problem to be solved

According to applicant's submissions the underlying problem is seen in the provision of a composition with improved stability.

However, the examining division cannot see any indication that this problem has been solved.

The application does not not contain any data relating to the stability.

With letter of 16.09.2011 the applicant provided data which should show the advantageous effect of the claimed compositions. These data relate to a composition comprising naproxen sodium, lactic acid and polyethylene glycol, and no water. No comparative data with a composition of D1 (or D3) or any other composition that does not contain an additional acid is provided. Therefore, the underlying problem simply can be seen in the provision of a further composition.

In order to solve the technical problem of providing an alternative composition the addition of any compound including an acid is obvious.

Applicant's arguments

D2 (p. 4) discusses that formulations of D1 were not stable due to the formation of PEG esters. Since the data provided with letter of 16.09.2011 show that compositions are stable, an unexpected effect was shown.

This, however, cannot be accepted for a number of reasons.

D2 does not disclose the exact composition of the tested formulation, but merely mentions that one formulation of ketoprofen with potassium hydroxide in a molar ration of 04. to 1 was not stable.

The number of difference or possible differences between the composition of D2 and the composition tested by the applicant is so high that it is not possible to deduce any conclusions from the test.

The compositions tested by the applicant differ or might differ by the following features which will influence the stability. Only some of the same are named.

Water content:

No water is added to the tested compositions (16.09.2011), whereas the compositions of D2 must include water due to the presence of NaOH. Water is known to favorise ester-formation.

Different active:

ketoprofen (which even is not mentioned in D1) might react differently than naproxen

Lactic acid

lactic acid (comp of 16.09.2011) is a carbonic acid which might form ester itself thereby displacing the pharmaceutically active acid/or competing with it. Further lactic acid contains an additional hydroxyl group which might have chelating properties or might form esters. Thus, an effect for lactic acid cannot be extrapolated to other acids.

Propylene glycol

Propylene glycol (comp of 16.09.2011) has hydroxyl groups which also might form esters, thus replacing PEG-OH groups. Since only the amount of PEG esters has been analysed, the formation of propylene glycol esters has not been considered.

PEG

For the composition of 16.09.2011 PEG 600 has been used, whereas in D2 PEG 400 has been used. PEG 600 has proportionally less hydroxyl groups that might form estergroups. Further, it is less viscous thus having a lower reaction rate.

pH-value and equimolar amount of acid

It is well known in chemistry that ester-formation is directly proportional to the H^+ ion concentration. Thus, if an effect was shown for one specific pH-value or relative acid amount it is not possible to extrapolate from this example (about 0.5 mole equivalent acid in the tested example) to any other H^+ concentration.

Storage conditions

No information about the storage conditions in D2 is given.

Summarising in view of these parameters (which only present a small list of all possible influences on the stability) it is not possible to conclude from the data provided with letter of 16.09.11 that the addition of an acid has any beneficial activity on the stability of the drug.

The applicant argued that the examining division has not provided scientific evidence that these parameters influence the stability.

First it has to be noted that all comments made above are part of the basic knowledge of a chemist. Second it is the duty of the applicant to make it plausible that the alleged effect is achieved over the whole breadth claimed. In particular, as in the present case, where it is well known that addition of an acid promotes ester-formation. D2 (p. 4), e.g. teaches that PEG-ester formation can be suppressed when the the pharmaceutically active agents is present as a salt. Consequently, if the applicant claims an effect, which goes

against the teaching of the prior art and against the general knowledge, the burden lies on him that this prejudice has been overcome over the whole breadth of the claims.

Provision of further data

On the telephone there was a discussion whether additional evidence could be provided and how they must look like. Although finally no such data were announced, some short remarks will be added.

The examining division is still of the opinion that all above mentioned parameters have to be taken into account when drafting comparative examples. All parameters will have have mutual influences on the stability.

Further, in view of the teaching of D2 (p.4) to which the applicant referred to with the submissions of 05.08.2011, it was not plausible that a formulation where the acid was only partially ionized had an improved stability. Therefore, the alleged improved stability is based on pure speculation. Such a lack of plausibility normally cannot be remedied by later evidence. Therefore, the examining division does not see how stability tests may look like in order to cover the breadth of the claims.

2 Auxiliary request 1

Claim 1 corresponds to claim 2 of the main request. This claim is not novel over D1. Further all clarity and inventive step objections equally apply to this request. Therefore, the first auxiliary request does not meet the requirements of the EPC.

3 Auxiliary request 2

Claim 1 relates to a product by process which gives the same product as defined in claim 1 of the main request. Therefore, all objections (clarity, novelty and inventive step) of the main request equally apply to this request.

4 Auxiliary request 3

Claims 1 of the third auxiliary request corresponds to claim 14 of the main request. Therefore, the same clarity and inventive step objections apply.

5 Auxiliary request 4

Claim 1 corresponds to claim 15 of the main request.

The composition is the same composition as in claim 1 of the main request. The use of these compositions in medicine is also disclosed in D1 or D3. Therefore claim 1 is not novel over D1 or D3. Further all clarity and inventive step objections equally apply to this request.

6 Auxiliary request 5

Claim 1 corresponds to claim 12 of the main request.

The composition is the same composition as in claim 12 of the main request. The composition in D1 comprises hydrochloric acid and the composition in D3 comprises propionate. Therefore claim 1 is not novel over D1 or D3. Further all clarity and inventive step objections equally apply to this request.

7 Auxiliary request 6

The subject matter of claim 1 differs from claim 1 of the main request in that the formulation is limited to Naproxen sodium and that the formulation must be liquid.

7.1 This amendment introduces subject-matter which extends beyond the content of the application as filed, contrary to Article 123(2) EPC. The amendment concerned is the following:

The invention relates to liquid and semi-solid formulations (see p. 3, l13). Naproxen sodium is only mentioned in the examples. The examples however relate to semi-solid and liquid formulations. As a consequence no disclosure can be found that naproxen sodium is to be used in liquid form.

7.2 Further claim 1 is not novel.

The composition in D3 is liquid and comprises naproxen sodium. Therefore claim 1 is not novel over D3. Further all clarity and inventive step objections equally apply to this request.

III DECISION

None of the requests meets the requirements of the EPC. Therefore, the application is refused pursuant to Article 97(2) EPC.

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European Patent Office
Office européen des brevets

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Application No. : 06 737 018.9

Minutes of the oral proceedings before the EXAMINING DIVISION

The proceedings were not public.

Proceedings opened on 07.10.2011 at 09:00 hours

Examining Division:

Chairman:	Borst, Markus
1st member:	Büttner, Ulf
2nd member:	Paul Soto, Raquel
Minute writer:	Paul Soto, Raquel

Present as/for the applicant/s:

Nobody had appeared for the applicant/s. The chairman confirmed that the applicant/s had been duly summoned.

Essentials of the oral proceedings and the relevant statements of the applicant/s:

After deliberation of the examining division, the chairman announced the following **decision**:

"The European patent application is refused."

The chairman **closed the proceedings** on 07.10.2011 at 09:25 hours.

signed:

Borst, Markus
. . . . . .
Chairman

signed:

Paul Soto, Raquel
. . . . . .
Minute Writer

Enclosure(s):

After deliberation of the examining division, the chairman announced the following ***decision****:*

"The European patent application is refused."

The chairman **closed the proceedings** on 07.10.2011 at 09:25 hours.

Borst, Markus
Chairman

Paul Soto, Raquel
Minute Writer

Annex(es):

It was noted that the applicant had informed the EPO that he would not be attending the oral proceedings.

As announced in the summons the requirements of Art. 84, 54 and 56 EPC were discussed. The examining division concluded that the main request lacked clarity, novelty and inventive step.

For the same reasons auxiliary requests 1-2 and 4-6 were found to lack clarity, novelty and inventive step. Auxiliary request 3 was found to lack clarity and inventive step. Auxiliary request 6 additionally lacked basis in the application as filed (Art. 123 (2) EPC).

Consequently, it was decided to refuse the application according to Article 97(2) EPC.

Article 106
Decisions subject to appeal

(1) An appeal shall lie from decisions of the Receiving Section, Examining Divisions, Opposition Divisions and the Legal Division. It shall have suspensive effect.

(2) A decision which does not terminate proceedings as regards one of the parties can only be appealed together with the final decision, unless the decision allows a separate appeal.

(3) The right to file an appeal against decisions relating to the apportionment or fixing of costs in opposition proceedings may be restricted in the Implementing Regulations.

Rule 97
Appeal against apportionment and fixing of costs

(1) The apportionment of costs of opposition proceedings cannot be the sole subject of an appeal.

(2) A decision fixing the amount of costs of opposition proceedings cannot be appealed unless the amount exceeds that of the fee for appeal.

Rule 98
Surrender or lapse of the patent

The decision of an Opposition Division may be appealed even if the European patent has been surrendered in all the designated Contracting States or has lapsed in all those States.

Article 107
Persons entitled to appeal and to be parties to appeal proceedings

Any party to proceedings adversely affected by a decision may appeal. Any other parties to the proceedings shall be parties to the appeal proceedings as of right.

Article 108
Time limit and form

Notice of appeal shall be filed in accordance with the Implementation Regulations, at the European Patent Office within **two months** of notification of the decision. Notice of appeal shall not be deemed to have been filed until the fee for appeal has been paid. Within **four months** of notification of the decision, a statement setting out the grounds of appeal shall be filed in accordance with the Implementing Regulations.

Further information concerning the filing of an appeal

(a) The appeal is to be filed with the European Patent Office either at its seat in Munich, at its branch at The Hague or at its Berlin sub-office. The postal addresses are as follows:

(i) European Patent Office 80298 MUNICH GERMANY	(ii) European Patent Office Postbus 5818 2280 HV Rijswijk NETHERLANDS	(iii) European Patent Office 10958 BERLIN GERMANY
Fax: +49 89 2399-4465	Fax: +31 70 340-3016	Fax: +49 30 259 01-840

(b) The notice of appeal must contain the name and address of the appellant in accordance with the provisions of Rule 41(2)(c) EPC, an indication of the decision impugned, and a request defining the subject of the appeal. In the statement of grounds of appeal the appellant shall indicate the reasons for setting aside the decision impugned, or the extent to which it is to be amended, and the facts and evidence on which the appeal is based (R. 99(1) and (2) EPC). The notice of appeal and any subsequent submissions stating the grounds for appeal must be signed (R. 50(3) EPC).

(c) Notice of appeal can be filed in accordance with Rule 1 and Rule 2(1) EPC, by delivery by hand, by post, or by technical means of communication. The filling has to comply with the details and conditions and, where appropriate, any special formal or technical requirements laid down by the President of the European Patent Office (R. 99(3) EPC).

(d) The fee for appeal is laid down in the Rules relating to Fees. The schedule of fees and expenses of the EPO or a reference to the current version is regularly published in the Official Journal of the European Patent Office under the heading "Guidance for the payment of fees, expenses and prices". It is also published on the EPO Internet page under http://www.epo.org/Patents/Grant-procedure/Filing-an-application/costs-and-fees.html.

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Date: 29-11-2011

Reference	Application No./Patent No.
PABCA/P38814EP	06737018.9 - 2123 / 1863458

Applicant/Proprietor: Banner Pharmacaps Inc.

EPA/EPO/OEB Formblatt/Form/Formulaire : 2007

Empfangsbescheinigung über den Zugang des vorstehend bezeichneten Schriftstücks
Acknowledgement of receipt of the document specified above
Récépissé du document spécifié ci-dessus

Unter Bezugnahme auf die Mitteilung im ABl EPA 7/2010, 377 wird gebeten, die Empfangsbescheinigung mit Empfangsdatum und Unterschrift zu versehen und **umgehend** an das EPA zurückzusenden:

With reference to the Notice in OJ EPO 7/2010, 377, you are requested to date and sign the acknowledgement of receipt and return it to the EPO **immediately**:

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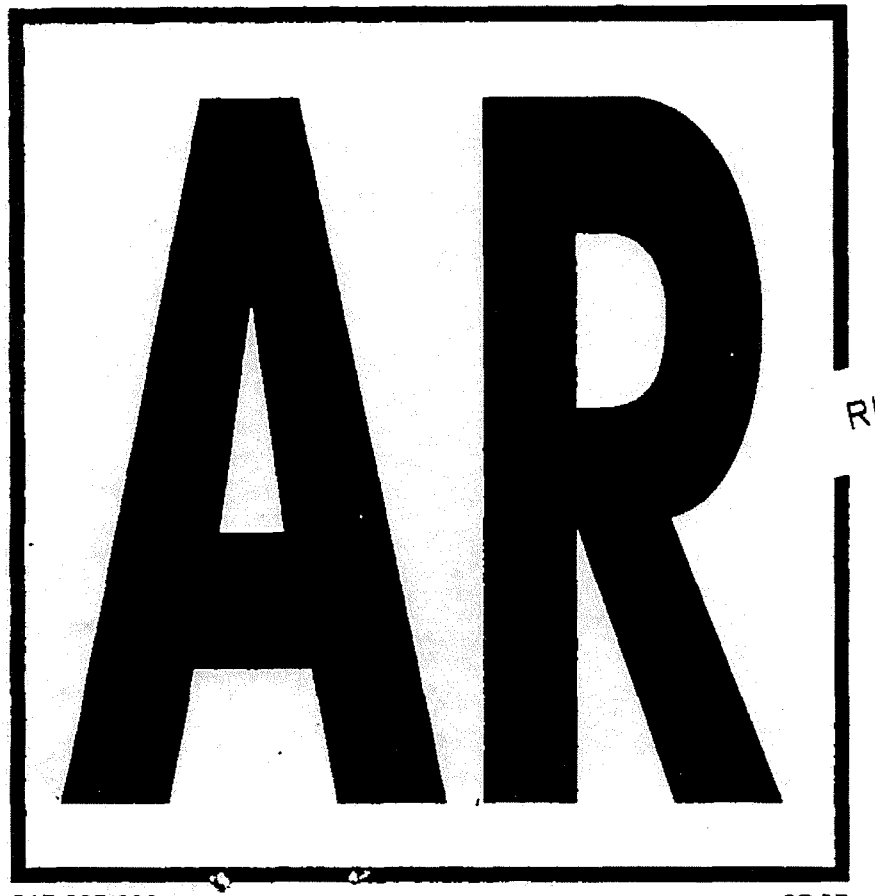

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Date: 29-11-2011

Reference	Application No./Patent No.
PABCA/P38814EP	06737018.9 - 2123 / 1863458
Applicant/Proprietor: Banner Pharmacaps Inc.	

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POTTER CLARKSON

To:	**European Patent Office**
Your Fax No:	00 49 89 2399 4465
From:	Charlotte Crowhurst PhD
Date:	27 January 2012
Our Ref:	PABCX/P38814EP
Your Ref:	European Patent Application No. 06737018.9-2123

Sheet 1 of 2 **Original by Post:** ✓

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European Patent Office
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27 January 20121

NOTICE OF APPEAL
(ARTICLE 106 EPC)
Sent by fax

Dear Sirs

European Patent Application No	:	06737018.9-2123
Appellant and Applicant	:	Banner Pharmacaps, Inc.
Address	:	4125 Premier Drive High Point, NC 27265-8144 USA

Our ref: PABCX/P38814EP

In a decision dated 7 October 2011 (with written notification dated 29 November 2011), the Examining Division refused the application. This is an appeal from that decision.

It is requested that:-

i) the decision is cancelled in its entirety to the extent that the appellant was adversely affected by it,

ii) the application is maintained in an unamended form, and

iii) oral proceedings under Article 116 EPC are held in the event that the Board of Appeal intends not to allow the appeal.

The fee for the appeal should be charged to the deposit account of Potter Clarkson LLP. This will be confirmed to your Accounts Department.

Yours faithfully

Charlotte Crowhurst PhD
For and on behalf of Potter Clarkson LLP

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27 January 2012

NOTICE OF APPEAL
(ARTICLE 106 EPC)
Sent by fax

Dear Sirs

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Yours faithfully

Charlotte Crowhurst PhD
For and on behalf of Potter Clarkson LLP

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URGENT

To:	**European Patent Office**
Your Fax No:	00 49 89 2399 4465
From:	Charlotte Crowhurst PhD
Date:	26 March 2012
Our Ref:	PABCX/P38814EP
Your Ref:	European Patent Application No. 06737018.9-2123

Sheet 1 of 56 **Original by Post:** ✓

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European Patent Office
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GERMANY

26 March 2012

URGENT

Sent by fax

Dear Sirs

European Patent Application No. 06737018.9-2123
BANNER PHARMACAPS, INC.
Our ref: PAECX/P38814EP

Further to our letter dated 27 January 2012, we hereby enclose a statement of the Grounds of Appeal, an Annex, a Main Request and Thirteen Auxiliary Requests.

Yours faithfully

Rob Pugh (ROBERT I PUGH)

Charlotte Crowhurst PhD
For and on behalf of Potter Clarkson LLP

js

Enc: Grounds of Appeal
Main Request
Thirteen Auxiliary Requests
Annex

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European Patent Application No. 06737018.9
(Publication No. 1863458)

Applicant and Appellant: Banner Pharmacaps, Inc.

GROUNDS OF APPEAL

26 MARCH 2012

26 March 2012

Potter Clarkson LLP
for Banner Pharmacaps, Inc.

CONTENTS

26 March 2012

Potter Clarkson LLP
for Banner Pharmacaps, Inc.

1. DECISION ON WHICH AN APPEAL HAS BEEN FILED

The applicant, Banner Pharmacaps, Inc., filed a Notice of Appeal on 27 January 2012 against the decision of the Examining Division (the written confirmation of which was dated 29 November 2011) rejecting European patent application no. 06737018.9.

2. REQUEST

It is requested that:

i) The decision is cancelled in its entirety to the extent that the Appellant was adversely affected by it.

ii) The application is maintained on the basis of the enclosed Main Request.

iii) If it is considered not possible to maintain the application on the basis of the Main Request it is maintained on the basis of one of the enclosed Auxiliary Requests.

iv) Oral proceedings under Article 16 EPC are held in the event that the Board of Appeal intends not to allow the appeal.

3. THE BASIS ON WHICH THE APPEAL IS FILED

The decision of the Examining Division is wrong in law and in fact.

As will be explained in more detail below, the Examining Division's understanding of the claims was incorrect. This led to an incorrect finding on the facts of the case.

4. CLAIM REQUESTS

We enclose a Main Request and 13 Auxiliary Claim Requests.

As will be explained below, the claims of the Main Request satisfy the requirements of the EPC. However, in case the Board of Appeal is not prepared to allow the application on the basis of the Main Request, we enclose 13 Auxiliary Claim Requests to be considered in the order presented. Each of these claim requests satisfies the requirements of the EPC.

5. THE MAIN REQUEST

The Main Request is based on Auxiliary Request 3 considered in the decision of the Examining Division (ED). However, the wording of the claims has been amended to address comments made by the ED.

Date 26 March 2012

Potter Clarkson LLP
for Banner Pharmacaps, Inc.

5.1 BASIS FOR THE CLAIMS

Claim 1 of the main request is directed to a method of making a softgel capsule and is based on original claims 14 and 15, which was directed to a method of making a mixture and encapsulating the mixture in a softgel capsule.

The pharmaceutically active agent has been limited to naproxen sodium. There is basis for this at page 5, line 1 and in the Examples.

The term "deionising agent" used in the original claims has been replaced by the acids disclosed at page 6, lines 17 to 21 as examples of deionising agents.

There is basis for the range for the amount of deionising agent at page 6, lines 14 to 16 and in original claim 3.

The other claims are based on the disclosure in the application as filed as follows:

Claim	Basis in application as originally filed
2	Claim 17
3	Page 6, lines 17 to 21 and the Examples
4	Page 6, lines 17 to 21 and the Examples
5 and 6	Claims 6 and 7
7	Claim 9
8 to 10	Claims 11 to 13

5.2. THE MAIN REQUEST SATISFIES THE REQUIREMENTS OF THE EPC

The rejections raised in the Examining Division's Decision dated 29 November 2011 are addressed below in the order presented in the decision.

5.2.1 Article 84 EPC – The Claims Clearly Defined The Invention

The Examining Division (ED) alleged that the wording of claim 1 of the Main Request (and the Auxiliary Requests) was indefinite. Specifically, the ED alleged that it is not clear what is meant by the term "deionizing agent". This objection does not apply to the claims of the main request because the term "deionizing agent" is not used in the claims of this request.

Claim 1 of the main request includes a list of acids, which has a very clear meaning. Claim 1 also clearly states that the acid is used in an amount of 0.2 to 1.0 mole equivalents per mole of naproxen sodium.

In summary, claim 1 of the main request is clear and the skilled person would know exactly what ingredients to use in order to carry out the claimed method and how to carry out that method.

Date 26 March 2012

Potter Clarkson LLP
for Banner Pharmacaps, Inc.

5.2.2 Novelty – The Claims Define Novel Subject Matter

The invention is novel.

As noted above, the main request is based on the third auxiliary request previously on file. We note that the ED did not raise an objection of lack of novelty against the subject matter of the third auxiliary request in its decision.

More particularly, none of the cited documents disclose a method of making a softgel capsule that comprises mixing naproxen sodium with polyethylene glycol and an acid as listed in claim 1 and then encapsulating the mixture.

It is an essential feature of the main request that the drug is naproxen sodium. The claimed method is therefore novel over the disclosure of US 5360015 (D1) relating to diclofenac containing compositions to which the examiner has referred.

In D1, the active agent is in the form of the free acid or base and an ionizing agent is added to the composition containing the active agent. In the case of Example IV, which uses naproxen this means that naproxen is mixed with potassium hydroxide and polyethylene glycol. These starting materials are clearly different to those used in the claimed method.

The claimed method is therefore novel over D1.

The claimed method is also novel in view of the disclosure of US2001/0007668 (D3). In particular, Example 17 of D3 does not disclose the method as claimed.

Example 17 in D3 discloses a solution of naproxen sodium, polyethylene glycol 300, sodium hydroxide, and sodium propionate. D3 uses this strongly basic environment to maintain ionization. An acid as listed in claim 1 of the main request is not used in the method described in Example 17. Also, the solution in Example 17 of D3 is not encapsulated and could not be readily encapsulated. High pH, as used in Example 17, can destabilize the capsule shell, as described in D2 and is discussed in more detail below.

Accordingly, the subject matter of the main request is novel over D3.

5.2.3 Inventive Step – The Invention Is Inventive Over The Cited Prior Art

The ED has indicated that either D1 or D3 could be considered as the closest prior art. In view of these documents, as the ED has correctly identified, the problem to be solved can be considered to be the reduction of the formation of PEG-esters of the active agent. This reduction in the formation of PEG-esters is relative to the amount that would be formed by following the teaching of D1 or D3. As will be discussed below, the method of the main request solves this problem.

The method of the main request is also prima facie not obvious in view of the teaching of D1 and D3. As discussed above, neither D1 nor D3 teaches or suggests the use of an acid in combination with the salt of an acid drug such as naproxen sodium and polyethylene glycol. In D1 and D3, when naproxen is used, whether in the form of the

free drug or in the form of a salt it is used in combination with a base. There is nothing in D1 or D3 that would have motivated the skilled person to go against the teaching of these documents and use naproxen sodium in combination with an acid as listed in claim 1. For this reason at least the claimed method is novel in view of the disclosure of D1 and D3.

In naproxen containing compositions, PEG-esters are formed as a result of an interaction between free naproxen and PEG. The compositions of D1 comprise a higher concentration of free naproxen than is present in the compositions of the present invention.

Enclosed with these Grounds of Appeal is additional data showing a direct comparison of formulations produced by the claimed method to formulations prepared in accordance with the teaching of D1.

The formulations were tested using two different amounts of naproxen sodium, 285 mg and 220 mg, and three different acid deionizing agents, HCl, citric acid, and lactic acid. These acids are representative of the different acids listed in claim 1. Formulations of the type described in D1 containing 200 or 260 mg of naproxen free acid and sodium hydroxide (in place of the potassium hydroxide used in D1) were also tested. All formulations contained PEG 600 and water. The acid or base was tested at three different concentrations: 0.2, 0.6, and 1.0 mole equivalents compared to the active agent. The samples were subjected to accelerated stability studies (60°C for 1 week). The compositions of the invention showed very low initial levels of PEG ester formation and also very low levels, if any, of PEG ester formation at the end of the stability study. In contrast, in the D1 formulations, the amount of PEG ester varied from 0.0093 to 0.014.

This study provides a direct comparison of the present invention and D1 and clearly shows that the method of the present invention provides unexpected results in that compositions obtained by this method contained lower amounts of PEG esters both initially and after the stability studies. This could not have been predicted from the prior art.

The subject matter claimed is inventive over D1 and D3.

In the decision, the ED identified variables they believed could affect the stability of the formulations. We note that the ED provided no evidence to support their conclusions. Although all of the ED's comments are not directly relevant to the method claims of the main request, for completeness we will comment on them below.

The ED alleged that the absence or presence of water could have an effect on PEG-ester formation. The formulations used for the comparative testing contained water and reduction in the formation of PEG-esters for the claimed formulations was observed compared to the D1 formulations.

The ED cited the differences in the active agent (ketoprofen in D2) and naproxen in D1 as having a possible affect on PEG-ester formation. Both actives contain a carboxylic acid group, which is the reactive functional group that participates in the reaction to form PEG-esters. One of ordinary skill in the art would expect these agents to react in a similar manner. In fact, the ED relied on this reasoning in attempting to extrapolate the

behavior of ketoprofen as described in D2 to naproxen in order to reject Applicant's claims. In any event, the data now provided show that the compositions of the invention provide reduced PEG-ester formation compared with the compositions of D1 even when the active agent is the same.

The ED also alleged that lactic acid might be unique in its ability to reduce the formation of PEG-esters by a mechanism different than that for other acids and therefore its behavior cannot be extrapolated to other acids. The ED provided no scientific data to support this conclusion. The enclosed data show a reduction in PEG-ester formation for lactic acid (organic acid having as single carboxylic acid group), citric acid (organic acid having multiple carboxylic acid groups), and hydrochloric acid (an inorganic acid). This data shows that the problem addressed by the invention is solved across the full breadth of the claims.

The ED also alleged that Applicant did not account for the formation of propylene glycol (PG) esters. However, it is not clear how this relates to the problem to be solved. As noted by the ED, PG also contains hydroxyl groups which can react with the free acid to form esters. Regardless of the type of ester formation, esterification of the active agent reduces the efficacy of the formulation. Therefore, reducing the reactivity of the active agent should reduce formation of all types of esters. The data enclosed herein shows that the claimed formulations exhibit much lower concentrations of PEG-ester formation compared to the compositions of D1. Such behaviour would also be observed with respect to PEG-ester formation.

The ED also suggested that differences in the molecular weight of the PEG used in D2 (PEG 400), which described the formation of PEG esters, and the PEG used in D1, which is PEG 600 may account for differences in PEG ester formation. In order to do a direct comparison, comparative studies of the claimed formulations and the D1 formulations were done using PEG 600. The data is enclosed. As discussed above, for formulations produced using the method of the present invention, the amount of PEG-esters was very low. In contrast, the amount of PEG-esters formed in the D1 formulations was substantially higher.

The ED also alleged that one could not extrapolate from a single relative acid concentration or pH value to other acid concentrations. We respectfully disagree. However, in order to facilitate allowance, the comparative studies submitted herein were conducted at three different acid/base concentrations, 0.2, 0.6, and 1.0 mole equivalent of acid/base to moles of active agent. The data show that at all concentrations the formulations produced using the claimed method exhibited significantly less PEG-ester formation than the D1 formulations.

The data described herein clearly show a significant reduction in PEG-ester formation when formulations are made using the claimed method compared to formulations made in accordance with the teaching of D1. Moreover, the results presented in the enclosed Annex show that such unexpected results are achieved over the full breadth of the claims.

The ED cited D2 for the notion that PEG-ester formation can be suppressed when the agent is present as a salt. The ED failed to consider the cited passage on page 4 in its entirety. D2 discloses that fill materials containing PEG 400 and potassium hydroxide at

Date 26 March 2012

Potter Clarkson LLP
for Banner Pharmacaps, Inc.

a mole ratio of 0.4 to 1 were unstable due to the formation of ketoprofen esters (page 4, lines 1-6). D2 discloses that in an attempt to completely ionize ketoprofen to prevent formation of undesirable esters, the potassium hydroxide to ketoprofen ratio was adjusted to 1.1 to 1 (page 4, lines 7-9). D2 goes on to state "With this second formulation, concerns arose that the ketoprofen salt thus formed and/or high pH caused by the excess potassium hydroxide used could effect the physical stability of the softgel capsule when the formulation was encapsulated. Additionally, if an equilibrium amount of the ketoprofen free acid remained in solution, it could form ketoprofen esters that could drive the reaction to form more ketoprofen free acid species which could eventually result in a chemically unstable formulation." D2 does not disclose or suggest forming more of the salt to minimize PEG-ester formation since doing so could (1) can destabilize the softgel capsule shell due to formation of large amounts of the salt and/or high pH; and (2) result in increased formation of PEG esters.

In the method now claimed, the active agent is naproxen sodium and it is used in combination with an acid. This method avoids the limitations discussed in D2.

None of the prior art discloses or suggest the method claimed in the main request or that such a method would solve the problem addressed by the present invention. Accordingly, the claims of the main request are inventive.

6. THE 1ST AUXILIARY REQUEST

The 1st auxiliary request is based on claim 2 of the main request considered by the ED and its dependent claims.

6.1 THE 1ST AUXILIARY REQUEST SATISFIES THE REQUIREMENTS OF THE EPC

6.1.1 Article 84 EPC – The Claims Clearly Defined The Invention

The Examining Division (ED) alleged that claim 1 of the Main Request (and the Auxiliary Requests) that they considered was indefinite. Specifically, the ED alleged that it is not clear what is meant by the term "deionizing agent". The ED alleged that it is not clear if the amount of deionizing agent should relate to the counter-ion or the final concentration of hydrogen ions. The ED has misunderstood the definition of the term "deionizing agent" and the amount of deionizing agent required according to the claims.

The application, as filed, states that "the deionizing agent functions by causing partial deionization (neutralization) of the salt of one or more pharmaceutically active agents" (page 6, lines 9 and 10). The claims specify that the active agent is a salt of an acidic pharmaceutically active agent, such as naproxen sodium. The deionizing agent is therefore a hydrogen-ion generating species (page 6, lines 11 and 12). Exemplary hydrogen-ion generating species are provided at page 6, lines 17-21.

The application as originally filed states "the deionizing agent is preferably present in an amount between 0.2 and 1.0 mole equivalents per mole of active agent" (page 6, lines 15-16). This range is an essential feature of the claims. The range clearly defines the amount of deionizing agent, not the amount of hydrogen ions or hydroxide ions produced in solution. It is also clear that the range for the amount of deionizing agent is relative to

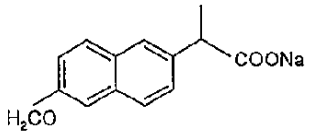
the amount of the salt of the acidic pharmaceutically active agent, such as naproxen sodium.

The dependent claim specifying the pH of the fill material has been deleted. Thus, any lack of clarity that the ED perceived resulted from the inclusion of claims specifying pH ranges has been removed.

The ED suggested that the molar range specified for the deionizing agent could relate to the amount of the anion.

However, this is not consistent with the information provided in the application and the applicant has not made any statement to suggest that this may be the case. From a knowledge of the basic chemistry of the interaction of a salt of an acidic pharmaceutically active agent such as naproxen sodium with a deionizing agent it would be abundantly clear to the skilled person that it is the amount of H^+ ions rather than the amount of the counter ion that is relevant to this invention.

Naproxen sodium has the structure



When naproxen sodium interacts with a deionizing agent the Na^+ is replaced by H^+ of the deionizing agent.

This basis chemistry would be self evident to the skilled reader, who would therefore appreciate what was meant by the quoted range for the amount of the deionizing agent.

The ED's statement that "The optional presence of water does not exclude the possibility that the H^+ ions are considered as deionizing agent" unnecessarily confuses and mistakenly complicates the situation. The wording of the claims makes it clear that the term "deionizing agent" does not encompass water.

In summary, claim 1 is clear and the skilled person would know exactly what is meant by the term deionizing agent and what the range for the amount of deionizing agent means.

6.1.2 Novelty – The Claims Define Novel Subject Matter

The invention is novel over the disclosure of US 5360015 (D1).

The claimed compositions are therefore novel over the disclosure of D1 relating to diclofenac containing compositions to which the examiner has referred. Diclofenac is not an acidic pharmaceutically active agent. It comprises both acidic and basic groups and it is therefore amphoteric. It is clear from the way in which acidic, basic and amphoteric active agents are discussed in the present application that the definition "acidic" does not encompass amphoteric molecules.

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Additionally, it is known in the art that acids such as hydrochloric acid catalyse the intramolecular cyclisation of diclofenac to form an indoline derivative. A copy of a paper that describes the intramolecular cyclisation of diclofenac, Palomo *et al*, "Analysis of diclofenac sodium and derivatives", Journal of Pharmaceutical and Biomedical Analysis, 21 (1999), 83-94, is already on file. As stated in the abstract of Palomo, the intramolecular cyclisation of diclofenac sodium causes the salt to become inactivated.

Thus, Example VII of D1 does not describe a pharmaceutical composition having the essential features of the compositions of the present invention. In particular, the composition of Example VII of D1 is not a composition comprising a salt of an acid or basic active agent and a deionizing agent that causes partial neutralization of the salt of the active agent resulting in enhanced bioavailability of the active agent. In fact, cyclization of the drug will have the opposite effect.

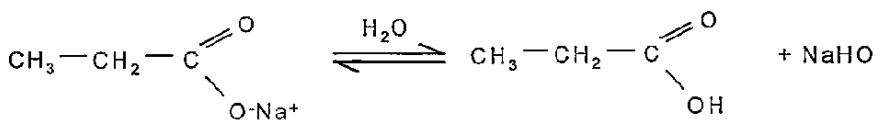
In assessing novelty, the ED alleged that because the compositions of the invention are typically in the form of a solution, it is not possible to distinguish whether the active agent and/or deionizing agent has been added in the form of a salt or a free acid. We respectfully disagree.

In D1, the active agent is in the form of the free acid or base and an ionizing agent is added to the composition containing the active agent. This means that in the case of an acidic drug the composition comprises the acidic drug and a base. The reaction of the active agent and ionizing agent is less than quantitative, so the composition will always comprise some of the acidic drug and some unreacted base. In contrast, in the pending claims, the active agent is in the form of a salt. The deionizing agent is added to a composition containing the salt of the active agent. Because reaction of the salt of the active agent and the deionizing agent is less the quantitative, the solution will always contain some of the salt and some unreacted deionizing agent but it will not contain a base as is present in the compositions of D1.

The ED raised an objection of lack of novelty on the basis of the disclosure of D3, particularly Example 17. The subject matter claimed is novel in view of the disclosure of D3.

Example 17 in D3 discloses a solution of naproxen sodium, polyethylene glycol 300, sodium hydroxide, and sodium propionate. Sodium propionate cannot deionize naproxen sodium since sodium propionate is not a hydrogen ion generating species. Therefore, regardless of whether the amount of sodium propionate in Example 1 is within the range of molar amounts specified in the claims, the formulation in Example 17 is not within the scope of the claims. Moreover, the solution is Example 17 in D3 is not encapsulated and could not be readily encapsulated. High pH, as used in Example 17, can destabilize the capsule shell as discussed in D2.

When sodium propionate is added to water, an equilibrium is established between propionate and propionic acid, as shown below:



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However, the amount of propionic acid present at equilibrium in the formulation of Example 17 of D3 is far below the 0.2 equivalents required by the claims. The formulation described in Example 17 of D3 contains 0.8153 g sodium propionate (K_b = 7.46 x 10^{-10}) dissolved in 800 mL of water (*i.e.*, an aqueous solution of approximately 0.0106 M sodium propionate). If we ignore the impact of the other species present in solution (including the naproxen sodium, PEG 300, and potassium hydroxide) on the equilibrium between propionate and propionic acid, the concentration of propionic acid at equilibrium can be calculated to be approximately 2.7 x 10^{-5} M (corresponding to roughly 2.2 x 10^{-5} moles propionic acid at equilibrium). The formulation in Example 17 of D3 contains 3.0033 g (0.0119 moles) of naproxen sodium. Therefore, if we ignore the impact of the other species present in solution, Example 17 describes a formulation containing roughly ***0.0018 mole equivalents*** of propionic acid per mole of naproxen sodium. In contrast, it is an essential feature of the present invention that the deionizing agent is present in an amount of from about 0.2 to 1.0 mole equivalents per mole of naproxen sodium.

Furthermore, the solution in Example 17 also contains 6.66 mg of potassium hydroxide. The pH of the sodium propionate solution is approximately 9.6. The addition of potassium hydroxide will make the solution more basic driving the equilibrium between proprionate and proprionic acid in the direction of proprionate. As a result, the actual amount of propionate present in the formulation described in Example 17 will be even less than 0.0018 mole equivalents per mole of naproxen sodium. Therefore, what small amounts of propionic acid may be present in Example 17 of D3 are not within the range for the amount of deionizing agent specified in the claims and thus are not effective to partially deionize naproxen sodium. Moreover, the solution in Example 17 of D3 is not encapsulated and could not be readily encapsulated. High pH, as used in Example 17, can destabilize the capsule shell, as discussed in D2. Accordingly, the subject matter claimed is novel over D3.

6.1.3 Inventive Step – The Invention Is Inventive Over The Cited Prior Art

The ED has indicated that either D1 or D3 could be considered as the closest prior art. In view of these documents, as the ED has correctly identified, the problem to be solved can be considered to be the reduction of the formation of PEG-esters of the active agent. This reduction in the formation of PEG-esters is relative to the amount that would be formed by following the teaching of D1 or D3.

In compositions containing an acidic pharmaceutically active agent, such as naproxen containing compositions, PEG-esters are formed as a result of an interaction between free acidic drug (e.g. naproxen) and PEG. The compositions of both D1 and D3 comprise a higher concentration of free naproxen than is present in the compositions of the present invention.

D1 is concerned with ionizing the free acid or free base, not deionizing the salt of the free acid or base. D1 describes ionizing naproxen not deionizing naproxen sodium. The ED has failed to show why one of ordinary skill in the art would have been motivated by the teaching of D1 to modify its teaching so as to deionize the drug rather than ionize it and thus arrive at the claimed compositions. D1 teaches the exact opposite of what is done

in the present invention and it cannot be considered to be obvious to go completely against the teaching of the prior art in this way.

Regarding D3, the ED alleges that D3 discloses that the formulations described therein are stable and robust. However, it is not clear in what context these solutions are described as stable. D3 discloses that no precipitate was observed but there is no disclosure related to PEG-ester formation. Such esters are likely to be soluble in PEG and therefore may not be observed visually, yet their formation affects the efficacy of the formulation.

The ED acknowledged the data submitted on 15 September 2011 but alleged that the date was not sufficient to directly compare the claimed compositions and the compositions of D1 (or D3).

Enclosed with these Grounds of Appeal is additional data showing a direct comparison of the claimed compositions to the compositions in D1.

The claimed formulations were tested using two different amounts of naproxen sodium, 285 mg and 220 mg, and three different acid deionizing agents, HCl, citric acid, and lactic acid. Formulations of the type described in D1 containing 200 or 260 mg of naproxen free acid and sodium hydroxide (in place of the potassium hydroxide used in D1) were also tested. All formulations contained PEG 600 and water. The acid or base was tested at three different concentrations: 0.2, 0.6, and 1.0 mole equivalents compared to the active agent. The samples were subjected to accelerated stability studies (60°C for 1 week). The compositions of the invention showed very low initial levels of PEG ester formation and also very low levels of PEG ester formation, if any, at the end of the stability study. In contrast, in the D1 formulations, the amount of PEG ester varied from 0.0093 to 0.014.

This study provides a direct comparison of the present invention and D1 and clearly shows that the method of the present invention provides unexpected results in that compositions obtained by this method contained lower amounts of PEG esters both initially and after the stability studies. This could not have been predicted from the prior art.

The subject matter claimed is therefore inventive.

In the decision, the ED identified variables they believed could affect the stability of the formulations. We note that the ED provided no evidence to support their conclusions.

The ED alleged that the absence or presence of water could have an effect on PEG-ester formation. As discussed above, the formulations used for the comparative testing contained water and reduction in the formation of PEG-esters for the claimed formulations was observed compared to the D1 formulations.

The ED cited the differences in the active agent (ketoprofen in D2) and naproxen in D1 as having a possible affect on PEG-ester formation. Both actives contain a carboxylic acid group, which is the reactive functional group that participates in the reaction to form PEG-esters. One of ordinary skill in the art would expect these agents to react in a similar manner. In fact, the ED relied on this reasoning in attempting to extrapolate the

behavior of ketoprofen as described in D2 to naproxen in order to reject Applicant's claims. In any event, the data now provided show that the compositions of the invention provide reduced PEG-ester formation compared with the compositions of D1 even when the active agent is the same.

The ED also alleged that lactic acid might be unique in its ability to reduce the formation of PEG-esters by a mechanism different than that for other acids and therefore its behavior cannot be extrapolated to other acids. The ED provided no scientific data to support this conclusion. The enclosed data show a reduction in PEG-ester formation for lactic acid (organic acid having as single carboxylic acid group), citric acid (organic acid having multiple carboxylic acid groups), and hydrochloric acid (an inorganic acid). This data shows that the problem addressed by the invention is solved across the full breadth of the claims.

The ED also alleged that Applicant did not account for the formation of propylene glycol (PG) esters. However, it is not clear how this relates to the problem to be solved. As noted by the ED, PG also contains hydroxyl groups which can react with the free acid to form esters. Regardless of the type of ester formation, esterification of the active agent reduces the efficacy of the formulation. Therefore, reducing the reactivity of the active agent should reduce formation of all types of esters. The data enclosed herein shows that the claimed formulations exhibit much lower concentrations of PEG-ester formation compared to the compositions of D1. Such behaviour would also be observed with respect to PEG-ester formation.

The ED also suggested that differences in the molecular weight of the PEG used in D2 (PEG 400), which described the formation of PEG esters, and the PEG used in D1, which is PEG 600 may account for differences in PEG ester formation. In order to do a direct comparison, comparative studies of the claimed formulations and the D1 formulations were done using PEG 600. The data is enclosed. As discussed above, for the claimed formulations, the amount of PEG-esters was very low. In contrast, the amount of PEG-esters formed in the D1 formulations was substantially higher.

The ED also alleged that one could not extrapolate from a single relative acid concentration or pH value to other acid concentrations. We respectfully disagree. However, in order to facilitate allowance, the comparative studies submitted herein were conducted at three different deionizing agent and ionizing agent concentrations, 0.2, 0.6, and 1.0 mole equivalent of deionizing or ionizing agent to moles of active agent. The data show that at all concentrations the claimed formulations exhibited significantly less PEG-ester formation than the D1 formulations.

The data described herein clearly show a significant reduction in PEG-ester formation for the claimed formulations compared to the formulations in of D1. Moreover, Applicants have shown that such unexpected results are achieved over the full breadth of the claims.

The ED cited D2 for the notion that PEG-ester formation can be suppressed when the agent is present as a salt. The ED failed to consider the cited passage on page 4 in its entirety. D2 discloses that fill materials containing PEG 400 and potassium hydroxide at a mole ratio of 0.4 to 1 were unstable due to the formation of ketoprofen esters (page 4, lines 1-6). D2 discloses that in an attempt to completely ionize ketoprofen to prevent

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formation of undesirable esters, the potassium hydroxide to ketoprofen ratio was adjusted to 1.1 to 1 (page 4, lines 7-9). D2 goes on to state "With this second formulation, concerns arose that the ketoprofen salt thus formed and/or high pH caused by the excess potassium hydroxide used could effect the physical stability of the softgel capsule when the formulation was encapsulated. Additionally, if an equilibrium amount of the ketoprofen free acid remained in solution, it could form ketoprofen esters that could drive the reaction to form more ketoprofen free acid species which could eventually result in a chemically unstable formulation." D2 does not disclose or suggest forming more of the salt to minimize PEG-ester formation since doing so could (1) can destabilize the softgel capsule shell due to formation of large amounts of the salt and/or high pH; and (2) result in increased formation of PEG esters.

None of the prior art discloses or suggest the claimed solution to the problem to be solved. Accordingly, the claims are inventive.

7. 2ND AUXILIARY REQUEST

The second auxiliary request is based on the first auxiliary request except that the term "deionizing agent which is a hydrogen ion species in an amount to cause partial deionization of the salt" has been replaced by a list of specify acids. Basis for this list can be found at page 6, lines 17 to 21 of the application as filed.

The comments of the ED relating to the clarity of wording relating to the deionizing agent are moot as this wording has been removed from the claims of this request. The claims of this request meet the other requirements of the EPC for the reasons set out above in relation to auxiliary request 1.

8. 3RD AUXILIARY REQUEST

The third auxiliary request is based on the first auxiliary request except that the active agent has been limited to naproxen sodium. The claims of this request satisfy the requirements of the EPC for the reasons set out above in relation to the first auxiliary request.

Additionally, it is noted that D1 does not disclose compositions comprising naproxen sodium. The two Examples of D1 that disclose compositions comprising naproxen, Examples IV and X both comprise naproxen and potassium hydroxide. In these compositions, potassium hydroxide acts as an ionizing agent and its interaction with naproxen results in the formation of naproxen potassium but these compositions do not comprise a compound that is a deionizing agent. For this reason, the subject matter of the claims of this request is novel in view of the disclosure of D1.

It is also noted that the data provided in the attached Annex clearly show that the problem addressed by the present invention is solved when the active agent is naproxen sodium.

In summary, this request satisfies the requirements of the EPC.

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9. 4TH AUXILIARY REQUEST

This request is based on the second and third auxiliary requests. That is the term "deionizing agent which is a hydrogen ion species in an amount to cause partial deionization of the salt" has been replaced by a list of acids and the active agent has been limited to naproxen sodium.

This request satisfies the requirements of the EPC for a combination of the reasons set out above in relation to the second and third auxiliary requests.

10. 5TH AUXILIARY REQUEST

This request is based on the fourth auxiliary request except that the list of acids has been reduced to include hydrochloric acid, citric acid and lactic acid only. These are the acids used in the Examples that were present in the application as originally filed and are also the acids that were used in the experiments reported in the attached Annex.

The claims of this request satisfy the requirements of the EPC for the reasons set out above in relation to the fifth auxiliary request.

It is also noted that the data provided in the attached Annex clearly show that the problem addressed by the present invention is solved when the active agent is naproxen sodium and an acid as listed in claim 1 is used.

In summary, this request satisfies the requirements of the EPC.

11. 6TH AUXILIARY REQUEST

This request is based on the fifth auxiliary request except that the acid has been limited to lactic acid. Lactic acid is used in the Examples that were present in the application as originally filed and the information included in attached Annex shows that formulations comprising lactic acid have a particularly favourable combination of properties.

The claims of this request satisfy the requirements of the EPC for the reasons set out above in relation to the fifth auxiliary request.

12. 7TH AUXILIARY REQUEST

This request is based on the third auxiliary request considered by the ED, except that the active agent has been limited to naproxen sodium.

It is noted that the ED considered that the claims of the third auxiliary request that they considered related to novel subject matter. The claims of this request are also novel.

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The claims of this request satisfy the other requirements of the EPC for the reasons set out about in relation to the main request, first auxiliary request and the third auxiliary request.

13. 8TH AUXILIARY REQUEST

This request is based on the main request except that the list of acids has been reduced to include hydrochloric acid, citric acid and lactic acid only. These are the acids used in the Examples that were present in the application as originally filed and are also the acids that were used in the experiments reported in the attached Annex.

The claims of this request satisfy the requirements of the EPC for the reasons set out above in relation to the main auxiliary request.

It is also noted that the data provided in the attached Annex clearly show that the problem addressed by the present invention is solved when the active agent is naproxen sodium and an acid as listed in claim 1 is used.

In summary, this request satisfies the requirements of the EPC.

14. 9TH AUXILIARY REQUEST

This request is based on the eighth auxiliary request except that the acid has been limited to lactic acid. Lactic acid is used in the Examples that were present in the application as originally filed and the information included in attached Annex shows that formulations comprising lactic acid have a particularly favourable combination of properties.

The claims of this request satisfy the requirements of the EPC for the reasons set out above in relation to the eighth auxiliary request.

15. 10TH, 11TH, 12TH AND 13TH AUXILIARY REQUESts

These requests are based on the main request and the 7th, 8th and 9th auxiliary requests respectively. In each of these requests claim 1 has been amended to state that step (a) of the claimed method is conducted at a temperature of from 50°C to 70°C. There is basis for this in original claim 17.

The subject matter of each of these requests satisfies the requirements of the EPC for the same reasons as each of the main request and the 7th, 8th and 9th auxiliary requests.

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16. CONCLUSION

For the reasons set out above the decision of the Examining Division should be overturned and a patent should be granted.

Charlotte Crowhurst PhD
For and on behalf of Potter Clarkson LLP
26 March 2012

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Potter Clarkson LLP
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Main Request

CLAIMS

1. A method of making a softgel capsule comprising

(a) making a fill mixture by mixing (i) naproxen sodium, (ii) polyethylene glycol, (iii) hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, fumaric acid, maleic acid, tartaric acid, citric acid, malic acid, acetic acid, proprionic acid, pyruvic acid, butanoic acid, or lactic acid; and

(b) encapsulating the mixture in a softgel capsule;

wherein (iii) is used in an amount of from 0.2 to 1.0 mole equivalents per mole of naproxen sodium.

2. A method of claim 1, wherein step (a) is conducted at a temperature of from 50°C to 70°C.

3. The method of claim 1 or claim 2, wherein (iii) is hydrochloric acid, citric acid or lactic acid.

4. The method of claim 3, wherein (iii) is lactic acid.

5. The method of any one of the preceding claims, wherein polyethylene glycol is present in an amount of from 10% to 80% by weight.

6. The method of any one of the preceding claims wherein the polyethylene glycol is one or more polyethylene glycols with a molecular weight between 300 and 1500.

7. The method of any one of the preceding claims, wherein water is present in an amount of from 1% to 18% by weight.

8. The method of any one of the preceding claims, wherein one or more excipients selected from the group consisting of plasticizers, crystallization inhibitors, wetting agents, bulk filling agents, solubilizers, bioavailability enhancers, solvents, dyes, preservatives, solvents, surfactants, and combinations thereof is added.

9. The method of claim 8, wherein the solubilizer is selected from the group consisting of glycerin, polyvinylpyrrolidone, propylene glycol and combinations thereof.

10. The method of claim 9, wherein the solubilizer is used in amount from 1% to 10% by weight.

11. A method according to any one of the preceding claims wherein the fill mixture produced in step (a) is liquid.

11th AUXILIARY REQUEST

CLAIMS

1. A method of making a softgel capsule comprising

(a) making a fill mixture by mixing (i) naproxen sodium, (ii) polyethylene glycol, (iii) a deionizing agent which is a hydrogen ion species in an amount to cause partial deionization of the salt, and (iv) optionally water at a temperature of from 50°C to 70°C; and

(b) encapsulating the mixture in a softgel capsule;

wherein (iii) is used in an amount to cause partial ionization of the naproxen sodium of from 0.2 to 1.0 mole equivalents per mole of naproxen sodium.

2. The method of claim 1, wherein the deionizing agent is selected from hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, fumaric acid, maleic acid, tartaric acid, methane sulfonate, ethane sulfonate, benzene sulfonate, citric acid, malic acid, acetic acid, proprionic acid, pyruvic acid, butanoic acid, or lactic acid,

3. The method of claim 1 or claim 2, wherein (iii) is hydrochloric acid, citric acid or lactic acid.

4. The method of claim 3, wherein (iii) is lactic acid.

5. The method of any one of the preceding claims, wherein polyethylene glycol is present in an amount of from 10% to 80% by weight.

6. The method of any one of the preceding claims wherein the polyethylene glycol is one or more polyethylene glycols with a molecular weight between 300 and 1500.

7. The method of any one of the preceding claims, wherein water is present in an amount of from 1% to 18% by weight.

8. The method of any one of the preceding claims, wherein one or more excipients selected from the group consisting of plasticizers, crystallization inhibitors, wetting agents, bulk filling agents, solubilizers, bioavailability enhancers, solvents, dyes, preservatives, solvents, surfactants, and combinations thereof is added.

9. The method of claim 8, wherein the solubilizer is selected from the group consisting of glycerin, polyvinylpyrrolidone, propylene glycol and combinations thereof.

10. The method of claim 9, wherein the solubilizer is used in amount from 1% to 10% by weight.

11. A method according to any one of the preceding claims wherein the fill mixture produced in step (a) is liquid.

12th AUXILIARY REQUEST

CLAIMS

1. A method of a softgel capsule comprising

(a) making a fill mixture by mixing (i) naproxen sodium, (ii) polyethylene glycol, (iii) hydrochloric acid, citric acid, or lactic acid, at a temperature of from 50°C to 70°C; and

(b) encapsulating the mixture in a softgel capsule;

wherein (iii) is used in an amount of from 0.2 to 1.0 mole equivalents per mole of naproxen sodium.

2. The method of claim 1, wherein (iii) is lactic acid.

3. The method claim 1 or claim 2, wherein polyethylene glycol is present in an amount of from 10% to 80% by weight.

4. The method of any one of the preceding claims wherein the polyethylene glycol is one or more polyethylene glycols with a molecular weight between 300 and 1500.

5. The method of any one of the preceding claims, wherein water is present in an amount of from 1% to 18% by weight.

6. The method of any one of the preceding claims, wherein one or more excipients selected from the group consisting of plasticizers, crystallization inhibitors, wetting agents, bulk filling agents, solubilizers, bioavailability enhancers, solvents, dyes, preservatives, solvents, surfactants, and combinations thereof is added.

7. The method of claim 6, wherein the solubilizer is selected from the group consisting of glycerin, polyvinylpyrrolidone, propylene glycol and combinations thereof.

8. The method of claim 7, wherein the solubilizer is used in amount from 1% to 10% by weight.

9. A method according to any one of the preceding claims wherein the fill mixture produced in step (a) is liquid.

13th AUXILIARY REQUEST

CLAIMS

1. A method of making a softgel capsule comprising

(a) making a fill mixture by mixing (i) naproxen sodium, (ii) polyethylene glycol, (iii) lactic acid, at a temperature of from 50°C to 70°C; and

(b) encapsulating the mixture in a softgel capsule;

wherein (iii) is used in an amount of from 0.2 to 1.0 mole equivalents per mole of naproxen sodium.

2. The method of claim 1, wherein polyethylene glycol is present in an amount of from 10% to 80% by weight.

3. The method of claim 1 or claim 2, wherein the polyethylene glycol is one or more polyethylene glycols with a molecular weight between 300 and 1500.

4. The method of any one of the preceding claims, wherein water is present in an amount of from 1% to 18% by weight.

5. The method of any one of the preceding claims, wherein one or more excipients selected from the group consisting of plasticizers, crystallization inhibitors, wetting agents, bulk filling agents, solubilizers, bioavailability enhancers, solvents, dyes, preservatives, solvents, surfactants, and combinations thereof is added.

6. The method of claim 5, wherein the solubilizer is selected from the group consisting of glycerin, polyvinylpyrrolidone, propylene glycol and combinations thereof.

7. The method of claim 6, wherein the solubilizer is used in amount from 1% to 10% by weight.

8. A method according to any one of the preceding claims wherein the fill mixture produced in step (a) is liquid.

5th AUXILIARY REQUEST

CLAIMS

1. A softgel capsule comprising a fill material wherein the fill material comprises
   (a) naproxen sodium;
   (b) hydrochloric acid, citric acid or lactic acid in an amount of from 0.2 to 1.0 mole equivalents per mole of the naproxen sodium;
   (c) polyethylene glycol.

2. The capsule of claim 1 wherein (b) is lactic acid.

3. The capsule of any one of the preceding claims wherein polyethylene glycol is present in an amount from 10% to 80% by weight.

4. The capsule of any one of the preceding claims wherein the polyethylene glycol is one or more polyethylene glycols with a molecular weight between 300 and 1500.

5. The capsule of any one of the preceding claims wherein water is present in an amount from 1% to 18% by weight.

6. The capsule of any one of the preceding claims 1 further comprising one or more excipients selected from the group consisting of plasticizers, crystallization inhibitors, wetting agents, bulk filling agents, solubilizers, bioavailability enhancers, solvents, dyes, preservatives, solvents, surfactants, and combinations thereof.

7. The capsule of claim 6 wherein the solubilizer is selected from the group consisting of glycerin, polyvinylpyrrolidone, propylene glycol and combinations thereof.

8. The capsule of claim 7 wherein the solubilizer is present in amount from 1% to 10% by weight.

9. The capsule of any one of the preceding claims wherein the fill material is liquid.

10. A capsule of any one of the preceding claims for use as a medicament.

11. A method of making the capsule of any one of the preceding claims comprising

(a) mixing naproxen sodium, the polyethylene glycol and the hydrochloric acid, citric acid or lactic acid; and

(b) encapsulating the mixture in a softgel capsule.

12. The method of claim 11, wherein step (a) is conducted at a temperature of from 50°C to 70°C

13. The use of

(a) naproxen sodium;

(b) hydrochloric acid, citric acid or lactic acid in an amount of from 0.2 to 1.0 mole equivalents per mole of the naproxen sodium; and

(c) polyethylene glycol;

in the manufacture of a medicament in the form of a capsule for administration of the naproxen sodium to a patient in need thereof.

14. A softgel capsule obtainable by a method which comprises

(I) producing a fill material by mixing

(a) naproxen sodium;

(b) hydrochloric acid, citric acid or lactic acid in an amount of from 0.2 to 1.0 mole equivalents per mole of the naproxen sodium; and

(c) polyethylene glycol; and

(III) encapsulating the mixture in a softgel capsule.

15. The softgel capsule of claim 14 obtainable by a method in which step (I) is conducted at a temperature of from 50°C to 70°C.

7th AUXILIARY REQUEST

CLAIMS

1. A method of making a softgel capsule comprising

(a) making a fill mixture by mixing (i) naproxen sodium, (ii) polyethylene glycol, (iii) a deionizing agent which is a hydrogen ion species in an amount to cause partial deionization of the salt, and (iv) optionally water; and

(b) encapsulating the mixture in a softgel capsule;

wherein (iii) is used in an amount to cause partial deionization of the naproxen sodium of from 0.2 to 1.0 mole equivalents per mole of naproxen sodium.

2. A method of claim 1, wherein step (a) is conducted at a temperature of from 50°C to 70°C.

3. The method of claim 1 or claim 2, wherein the deionizing agent is selected from hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, fumaric acid, maleic acid, tartaric acid, methane sulfonate, ethane sulfonate, benzene sulfonate, citric acid, malic acid, acetic acid, proprionic acid, pyruvic acid, butanoic acid, or lactic acid,

4. The method of any one of the preceding claims, wherein (iii) is hydrochloric acid, citric acid or lactic acid.

5. The method of claim 4, wherein (iii) is lactic acid.

6. The method of any one of the preceding claims, wherein polyethylene glycol is present in an amount of from 10% to 80% by weight.

7. The method of any one of the preceding claims wherein the polyethylene glycol is one or more polyethylene glycols with a molecular weight between 300 and 1500.

8. The method of any one of the preceding claims, wherein water is present in an amount of from 1% to 18% by weight.

9. The method of any one of the preceding claims, wherein one or more excipients selected from the group consisting of plasticizers, crystallization inhibitors, wetting agents, bulk filling agents, solubilizers, bioavailability enhancers, solvents, dyes, preservatives, solvents, surfactants, and combinations thereof is added.

10. The method of claim 9, wherein the solubilizer is selected from the group consisting of glycerin, polyvinylpyrrolidone, propylene glycol and combinations thereof.

11. The method of claim 10, wherein the solubilizer is used in amount from 1% to 10% by weight.

12. A method according to any one of the preceding claims wherein the fill mixture produced in step (a) is liquid.

1st AUXILIARY REQUEST

CLAIMS

1. A softgel capsule comprising a fill material wherein the fill material comprises
   (a) a salt of an acidic pharmaceutically active agent;
   (b) a deionizing agent which is a hydrogen ion species in an amount to cause partial deionization of the salt of from 0.2 to 1.0 mole equivalents per mole of the pharmaceutically active agent;
   (c) polyethylene glycol; and optionally
   (d) water.

2. The capsule of claim 1 wherein the pharmaceutically active agent is selected from the group consisting of therapeutically active agents, diagnostic agents, and prophylactic agents.

3. The capsule of claim 1 or claim 2 wherein polyethylene glycol is present in an amount from 10% to 80% by weight.

4. The capsule of any one of the preceding claims wherein the polyethylene glycol is one or more polyethylene glycols with a molecular weight between 300 and 1500.

5. The capsule of any one of the preceding claims wherein water is present in an amount from 1% to 18% by weight.

6. The capsule of any one of the preceding claims further comprising one or more excipients selected from the group consisting of plasticizers, crystallization inhibitors, wetting agents, bulk filling agents, solubilizers, bioavailability enhancers, solvents, dyes, preservatives, solvents, surfactants, and combinations thereof.

7. The capsule of claim 6 wherein the solubilizer is selected from the group consisting of glycerin, polyvinylpyrrolidone, propylene glycol and combinations thereof.

8. The capsule of claim 7 wherein the solubilizer is present in amount from 1% to 10% by weight.

9. The capsule of any one of the preceding claims wherein the salt (a) is naproxen sodium.

10. The capsule of any one of the preceding claims wherein the hydrogen ion species is selected from hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, fumaric acid, maleic acid, tartaric acid, methane-, ethane-, and benzene sulfonates, citric acid, malic acid, acetic acid, proprionic acid, pyruvic acid, butanoic acid, and lactic acid.

11. The capsule of claim 10 wherein the hydrogen ion species is hydrochloric acid, citric acid or lactic acid.

12. The capsule of claim 11 wherein the hydrogen ion species is lactic acid.

13. The capsule of any one of the preceding claims wherein the fill material is liquid.

14. A capsule of any one of the preceding claims 1 for use as a medicament.

15. A method of making the capsule of any one of the preceding claims comprising
(a) mixing the salt of an acidic pharmaceutically active agent, the polyethylene glycol and the deionizing agent and optionally water; and
(b) encapsulating the mixture in a softgel capsule.

16. The method of claim 15 wherein step (a) is conducted at a temperature of from 50 °C to 70 °C.

17. The use of
(a) a salt of an acidic pharmaceutically active agent;
(b) a deionizing agent which is a hydrogen ion species in an amount to cause partial deionization of the salt of from 0.2 to 1.0 mole equivalents per mole of the pharmaceutically active agent;
(c) polyethylene glycol; and optionally
(d) water
in the manufacture of a softgel capsule medicament for administration of the pharmaceutically active agent to a patient in need thereof.

18. A softgel capsule obtainable by a method which comprises

(I) producing a fill material by mixing

(a) a salt of an acidic pharmaceutically active agent;

(b) a deionizing agent which is a hydrogen ion species in an amount to cause partial deionization of the salt of from 0.2 to 1.0 mole equivalents per mole of the pharmaceutically active agent;

(c) polyethylene glycol; and optionally

(d) water; and

(II) encapsulating the mixture in a softgel capsule.

19. The softgel capsule of claim 18, obtainable by a process in which step (I) is conducted at a temperature of from 50°C to 70°C.

2nd AUXILIARY REQUEST

CLAIMS

1. A softgel capsule comprising a fill material wherein the fill material comprises
   (a) a salt of an acidic pharmaceutically active agent;
   (b) hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, fumaric acid, maleic acid, citric acid, malic acid, acetic acid, proprionic acid, pyruvic acid, butanoic acid or lactic acid in an amount of from 0.2 to 1.0 mole equivalents per mole of the pharmaceutically active agent; and
   (c) polyethylene glycol.

2. The capsule of claim 1 wherein the pharmaceutically active agent is selected from the group consisting of therapeutically active agents, diagnostic agents, and prophylactic agents.

3. The capsule of claim 1 or claim 2 wherein polyethylene glycol is present in an amount from 10% to 80% by weight.

4. The capsule of any one of the preceding claims wherein the polyethylene glycol is one or more polyethylene glycols with a molecular weight between 300 and 1500.

5. The capsule of any one of the preceding claims wherein water is present in an amount from 1% to 18% by weight.

6. The capsule of any one of the preceding claims further comprising one or more excipients selected from the group consisting of plasticizers, crystallization inhibitors, wetting agents, bulk filling agents, solubilizers, bioavailability enhancers, solvents, dyes, preservatives, solvents, surfactants, and combinations thereof.

7. The capsule of claim 6 wherein the solubilizer is selected from the group consisting of glycerin, polyvinylpyrrolidone, propylene glycol and combinations thereof.

8. The capsule of claim 7 wherein the solubilizer is present in amount from 1% to 10% by weight.

9. The capsule of any one of the preceding claims wherein the salt (a) is naproxen sodium.

10. The capsule of any one of the preceding claims wherein (b) is hydrochloric acid, citric acid or lactic acid.

11. The capsule of claim 10 wherein (b) is lactic acid.

12. The capsule of any one of the preceding claims wherein the fill material is liquid.

13. A capsule of any one of the preceding claims for use as a medicament.

14. A method of making the capsule as defined in claim 1 comprising
(a) mixing components (a), (b), (c) as defined in claim 1; and
(b) encapsulating the mixture in a softgel capsule.

15. The method of claim 14 wherein step (a) is conducted at a temperature of from 50 °C to 70 °C.

16. The use of
(a) a salt of an acidic pharmaceutically active agent;
(b) hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, fumaric acid, maleic acid, citric acid, malic acid, acetic acid, proprionic acid, pyruvic acid, butanoic acid or lactic acid in an amount of from 0.2 to 1.0 mole equivalents per mole of the pharmaceutically active agent; and
(c) polyethylene glycol;
in the manufacture of a softgel capsule medicament for administration of the pharmaceutically active agent to a patient in need thereof.

17. A softgel capsule obtainable by a method which comprises
(I) producing a fill material by mixing
(a) a salt of an acidic pharmaceutically active agent;
(b) hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, fumaric acid, maleic acid, citric acid, malic acid, acetic acid, proprionic acid, pyruvic acid,

butanoic acid or lactic acid in an amount of from 0.2 to 1.0 mole equivalents per mole of the pharmaceutically active agent;

(c) polyethylene glycol; and

(II) encapsulating the mixture in a softgel capsule.

18. The softgel capsule of claim 17 obtainable by a method in which step (I) is conducted at a temperature of from 50°C to 70°C.

3rd AUXILIARY REQUEST

CLAIMS

1. A softgel capsule comprising a fill material wherein the fill material comprises

(a) naproxen sodium;

(b) a deionizing agent in an amount to cause partial deionization of the salt of from 0.2 to 1.0 mole equivalents per mole of the naproxen sodium;

(c) polyethylene glycol; and optionally

(d) water.

2. The capsule of claim 1 wherein the deionizing is selected from hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, fumaric acid, maleic acid, tartaric acid, methane-, ethane-, and benzene sulfonates, citric acid, malic acid, acetic acid, proprionic acid, pyruvic acid, butanoic acid, and lactic acid.

3. The capsule of claim 2 wherein the deionizing agent is hydrochloric acid, citric acid or lactic acid.

4. The capsule of claim 3 wherein the deionizing agent is lactic acid

5. The capsule of any one of the preceding claims wherein polyethylene glycol is present in an amount from 10% to 80% by weight.

6. The capsule of any one of the preceding claims wherein the polyethylene glycol is one or more polyethylene glycols with a molecular weight between 300 and 1500.

7. The capsule of any one of the preceding claims wherein water is present in an amount from 1% to 18% by weight.

8. The capsule of any one of the preceding claims further comprising one or more excipients selected from the group consisting of plasticizers, crystallization inhibitors, wetting agents, bulk filling agents, solubilizers, bioavailability enhancers, solvents, dyes, preservatives, solvents, surfactants, and combinations thereof.

9. The capsule of claim 8 wherein the solubilizer is selected from the group consisting of glycerin, polyvinylpyrrolidone, propylene glycol and combinations thereof.

10. The capsule of claim 9 wherein the solubilizer is present in amount from 1% to 10% by weight.

11. The capsule of any one of the preceding claims wherein the fill material is liquid.

12. A capsule of any one of the preceding claims for use as a medicament.

13. A method of making the capsule of any of the preceding claims comprising

(a) mixing naproxen sodium, the polyethylene glycol and the deionizing agent and optionally water; and

(b) encapsulating the mixture in a softgel capsule.

14. The method of claim 13, wherein step (a) is conducted at a temperature of from 50°C to 70°C.

15. The use of

(a) naproxen sodium;

(b) a deionizing agent in an amount to cause partial deionization of the naproxen sodium from 0.2 to 1.0 mole equivalents per mole of the pharmaceutically active agent(s);

(c) polyethylene glycol: and optionally

(d) water

in the manufacture of a medicament in the form of a capsule for administration of the naproxen sodium to a patient in need thereof.

16. A softgel capsule obtainable by a method which comprises

(I) producing a fill material by mixing

(a) naproxen sodium;

(b) a deionizing agent in an amount to cause partial deionization of the naproxen sodium from 0.2 to 1.0 mole equivalents per mole of the pharmaceutically active agent(s);

(c) polyethylene glycol: and optionally

(d) water; and

(II) encapsulating the mixture in a softgel capsule.

17. The softgel capsule of claim 16 obtainable by a method in which step (I) is conducted at a temperature of from 50°C to 70°C.

4th AUXILIARY REQUEST

CLAIMS

1. A softgel capsule comprising a fill material wherein the fill material comprises

(a) naproxen sodium;

(b) hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, fumaric acid, maleic acid, tartaric acid, citric acid, malic acid, acetic acid, proprionic acid, pyruvic acid, butanoic acid or lactic acid in an amount of from 0.2 to 1.0 mole equivalents per mole of the naproxen sodium;

(c) polyethylene glycol.

2. The capsule of claim 1 wherein (b) is hydrochloric acid, citric acid or lactic acid.

3. The capsule of claim 2 wherein (b) is lactic acid.

4. The capsule of any one of the preceding claims wherein polyethylene glycol is present in an amount from 10% to 80% by weight.

5. The capsule of any one of the preceding claims wherein the polyethylene glycol is one or more polyethylene glycols with a molecular weight between 300 and 1500.

6. The capsule of any one of the preceding claims wherein water is present in an amount from 1% to 18% by weight.

7. The capsule of any one of the preceding claims further comprising one or more excipients selected from the group consisting of plasticizers, crystallization inhibitors, wetting agents, bulk filling agents, solubilizers, bioavailability enhancers, solvents, dyes, preservatives, solvents, surfactants, and combinations thereof.

8. The capsule of claim 7 wherein the solubilizer is selected from the group consisting of glycerin, polyvinylpyrrolidone, propylene glycol and combinations thereof.

9. The capsule of claim 8 wherein the solubilizer is present in amount from 1% to 10% by weight.

10. The capsule of any one of the preceding claims wherein the fill material is liquid.

11. A capsule of any of the preceding claims for use as a medicament.

12. A method of making the capsule of claim 1 comprising

(a) mixing components (a), (b) and (c) as defined in claim 1; and

(b) encapsulating the mixture in a softgel capsule.

13. The method of claim 12, wherein step (a) is conducted at a temperature of from 50°C to 70°C

14. The use of

(a) naproxen sodium;

(b) hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, fumaric acid, maleic acid, tartaric acid, citric acid, malic acid, acetic acid, proprionic acid, pyruvic acid, butanoic acid or lactic acid in an amount of from 0.2 to 1.0 mole equivalents per mole of the naproxen sodium; and

(c) polyethylene glycol;

in the manufacture of a medicament in the form of a capsule for administration of the naproxen sodium to a patient in need thereof.

15. A softgel capsule obtainable by a method which comprises

(I) producing a fill material by mixing

(a) naproxen sodium;

(b) hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, fumaric acid, maleic acid, tartaric acid, citric acid, malic acid, acetic acid, proprionic acid, pyruvic acid, butanoic acid or lactic acid in an amount of from 0.2 to 1.0 mole equivalents per mole of the naproxen sodium; and

(c) polyethylene glycol; and

(II) encapsulating the mixture in a softgel capsule.

16. The softgel capsule of claim 15 obtainable by a method in which step (I) is conducted at a temperature of from 50°C to 70°C.

6th AUXILIARY REQUEST

CLAIMS

1. A softgel capsule comprising a fill material wherein the fill material comprises

(a) naproxen sodium;

(b) lactic acid in an amount of from 0.2 to 1.0 mole equivalents per mole of the naproxen sodium;

(c) polyethylene glycol.

2. The capsule of claim 1 wherein polyethylene glycol is present in an amount from 10% to 80% by weight.

3. The capsule of claim 1 wherein the polyethylene glycol is one or more polyethylene glycols with a molecular weight between 300 and 1500.

4. The capsule of claim 1 wherein water is present in an amount from 1% to 18% by weight.

5. The capsule of claim 1 further comprising one or more excipients selected from the group consisting of plasticizers, crystallization inhibitors, wetting agents, bulk filling agents, solubilizers, bioavailability enhancers, solvents, dyes, preservatives, solvents, surfactants, and combinations thereof.

6. The capsule of claim 5 wherein the solubilizer is selected from the group consisting of glycerin, polyvinylpyrrolidone, propylene glycol and combinations thereof.

7. The capsule of claim 6 wherein the solubilizer is present in amount from 1% to 10% by weight.

8. The capsule of any one of the preceding claims wherein the fill material is liquid.

9. A capsule of any one of the preceding claims for use as a medicament.

10. A method of making the capsule of any one of the preceding claims comprising

(a) mixing naproxen sodium, the polyethylene glycol and the lactic acid and optionally water; and

(b) encapsulating the mixture in a softgel capsule.

11. The method of claim 10, wherein step (a) is conducted at a temperature of from 50°C to 70°C.

12. The use of

(a) naproxen sodium;

(b) lactic acid in an amount to cause partial deionization of the naproxen sodium from 0.2 to 1.0 mole equivalents per mole of the pharmaceutically active agent(s);

(c) polyethylene glycol: and optionally

(d) water

in the manufacture of a medicament in the form of a capsule for administration of the naproxen sodium to a patient in need thereof.

13. A softgel capsule obtainable by a method which comprises

(I) producing a fill material by mixing

(a) naproxen sodium;

(b) lactic acid in an amount to cause partial deionization of the naproxen sodium from 0.2 to 1.0 mole equivalents per mole of the pharmaceutically active agent(s);

(c) polyethylene glycol: and optionally

(d) water; and

(II) encapsulating the mixture in a softgel capsule.

14. The softgel capsule of claim 13 obtainable by a method in which step (I) is conducted at a temperature of from 50°C to 70°C.

8th AUXILIARY REQUEST

CLAIMS

1. A method of making a softgel capsule comprising

(a) making a fill mixture by mixing (i) naproxen sodium, (ii) polyethylene glycol, (iii) hydrochloric acid, citric acid or lactic acid; and

(b) encapsulating the mixture in a softgel capsule;

wherein (iii) is used in an amount of from 0.2 to 1.0 mole equivalents per mole of naproxen sodium.

2. A method of claim 1, wherein step (a) is conducted at a temperature of from 50°C to 70°C.

3. The method claim 1 or claim 2, wherein (iii) is lactic acid.

4. The method of any one of the preceding claims, wherein polyethylene glycol is present in an amount of from 10% to 80% by weight.

5. The method of any one of the preceding claims wherein the polyethylene glycol is one or more polyethylene glycols with a molecular weight between 300 and 1500.

6. The method of any one of the preceding claims, wherein water is present in an amount of from 1% to 18% by weight.

7. The method of any one of the preceding claims, wherein one or more excipients selected from the group consisting of plasticizers, crystallization inhibitors, wetting agents, bulk filling agents, solubilizers, bioavailability enhancers, solvents, dyes, preservatives, solvents, surfactants, and combinations thereof is added.

8. The method of claim 7, wherein the solubilizer is selected from the group consisting of glycerin, polyvinylpyrrolidone, propylene glycol and combinations thereof.

9. The method of claim 8, wherein the solubilizer is used in amount from 1% to 10% by weight.

10. A method according to any one of the preceding claims wherein the fill mixture produced in step (a) is liquid.

9th AUXILIARY REQUEST

CLAIMS

1. A method of making a softgel capsule comprising

(a) making a fill mixture by mixing (i) naproxen sodium, (ii) polyethylene glycol, (iii) lactic acid; and

(b) encapsulating the mixture in a softgel capsule;

wherein (iii) is used in an amount of from 0.2 to 1.0 mole equivalents per mole of naproxen sodium.

2. A method of claim 1, wherein step (a) is conducted at a temperature of from 50°C to 70°C.

3. The method of claim 1 or claim 2, wherein polyethylene glycol is present in an amount of from 10% to 80% by weight.

4. The method of any one of the preceding claims wherein the polyethylene glycol is one or more polyethylene glycols with a molecular weight between 300 and 1500.

5. The method of any one of the preceding claims, wherein water is present in an amount of from 1% to 18% by weight.

6. The method of any one of the preceding claims, wherein one or more excipients selected from the group consisting of plasticizers, crystallization inhibitors, wetting agents, bulk filling agents, solubilizers, bioavailability enhancers, solvents, dyes, preservatives, solvents, surfactants, and combinations thereof is added.

7. The method of claim 6, wherein the solubilizer is selected from the group consisting of glycerin, polyvinylpyrrolidone, propylene glycol and combinations thereof.

8. The method of claim 7, wherein the solubilizer is used in amount from 1% to 10% by weight.

9. A method according to any one of the preceding claims wherein the fill mixture produced in step (a) is liquid.

10th AUXILIARY REQUEST

CLAIMS

1. A method of making a softgel capsule comprising

(a) making a fill mixture by mixing (i) naproxen sodium, (ii) polyethylene glycol, (iii) hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, fumaric acid, maleic acid, tartaric acid, citric acid, malic acid, acetic acid, proprionic acid, pyruvic acid, butanoic acid, or lactic acid, at a temperature of from 50°C to 70°C; and

(b) encapsulating the mixture in a softgel capsule;

wherein (iii) is used in an amount of from 0.2 to 1.0 mole equivalents per mole of naproxen sodium.

2. The method of claim 1, wherein (iii) is hydrochloric acid, citric acid or lactic acid.

3. The method of claim 2, wherein (iii) is lactic acid.

4. The method of any one of the preceding claims, wherein polyethylene glycol is present in an amount of from 10% to 80% by weight.

5. The method of any one of the preceding claims wherein the polyethylene glycol is one or more polyethylene glycols with a molecular weight between 300 and 1500.

6. The method of any one of the preceding claims, wherein water is present in an amount of from 1% to 18% by weight.

7. The method of any one of the preceding claims, wherein one or more excipients selected from the group consisting of plasticizers, crystallization inhibitors, wetting agents, bulk filling agents, solubilizers, bioavailability enhancers, solvents, dyes, preservatives, solvents, surfactants, and combinations thereof is added.

8. The method of claim 7, wherein the solubilizer is selected from the group consisting of glycerin, polyvinylpyrrolidone, propylene glycol and combinations thereof.

9. The method of claim 8, wherein the solubilizer is used in amount from 1% to 10% by weight.

10. A method according to any one of the preceding claims wherein the fill mixture produced in step (a) is liquid.

European Patent Application No.06737018.9
Banner Pharmacaps, Inc
PC Ref: PABCX/P38814EP

ANNEX TO GROUNDS OF APPEAL

REPORT OF COMPARATIVE STUDIES CONDUCTED TO COMPARE THE PROPERTIES OF COMPOSITIONS OBTAINED IN ACCORDANCE WITH THE INVENTION AND THE COMPOSITIONS DESCRIBED IN US 5,360,615

1.0 INTRODUCTION

European patent application no. 06737018.9 is directed to a method of preparing a pharmaceutical composition. This method comprises mixing (i) naproxen sodium, (ii) polyethylene glycol, (iii) hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, fumaric acid, maleic acid, tartaric acid, citric acid, malic acid, acetic acid, proprionic acid, pyruvic acid, butanoic acid, or lactic acid. Component (iii) is used in an amount of from 0.2 to 1.0 mole equivalents per mole of naproxen sodium.

An advantage of the present invention is that it provides a reduction in the production of undesired degradation products such as polyethylene glycol (PEG) esters compared with the prior art.

The applicant company conducted experiments to demonstrate that preparing a pharmaceutical composition in accordance with the present invention results in reduced formation of polyethylene glycol (PEG) esters compared to producing a composition in accordance with the teaching of D1.

Accordingly, the study was designed based on the information provided in D1 and the teaching of European patent application no. 06737018.9. The compositions tested are summarized in Tables 1, 2 and 3 below.

Table 1: Study of compositions prepared in accordance with the present invention

Naproxen Form	Naproxen amount	Acid	Approximate mole equivalent level (amount of acid)		
Naproxen Sodium	285 mg	HCl	0.2	0.6	1.0
	220 mg	HCl	0.2	0.6	1.0
Naproxen Sodium	285 mg	Lactic acid	0.2	0.6	1.0
	220 mg	Lactic acid	0.2	0.6	1.0
Naproxen Sodium	285 mg	Citric acid	0.2		1.0
	220 mg	Citric acid	0.2		

285 mg of Naproxen Sodium is equivalent to 260 mg of the free acid.

220 mg of Naproxen Sodium is equivalent to 200 mg of the free acid.

Table 2: Study based on the teaching of D1

Naproxen Form	Naproxen amount	Base	Approximate mole equivalent level (amount of base)		
Naproxen free acid	260 mg	KOH	0.2	0.6	1.0
	200 mg	KOH	0.2	0.6	1.0

All the experiments were performed using PEG 600. This is a representative example of a PEG that can be used in the present invention and was used in some of the Examples of the application as filed and was also used in Example IV of D1.

Table 3: Study based of compositions containing water

Naproxen Form	Naproxen Amount	Acid/Base	Water	Approximate mole equivalent level (amount of acid/base)		
Naproxen Sodium	285 mg	Lactic acid	8.5%	0.2	0.6	1.0
	220 mg	Lactic acid	8.5%	0.2	0.6	1.0
Naproxen free acid	260 mg	KOH	8.5%	0.2	0.6	1.0
	200 mg	KOH	8.5%	0.2	0.6	1.0

2.0 MATERIALS

Material	Lot #	Supplier
6N Hydrochloric Acid	E05P01	J.T. Baker
PEG-600	100009129	Banner
Lactic Acid	20010740	Banner
Citric Acid	08-0091	Banner
Potassium Hydroxide	E17K52	J.T. Baker
Naproxen Sodium	SO60103	RoChemical International
Naproxen	081M1091V	Sigma-Aldrich

3.0 PROCEDURE

Naproxen sodium or free acid was added to PEG 600 followed by addition of molar equivalent of the appropriate acid or based in accordance with the method of the present invention and the teaching of D1, respectively.

The compositions produced in this manner were subjected to an accelerated stability study. In this study the compositions were heated to 60°C for 1 week and analyzed for the amount of PEG esters initially and at the end of the accelerated stability study.

The following formulations were prepared:

- Two series of formulations identical to that described in D1 and in the present application.
- Two series of modified formulations prepared using:
  (1) 220 mg Naproxen Sodium and PEG 600, PG and Povidone were replaced with PEG 600. Three mole ratios of acid or base such as 0.2, 0.6 and 1 were used as illustrative of the range specified in the claims of the present application.

(2) Formulations based on the teaching of D1 comprising Naproxen free acid in an amount equivalent to the molar amount used in the formulations representative of the invention, with the same amount of PEG 600 and with KOH.

Samples were analyzed by HPLC:

Agilent 1100 Series HPLC System

Column: DeactiSil ODS-3 5u 100A, 25cm X 4.6mm (ES Industries)

Column Oven Temperature: ambient

Flow Rate: 1.5 mL/min

Injection Volume: 25 uL

UV Detector at 272 nm

Run Time: 60 minutes

Mobile Phase A:

Phosphate Buffer:Acetonitrile (3:2 ratio)

Mobile Phase B:

Phosphate Buffer:Acetonitrile (1:3 ratio)

Limit of quantitation was approximated to be 0.00011 mg/mL

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Banner's Formulations

Sample #	Name	Naproxen Na (g)	6N HCl (mL)	PEG-600 (g)
1	NS 285-0.2 HCl	7.128	0.95	16.950
2	NS 285-0.6 HCl	7.120	2.80	15.024
3	NS 285-1.0 HCl	7.152	4.70	13.514
4	NS 220-0.2 HCl	5.512	0.70	18.790
5	NS 220-0.6 HCl	5.521	2.15	17.413
6	NS 220-1.0 HCl	5.548	3.60	15.891

		Naproxen Na (g)	Lactic Acid (g)	DI H20 (g)	PEG-600 (g)
7	NS 285-0.2 lactic	7.133	0.513	0.434	16.947
8	NS 285-0.6 Lactic	7.150	1.528	1.295	15.053
9	NS 285-1.0 Lactic	7.132	2.544	2.167	13.188
10	NS 220-0.2 Lactic	5.559	0.388	0.460	18.789
11	NS 220-0.6 Lactic	5.518	1.186	1.030	17.339
12	NS 220-1.0 Lactic	5.523	1.972	1.660	15.899

		Naproxen Na (g)	Citric Acid (g)	DI H20 (g)	PEG-600 (g)
13	NS 285-0.2 Citric	7.129	1.020	0.439	16.364
14	NS 285-1.0 Citric	7.128	5.436	2.519	10.350
15	NS 220-0.2 Citric	5.012	0.865	0.364	18.355

Yu's Formulations

	Naproxen API	Naproxen (g)	50% KOH (9)	PEG-GOO (g)
16	Yu 260-0.2 KOH	6.499	0.330	17.892
17	Yu 260-0.6 KOH	6.497	0.957	16.681
18	Yu 260-1.0 KOH	6.510	1.594	15.357
19	Yu 200-0.2 KOH	5.027	0.286	19.555
20	Yu 200-0.6 KOH	5.100	0.757	18.580
21	Yu 200-1.0 KOH	5.134	1.230	17.540

In the tables above, "Banner's formulations" refers to formulations prepared using the method of the present invention and "Yu's formulations" refers to formulations that are representative of the teaching of D1.

4.0 RESULTS

The results are summarized in the Table below.

Banner's Formulations		Room Temperature		Stress at 60C for 7-Days		Physical Observations of Formulations	
Sample #	Name	Peaks RT	% Area	Peaks RT	% Area	Room Temp	Stress at 60C 7-Days
1	NS 285-0.2 HCl	*10.78 **14.347	0.0084% 99.9916%	14.36	100.0000%	Phase Separate, precipitate	Phase Separate, precipitate
2	NS 285-0.6 HCl	10.787 14.34	0.0101% 99.9899%	10.78 14.38	0.0030% 99.9970%	Phase Separate, precipitate	Phase Separate, precipitate
3	NS 285-1.0 HCl	10.753 14.36	0.0076% 99.9924%	10.8 14.4	0.0069% 99.9931%	Phase Separate, precipitate	Phase Separate, precipitate
4	NS 220-0.2 HCl	10.773 14.347	0.0076% 99.9924%	14.4	100.0000%	Phase Separate, precipitate	Phase Separate, precipitate
5	NS 220-0.6 HCl	14.36	100.0000%	14.427	100.0000%	Phase Separate, precipitate	Phase Separate, precipitate
6	NS 220-1.0 HCl	10.773 14.36	0.0082% 99.9918%	10.793 14.413	0.0048% 99.9952%	Phase Separate, precipitate	Phase Separate, precipitate
7	NS 285-0.2 Lactic	10.78 14.293	0.0075% 99.9925%	14.36	100.0000%	Phase Separate, precipitate	Phase Separate, precipitate
8	NS 285-0.6 Lactic	10.773 14.287	0.0072% 99.9928%	14.36	100.0000%	Clear Solution, crystallize at bottom	Clear Solution
9	NS 285-1.0 Lactic	10.767 14.327	0.0073% 99.9927%	14.413	100.0000%	Phase Separate, precipitate	Phase Separate, precipitate

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Banner Pharmacaps, Inc
PC Ref: PABCX/P38814EP

10	NS 220-0.2 Lactic	10.767 14.327	0.0069% 99.9931%	14.42	100.0000%	Phase Separate, precipitate	Phase Separate, precipitate
11	NS 220-0.6 Lactic	10.773 14.347	0.0067% 99.9933%	14.407	100.0000%	Clear solution	Clear solution
12	NS 220-1.0 Lactic	10.773 14.367	0.0064% 99.9936%	14.393	100.0000%	White semi-solid crystallized	Phase Separate, precipitate
13	NS 285-0.2 Citric	10.747 14.327	0.0087% 99.9913%	10.76 14.38	0.0038% 99.9962%	White semi-solid crystallized	Phase Separate, precipitate
14	NS 285-1.0 Citric	10.78 14.32	0.0021% 30.4552%	10.78 14.373	0.0107% 99.9893%	White semi-solid paste	White semi-solid paste
15	NS 220-0.2 Citric	10.787 14.353	0.0061% 99.9939%	14.393	100.0000%	Opaque solution fill, viscuous	Phase Separate, precipitate

Yu's Formulations		Room Temperature		Stress at 60C for 7-Days		Physical Observations of Formulations	
Sample #	Name	Peaks RT	% Area	Peaks RT	% Area	Room Temp	Stress at 60C 7-Days
16	Yu 260-0.2 KOH	*10.773 **14.333	0.0178% 99.8580%	10.793 14.387	0.0132% 99.8658%	Phase Separate, precipitate	Clear solution
17	Yu 260-0.6 KOH	10.767 14.367	0.0154% 99.8745%	10.807 14.387	0.0133% 99.8689%	Clear solution	Clear solution
18	Yu 260-1.0 KOH	10.793 14.36	0.0160% 99.8751%	10.813 14.373	0.0140% 99.8647%	Clear solution	Clear solution
19	Yu 200-0.2 KOH	10.793 14.393	0.0144% 99.8879%	10.8 14.413	0.0093% 99.8861%	Clear solution	Clear solution
20	Yu 200-0.6 KOH	10.787 14.387	0.0146% 99.8797%	10.793 14.4	0.0128% 99.8784%	Clear solution	Clear solution
21	Yu 200-1.0 KOH	10.787 14.38	0.0148% 99.8635%	10.807 14.387	0.0135% 99.8750%	Clear solution	Clear solution

* PEG ester peak retention time.

** Naproxen peak retention time.

In general, the amount of PEG ester in the formulations prepared in accordance with the teaching of D1 when subjected to stressed conditions varied from 0.0093 to 0.014. The compositions prepared by the method of the present invention exhibited lower levels of PEG esters at room temperature and after the stress study.

5.0 CONCLUSION

The results of these experiments show that formulations prepared in accordance with the teaching of the present invention surprisingly contain lower amounts of PEG esters that formulations prepared following the teaching of D1.

ANNEX TO GROUNDS OF APPEAL

REPORT OF COMPARATIVE STUDIES CONDUCTED TO COMPARE THE PROPERTIES OF COMPOSITIONS OBTAINED IN ACCORDANCE WITH THE INVENTION AND THE COMPOSITIONS DESCRIBED IN US 5,360,615

1.0 INTRODUCTION

European patent application no. 06737018.9 is directed to a method of preparing a pharmaceutical composition. This method comprises mixing (i) naproxen sodium, (ii) polyethylene glycol, (iii) hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, fumaric acid, maleic acid, tartaric acid, citric acid, malic acid, acetic acid, proprionic acid, pyruvic acid, butanoic acid, or lactic acid. Component (iii) is used in an amount of from 0.2 to 1.0 mole equivalents per mole of naproxen sodium.

An advantage of the present invention is that it provides a reduction in the production of undesired degradation products such as polyethylene glycol (PEG) esters compared with the prior art.

The applicant company conducted experiments to demonstrate that preparing a pharmaceutical composition in accordance with the present invention results in reduced formation of polyethylene glycol (PEG) esters compared to producing a composition in accordance with the teaching of D1.

Accordingly, the study was designed based on the information provided in D1 and the teaching of European patent application no. 06737018.9. The compositions tested are summarized in Tables 1, 2 and 3 below.

Table 1: Study of compositions prepared in accordance with the present invention

Naproxen Form	Naproxen amount	Acid	Approximate mole equivalent level (amount of acid)		
Naproxen Sodium	285 mg	HCl	0.2	0.6	1.0
	220 mg	HCl	0.2	0.6	1.0
Naproxen Sodium	285 mg	Lactic acid	0.2	0.6	1.0
	220 mg	Lactic acid	0.2	0.6	1.0
Naproxen Sodium	285 mg	Citric acid	0.2		1.0
	220 mg	Citric acid	0.2		

285 mg of Naproxen Sodium is equivalent to 260 mg of the free acid.

220 mg of Naproxen Sodium is equivalent to 200 mg of the free acid.

Table 2: Study based on the teaching of D1

Naproxen Form	Naproxen amount	Base	Approximate mole equivalent level (amount of base)		
Naproxen free acid	260 mg	KOH	0.2	0.6	1.0
	200 mg	KOH	0.2	0.6	1.0

All the experiments were performed using PEG 600. This is a representative example of a PEG that can be used in the present invention and was used in some of the Examples of the application as filed and was also used in Example IV of D1.

Table 3: Study based of compositions containing water

Naproxen Form	Naproxen Amount	Acid/Base	Water	Approximate mole equivalent level (amount of acid/base)		
Naproxen Sodium	285 mg	Lactic acid	8.5%	0.2	0.6	1.0
	220 mg	Lactic acid	8.5%	0.2	0.6	1.0
Naproxen free acid	260 mg	KOH	8.5%	0.2	0.6	1.0
	200 mg	KOH	8.5%	0.2	0.6	1.0

2.0 MATERIALS

Material	Lot #	Supplier
6N Hydrochloric Acid	E05P01	J.T. Baker
PEG-600	100009129	Banner
Lactic Acid	20010740	Banner
Citric Acid	08-0091	Banner
Potassium Hydroxide	E17K52	J.T. Baker
Naproxen Sodium	SO60103	RoChemical International
Naproxen	081M1091V	Sigma-Aldrich

3.0 PROCEDURE

Naproxen sodium or free acid was added to PEG 600 followed by addition of molar equivalent of the appropriate acid or based in accordance with the method of the present invention and the teaching of D1, respectively.

The compositions produced in this manner were subjected to an accelerated stability study. In this study the compositions were heated to 60°C for 1 week and analyzed for the amount of PEG esters initially and at the end of the accelerated stability study.

The following formulations were prepared:

- Two series of formulations identical to that described in D1 and in the present application.
- Two series of modified formulations prepared using:

  (1) 220 mg Naproxen Sodium and PEG 600, PG and Povidone were replaced with PEG 600. Three mole ratios of acid or base such as 0.2, 0.6 and 1 were used as illustrative of the range specified in the claims of the present application.

(2) Formulations based on the teaching of D1 comprising Naproxen free acid in an amount equivalent to the molar amount used in the formulations representative of the invention, with the same amount of PEG 600 and with KOH.

Samples were analyzed by HPLC:

Agilent 1100 Series HPLC System

Column: DeactiSil ODS-3 5u 100A, 25cm X 4.6mm (ES Industries)

Column Oven Temperature: ambient

Flow Rate: 1.5 mL/min

Injection Volume: 25 uL

UV Detector at 272 nm

Run Time: 60 minutes

Mobile Phase A:

Phosphate Buffer:Acetonitrile (3:2 ratio)

Mobile Phase B:

Phosphate Buffer:Acetonitrile (1:3 ratio)

Limit of quantitation was approximated to be 0.00011 mg/mL

Banner's Formulations

Sample #	Name	Naproxen Na (g)	6N HCl (mL)	PEG-600 (g)
1	NS 285-0.2 HCl	7.128	0.95	16.950
2	NS 285-0.6 HCl	7.120	2.80	15.024
3	NS 285-1.0 HCl	7.152	4.70	13.514
4	NS 220-0.2 HCl	5.512	0.70	18.790
5	NS 220-0.6 HCl	5.521	2.15	17.413
6	NS 220-1.0 HCl	5.548	3.60	15.891

		Naproxen Na (g)	Lactic Acid (g)	DI H20 (g)	PEG-600 (g)
7	NS 285-0.2 lactic	7.133	0.513	0.434	16.947
8	NS 285-0.6 Lactic	7.150	1.528	1.295	15.053
9	NS 285-1.0 Lactic	7.132	2.544	2.167	13.188
10	NS 220-0.2 Lactic	5.559	0.388	0.460	18.789
11	NS 220-0.6 Lactic	5.518	1.186	1.030	17.339
12	NS 220-1.0 Lactic	5.523	1.972	1.660	15.899

		Naproxen Na (g)	Citric Acid (g)	DI H20 (g)	PEG-600 (g)
13	NS 285-0.2 Citric	7.129	1.020	0.439	16.364
14	NS 285-1.0 Citric	7.128	5.436	2.519	10.350
15	NS 220-0.2 Citric	5.012	0.865	0.364	18.355

Yu's Formulations

	Naproxen API	Naproxen (g)	50% KOH (9)	PEG-GOO (g)
16	Yu 260-0.2 KOH	6.499	0.330	17.892
17	Yu 260-0.6 KOH	6.497	0.957	16.681
18	Yu 260-1.0 KOH	6.510	1.594	15.357
19	Yu 200-0.2 KOH	5.027	0.286	19.555
20	Yu 200-0.6 KOH	5.100	0.757	18.580
21	Yu 200-1.0 KOH	5.134	1.230	17.540

In the tables above, "Banner's formulations" refers to formulations prepared using the method of the present invention and "Yu's formulations" refers to formulations that are representative of the teaching of D1.

4.0 RESULTS

The results are summarized in the Table below.

Banner's Formulations		Room Temperature		Stress at 60C for 7-Days		Physical Observations of Formulations	
Sample #	Name	Peaks RT	% Area	Peaks RT	% Area	Room Temp	Stress at 60C 7-Days
1	NS 285-0.2 HCl	*10.78 **14.347	0.0084% 99.9916%	14.36	100.0000%	Phase Separate, precipitate	Phase Separate, precipitate
2	NS 285-0.6 HCl	10.787 14.34	0.0101% 99.9899%	10.78 14.38	0.0030% 99.9970%	Phase Separate, precipitate	Phase Separate, precipitate
3	NS 285-1.0 HCl	10.753 14.36	0.0076% 99.9924%	10.8 14.4	0.0069% 99.9931%	Phase Separate, precipitate	Phase Separate, precipitate
4	NS 220-0.2 HCl	10.773 14.347	0.0076% 99.9924%	14.4	100.0000%	Phase Separate, precipitate	Phase Separate, precipitate
5	NS 220-0.6 HCl	14.36	100.0000%	14.427	100.0000%	Phase Separate, precipitate	Phase Separate, precipitate
6	NS 220-1.0 HCl	10.773 14.36	0.0082% 99.9918%	10.793 14.413	0.0048% 99.9952%	Phase Separate, precipitate	Phase Separate, precipitate
7	NS 285-0.2 Lactic	10.78 14.293	0.0075% 99.9925%	14.36	100.0000%	Phase Separate, precipitate	Phase Separate, precipitate
8	NS 285-0.6 Lactic	10.773 14.287	0.0072% 99.9928%	14.38	100.0000%	Clear Solution, crystallize at bottom	Clear Solution
9	NS 285-1.0 Lactic	10.767 14.327	0.0073% 99.9927%	14.413	100.0000%	Phase Separate, precipitate	Phase Separate, precipitate

10	NS 220-0.2 Lactic	10.767 14.327	0.0069% 99.9931%	14.42	100.0000%	Phase Separate, precipitate	Phase Separate, precipitate
11	NS 220-0.6 Lactic	10.773 14.347	0.0067% 99.9933%	14.407	100.0000%	Clear solution	Clear solution
12	NS 220-1.0 Lactic	10.773 14.367	0.0064% 99.9936%	14.393	100.0000%	White semi-solid crystallized	Phase Separate, precipitate
13	NS 285-0.2 Citric	10.747 14.327	0.0087% 99.9913%	10.76 14.38	0.0038% 99.9962%	White semi-solid crystallized	Phase Separate, precipitate
14	NS 285-1.0 Citric	10.78 14.32	0.0021% 30.4552%	10.78 14.373	0.0107% 99.9893%	White semi-solid paste	White semi-solid paste
15	NS 220-0.2 Citric	10.787 14.353	0.0061% 99.9939%	14.393	100.0000%	Opaque solution fill, viscuous	Phase Separate, precipitate

Yu's Formulations		Room Temperature		Stress at 60C for 7-Days		Physical Observations of Formulations	
Sample #	**Name**	**Peaks RT**	**% Area**	**Peaks RT**	**% Area**	**Room Temp**	**Stress at 60C 7-Days**
16	Yu 260-0.2 KOH	*10.773 **14.333	0.0178% 99.8580%	10.793 14.387	0.0132% 99.8658%	Phase Separate, precipitate	Clear solution
17	Yu 260-0.6 KOH	10.767 14.367	0.0154% 99.8745%	10.807 14.387	0.0133% 99.8689%	Clear solution	Clear solution
18	Yu 260-1.0 KOH	10.793 14.36	0.0160% 99.8751%	10.813 14.373	0.0140% 99.8647%	Clear solution	Clear solution
19	Yu 200-0.2 KOH	10.793 14.393	0.0144% 99.8879%	10.8 14.413	0.0093% 99.8861%	Clear solution	Clear solution
20	Yu 200-0.6 KOH	10.787 14.387	0.0146% 99.8797%	10.793 14.4	0.0128% 99.8784%	Clear solution	Clear solution
21	Yu 200-1.0 KOH	10.787 14.38	0.0148% 99.8835%	10.807 14.387	0.0135% 99.8750%	Clear solution	Clear solution

* PEG ester peak retention time.

** Naproxen peak retention time.

In general, the amount of PEG ester in the formulations prepared in accordance with the teaching of D1 when subjected to stressed conditions varied from 0.0093 to 0.014. The compositions prepared by the method of the present invention exhibited lower levels of PEG esters at room temperature and after the stress study.

5.0 CONCLUSION

The results of these experiments show that formulations prepared in accordance with the teaching of the present invention surprisingly contain lower amounts of PEG esters that formulations prepared following the teaching of D1.

POTTER CLARKSON

EPO - Munich
35
27. März 2012

CONFIRMATION COPY

European Patent Office
Erhardtstraße 27
D-80298 München
GERMANY

26 March 2012

URGENT

Sent by fax

Dear Sirs

European Patent Application No. 06737018.9-2123
BANNER PHARMACAPS, INC.
Our ref: PABCX/P38814EP

Further to our letter dated 27 January 2012, we hereby enclose a statement of the Grounds of Appeal, an Annex, a Main Request and Thirteen Auxiliary Requests.

Yours faithfully

Rob Pugh (ROBERT I PUGH)

Charlotte Crowhurst PhD
For and on behalf of Potter Clarkson LLP

js

Enc: Grounds of Appeal
Main Request
Thirteen Auxiliary Requests
Annex

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European Patent Application No. 06737018.9
(Publication No. 1863458)

Applicant and Appellant: Banner Pharmacaps, Inc.

GROUNDS OF APPEAL

26 MARCH 2012

26 March 2012

Potter Clarkson LLP
for Banner Pharmacaps, Inc.

CONTENTS

26 March 2012

Potter Clarkson LLP
for Banner Pharmacaps, Inc.

1. DECISION ON WHICH AN APPEAL HAS BEEN FILED

The applicant, Banner Pharmacaps, Inc., filed a Notice of Appeal on 27 January 2012 against the decision of the Examining Division (the written confirmation of which was dated 29 November 2011) rejecting European patent application no. 06737018.9.

2. REQUEST

It is requested that:

i) The decision is cancelled in its entirety to the extent that the Appellant was adversely affected by it.

ii) The application is maintained on the basis of the enclosed Main Request.

iii) If it is considered not possible to maintain the application on the basis of the Main Request it is maintained on the basis of one of the enclosed Auxiliary Requests.

iv) Oral proceedings under Article 16 EPC are held in the event that the Board of Appeal intends not to allow the appeal.

3. THE BASIS ON WHICH THE APPEAL IS FILED

The decision of the Examining Division is wrong in law and in fact.

As will be explained in more detail below, the Examining Division's understanding of the claims was incorrect. This led to an incorrect finding on the facts of the case.

4. CLAIM REQUESTS

We enclose a Main Request and 13 Auxiliary Claim Requests.

As will be explained below, the claims of the Main Request satisfy the requirements of the EPC. However, in case the Board of Appeal is not prepared to allow the application on the basis of the Main Request, we enclose 13 Auxiliary Claim Requests to be considered in the order presented. Each of these claim requests satisfies the requirements of the EPC.

5. THE MAIN REQUEST

The Main Request is based on Auxiliary Request 3 considered in the decision of the Examining Division (ED). However, the wording of the claims has been amended to address comments made by the ED.

Date 26 March 2012

Potter Clarkson LLP
for Banner Pharmacaps, Inc.

5.1 BASIS FOR THE CLAIMS

Claim 1 of the main request is directed to a method of making a softgel capsule and is based on original claims 14 and 15, which was directed to a method of making a mixture and encapsulating the mixture in a softgel capsule.

The pharmaceutically active agent has been limited to naproxen sodium. There is basis for this at page 5, line 1 and in the Examples.

The term "deionising agent" used in the original claims has been replaced by the acids disclosed at page 6, lines 17 to 21 as examples of deionising agents.

There is basis for the range for the amount of deionising agent at page 6, lines 14 to 16 and in original claim 3.

The other claims are based on the disclosure in the application as filed as follows:

Claim	Basis in application as originally filed
2	Claim 17
3	Page 6, lines 17 to 21 and the Examples
4	Page 6, lines 17 to 21 and the Examples
5 and 6	Claims 6 and 7
7	Claim 9
8 to 10	Claims 11 to 13

5.2. THE MAIN REQUEST SATISFIES THE REQUIREMENTS OF THE EPC

The rejections raised in the Examining Division's Decision dated 29 November 2011 are addressed below in the order presented in the decision.

5.2.1 Article 84 EPC – The Claims Clearly Defined The Invention

The Examining Division (ED) alleged that the wording of claim 1 of the Main Request (and the Auxiliary Requests) was indefinite. Specifically, the ED alleged that it is not clear what is meant by the term "deionizing agent". This objection does not apply to the claims of the main request because the term "deionizing agent" is not used in the claims of this request.

Claim 1 of the main request includes a list of acids, which has a very clear meaning. Claim 1 also clearly states that the acid is used in an amount of 0.2 to 1.0 mole equivalents per mole of naproxen sodium.

In summary, claim 1 of the main request is clear and the skilled person would know exactly what ingredients to use in order to carry out the claimed method and how to carry out that method.

Date 26 March 2012

Potter Clarkson LLP
for Banner Pharmacaps, Inc.

5.2.2 Novelty – The Claims Define Novel Subject Matter

The invention is novel.

As noted above, the main request is based on the third auxiliary request previously on file. We note that the ED did not raise an objection of lack of novelty against the subject matter of the third auxiliary request in its decision.

More particularly, none of the cited documents disclose a method of making a softgel capsule that comprises mixing naproxen sodium with polyethylene glycol and an acid as listed in claim 1 and then encapsulating the mixture.

It is an essential feature of the main request that the drug is naproxen sodium. The claimed method is therefore novel over the disclosure of US 5360015 (D1) relating to diclofenac containing compositions to which the examiner has referred.

In D1, the active agent is in the form of the free acid or base and an ionizing agent is added to the composition containing the active agent. In the case of Example IV, which uses naproxen this means that naproxen is mixed with potassium hydroxide and polyethylene glycol. These starting materials are clearly different to those used in the claimed method.

The claimed method is therefore novel over D1.

The claimed method is also novel in view of the disclosure of US2001/0007668 (D3). In particular, Example 17 of D3 does not disclose the method as claimed.

Example 17 in D3 discloses a solution of naproxen sodium, polyethylene glycol 300, sodium hydroxide, and sodium propionate. D3 uses this strongly basic environment to maintain ionization. An acid as listed in claim 1 of the main request is not used in the method described in Example 17. Also, the solution in Example 17 of D3 is not encapsulated and could not be readily encapsulated. High pH, as used in Example 17, can destabilize the capsule shell, as described in D2 and is discussed in more detail below.

Accordingly, the subject matter of the main request is novel over D3.

5.2.3 Inventive Step – The Invention Is Inventive Over The Cited Prior Art

The ED has indicated that either D1 or D3 could be considered as the closest prior art. In view of these documents, as the ED has correctly identified, the problem to be solved can be considered to be the reduction of the formation of PEG-esters of the active agent. This reduction in the formation of PEG-esters is relative to the amount that would be formed by following the teaching of D1 or D3. As will be discussed below, the method of the main request solves this problem.

The method of the main request is also prima facie not obvious in view of the teaching of D1 and D3. As discussed above, neither D1 nor D3 teaches or suggests the use of an acid in combination with the salt of an acid drug such as naproxen sodium and polyethylene glycol. In D1 and D3, when naproxen is used, whether in the form of the

free drug or in the form of a salt it is used in combination with a base. There is nothing in D1 or D3 that would have motivated the skilled person to go against the teaching of these documents and use naproxen sodium in combination with an acid as listed in claim 1. For this reason at least the claimed method is novel in view of the disclosure of D1 and D3.

In naproxen containing compositions, PEG-esters are formed as a result of an interaction between free naproxen and PEG. The compositions of D1 comprise a higher concentration of free naproxen than is present in the compositions of the present invention.

Enclosed with these Grounds of Appeal is additional data showing a direct comparison of formulations produced by the claimed method to formulations prepared in accordance with the teaching of D1.

The formulations were tested using two different amounts of naproxen sodium, 285 mg and 220 mg, and three different acid deionizing agents, HCl, citric acid, and lactic acid. These acids are representative of the different acids listed in claim 1. Formulations of the type described in D1 containing 200 or 260 mg of naproxen free acid and sodium hydroxide (in place of the potassium hydroxide used in D1) were also tested. All formulations contained PEG 600 and water. The acid or base was tested at three different concentrations: 0.2, 0.6, and 1.0 mole equivalents compared to the active agent. The samples were subjected to accelerated stability studies (60°C for 1 week). The compositions of the invention showed very low initial levels of PEG ester formation and also very low levels, if any, of PEG ester formation at the end of the stability study. In contrast, in the D1 formulations, the amount of PEG ester varied from 0.0093 to 0.014.

This study provides a direct comparison of the present invention and D1 and clearly shows that the method of the present invention provides unexpected results in that compositions obtained by this method contained lower amounts of PEG esters both initially and after the stability studies. This could not have been predicted from the prior art.

The subject matter claimed is inventive over D1 and D3.

In the decision, the ED identified variables they believed could affect the stability of the formulations. We note that the ED provided no evidence to support their conclusions. Although all of the ED's comments are not directly relevant to the method claims of the main request, for completeness we will comment on them below.

The ED alleged that the absence or presence of water could have an effect on PEG-ester formation. The formulations used for the comparative testing contained water and reduction in the formation of PEG-esters for the claimed formulations was observed compared to the D1 formulations.

The ED cited the differences in the active agent (ketoprofen in D2) and naproxen in D1 as having a possible affect on PEG-ester formation. Both actives contain a carboxylic acid group, which is the reactive functional group that participates in the reaction to form PEG-esters. One of ordinary skill in the art would expect these agents to react in a similar manner. In fact, the ED relied on this reasoning in attempting to extrapolate the

behavior of ketoprofen as described in D2 to naproxen in order to reject Applicant's claims. In any event, the data now provided show that the compositions of the invention provide reduced PEG-ester formation compared with the compositions of D1 even when the active agent is the same.

The ED also alleged that lactic acid might be unique in its ability to reduce the formation of PEG-esters by a mechanism different than that for other acids and therefore its behavior cannot be extrapolated to other acids. The ED provided no scientific data to support this conclusion. The enclosed data show a reduction in PEG-ester formation for lactic acid (organic acid having as single carboxylic acid group), citric acid (organic acid having multiple carboxylic acid groups), and hydrochloric acid (an inorganic acid). This data shows that the problem addressed by the invention is solved across the full breadth of the claims.

The ED also alleged that Applicant did not account for the formation of propylene glycol (PG) esters. However, it is not clear how this relates to the problem to be solved. As noted by the ED, PG also contains hydroxyl groups which can react with the free acid to form esters. Regardless of the type of ester formation, esterification of the active agent reduces the efficacy of the formulation. Therefore, reducing the reactivity of the active agent should reduce formation of all types of esters. The data enclosed herein shows that the claimed formulations exhibit much lower concentrations of PEG-ester formation compared to the compositions of D1. Such behaviour would also be observed with respect to PEG-ester formation.

The ED also suggested that differences in the molecular weight of the PEG used in D2 (PEG 400), which described the formation of PEG esters, and the PEG used in D1, which is PEG 600 may account for differences in PEG ester formation. In order to do a direct comparison, comparative studies of the claimed formulations and the D1 formulations were done using PEG 600. The data is enclosed. As discussed above, for formulations produced using the method of the present invention, the amount of PEG-esters was very low. In contrast, the amount of PEG-esters formed in the D1 formulations was substantially higher.

The ED also alleged that one could not extrapolate from a single relative acid concentration or pH value to other acid concentrations. We respectfully disagree. However, in order to facilitate allowance, the comparative studies submitted herein were conducted at three different acid/base concentrations, 0.2, 0.6, and 1.0 mole equivalent of acid/base to moles of active agent. The data show that at all concentrations the formulations produced using the claimed method exhibited significantly less PEG-ester formation than the D1 formulations.

The data described herein clearly show a significant reduction in PEG-ester formation when formulations are made using the claimed method compared to formulations made in accordance with the teaching of D1. Moreover, the results presented in the enclosed Annex show that such unexpected results are achieved over the full breadth of the claims.

The ED cited D2 for the notion that PEG-ester formation can be suppressed when the agent is present as a salt. The ED failed to consider the cited passage on page 4 in its entirety. D2 discloses that fill materials containing PEG 400 and potassium hydroxide at

a mole ratio of 0.4 to 1 were unstable due to the formation of ketoprofen esters (page 4, lines 1-6). D2 discloses that in an attempt to completely ionize ketoprofen to prevent formation of undesirable esters, the potassium hydroxide to ketoprofen ratio was adjusted to 1.1 to 1 (page 4, lines 7-9). D2 goes on to state "With this second formulation, concerns arose that the ketoprofen salt thus formed and/or high pH caused by the excess potassium hydroxide used could effect the physical stability of the softgel capsule when the formulation was encapsulated. Additionally, if an equilibrium amount of the ketoprofen free acid remained in solution, it could form ketoprofen esters that could drive the reaction to form more ketoprofen free acid species which could eventually result in a chemically unstable formulation." D2 does not disclose or suggest forming more of the salt to minimize PEG-ester formation since doing so could (1) can destabilize the softgel capsule shell due to formation of large amounts of the salt and/or high pH; and (2) result in increased formation of PEG esters.

In the method now claimed, the active agent is naproxen sodium and it is used in combination with an acid. This method avoids the limitations discussed in D2.

None of the prior art discloses or suggest the method claimed in the main request or that such a method would solve the problem addressed by the present invention. Accordingly, the claims of the main request are inventive.

6. THE 1ST AUXILIARY REQUEST

The 1st auxiliary request is based on claim 2 of the main request considered by the ED and its dependent claims.

6.1 THE 1ST AUXILIARY REQUEST SATISFIES THE REQUIREMENTS OF THE EPC

6.1.1 Article 84 EPC – The Claims Clearly Defined The Invention

The Examining Division (ED) alleged that claim 1 of the Main Request (and the Auxiliary Requests) that they considered was indefinite. Specifically, the ED alleged that it is not clear what is meant by the term "deionizing agent". The ED alleged that it is not clear if the amount of deionizing agent should relate to the counter-ion or the final concentration of hydrogen ions. The ED has misunderstood the definition of the term "deionizing agent" and the amount of deionizing agent required according to the claims.

The application, as filed, states that "the deionizing agent functions by causing partial deionization (neutralization) of the salt of one or more pharmaceutically active agents" (page 6, lines 9 and 10). The claims specify that the active agent is a salt of an acidic pharmaceutically active agent, such as naproxen sodium. The deionizing agent is therefore a hydrogen-ion generating species (page 6, lines 11 and 12). Exemplary hydrogen-ion generating species are provided at page 6, lines 17-21.

The application as originally filed states "the deionizing agent is preferably present in an amount between 0.2 and 1.0 mole equivalents per mole of active agent" (page 6, lines 15-16). This range is an essential feature of the claims. The range clearly defines the amount of deionizing agent, not the amount of hydrogen ions or hydroxide ions produced in solution. It is also clear that the range for the amount of deionizing agent is relative to

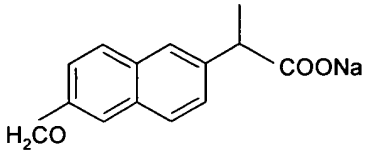
the amount of the salt of the acidic pharmaceutically active agent, such as naproxen sodium.

The dependent claim specifying the pH of the fill material has been deleted. Thus, any lack of clarity that the ED perceived resulted from the inclusion of claims specifying pH ranges has been removed.

The ED suggested that the molar range specified for the deionizing agent could relate to the amount of the anion.

However, this is not consistent with the information provided in the application and the applicant has not made any statement to suggest that this may be the case. From a knowledge of the basic chemistry of the interaction of a salt of an acidic pharmaceutically active agent such as naproxen sodium with a deionizing agent it would be abundantly clear to the skilled person that it is the amount of H^+ ions rather than the amount of the counter ion that is relevant to this invention.

Naproxen sodium has the structure



When naproxen sodium interacts with a deionizing agent the Na^+ is replaced by H^+ of the deionizing agent.

This basis chemistry would be self evident to the skilled reader, who would therefore appreciate what was meant by the quoted range for the amount of the deionizing agent.

The ED's statement that "The optional presence of water does not exclude the possibility that the H^+ ions are considered as deionizing agent" unnecessarily confuses and mistakenly complicates the situation. The wording of the claims makes it clear that the term "deionizing agent" does not encompass water.

In summary, claim 1 is clear and the skilled person would know exactly what is meant by the term deionizing agent and what the range for the amount of deionizing agent means.

6.1.2 Novelty – The Claims Define Novel Subject Matter

The invention is novel over the disclosure of US 5360015 (D1).

The claimed compositions are therefore novel over the disclosure of D1 relating to diclofenac containing compositions to which the examiner has referred. Diclofenac is not an acidic pharmaceutically active agent. It comprises both acidic and basic groups and it is therefore amphoteric. It is clear from the way in which acidic, basic and amphoteric active agents are discussed in the present application that the definition "acidic" does not encompass amphoteric molecules.

Additionally, it is known in the art that acids such as hydrochloric acid catalyse the intramolecular cyclisation of diclofenac to form an indoline derivative. A copy of a paper that describes the intramolecular cyclisation of diclofenac, Palomo *et al*, "Analysis of diclofenac sodium and derivatives", Journal of Pharmaceutical and Biomedical Analysis, 21 (1999), 83-94, is already on file. As stated in the abstract of Palomo, the intramolecular cyclisation of diclofenac sodium causes the salt to become inactivated.

Thus, Example VII of D1 does not describe a pharmaceutical composition having the essential features of the compositions of the present invention. In particular, the composition of Example VII of D1 is not a composition comprising a salt of an acid or basic active agent and a deionizing agent that causes partial neutralization of the salt of the active agent resulting in enhanced bioavailability of the active agent. In fact, cyclization of the drug will have the opposite effect.

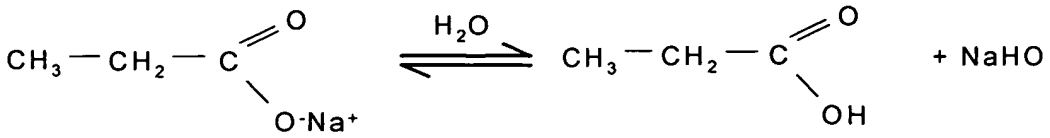
In assessing novelty, the ED alleged that because the compositions of the invention are typically in the form of a solution, it is not possible to distinguish whether the active agent and/or deionizing agent has been added in the form of a salt or a free acid. We respectfully disagree.

In D1, the active agent is in the form of the free acid or base and an ionizing agent is added to the composition containing the active agent. This means that in the case of an acidic drug the composition comprises the acidic drug and a base. The reaction of the active agent and ionizing agent is less than quantitative, so the composition will always comprise some of the acidic drug and some unreacted base. In contrast, in the pending claims, the active agent is in the form of a salt. The deionizing agent is added to a composition containing the salt of the active agent. Because reaction of the salt of the active agent and the deionizing agent is less the quantitative, the solution will always contain some of the salt and some unreacted deionizing agent but it will not contain a base as is present in the compositions of D1.

The ED raised an objection of lack of novelty on the basis of the disclosure of D3, particularly Example 17. The subject matter claimed is novel in view of the disclosure of D3.

Example 17 in D3 discloses a solution of naproxen sodium, polyethylene glycol 300, sodium hydroxide, and sodium propionate. Sodium propionate cannot deionize naproxen sodium since sodium propionate is not a hydrogen ion generating species. Therefore, regardless of whether the amount of sodium propionate in Example 1 is within the range of molar amounts specified in the claims, the formulation in Example 17 is not within the scope of the claims. Moreover, the solution is Example 17 in D3 is not encapsulated and could not be readily encapsulated. High pH, as used in Example 17, can destabilize the capsule shell as discussed in D2.

When sodium propionate is added to water, an equilibrium is established between propionate and propionic acid, as shown below:



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However, the amount of propionic acid present at equilibrium in the formulation of Example 17 of D3 is far below the 0.2 equivalents required by the claims. The formulation described in Example 17 of D3 contains 0.8153 g sodium propionate (K_b = 7.46 x 10^{-10}) dissolved in 800 mL of water (*i.e.*, an aqueous solution of approximately 0.0106 M sodium propionate). If we ignore the impact of the other species present in solution (including the naproxen sodium, PEG 300, and potassium hydroxide) on the equilibrium between propionate and propionic acid, the concentration of propionic acid at equilibrium can be calculated to be approximately 2.7 x 10^{-5} M (corresponding to roughly 2.2 x 10^{-5} moles propionic acid at equilibrium). The formulation in Example 17 of D3 contains 3.0033 g (0.0119 moles) of naproxen sodium. Therefore, if we ignore the impact of the other species present in solution, Example 17 describes a formulation containing roughly ***0.0018 mole equivalents*** of propionic acid per mole of naproxen sodium. In contrast, it is an essential feature of the present invention that the deionizing agent is present in an amount of from about 0.2 to 1.0 mole equivalents per mole of naproxen sodium.

Furthermore, the solution in Example 17 also contains 6.66 mg of potassium hydroxide. The pH of the sodium propionate solution is approximately 9.6. The addition of potassium hydroxide will make the solution more basic driving the equilibrium between proprionate and proprionic acid in the direction of proprionate. As a result, the actual amount of propionate present in the formulation described in Example 17 will be even less than 0.0018 mole equivalents per mole of naproxen sodium. Therefore, what small amounts of propionic acid may be present in Example 17 of D3 are not within the range for the amount of deionizing agent specified in the claims and thus are not effective to partially deionize naproxen sodium. Moreover, the solution in Example 17 of D3 is not encapsulated and could not be readily encapsulated. High pH, as used in Example 17, can destabilize the capsule shell, as discussed in D2. Accordingly, the subject matter claimed is novel over D3.

6.1.3 Inventive Step – The Invention Is Inventive Over The Cited Prior Art

The ED has indicated that either D1 or D3 could be considered as the closest prior art. In view of these documents, as the ED has correctly identified, the problem to be solved can be considered to be the reduction of the formation of PEG-esters of the active agent. This reduction in the formation of PEG-esters is relative to the amount that would be formed by following the teaching of D1 or D3.

In compositions containing an acidic pharmaceutically active agent, such as naproxen containing compositions, PEG-esters are formed as a result of an interaction between free acidic drug (e.g. naproxen) and PEG. The compositions of both D1 and D3 comprise a higher concentration of free naproxen than is present in the compositions of the present invention.

D1 is concerned with ionizing the free acid or free base, not deionizing the salt of the free acid or base. D1 describes ionizing naproxen not deionizing naproxen sodium. The ED has failed to show why one of ordinary skill in the art would have been motivated by the teaching of D1 to modify its teaching so as to deionize the drug rather than ionize it and thus arrive at the claimed compositions. D1 teaches the exact opposite of what is done

in the present invention and it cannot be considered to be obvious to go completely against the teaching of the prior art in this way.

Regarding D3, the ED alleges that D3 discloses that the formulations described therein are stable and robust. However, it is not clear in what context these solutions are described as stable. D3 discloses that no precipitate was observed but there is no disclosure related to PEG-ester formation. Such esters are likely to be soluble in PEG and therefore may not be observed visually, yet their formation affects the efficacy of the formulation.

The ED acknowledged the data submitted on 15 September 2011 but alleged that the date was not sufficient to directly compare the claimed compositions and the compositions of D1 (or D3).

Enclosed with these Grounds of Appeal is additional data showing a direct comparison of the claimed compositions to the compositions in D1.

The claimed formulations were tested using two different amounts of naproxen sodium, 285 mg and 220 mg, and three different acid deionizing agents, HCl, citric acid, and lactic acid. Formulations of the type described in D1 containing 200 or 260 mg of naproxen free acid and sodium hydroxide (in place of the potassium hydroxide used in D1) were also tested. All formulations contained PEG 600 and water. The acid or base was tested at three different concentrations: 0.2, 0.6, and 1.0 mole equivalents compared to the active agent. The samples were subjected to accelerated stability studies (60°C for 1 week). The compositions of the invention showed very low initial levels of PEG ester formation and also very low levels of PEG ester formation, if any, at the end of the stability study. In contrast, in the D1 formulations, the amount of PEG ester varied from 0.0093 to 0.014.

This study provides a direct comparison of the present invention and D1 and clearly shows that the method of the present invention provides unexpected results in that compositions obtained by this method contained lower amounts of PEG esters both initially and after the stability studies. This could not have been predicted from the prior art.

The subject matter claimed is therefore inventive.

In the decision, the ED identified variables they believed could affect the stability of the formulations. We note that the ED provided no evidence to support their conclusions.

The ED alleged that the absence or presence of water could have an effect on PEG-ester formation. As discussed above, the formulations used for the comparative testing contained water and reduction in the formation of PEG-esters for the claimed formulations was observed compared to the D1 formulations.

The ED cited the differences in the active agent (ketoprofen in D2) and naproxen in D1 as having a possible affect on PEG-ester formation. Both actives contain a carboxylic acid group, which is the reactive functional group that participates in the reaction to form PEG-esters. One of ordinary skill in the art would expect these agents to react in a similar manner. In fact, the ED relied on this reasoning in attempting to extrapolate the

behavior of ketoprofen as described in D2 to naproxen in order to reject Applicant's claims. In any event, the data now provided show that the compositions of the invention provide reduced PEG-ester formation compared with the compositions of D1 even when the active agent is the same.

The ED also alleged that lactic acid might be unique in its ability to reduce the formation of PEG-esters by a mechanism different than that for other acids and therefore its behavior cannot be extrapolated to other acids. The ED provided no scientific data to support this conclusion. The enclosed data show a reduction in PEG-ester formation for lactic acid (organic acid having as single carboxylic acid group), citric acid (organic acid having multiple carboxylic acid groups), and hydrochloric acid (an inorganic acid). This data shows that the problem addressed by the invention is solved across the full breadth of the claims.

The ED also alleged that Applicant did not account for the formation of propylene glycol (PG) esters. However, it is not clear how this relates to the problem to be solved. As noted by the ED, PG also contains hydroxyl groups which can react with the free acid to form esters. Regardless of the type of ester formation, esterification of the active agent reduces the efficacy of the formulation. Therefore, reducing the reactivity of the active agent should reduce formation of all types of esters. The data enclosed herein shows that the claimed formulations exhibit much lower concentrations of PEG-ester formation compared to the compositions of D1. Such behaviour would also be observed with respect to PEG-ester formation.

The ED also suggested that differences in the molecular weight of the PEG used in D2 (PEG 400), which described the formation of PEG esters, and the PEG used in D1, which is PEG 600 may account for differences in PEG ester formation. In order to do a direct comparison, comparative studies of the claimed formulations and the D1 formulations were done using PEG 600. The data is enclosed. As discussed above, for the claimed formulations, the amount of PEG-esters was very low. In contrast, the amount of PEG-esters formed in the D1 formulations was substantially higher.

The ED also alleged that one could not extrapolate from a single relative acid concentration or pH value to other acid concentrations. We respectfully disagree. However, in order to facilitate allowance, the comparative studies submitted herein were conducted at three different deionizing agent and ionizing agent concentrations, 0.2, 0.6, and 1.0 mole equivalent of deionizing or ionizing agent to moles of active agent. The data show that at all concentrations the claimed formulations exhibited significantly less PEG-ester formation than the D1 formulations.

The data described herein clearly show a significant reduction in PEG-ester formation for the claimed formulations compared to the formulations in of D1. Moreover, Applicants have shown that such unexpected results are achieved over the full breadth of the claims.

The ED cited D2 for the notion that PEG-ester formation can be suppressed when the agent is present as a salt. The ED failed to consider the cited passage on page 4 in its entirety. D2 discloses that fill materials containing PEG 400 and potassium hydroxide at a mole ratio of 0.4 to 1 were unstable due to the formation of ketoprofen esters (page 4, lines 1-6). D2 discloses that in an attempt to completely ionize ketoprofen to prevent

formation of undesirable esters, the potassium hydroxide to ketoprofen ratio was adjusted to 1.1 to 1 (page 4, lines 7-9). D2 goes on to state "With this second formulation, concerns arose that the ketoprofen salt thus formed and/or high pH caused by the excess potassium hydroxide used could effect the physical stability of the softgel capsule when the formulation was encapsulated. Additionally, if an equilibrium amount of the ketoprofen free acid remained in solution, it could form ketoprofen esters that could drive the reaction to form more ketoprofen free acid species which could eventually result in a chemically unstable formulation." D2 does not disclose or suggest forming more of the salt to minimize PEG-ester formation since doing so could (1) can destabilize the softgel capsule shell due to formation of large amounts of the salt and/or high pH; and (2) result in increased formation of PEG esters.

None of the prior art discloses or suggest the claimed solution to the problem to be solved. Accordingly, the claims are inventive.

7. 2ND AUXILIARY REQUEST

The second auxiliary request is based on the first auxiliary request except that the term "deionizing agent which is a hydrogen ion species in an amount to cause partial deionization of the salt" has been replaced by a list of specify acids. Basis for this list can be found at page 6, lines 17 to 21 of the application as filed.

The comments of the ED relating to the clarity of wording relating to the deionizing agent are moot as this wording has been removed from the claims of this request. The claims of this request meet the other requirements of the EPC for the reasons set out above in relation to auxiliary request 1.

8. 3RD AUXILIARY REQUEST

The third auxiliary request is based on the first auxiliary request except that the active agent has been limited to naproxen sodium. The claims of this request satisfy the requirements of the EPC for the reasons set out above in relation to the first auxiliary request.

Additionally, it is noted that D1 does not disclose compositions comprising naproxen sodium. The two Examples of D1 that disclose compositions comprising naproxen, Examples IV and X both comprise naproxen and potassium hydroxide. In these compositions, potassium hydroxide acts as an ionizing agent and its interaction with naproxen results in the formation of naproxen potassium but these compositions do not comprise a compound that is a deionizing agent. For this reason, the subject matter of the claims of this request is novel in view of the disclosure of D1.

It is also noted that the data provided in the attached Annex clearly show that the problem addressed by the present invention is solved when the active agent is naproxen sodium.

In summary, this request satisfies the requirements of the EPC.

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for Banner Pharmacaps, Inc.

9. 4TH AUXILIARY REQUEST

This request is based on the second and third auxiliary requests. That is the term "deionizing agent which is a hydrogen ion species in an amount to cause partial deionization of the salt" has been replaced by a list of acids and the active agent has been limited to naproxen sodium.

This request satisfies the requirements of the EPC for a combination of the reasons set out above in relation to the second and third auxiliary requests.

10. 5TH AUXILIARY REQUEST

This request is based on the fourth auxiliary request except that the list of acids has been reduced to include hydrochloric acid, citric acid and lactic acid only. These are the acids used in the Examples that were present in the application as originally filed and are also the acids that were used in the experiments reported in the attached Annex.

The claims of this request satisfy the requirements of the EPC for the reasons set out above in relation to the fifth auxiliary request.

It is also noted that the data provided in the attached Annex clearly show that the problem addressed by the present invention is solved when the active agent is naproxen sodium and an acid as listed in claim 1 is used.

In summary, this request satisfies the requirements of the EPC.

11. 6TH AUXILIARY REQUEST

This request is based on the fifth auxiliary request except that the acid has been limited to lactic acid. Lactic acid is used in the Examples that were present in the application as originally filed and the information included in attached Annex shows that formulations comprising lactic acid have a particularly favourable combination of properties.

The claims of this request satisfy the requirements of the EPC for the reasons set out above in relation to the fifth auxiliary request.

12. 7TH AUXILIARY REQUEST

This request is based on the third auxiliary request considered by the ED, except that the active agent has been limited to naproxen sodium.

It is noted that the ED considered that the claims of the third auxiliary request that they considered related to novel subject matter. The claims of this request are also novel.

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The claims of this request satisfy the other requirements of the EPC for the reasons set out about in relation to the main request, first auxiliary request and the third auxiliary request.

13. 8TH AUXILIARY REQUEST

This request is based on the main request except that the list of acids has been reduced to include hydrochloric acid, citric acid and lactic acid only. These are the acids used in the Examples that were present in the application as originally filed and are also the acids that were used in the experiments reported in the attached Annex.

The claims of this request satisfy the requirements of the EPC for the reasons set out above in relation to the main auxiliary request.

It is also noted that the data provided in the attached Annex clearly show that the problem addressed by the present invention is solved when the active agent is naproxen sodium and an acid as listed in claim 1 is used.

In summary, this request satisfies the requirements of the EPC.

14. 9TH AUXILIARY REQUEST

This request is based on the eighth auxiliary request except that the acid has been limited to lactic acid. Lactic acid is used in the Examples that were present in the application as originally filed and the information included in attached Annex shows that formulations comprising lactic acid have a particularly favourable combination of properties.

The claims of this request satisfy the requirements of the EPC for the reasons set out above in relation to the eighth auxiliary request.

15. 10TH, 11TH, 12TH AND 13TH AUXILIARY REQUESTs

These requests are based on the main request and the 7th, 8th and 9th auxiliary requests respectively. In each of these requests claim 1 has been amended to state that step (a) of the claimed method is conducted at a temperature of from 50°C to 70°C. There is basis for this in original claim 17.

The subject matter of each of these requests satisfies the requirements of the EPC for the same reasons as each of the main request and the 7th, 8th and 9th auxiliary requests.

Date 26 March 2012

Potter Clarkson LLP
for Banner Pharmacaps, Inc.

16. CONCLUSION

For the reasons set out above the decision of the Examining Division should be overturned and a patent should be granted.

Charlotte Crowhurst PhD
For and on behalf of Potter Clarkson LLP
26 March 2012

Date 26 March 2012

Potter Clarkson LLP
for Banner Pharmacaps, Inc.

Main Request

CLAIMS

1. A method of making a softgel capsule comprising

(a) making a fill mixture by mixing (i) naproxen sodium, (ii) polyethylene glycol, (iii) hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, fumaric acid, maleic acid, tartaric acid, citric acid, malic acid, acetic acid, proprionic acid, pyruvic acid, butanoic acid, or lactic acid; and

(b) encapsulating the mixture in a softgel capsule;

wherein (iii) is used in an amount of from 0.2 to 1.0 mole equivalents per mole of naproxen sodium.

2. A method of claim 1, wherein step (a) is conducted at a temperature of from 50°C to 70°C.

3. The method of claim 1 or claim 2, wherein (iii) is hydrochloric acid, citric acid or lactic acid.

4. The method of claim 3, wherein (iii) is lactic acid.

5. The method of any one of the preceding claims, wherein polyethylene glycol is present in an amount of from 10% to 80% by weight.

6. The method of any one of the preceding claims wherein the polyethylene glycol is one or more polyethylene glycols with a molecular weight between 300 and 1500.

7. The method of any one of the preceding claims, wherein water is present in an amount of from 1% to 18% by weight.

8. The method of any one of the preceding claims, wherein one or more excipients selected from the group consisting of plasticizers, crystallization inhibitors, wetting agents, bulk filling agents, solubilizers, bioavailability enhancers, solvents, dyes, preservatives, solvents, surfactants, and combinations thereof is added.

9. The method of claim 8, wherein the solubilizer is selected from the group consisting of glycerin, polyvinylpyrrolidone, propylene glycol and combinations thereof.

10. The method of claim 9, wherein the solubilizer is used in amount from 1% to 10% by weight.

11. A method according to any one of the preceding claims wherein the fill mixture produced in step (a) is liquid.

9th AUXILIARY REQUEST

CLAIMS

1. A method of making a softgel capsule comprising

(a) making a fill mixture by mixing (i) naproxen sodium, (ii) polyethylene glycol, (iii) lactic acid; and

(b) encapsulating the mixture in a softgel capsule;

wherein (iii) is used in an amount of from 0.2 to 1.0 mole equivalents per mole of naproxen sodium.

2. A method of claim 1, wherein step (a) is conducted at a temperature of from 50°C to 70°C.

3. The method of claim 1 or claim 2, wherein polyethylene glycol is present in an amount of from 10% to 80% by weight.

4. The method of any one of the preceding claims wherein the polyethylene glycol is one or more polyethylene glycols with a molecular weight between 300 and 1500.

5. The method of any one of the preceding claims, wherein water is present in an amount of from 1% to 18% by weight.

6. The method of any one of the preceding claims, wherein one or more excipients selected from the group consisting of plasticizers, crystallization inhibitors, wetting agents, bulk filling agents, solubilizers, bioavailability enhancers, solvents, dyes, preservatives, solvents, surfactants, and combinations thereof is added.

7. The method of claim 6, wherein the solubilizer is selected from the group consisting of glycerin, polyvinylpyrrolidone, propylene glycol and combinations thereof.

8. The method of claim 7, wherein the solubilizer is used in amount from 1% to 10% by weight.

9. A method according to any one of the preceding claims wherein the fill mixture produced in step (a) is liquid.

10th AUXILIARY REQUEST

CLAIMS

1. A method of making a softgel capsule comprising

(a) making a fill mixture by mixing (i) naproxen sodium, (ii) polyethylene glycol, (iii) hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, fumaric acid, maleic acid, tartaric acid, citric acid, malic acid, acetic acid, proprionic acid, pyruvic acid, butanoic acid, or lactic acid, at a temperature of from 50°C to 70°C; and

(b) encapsulating the mixture in a softgel capsule;

wherein (iii) is used in an amount of from 0.2 to 1.0 mole equivalents per mole of naproxen sodium.

2. The method of claim 1, wherein (iii) is hydrochloric acid, citric acid or lactic acid.

3. The method of claim 2, wherein (iii) is lactic acid.

4. The method of any one of the preceding claims, wherein polyethylene glycol is present in an amount of from 10% to 80% by weight.

5. The method of any one of the preceding claims wherein the polyethylene glycol is one or more polyethylene glycols with a molecular weight between 300 and 1500.

6. The method of any one of the preceding claims, wherein water is present in an amount of from 1% to 18% by weight.

7. The method of any one of the preceding claims, wherein one or more excipients selected from the group consisting of plasticizers, crystallization inhibitors, wetting agents, bulk filling agents, solubilizers, bioavailability enhancers, solvents, dyes, preservatives, solvents, surfactants, and combinations thereof is added.

8. The method of claim 7, wherein the solubilizer is selected from the group consisting of glycerin, polyvinylpyrrolidone, propylene glycol and combinations thereof.

9. The method of claim 8, wherein the solubilizer is used in amount from 1% to 10% by weight.

10. A method according to any one of the preceding claims wherein the fill mixture produced in step (a) is liquid.

11th AUXILIARY REQUEST

CLAIMS

1. A method of making a softgel capsule comprising

(a) making a fill mixture by mixing (i) naproxen sodium, (ii) polyethylene glycol, (iii) a deionizing agent which is a hydrogen ion species in an amount to cause partial deionization of the salt, and (iv) optionally water at a temperature of from 50°C to 70°C; and

(b) encapsulating the mixture in a softgel capsule;

wherein (iii) is used in an amount to cause partial ionization of the naproxen sodium of from 0.2 to 1.0 mole equivalents per mole of naproxen sodium.

2. The method of claim 1, wherein the deionizing agent is selected from hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, fumaric acid, maleic acid, tartaric acid, methane sulfonate, ethane sulfonate, benzene sulfonate, citric acid, malic acid, acetic acid, proprionic acid, pyruvic acid, butanoic acid, or lactic acid,

3. The method of claim 1 or claim 2, wherein (iii) is hydrochloric acid, citric acid or lactic acid.

4. The method of claim 3, wherein (iii) is lactic acid.

5. The method of any one of the preceding claims, wherein polyethylene glycol is present in an amount of from 10% to 80% by weight.

6. The method of any one of the preceding claims wherein the polyethylene glycol is one or more polyethylene glycols with a molecular weight between 300 and 1500.

7. The method of any one of the preceding claims, wherein water is present in an amount of from 1% to 18% by weight.

8. The method of any one of the preceding claims, wherein one or more excipients selected from the group consisting of plasticizers, crystallization inhibitors, wetting agents, bulk filling agents, solubilizers, bioavailability enhancers, solvents, dyes, preservatives, solvents, surfactants, and combinations thereof is added.

9. The method of claim 8, wherein the solubilizer is selected from the group consisting of glycerin, polyvinylpyrrolidone, propylene glycol and combinations thereof.

10. The method of claim 9, wherein the solubilizer is used in amount from 1% to 10% by weight.

11. A method according to any one of the preceding claims wherein the fill mixture produced in step (a) is liquid.

12th AUXILIARY REQUEST

CLAIMS

1. A method of a softgel capsule comprising

(a) making a fill mixture by mixing (i) naproxen sodium, (ii) polyethylene glycol, (iii) hydrochloric acid, citric acid, or lactic acid, at a temperature of from 50°C to 70°C; and

(b) encapsulating the mixture in a softgel capsule;

wherein (iii) is used in an amount of from 0.2 to 1.0 mole equivalents per mole of naproxen sodium.

2. The method of claim 1, wherein (iii) is lactic acid.

3. The method claim 1 or claim 2, wherein polyethylene glycol is present in an amount of from 10% to 80% by weight.

4. The method of any one of the preceding claims wherein the polyethylene glycol is one or more polyethylene glycols with a molecular weight between 300 and 1500.

5. The method of any one of the preceding claims, wherein water is present in an amount of from 1% to 18% by weight.

6. The method of any one of the preceding claims, wherein one or more excipients selected from the group consisting of plasticizers, crystallization inhibitors, wetting agents, bulk filling agents, solubilizers, bioavailability enhancers, solvents, dyes, preservatives, solvents, surfactants, and combinations thereof is added.

7. The method of claim 6, wherein the solubilizer is selected from the group consisting of glycerin, polyvinylpyrrolidone, propylene glycol and combinations thereof.

8. The method of claim 7, wherein the solubilizer is used in amount from 1% to 10% by weight.

9. A method according to any one of the preceding claims wherein the fill mixture produced in step (a) is liquid.

13th AUXILIARY REQUEST

CLAIMS

1. A method of making a softgel capsule comprising

(a) making a fill mixture by mixing (i) naproxen sodium, (ii) polyethylene glycol, (iii) lactic acid, at a temperature of from 50°C to 70°C; and

(b) encapsulating the mixture in a softgel capsule;

wherein (iii) is used in an amount of from 0.2 to 1.0 mole equivalents per mole of naproxen sodium.

2. The method of claim 1, wherein polyethylene glycol is present in an amount of from 10% to 80% by weight.

3. The method of claim 1 or claim 2, wherein the polyethylene glycol is one or more polyethylene glycols with a molecular weight between 300 and 1500.

4. The method of any one of the preceding claims, wherein water is present in an amount of from 1% to 18% by weight.

5. The method of any one of the preceding claims, wherein one or more excipients selected from the group consisting of plasticizers, crystallization inhibitors, wetting agents, bulk filling agents, solubilizers, bioavailability enhancers, solvents, dyes, preservatives, solvents, surfactants, and combinations thereof is added.

6. The method of claim 5, wherein the solubilizer is selected from the group consisting of glycerin, polyvinylpyrrolidone, propylene glycol and combinations thereof.

7. The method of claim 6, wherein the solubilizer is used in amount from 1% to 10% by weight.

8. A method according to any one of the preceding claims wherein the fill mixture produced in step (a) is liquid.

1st AUXILIARY REQUEST

CLAIMS

1. A softgel capsule comprising a fill material wherein the fill material comprises
   (a) a salt of an acidic pharmaceutically active agent;
   (b) a deionizing agent which is a hydrogen ion species in an amount to cause partial deionization of the salt of from 0.2 to 1.0 mole equivalents per mole of the pharmaceutically active agent;
   (c) polyethylene glycol; and optionally
   (d) water.

2. The capsule of claim 1 wherein the pharmaceutically active agent is selected from the group consisting of therapeutically active agents, diagnostic agents, and prophylactic agents.

3. The capsule of claim 1 or claim 2 wherein polyethylene glycol is present in an amount from 10% to 80% by weight.

4. The capsule of any one of the preceding claims wherein the polyethylene glycol is one or more polyethylene glycols with a molecular weight between 300 and 1500.

5. The capsule of any one of the preceding claims wherein water is present in an amount from 1% to 18% by weight.

6. The capsule of any one of the preceding claims further comprising one or more excipients selected from the group consisting of plasticizers, crystallization inhibitors, wetting agents, bulk filling agents, solubilizers, bioavailability enhancers, solvents, dyes, preservatives, solvents, surfactants, and combinations thereof.

7. The capsule of claim 6 wherein the solubilizer is selected from the group consisting of glycerin, polyvinylpyrrolidone, propylene glycol and combinations thereof.

8. The capsule of claim 7 wherein the solubilizer is present in amount from 1% to 10% by weight.

9. The capsule of any one of the preceding claims wherein the salt (a) is naproxen sodium.

10. The capsule of any one of the preceding claims wherein the hydrogen ion species is selected from hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, fumaric acid, maleic acid, tartaric acid, methane-, ethane-, and benzene sulfonates, citric acid, malic acid, acetic acid, proprionic acid, pyruvic acid, butanoic acid, and lactic acid.

11. The capsule of claim 10 wherein the hydrogen ion species is hydrochloric acid, citric acid or lactic acid.

12. The capsule of claim 11 wherein the hydrogen ion species is lactic acid.

13. The capsule of any one of the preceding claims wherein the fill material is liquid.

14. A capsule of any one of the preceding claims 1 for use as a medicament.

15. A method of making the capsule of any one of the preceding claims comprising
    (a) mixing the salt of an acidic pharmaceutically active agent, the polyethylene glycol and the deionizing agent and optionally water; and
    (b) encapsulating the mixture in a softgel capsule.

16. The method of claim 15 wherein step (a) is conducted at a temperature of from 50 °C to 70 °C.

17. The use of
    (a) a salt of an acidic pharmaceutically active agent;
    (b) a deionizing agent which is a hydrogen ion species in an amount to cause partial deionization of the salt of from 0.2 to 1.0 mole equivalents per mole of the pharmaceutically active agent;
    (c) polyethylene glycol; and optionally
    (d) water
    in the manufacture of a softgel capsule medicament for administration of the pharmaceutically active agent to a patient in need thereof.

18. A softgel capsule obtainable by a method which comprises

(I) producing a fill material by mixing

(a) a salt of an acidic pharmaceutically active agent;

(b) a deionizing agent which is a hydrogen ion species in an amount to cause partial deionization of the salt of from 0.2 to 1.0 mole equivalents per mole of the pharmaceutically active agent;

(c) polyethylene glycol; and optionally

(d) water; and

(II) encapsulating the mixture in a softgel capsule.

19. The softgel capsule of claim 18, obtainable by a process in which step (I) is conducted at a temperature of from 50°C to 70°C.

2nd AUXILIARY REQUEST

CLAIMS

1. A softgel capsule comprising a fill material wherein the fill material comprises
   (a) a salt of an acidic pharmaceutically active agent;
   (b) hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, fumaric acid, maleic acid, citric acid, malic acid, acetic acid, proprionic acid, pyruvic acid, butanoic acid or lactic acid in an amount of from 0.2 to 1.0 mole equivalents per mole of the pharmaceutically active agent; and
   (c) polyethylene glycol.

2. The capsule of claim 1 wherein the pharmaceutically active agent is selected from the group consisting of therapeutically active agents, diagnostic agents, and prophylactic agents.

3. The capsule of claim 1 or claim 2 wherein polyethylene glycol is present in an amount from 10% to 80% by weight.

4. The capsule of any one of the preceding claims wherein the polyethylene glycol is one or more polyethylene glycols with a molecular weight between 300 and 1500.

5. The capsule of any one of the preceding claims wherein water is present in an amount from 1% to 18% by weight.

6. The capsule of any one of the preceding claims further comprising one or more excipients selected from the group consisting of plasticizers, crystallization inhibitors, wetting agents, bulk filling agents, solubilizers, bioavailability enhancers, solvents, dyes, preservatives, solvents, surfactants, and combinations thereof.

7. The capsule of claim 6 wherein the solubilizer is selected from the group consisting of glycerin, polyvinylpyrrolidone, propylene glycol and combinations thereof.

8. The capsule of claim 7 wherein the solubilizer is present in amount from 1% to 10% by weight.

9. The capsule of any one of the preceding claims wherein the salt (a) is naproxen sodium.

10. The capsule of any one of the preceding claims wherein (b) is hydrochloric acid, citric acid or lactic acid.

11. The capsule of claim 10 wherein (b) is lactic acid.

12. The capsule of any one of the preceding claims wherein the fill material is liquid.

13. A capsule of any one of the preceding claims for use as a medicament.

14. A method of making the capsule as defined in claim 1 comprising

(a) mixing components (a), (b), (c) as defined in claim 1; and

(b) encapsulating the mixture in a softgel capsule.

15. The method of claim 14 wherein step (a) is conducted at a temperature of from 50 °C to 70 °C.

16. The use of

(a) a salt of an acidic pharmaceutically active agent;

(b) hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, fumaric acid, maleic acid, citric acid, malic acid, acetic acid, proprionic acid, pyruvic acid, butanoic acid or lactic acid in an amount of from 0.2 to 1.0 mole equivalents per mole of the pharmaceutically active agent; and

(c) polyethylene glycol;

in the manufacture of a softgel capsule medicament for administration of the pharmaceutically active agent to a patient in need thereof.

17. A softgel capsule obtainable by a method which comprises

(I) producing a fill material by mixing

(a) a salt of an acidic pharmaceutically active agent;

(b) hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, fumaric acid, maleic acid, citric acid, malic acid, acetic acid, proprionic acid, pyruvic acid,

butanoic acid or lactic acid in an amount of from 0.2 to 1.0 mole equivalents per mole of the pharmaceutically active agent;

(c) polyethylene glycol; and

(II) encapsulating the mixture in a softgel capsule.

18. The softgel capsule of claim 17 obtainable by a method in which step (I) is conducted at a temperature of from 50°C to 70°C.

3rd AUXILIARY REQUEST

CLAIMS

1. A softgel capsule comprising a fill material wherein the fill material comprises

(a) naproxen sodium;

(b) a deionizing agent in an amount to cause partial deionization of the salt of from 0.2 to 1.0 mole equivalents per mole of the naproxen sodium;

(c) polyethylene glycol; and optionally

(d) water.

2. The capsule of claim 1 wherein the deionizing is selected from hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, fumaric acid, maleic acid, tartaric acid, methane-, ethane-, and benzene sulfonates, citric acid, malic acid, acetic acid, proprionic acid, pyruvic acid, butanoic acid, and lactic acid.

3. The capsule of claim 2 wherein the deionizing agent is hydrochloric acid, citric acid or lactic acid.

4. The capsule of claim 3 wherein the deionizing agent is lactic acid

5. The capsule of any one of the preceding claims wherein polyethylene glycol is present in an amount from 10% to 80% by weight.

6. The capsule of any one of the preceding claims wherein the polyethylene glycol is one or more polyethylene glycols with a molecular weight between 300 and 1500.

7. The capsule of any one of the preceding claims wherein water is present in an amount from 1% to 18% by weight.

8. The capsule of any one of the preceding claims further comprising one or more excipients selected from the group consisting of plasticizers, crystallization inhibitors, wetting agents, bulk filling agents, solubilizers, bioavailability enhancers, solvents, dyes, preservatives, solvents, surfactants, and combinations thereof.

9. The capsule of claim 8 wherein the solubilizer is selected from the group consisting of glycerin, polyvinylpyrrolidone, propylene glycol and combinations thereof.

10. The capsule of claim 9 wherein the solubilizer is present in amount from 1% to 10% by weight.

11. The capsule of any one of the preceding claims wherein the fill material is liquid.

12. A capsule of any one of the preceding claims for use as a medicament.

13. A method of making the capsule of any of the preceding claims comprising

(a) mixing naproxen sodium, the polyethylene glycol and the deionizing agent and optionally water; and

(b) encapsulating the mixture in a softgel capsule.

14. The method of claim 13, wherein step (a) is conducted at a temperature of from 50°C to 70°C.

15. The use of

(a) naproxen sodium;

(b) a deionizing agent in an amount to cause partial deionization of the naproxen sodium from 0.2 to 1.0 mole equivalents per mole of the pharmaceutically active agent(s);

(c) polyethylene glycol: and optionally

(d) water

in the manufacture of a medicament in the form of a capsule for administration of the naproxen sodium to a patient in need thereof.

16. A softgel capsule obtainable by a method which comprises

(I) producing a fill material by mixing

(a) naproxen sodium;

(b) a deionizing agent in an amount to cause partial deionization of the naproxen sodium from 0.2 to 1.0 mole equivalents per mole of the pharmaceutically active agent(s);

(c) polyethylene glycol: and optionally

(d) water; and

(II) encapsulating the mixture in a softgel capsule.

17. The softgel capsule of claim 16 obtainable by a method in which step (I) is conducted at a temperature of from 50°C to 70°C.

4th AUXILIARY REQUEST

CLAIMS

1. A softgel capsule comprising a fill material wherein the fill material comprises

(a) naproxen sodium;

(b) hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, fumaric acid, maleic acid, tartaric acid, citric acid, malic acid, acetic acid, proprionic acid, pyruvic acid, butanoic acid or lactic acid in an amount of from 0.2 to 1.0 mole equivalents per mole of the naproxen sodium;

(c) polyethylene glycol.

2. The capsule of claim 1 wherein (b) is hydrochloric acid, citric acid or lactic acid.

3. The capsule of claim 2 wherein (b) is lactic acid.

4. The capsule of any one of the preceding claims wherein polyethylene glycol is present in an amount from 10% to 80% by weight.

5. The capsule of any one of the preceding claims wherein the polyethylene glycol is one or more polyethylene glycols with a molecular weight between 300 and 1500.

6. The capsule of any one of the preceding claims wherein water is present in an amount from 1% to 18% by weight.

7. The capsule of any one of the preceding claims further comprising one or more excipients selected from the group consisting of plasticizers, crystallization inhibitors, wetting agents, bulk filling agents, solubilizers, bioavailability enhancers, solvents, dyes, preservatives, solvents, surfactants, and combinations thereof.

8. The capsule of claim 7 wherein the solubilizer is selected from the group consisting of glycerin, polyvinylpyrrolidone, propylene glycol and combinations thereof.

9. The capsule of claim 8 wherein the solubilizer is present in amount from 1% to 10% by weight.

10. The capsule of any one of the preceding claims wherein the fill material is liquid.

11. A capsule of any of the preceding claims for use as a medicament.

12. A method of making the capsule of claim 1 comprising

(a) mixing components (a), (b) and (c) as defined in claim 1; and

(b) encapsulating the mixture in a softgel capsule.

13. The method of claim 12, wherein step (a) is conducted at a temperature of from 50°C to 70°C

14. The use of

(a) naproxen sodium;

(b) hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, fumaric acid, maleic acid, tartaric acid, citric acid, malic acid, acetic acid, proprionic acid, pyruvic acid, butanoic acid or lactic acid in an amount of from 0.2 to 1.0 mole equivalents per mole of the naproxen sodium; and

(c) polyethylene glycol;

in the manufacture of a medicament in the form of a capsule for administration of the naproxen sodium to a patient in need thereof.

15. A softgel capsule obtainable by a method which comprises

(I) producing a fill material by mixing

(a) naproxen sodium;

(b) hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, fumaric acid, maleic acid, tartaric acid, citric acid, malic acid, acetic acid, proprionic acid, pyruvic acid, butanoic acid or lactic acid in an amount of from 0.2 to 1.0 mole equivalents per mole of the naproxen sodium; and

(c) polyethylene glycol; and

(II) encapsulating the mixture in a softgel capsule.

16. The softgel capsule of claim 15 obtainable by a method in which step (I) is conducted at a temperature of from 50°C to 70°C.

5th AUXILIARY REQUEST

CLAIMS

1. A softgel capsule comprising a fill material wherein the fill material comprises
   (a) naproxen sodium;
   (b) hydrochloric acid, citric acid or lactic acid in an amount of from 0.2 to 1.0 mole equivalents per mole of the naproxen sodium;
   (c) polyethylene glycol.

2. The capsule of claim 1 wherein (b) is lactic acid.

3. The capsule of any one of the preceding claims wherein polyethylene glycol is present in an amount from 10% to 80% by weight.

4. The capsule of any one of the preceding claims wherein the polyethylene glycol is one or more polyethylene glycols with a molecular weight between 300 and 1500.

5. The capsule of any one of the preceding claims wherein water is present in an amount from 1% to 18% by weight.

6. The capsule of any one of the preceding claims 1 further comprising one or more excipients selected from the group consisting of plasticizers, crystallization inhibitors, wetting agents, bulk filling agents, solubilizers, bioavailability enhancers, solvents, dyes, preservatives, solvents, surfactants, and combinations thereof.

7. The capsule of claim 6 wherein the solubilizer is selected from the group consisting of glycerin, polyvinylpyrrolidone, propylene glycol and combinations thereof.

8. The capsule of claim 7 wherein the solubilizer is present in amount from 1% to 10% by weight.

9. The capsule of any one of the preceding claims wherein the fill material is liquid.

10. A capsule of any one of the preceding claims for use as a medicament.

11. A method of making the capsule of any one of the preceding claims comprising

(a) mixing naproxen sodium, the polyethylene glycol and the hydrochloric acid, citric acid or lactic acid; and

(b) encapsulating the mixture in a softgel capsule.

12. The method of claim 11, wherein step (a) is conducted at a temperature of from 50°C to 70°C

13. The use of

(a) naproxen sodium;

(b) hydrochloric acid, citric acid or lactic acid in an amount of from 0.2 to 1.0 mole equivalents per mole of the naproxen sodium; and

(c) polyethylene glycol;

in the manufacture of a medicament in the form of a capsule for administration of the naproxen sodium to a patient in need thereof.

14. A softgel capsule obtainable by a method which comprises

(I) producing a fill material by mixing

(a) naproxen sodium;

(b) hydrochloric acid, citric acid or lactic acid in an amount of from 0.2 to 1.0 mole equivalents per mole of the naproxen sodium; and

(c) polyethylene glycol; and

(III) encapsulating the mixture in a softgel capsule.

15. The softgel capsule of claim 14 obtainable by a method in which step (I) is conducted at a temperature of from 50°C to 70°C.

6th AUXILIARY REQUEST

CLAIMS

1. A softgel capsule comprising a fill material wherein the fill material comprises

(a) naproxen sodium;

(b) lactic acid in an amount of from 0.2 to 1.0 mole equivalents per mole of the naproxen sodium;

(c) polyethylene glycol.

2. The capsule of claim 1 wherein polyethylene glycol is present in an amount from 10% to 80% by weight.

3. The capsule of claim 1 wherein the polyethylene glycol is one or more polyethylene glycols with a molecular weight between 300 and 1500.

4. The capsule of claim 1 wherein water is present in an amount from 1% to 18% by weight.

5. The capsule of claim 1 further comprising one or more excipients selected from the group consisting of plasticizers, crystallization inhibitors, wetting agents, bulk filling agents, solubilizers, bioavailability enhancers, solvents, dyes, preservatives, solvents, surfactants, and combinations thereof.

6. The capsule of claim 5 wherein the solubilizer is selected from the group consisting of glycerin, polyvinylpyrrolidone, propylene glycol and combinations thereof.

7. The capsule of claim 6 wherein the solubilizer is present in amount from 1% to 10% by weight.

8. The capsule of any one of the preceding claims wherein the fill material is liquid.

9. A capsule of any one of the preceding claims for use as a medicament.

10. A method of making the capsule of any one of the preceding claims comprising

(a) mixing naproxen sodium, the polyethylene glycol and the lactic acid and optionally water; and

(b) encapsulating the mixture in a softgel capsule.

11. The method of claim 10, wherein step (a) is conducted at a temperature of from 50°C to 70°C.

12. The use of

(a) naproxen sodium;

(b) lactic acid in an amount to cause partial deionization of the naproxen sodium from 0.2 to 1.0 mole equivalents per mole of the pharmaceutically active agent(s);

(c) polyethylene glycol: and optionally

(d) water

in the manufacture of a medicament in the form of a capsule for administration of the naproxen sodium to a patient in need thereof.

13. A softgel capsule obtainable by a method which comprises

(I) producing a fill material by mixing

(a) naproxen sodium;

(b) lactic acid in an amount to cause partial deionization of the naproxen sodium from 0.2 to 1.0 mole equivalents per mole of the pharmaceutically active agent(s);

(c) polyethylene glycol: and optionally

(d) water; and

(II) encapsulating the mixture in a softgel capsule.

14. The softgel capsule of claim 13 obtainable by a method in which step (I) is conducted at a temperature of from 50°C to 70°C.

7th AUXILIARY REQUEST

CLAIMS

1. A method of making a softgel capsule comprising

(a) making a fill mixture by mixing (i) naproxen sodium, (ii) polyethylene glycol, (iii) a deionizing agent which is a hydrogen ion species in an amount to cause partial deionization of the salt, and (iv) optionally water; and

(b) encapsulating the mixture in a softgel capsule;

wherein (iii) is used in an amount to cause partial deionization of the naproxen sodium of from 0.2 to 1.0 mole equivalents per mole of naproxen sodium.

2. A method of claim 1, wherein step (a) is conducted at a temperature of from 50°C to 70°C.

3. The method of claim 1 or claim 2, wherein the deionizing agent is selected from hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, fumaric acid, maleic acid, tartaric acid, methane sulfonate, ethane sulfonate, benzene sulfonate, citric acid, malic acid, acetic acid, proprionic acid, pyruvic acid, butanoic acid, or lactic acid,

4. The method of any one of the preceding claims, wherein (iii) is hydrochloric acid, citric acid or lactic acid.

5. The method of claim 4, wherein (iii) is lactic acid.

6. The method of any one of the preceding claims, wherein polyethylene glycol is present in an amount of from 10% to 80% by weight.

7. The method of any one of the preceding claims wherein the polyethylene glycol is one or more polyethylene glycols with a molecular weight between 300 and 1500.

8. The method of any one of the preceding claims, wherein water is present in an amount of from 1% to 18% by weight.

9. The method of any one of the preceding claims, wherein one or more excipients selected from the group consisting of plasticizers, crystallization inhibitors, wetting agents, bulk filling agents, solubilizers, bioavailability enhancers, solvents, dyes, preservatives, solvents, surfactants, and combinations thereof is added.

10. The method of claim 9, wherein the solubilizer is selected from the group consisting of glycerin, polyvinylpyrrolidone, propylene glycol and combinations thereof.

11. The method of claim 10, wherein the solubilizer is used in amount from 1% to 10% by weight.

12. A method according to any one of the preceding claims wherein the fill mixture produced in step (a) is liquid.

8th AUXILIARY REQUEST

CLAIMS

1. A method of making a softgel capsule comprising

(a) making a fill mixture by mixing (i) naproxen sodium, (ii) polyethylene glycol, (iii) hydrochloric acid, citric acid or lactic acid; and

(b) encapsulating the mixture in a softgel capsule;

wherein (iii) is used in an amount of from 0.2 to 1.0 mole equivalents per mole of naproxen sodium.

2. A method of claim 1, wherein step (a) is conducted at a temperature of from 50°C to 70°C.

3. The method claim 1 or claim 2, wherein (iii) is lactic acid.

4. The method of any one of the preceding claims, wherein polyethylene glycol is present in an amount of from 10% to 80% by weight.

5. The method of any one of the preceding claims wherein the polyethylene glycol is one or more polyethylene glycols with a molecular weight between 300 and 1500.

6. The method of any one of the preceding claims, wherein water is present in an amount of from 1% to 18% by weight.

7. The method of any one of the preceding claims, wherein one or more excipients selected from the group consisting of plasticizers, crystallization inhibitors, wetting agents, bulk filling agents, solubilizers, bioavailability enhancers, solvents, dyes, preservatives, solvents, surfactants, and combinations thereof is added.

8. The method of claim 7, wherein the solubilizer is selected from the group consisting of glycerin, polyvinylpyrrolidone, propylene glycol and combinations thereof.

9. The method of claim 8, wherein the solubilizer is used in amount from 1% to 10% by weight.

10. A method according to any one of the preceding claims wherein the fill mixture produced in step (a) is liquid.

Europäisches Patentamt
European Patent Office
Office européen des brevets

European patent application No. 06737018.9

Appeal - for immediate attention

I. Findings

1. ☐ Appeal in which **more than one party** is involved (opposition procedure, except when all oppositions have been withdrawn). Refer the case to the Board of Appeal without delay using EPO Form 2703.

2. ☑ Appeal in which **only one party** is involved (examination procedure and opposition procedure if all oppositions have been withdrawn).

2.1 Requirements of Article 108 EPC

The **notice of appeal** has been filed within the time limit.	yes ☒	no ☐
The **appeal fee** has been paid within the time limit.	yes ☒	no ☐
The **statement of grounds** has been filed within the time limit.	yes ☒	no ☐

If one of the answers set out above is "no", refer the case to the Board of Appeal without delay using EPO Form 2703. The Board of Appeal decides on the admissibility of the appeal.

2.2 Special cases which have to be referred to the Board of Appeal without delay using EPO Form 2703

☐ Request for re-establishment of rights into the appeal period (Art. 122 EPC)
☐ Withdrawal of the appeal
☐ Expiry of the three-month time limit for Interlocutory revision (Art. 109(2) EPC)
☐ Request for correction of the appeal (R. 139 EPC)

27-03-2012	Hodzic, Iris	
Date	Formalities Officer	Director/SCAPE (for information)

II. Appeal against the decision of the Formalities Officer

☐ The appeal is allowable and well-founded. The decision under appeal is rectified (Art. 109(1) EPC). EPO Form 2710 is to be dispatched.
  ☐ No request for reimbursement of the appeal fee has been filed.
  ☐ A request for reimbursement of the appeal fee has been filed.
    ☐ Reimbursement of the appeal fee is ordered (R. 103 EPC).
    ☐ The request for reimbursement of the appeal fee cannot be allowed. **Refer the case to the Board of Appeal without delay using Form 2703 (R. 103(2) EPC).**
☐ The decision under appeal is not rectified. Refer the case to the Board of Appeal without delay using EPO Form 2703 (Art. 109(2) EPC).

Date	Formalities Officer	SCAPE (for information)

III. Appeal against the decision of the Examining/Opposition Division

☑ To the Examining Division ☐ To the Opposition Division

27-03-2012	Hodzic, Iris
Date	Formalities Officer

SS51521

To the Formalities Officer

☐ The appeal is allowable and well-founded. The decision under appeal is rectified (Art. 109(1) EPC). EPO Form 2710 is to be dispatched.

- ☐ No request for reimbursement of the appeal fee has been filed.
- ☐ A request for reimbursement of the appeal fee has been filed.
  - ☐ Reimbursement of the appeal fee is ordered (R. 103 EPC).
  - ☐ The request for reimbursement of the appeal fee cannot be allowed. **Refer the case to the Board of Appeal without delay using EPO Form 2703 (R. 103(2) EPC).**

☒ The decision under appeal is not rectified. Refer the case to the Board of Appeal without delay using EPO Form 2703 (Art. 109(2) EPC).

36.3.12
Date

☒ Examining Division ☐ Opposition Division

Chairman	2nd Examiner	Primary Examiner	Legal Member

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Datum/Date
18.04.12

Zeichen/Reference/Référence	Anmeldung Nr./Application No./Demande n°/Patent Nr./Patent No./Brevet n°
PABCA/P38814EP APPR	06737018.9 / 1863458
Anmelder/Applicant/Demandeur//Patentinhaber/Proprietor/Titulaire	
Banner Pharmacaps Inc.	

File number: **T0826/12-3.3.02**

Commencement of Proceedings before the Board of Appeal

The letter dated 27.01.12 filed by the applicant
against the decision of the European Patent Office of 29.11.11
has been referred to Board of Appeal 3.3.02.

The reference number is mentioned above.

Any further communications should be addressed to Directorate-General 3 of the European Patent Office and should quote this reference number.

The Registrar G. Magouliotis
Tel.: 089 / 2399 - 3321

Annex: letter dated
Registered letter

Europäisches Patentamt
European Patent Office
Office européen des brevets

Beschwerdekammern
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Appeal number: T0826/12-3.3.02

Order

1. In accordance with the business distribution scheme of the Technical Boards of Appeal, the following shall hear the above appeal:

Chairman: U. Oswald

technically qualified member: D. Boulois

legally qualified member: R. Cramer

In the case of an extended Board:

technically qualified member: _____

legally qualified member: _____

2. The rapporteur shall be: D. Boulois

3. The additional rapporteur shall be: _____

4. Back to the Registry for further action.

Munich, 10.07.12

Chairman U. Oswald

POTTER CLARKSON

European Patent Office
Erhardtstraße 27
D-80298 München
GERMANY

EPO - Munich
27
28. Sep. 2012

27 September 2012

Dear Sirs

CHANGE OF ADDRESS FOR POTTER CLARKSON LLP
Our Ref: GEN/RSB

Please note that, as of 1 October 2012, this firm (Association No 414) will be located at:

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Please update your records.

Yours faithfully

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Appeal number: T0826/12-3.3.07

Order

1. In accordance with the business distribution scheme of the Technical Boards of Appeal, the following shall hear the above appeal:

Chairman: J. Riolo

technically qualified member: D. Boulois

legally qualified member: W. Ungler

In the case of an extended Board:

technically qualified member: _____

legally qualified member: _____

2. The rapporteur shall be: D. Boulois

3. The additional rapporteur shall be: _____

4. Back to the Registry for further action.

Munich, 16.04.13

Chairman J. Riolo

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The Belgrave Centre
Talbot Street
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ROYAUME UNI

Datum/Date
19.04.13

Zeichen/Reference/Référence	Anmeldung Nr./Application No./Demande n°//Patent Nr./Patent No./Brevet n°
PABCA/P38814EP APPR01	06737018.9 / 1863458
Anmelder/Applicant/Demandeur//Patentinhaber/Proprietor/Titulaire	
Banner Pharmacaps Inc.	

Appeal number: **T0826/12-3.3.07**

Change of responsibility of a Board of Appeal
Article 1(2) Business Distribution Scheme for the Technical Boards of Appeal

According to the amended business distribution scheme for the Technical Boards of Appeal for the year 2013 , this case has been transferred to Board 3307 as from 02.01.13.

The new reference number is: **T0826/12-3.3.07**

Please quote the new reference number cited above in any further communications.

The Registrar I. Aperribay
Tel.: 089 / 2399 - 3371

POTTER CLARKSON

Claudia Weber & Eric Bihl (CDR)
European Patent Office
80298 MUNICH
GERMANY

31 July 2013

Sent by Fax

Dear Claudia & Eric

REGISTERED ASSOCIATION NO. 414

I understand from Richard Garvey that you are the correct people to contact concerning the transfer of all cases for Potter Clarkson LLP to our Registered Association. Potter Clarkson LLP is Registered Association No. 414. I would be grateful if you could transfer all our cases to our Registered Association, so that we may then proceed in setting up an EPO Mailbox for receiving official notifications.

Please let me know if you require any further information from me. I look forward to receiving confirmation that the transfer has been made.

Yours sincerely

Gareth D Probert PhD
For and on behalf of Potter Clarkson LLP

seb

Potter Clarkson LLP
The Belgrave Centre
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W:www.potterclarkson.com

POTTER CLARKSON

Claudia Weber & Eric Bihl (CDR)
European Patent Office
80298 MUNICH
GERMANY

31 July 2013

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Date
08.08.13

Reference	Application No./Patent No.
PABCA/P38814EP	06737018.9 - 1464 / 1863458

Applicant/Proprietor
Banner Pharmacaps Inc.

Communication of amended entries concerning the representative (R. 143(1)(h) EPC)

As requested, for the above-mentioned European patent application / European patent the entries concerning the representative have been amended as follows:

Potter Clarkson LLP
The Belgrave Centre
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The amendment will be recorded in the Register of European Patents.

For the Examining Division

Europäisches Patentamt • European Patent Office • Office européen des brevets

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Appeal number: **T0826/12-3.3.07**

Order

Oral proceedings are to be held

on 16.09.14

at 09:00 hours

Room N° 0132

Munich 15.11.13

Chairman J. Riolo

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Zeichen/Reference/Référence	Anmeldung Nr./Application No./Demande n°//Patent Nr./Patent No./Brevet n°
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Banner Pharmacaps Inc.	

Appeal number: **T0826/12-3.3.07**

Summons to oral proceedings pursuant to Rule 115(1) EPC

You are hereby summoned to the oral proceedings concerning the above appeal.
The proceedings are scheduled to take place

on 16.09.14 at 9:00 hrs in Room 0132

Bob-van-Benthem-Platz 1, 80469 Munich (DE)

The proceedings will be public.

Room 115 is available as a waiting-room.

You are requested to attend outside the appointed room **10 minutes** before the hearing.

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Appeal number: **T0826/12-3.3.07**

You are reminded that

- if a party who has been duly summoned to oral proceedings does not appear, the proceedings may continue without that party (Rule 115(2) EPC).

- oral proceedings will only be postponed at the request of a party for serious reasons (see Notice in Special edition No. 3 OJ EPO 2007, 115).

- as regards filing authorisations for representatives or company employees, see Decision of the President of the EPO dated 12.7.2007 on the filing of authorisations in Special edition No. 3 OJ EPO 2007, 128.

- concerning the language of the proceedings, attention is drawn to Rule 4 EPC. Notice given pursuant to Rule 4(1) EPC before the first instance is not valid in proceedings before the Boards of Appeal.

Composition of the Board

Chairman: J. Riolo

Member: D. Boulois

Member: W. Ungler

For all urgent communications in connection with the oral proceedings please use <u>only</u> fax No. + 49 (0) 89 2399 3014.

If you are planning not to attend the oral proceedings or if you are aware of any matter that could have a bearing on the appointment of interpreters, you are requested to inform the Board of this, preferably in writing, at the earliest possible opportunity.

The Registrar S. Fabiani

Tel.: 089 / 2399 - 3371

Annex(es): ☑ Confirmation of receipt Form 2936

☐ Communication pursuant to Article 15(1) of the Rules of Procedure of the Boards of Appeal

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Sendungsnummer / No de l'envoi / Item number

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Boards of Appeal

The Registry

Name: S. Fabiani

Tel.: 089 / 2399 - 3371

Date: 20.11.13

Zeichen/Reference/Référence	Anmeldung Nr./Application No./Demande n°//Patent Nr./Patent No./Brevet n°
PABCA/P38814EP APPR	06737018.9 / 1863458
Anmelder/Applicant/Demandeur//Patentinhaber/Proprietor/Titulaire	
Banner Pharmacaps Inc.	

Appeal number: T0826/12-3.3.07

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(11) International Publication Number: **WO 95/31979**

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08/247,028 19 May 1994 (19.05.94) US

(60) Parent Application or Grant
(63) Related by Continuation
US 08/247,028 (CIP)
Filed on 19 May 1994 (19.05.94)

(71) Applicant *(for all designated States except US)*: R.P. SCHERER INTERNATIONAL CORPORATION [US/US]; 2075 West Big Beaver Road, P.O. Box 7060, Troy, MI 48007-7060 (US).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: SHELLEY, Rickey, S. [US/US]; 986 Wood Street, Largo, FL 31640 (US). WEI, Youching [US/US]; 2275 Willowbrook Drive, Clearwater, FL 34624 (US).

(74) Agents: SARUSSI, Steven, J.; Banner & Allegretti, Ltd., Ten South Wacker Drive, Chicago, IL 60606 (US).

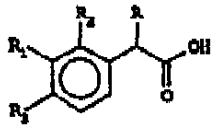
(81) Designated States: AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LT, LU, LV, MD, MG, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TT, UA, UG, US, UZ, VN, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG), ARIPO patent (KE, MW, SD, SZ, UG).

Published
With international search report.
Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: SOLUTIONS OF ARYL OR HETEROARYL SUBSTITUTED ALKANOIC ACIDS IN LIPOPHILIC SOLVENTS AND SOFT GELATIN CAPSULES CONTAINING SUCH SOLUTIONS

(57) Abstract

Methods and compositions are disclosed for preparing liquid mixtures of aryl or heteroaryl alkanoic acids suitable for encapsulation in soft gelatin capsules. The compositions comprise alkanoic acids of formulas (I), (Ia), (Ib) or pharmaceutically acceptable salts thereof, wherein R, R_1, R_2, R_3, and R_5 represent hydrogen or various organic substituents, and an effective solubilizing amount of at least one lipophilic solvent.



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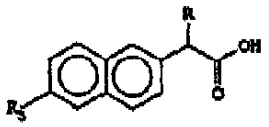

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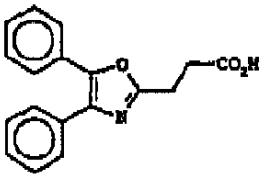

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SOLUTIONS OF ARYL OR HETEROARYL SUBSTITUTED ALKANOIC ACIDS IN LIPOPHILIC SOLVENTS AND SOFT GELATIN CAPSULES CONTAINING SUCH SOLUTIONS

BACKGROUND OF THE INVENTION

Field of the Invention

The present invention relates to solutions containing therapeutically useful substituted alkanoic acids in combination with at least one lipophilic solvent for encapsulation in soft gelatin capsules (softgel capsules).

Description of the Related Art

Hydrophilic softgels are well known for the oral administration of pharmaceutical agents. Typically, softgel capsules consist of an outer shell of gelatin containing a plasticizer and an inner filling of hydrophilic liquid containing a dissolved hydrophobic pharmaceutical agent. The plasticizer is chosen so that the solubility in the fill liquid is as low as possible. If the plasticizer is soluble in the fill liquid, it can migrate out of the shell over time into the fill, leaving the shell brittle and subject to rupture.

With respect to pharmaceutical agents of relatively low solubility and/or relatively high dosage amount, softgel capsules can pose problems for the pharmaceutical formulator. For example, if a given pharmaceutical agent has a relatively low solubility, it may need a relatively large volume of solution in order to deliver a pharmaceutically acceptable unit dose. While theoretically possible to encapsulate such a large volume of solution in a softgel capsule, for example, the practical

limitations on the size of capsules suitable for conventional oral administration to human patients could well preclude pharmaceutical use of the resulting softgel.

Similarly, if a pharmaceutical agent requires a relatively high dose, a large volume of solution may again be a necessity for delivery of the require dosage. Softgel encapsulation of such a large solution volume may be impractical because the size of the needed softgel would likely exceed the maximum limit for conventional oral administration to human patients.

As one approach to handling the problems of encapsulating low solubility or high dose pharmaceutical agents, U.S. Patent No. 5,071,643 (Yu et. al.) discloses the use of polyethylene glycol based solutions for acidic, basic and amphoteric pharmaceutical agents. These polyethylene glycol based solutions contain either an hydroxide species or a hydrogen ion species that causes the appropriate pharmaceutical agent to partially ionize, i.e., the pharmaceutical agent is present in both the free form and the salt form. The partial ionization described in Yu et al. results in enhanced solubility for the acidic, basic or amphoteric pharmaceutical agent. This enhanced solubility, in turn, may permit the preparation of a solution of pharmaceutical agent that is highly concentrated enough to be encapsulated in a capsule acceptably sized for oral administration to human patients. The Yu et al. patent discloses that enhanced solubility solutions can be prepared using polyethylene glycol and contemplated equivalents of polyethylene

glycol, such as polyethylene glycol ethers or various alcohols and copolymers of polyethylene glycol.

Softgel encapsulation is sometimes the preferred delivery system for many pharmaceutical agents that are administered orally to human patients. Generally, to be suitable for softgel encapsulation, a pharmaceutical formulation should be in the form of a clear, stable solution. The present inventors have discovered that the enhanced solubility solutions disclosed by the Yu et al. patent are not as effective with various substituted alkanoic acid pharmaceutical agents.

Therapeutically useful 2- or 3-aryl or 2- or 3-heteroaryl substituted alkanoic acids function as anti-inflammatory and analgesic agents and may be administered orally. They are also essentially insoluble in water. An example of such a useful alkanoic acid suitable for use in the present invention is ketoprofen which is 2-(3-benzoylphenyl) propionic acid.

Ketoprofen is an anti-inflammatory, analgesic agent that is principally indicated for the acute and long-term management of rheumatoid arthritis and osteoarthritis. Additionally it is a nonsteroidal compound and poorly water soluble. Some gastrointestinal irritation is ordinarily associated with oral dosage forms of ketoprofen. The properties of ketoprofen render it a good candidate for formulation with the enhanced solubility solutions disclosed in the Yu et al. patent. In a number of experiments, the present inventors applied the Yu et al. enhanced solubility solutions in formulations of ketoprofen for softgel encapsulation.

In one formulation, polyethylene glycol 400 and potassium hydroxide were used to solubilize the ketoprofen, with the mole ratio of potassium hydroxide to ketoprofen being in the range of 0.4 to 1. It was surprisingly found that the resulting formulation was not sufficiently stable for softgel encapsulation due to the undesirable formation of ketoprofen esters.

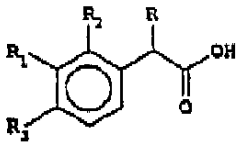
In an attempt to completely ionize the ketoprofen to prevent the formation of undesirable esters, the potassium hydroxide to ketoprofen mole ratio was adjusted to range from 1.1 to 1. With this second formulation, concerns arose that the ketoprofen salt thus formed and/or the high pH caused by the excess potassium hydroxide used could affect the physical stability of the softgel capsule when the formulation was encapsulated. Additionally, if an equilibrium amount of the ketoprofen free acid remained in the solution, it could form ketoprofen esters that could drive the reaction to form more ketoprofen free acid species, which could eventually result in a chemically unstable formulation.

The present inventors have discovered that non-hydroxyl containing solvents may be used to form pharmaceutically acceptable solutions of 2- or 3-aryl or 3-heteroaryl substituted alkanoic acids that are stable and suitable for softgel encapsulation.

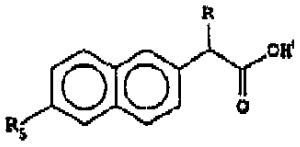
SUMMARY OF THE INVENTION

The present invention provides enhanced solubility pharmaceutically acceptable solutions of therapeutically useful substituted alkanoic acids, preferably 2- or 3-aryl or 2- or 3-heteroaryl alkanoic acids, that can be encapsulated in softgel capsules of a size suitable for subsequent oral administration to human patients, having improved chemical stability compared with polyethylene glycol water miscible formulations of the alkanoic acids.

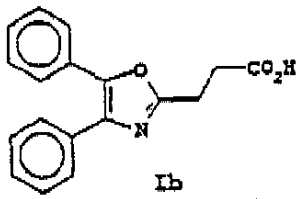
The therapeutically useful active agents, i.e., substituted alkanoic acids, preferred for use in the present invention have general formulas I, Ia or Ib:



I



Ia

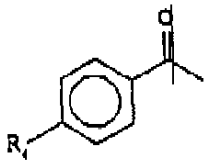


Ib

or pharmaceutically acceptable salts thereof, wherein

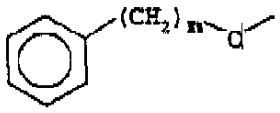
R represents a hydrogen atom or an alkyl group containing 1 to 4 carbon atoms;

R_1 represents hydrogen, halogen, C_1-C_6 alkyl, phenylalkyl where the alkyl is C_1-C_6 alkyl, a benzoyl group of the formula:



where R_4 represents hydrogen, C_1-C_6 alkyl, or an alkylthio group having 1 to 6 carbon atoms; or

R_1 represents a group of the formula:



where n is 0, 1 or 2;

R_2 represents hydrogen, hydroxy or C_1-C_6 alkoxy;

R_3 represents hydrogen, C_1-C_5 alkyl or phenyl; and

R_5 is C_1-C_6 alkoxy.

The enhanced solubility pharmaceutically acceptable solutions of therapeutically useful alkanoic acids can be encapsulated in softgel capsules of a size suitable for subsequent oral administration to human patients, which improves the physical stability of the softgel capsules used to encapsulate the pharmaceutical solutions compared with polyethylene glycol water miscible formulations of the alkanoic acids.

The present invention also provides enhanced solubility pharmaceutically acceptable solutions of alkanoic acids that unexpectedly can be encapsulated in a softgel capsule of a size smaller than what is required to encapsulate the same dose of the acid in polyethylene glycol water miscible formulations.

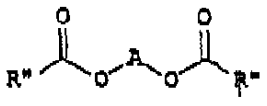
The enhanced solubility pharmaceutically acceptable solutions of 2- or 3-aryl or 3-heteroaryl alkanoic acids provided

by the present invention may reduce or eliminate the gastrointestinal irritation associated with oral dosage forms of these agents.

The lipophilic solvent and the hydroxyl containing softgel capsule plasticizers, such as glycerin, are immiscible, thereby improving both the chemical stability of the acid solution and improving the physical stability of the softgel capsule by greatly reducing the migration of capsule plasticizers into the encapsulated pharmaceutical formulation. Additionally, the use of the lipophilic solvent prevents the formation of esters which can decrease the chemical stability of the alkanoic acid solution.

Suitable lipophilic solvents are polyol esters of fatty acids. The polyol esters of fatty acids may be mono-, di-, tri-, etc, esters of the polyols. Thus, there may be free hydroxyl groups present in the polyol esters of fatty acids useful as lipophilic solvents of the invention.

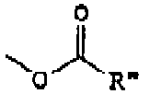
The lipophilic solvent preferred for use in the present invention is an alkylene glycol derivative of formula II:



II

wherein

A represents C_1-C_4 alkylene optionally substituted with alkyl or a group of the formula



; and

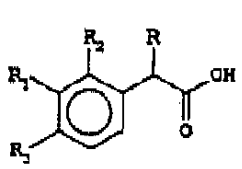
the R^m groups are the same of different and represent C_1-C_{12} alkyl.

Further objects and embodiments of the present invention will be described in the following description of the preferred embodiments.

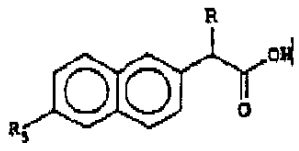
DESCRIPTION OF THE PREFERRED EMBODIMENTS

The present invention is useful for providing pharmaceutically acceptable solutions of substituted alkanoic acids dissolved in at least one lipophilic solvent, which are chemically stable and suitable for softgel encapsulation.

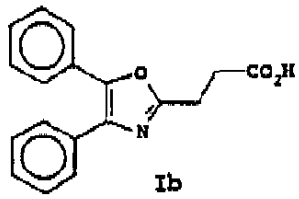
The therapeutically useful active agents, i.e., substituted alkanoic acids, preferred for use in the present invention have general formulas I, Ia or Ib:



I



Ia



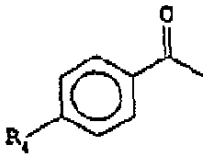
Ib

or pharmaceutically acceptable salts thereof,

wherein

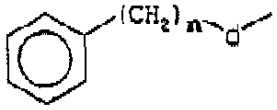
R represents a hydrogen atom or an alkyl group containing 1 to 4 carbon atoms;

R_1 represents hydrogen, halogen, C_1-C_6 alkyl, phenylalkyl where the alkyl is C_1-C_6 alkyl, a benzoyl group of the formula:



where R_4 represents hydrogen, C_1-C_6 alkyl, or an alkylthio group having 1 to 4 carbon atoms; or

R_1 represents a group of the formula:



where n is 0, 1 or 2;

R_2 represents hydrogen, hydroxy or C_1-C_6 alkoxy;

R_3 represents hydrogen, C_1-C_6 alkyl or phenyl; and

R_5 is C_1-C_6 alkoxy.

Suitable pharmaceutically acceptable, non-toxic salts include salts such as, for example, alkali metal, alkaline earth metal, ammonium and amine salts. Compounds of general formulas I, Ia, and Ib in which R represents an alkyl group can exist in optically active forms, including isomers and racemates thereof. Preferred alkanoic acids suitable for use in the present invention include ketoprofen (formula I where R is methyl, R_1 is benzoyl, and R_2 and R_3 are hydrogen, i.e., 2-(3-benzoylphenyl)propionic acid); ibuprofen (formula I where R is methyl, R_1 and R_2 are hydrogen, and R_3 is isobutyl, i.e., 2-(4-isobutylphenyl)propionic acid); naproxen (formula Ia where R is methyl and R_5 is methoxy, i.e., 2-(6-methoxy naphthyl)propionic acid); and oxaprozin, (formula Ib, i.e., 4,5-diphenyl-2-oxazolepropionic acid).

The enhanced solubility pharmaceutically acceptable solutions of therapeutically useful substituted alkanoic acids can be encapsulated in softgel capsules of a size suitable for

subsequent oral administration to human patients, which improves the physical stability of the softgel capsules used to encapsulate the pharmaceutical solutions compared with polyethylene glycol water miscible formulations of the alkanoic acids.

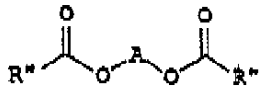
The present invention also provides enhanced solubility pharmaceutically acceptable solutions of ketoprofen that can be encapsulated in a softgel capsule of a size smaller than what is required to encapsulate the same dose of the acids in polyethylene glycol water miscible formulations.

The present invention provides pharmaceutically acceptable solutions containing from about 0.1 to 1000 mg, preferably about 5 to 200 mg, and most preferably about 10 to 100 mg, of an alkanoic acid dissolved in at least one lipophilic solvent, resulting in a clear solution suitable for softgel encapsulation. The lipophilic solvent and the hydroxyl containing softgel capsule plasticizers, such as glycerin, are immiscible, thereby improving both the chemical stability of the alkanoic acid solution and improving the physical stability of the softgel capsule by greatly reducing the migration of capsule plasticizers into the encapsulated pharmaceutical formulation. Additionally, the use of the lipophilic solvent prevents the formation of esters which can decrease the chemical stability of the alkanoic acid solution.

Suitable lipophilic solvents are polyol esters of fatty acids. The polyol esters of fatty acids may be mono-, di-, tri-, etc, esters of the polyols. Thus, there may be free hydroxyl

groups present in the polyol esters of fatty acids useful as lipophilic solvents of the invention.

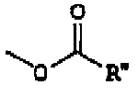
The lipophilic solvent preferred for use in the present invention is an alkylene glycol derivative of formula II:



II

wherein

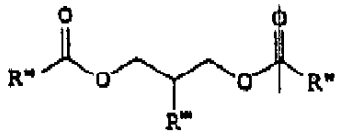
A represents C_1-C_4 alkylene optionally substituted with alkyl or



; and

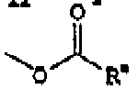
the R" groups are the same or different and represent C_1-C_{12} alkyl,

Suitable lipophilic solvents include those of formula III:



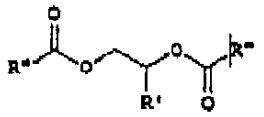
III

where the R" groups are the same or different and represent C_1-C_{12} alkyl and R''' is hydrogen or



.

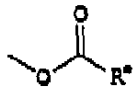
Suitable lipophilic solvents also include those of formula IV:



IV

where the R" groups are the same or different and represent C_1-C_{12} alkyl and R' is C_1-C_6 alkyl.

Other suitable lipophilic solvents are those of formula III where the R" groups are the same and represent C_1-C_4 alkyl and R''' is



Still other suitable lipophilic solvents are those of formula IV where the R" groups are the same or different and represent C_1-C_4 alkyl and R' is methyl.

Most preferred lipophilic solvents of formula III are those where R" is methyl. Most preferred lipophilic solvents of formula IV are those where the R" groups are the same or different and represent $CH_3(CH_2)_6$ or $CH_3(CH_2)_8$.

Particularly preferred solvents are selected from the group consisting of propylene glycol dicaprylate/dicaprate, 1,2,3-propanetriol triacetate and mixtures thereof. Most preferably the solvents suitable for use in the present invention include

propylene glycol dicaprylate/dicaprate, 1,2,3-propanetriol triacetate and mixtures thereof. Propylene glycol dicaprylate/dicaprate is available under the trade name Captex 200 from Karlshamn Lipid Specialties and 1,2,3-propanetriol triacetate is available under the trade name Triacetin from Eastman Chemicals.

The inventive solutions may also contain optional, additional ingredients to improve the dispersivity and dissolution of the substituted alkanoic acid. Suitable additional components include surfactants such as, for example, polyglyceryl esters of fatty acids, polyglycolyzed glycerides, propylene glycol esters, mono- and di-glycerides, sorbitan fatty acid esters, polyoxyethylene sorbitan fatty acid esters, polyoxyethylene sorbitol esters, polyoxyethylene acids, polyoxyethylene alcohols, and mixtures thereof. A preferred class of surfactants for use in combination with the lipophilic solvents is the polyoxyethylene sorbitan fatty acid esters. Suitable sorbitan esters are sold under the trade name Tween. A particularly useful Tween is polyoxyethylene (20) sorbitan mono-oleate (Tween 80).

The active substituted alkanoic acid pharmaceutical agent may be present in the solution in amounts ranging up to about 30% by weight of the solution. Preferred concentrations of the active agent are from about 5-20%, more preferably about 10-15%, by weight of the final solution. Combinations of lipophilic solvents may be used to obtain a desired final concentration.

For example, ketoprofen may be present in the solution in amounts ranging up to about 5% by weight of the solution when dissolved only in propylene glycol dicaprylate/dicaprate. Ketoprofen may be present in the solution in amounts ranging up to about 14% by weight of the solution when dissolved only in 1,2,3-propanetriol triacetate. When dissolved in a mixture of propylene glycol dicaprylate/dicaprate, 1,2,3-propanetriol triacetate and Tween, the ketoprofen pharmaceutical agent may be present in solution in amounts ranging up to about 22% by weight of solution.

In addition to the ketoprofen pharmaceutical agent and the lipophilic solvents, other adjuncts may optionally be present. Polyoxyethylene (20) sorbitan mono-oleate (Tween 80) may be included in the solution up to about 50% by weight of the solution.

Once the appropriate pharmaceutically acceptable solution of the substituted alkanoic acid is formulated, it can be encapsulated into conventional softgel capsules using any suitable encapsulation method, such as for example, the rotary die process.

All documents, e.g., patents and journal articles, cited above or below are hereby incorporated by reference in their entirety.

One skilled in the art will recognize that modifications may be made in the present invention without deviating from the spirit or scope of the invention. The invention is illustrated further by the following examples which are not to be construed

as limiting the invention or scope of the specific procedures described herein.

Example 1

Pharmaceutically acceptable solutions containing ketoprofen are prepared in the following manner. First, mix the following until homogeneous:

(1) about 92 mg of propylene glycol dicaprylate/dicaprate;

(2) about 92mg of 1,2,3-propanetriol acetate; and

(3) about 10 mg of polyoxyethylene (20) sorbitan mono-oleate.

Second, add about 25 mg of ketoprofen to the homogeneous mixture of propylene glycol dicaprylate, 1,2,3-propanetriol acetate and polyoxyethylene (20) sorbitan mono-oleate, and mix again. While mixing in the ketoprofen, heat the mixture and maintain the temperature between 110-125°F until the ketoprofen is dissolved. Once the ketoprofen is fully dissolved, the solution is then cooled and deaerated. After being cooled and deaerated, the ketoprofen solution can be encapsulated in suitable softgel capsules, such as 4 oval softgel. The filled softgel capsules are thereafter dry finished to the appropriate hardness.

Example 2

Pharmaceutically acceptable solutions containing ketoprofen are prepared in the following manner. First, mix the following until homogeneous:

(1) about 112 mg of propylene glycol dicaprylate/dicaprate;

(2) about 72 mg of 1,2,3-propanetriol acetate; and

(3) about 14 mg of polyoxyethylene (20) sorbitan mono-oleate.

Second, add about 25 mg of ketoprofen to the homogeneous mixture of propylene glycol dicaprylate, 1,2,3-propanetriol acetate and polyoxyethylene (20) sorbitan mono-oleate, and mix again. While mixing in the ketoprofen, heat the mixture and maintain the temperature between 110-125°F until the ketoprofen is dissolved. Once the ketoprofen is fully dissolved, the solution is then cooled and deaerated. After being cooled and deaerated, the ketoprofen solution can be encapsulated in suitable softgel capsules, such as 4 oval softgel. The filled softgel capsules are thereafter dry finished to the appropriate hardness.

Example 3

Pharmaceutically acceptable solutions containing up to about 22% ketoprofen by weight of solution are prepared in the following manner, which provides a self-emulsifying system. First, mix the following until homogeneous:

(1) propylene glycol dicaprylate/dicaprate in an amount ranging from about 40% to about 98% by weight;

(2) 1,2,3-propanetriol acetate in an amount ranging from about 1% to about 55% by weight; and

(3) polyoxyethylene (20) sorbitan mono-oleate in an amount ranging from about 1% to about 50% by weight.

Second, add ketoprofen to the homogeneous mixture of propylene glycol dicaprylate, 1,2,3-propanetriol triacetate and polyoxyethylene (20) sorbitan mono-oleate, and mix again. While mixing in the ketoprofen, heat the mixture and maintain the temperature between 110-125°F until the ketoprofen is dissolved. Once the ketoprofen is fully dissolved, the solution is then cooled and deaerated. After being cooled and deaerated, the ketoprofen solution can be encapsulated in suitable softgel capsules. The filled softgel capsules are thereafter dry finished to the appropriate hardness.

Example 4

Pharmaceutically acceptable solutions containing up to about 14% ketoprofen by weight of solution are prepared in the following manner. First, mix the following until homogeneous:

(1) propylene glycol dicaprylate/dicaprate in an amount ranging from about 1% to about 50% by weight; and

(2) 1,2,3-propanetriol acetate in an amount ranging from about 50% to about 99% by weight.

Second, add ketoprofen to the homogeneous mixture of propylene glycol dicaprylate and 1,2,3-propanetriol acetate and mix again. While mixing in the ketoprofen, heat the mixture and maintain the temperature between 110-125°F until the ketoprofen is dissolved. Once the ketoprofen is fully dissolved, the solution is then cooled and deaerated. After being cooled and deaerated, the ketoprofen solution can be encapsulated in suitable softgel

capsules. The filled softgel capsules are thereafter dry finished to the appropriate hardness.

Example 5

Pharmaceutically acceptable solutions containing up to about 5% ketoprofen by weight of solution are prepared by mixing the ketoprofen with propylene glycol dicaprylate/dicaprate while heating the mixture. The temperature of the mixture should be maintained between 110-125°F until the ketoprofen is dissolved. Once the ketoprofen is fully dissolved, the solution is then cooled and deaerated. After being cooled and deaerated, the ketoprofen solution can be encapsulated in suitable softgel capsules. The filled softgel capsules are thereafter dry finished to the appropriate hardness.

Example 6

Pharmaceutically acceptable solutions containing up to about 14% ketoprofen by weight of solution are prepared by mixing the ketoprofen with 1,2,3-propanetriol acetate while heating the mixture. The temperature of the mixture should be maintained between 110-125°F until the ketoprofen is dissolved. Once the ketoprofen is fully dissolved, the solution is then cooled and deaerated. After being cooled and deaerated, the ketoprofen solution can be encapsulated in suitable softgel capsules. The filled softgel capsules are thereafter dry finished to the appropriate hardness.

Example 7

The following formulations are prepared according to the invention using the procedure set forth above in Example 1.

Ingredient	A (mg)	B (mg)	C (mg)
Propylene glycol dicaprylate/dicaprate	92	184	276
1,2,3-Propanetriol triacetate	92	184	276
Polyoxyethylene (20) sorbitan mono-oleate	10	20	30
Ketoprofen	25	50	75
Final softgel size	4 oval	7.5 oval	12 oval

Example 8

The following comparative formulations are prepared essentially as in the procedure set forth above in Example 1 but do not include the lipophilic solvent according to the invention.

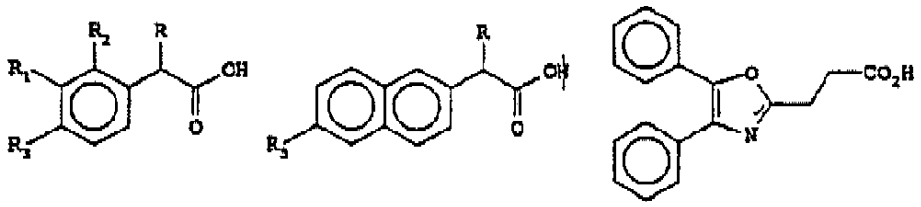
Ingredient	D (mg)	E (mg)	F (mg)
Water	5.46	10.92	16.38
Potassium hydroxide	6.06	12.12	18.18
Polyoxyethylene glycol 400	438.48	876.96	1315.44
Propylene glycol	25	50	75
Ketoprofen	25	50	75
Final softgel size	12 oval	20 oval	30 oval

Certain specific embodiments of the present invention have been discussed and disclosed in detail. Many other embodiments

that have not been disclosed or described are nevertheless the equivalent of and fall within the scope of the present invention and/or the following claims.

WE CLAIM:

1. A pharmaceutical composition comprising alkanoic acids selected from the group consisting of alkanoic acids of the formulas:

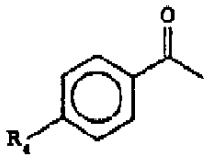


or pharmaceutically acceptable salts thereof,

wherein

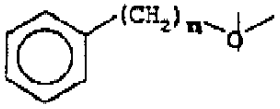
R represents a hydrogen atom or an alkyl group containing 1 to 4 carbon atoms;

R_1 represents hydrogen, halogen, C_1-C_6 alkyl, phenylalkyl where the alkyl is C_1-C_6 alkyl, a benzoyl group of the formula:



where R_4 represents hydrogen, C_1-C_6 alkyl, or an alkylthio group having 1 to 4 carbon atoms; or

R_1 represents a group of the formula:



where n is 0, 1 or 2;

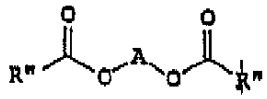
R_2 represents hydrogen, hydroxy or C_1-C_6 alkoxy;

R_3 represents hydrogen, C_1-C_6 alkyl or phenyl; and

R_4 is C_1-C_6 alkoxy.

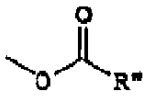
the 2-phenyl or naphthyl alkanoic acid being solubilized in a lipophilic solvent.

2. A pharmaceutical composition according to Claim 1 wherein the lipophilic solvent has the formula:



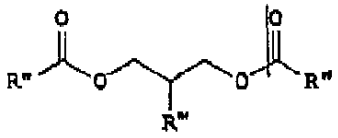
wherein

A represents C_1-C_4 alkylene optionally substituted with alkyl or

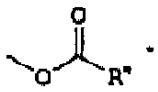
 ; and

the R" groups are the same of different and represent C_1-C_{12} alkyl.

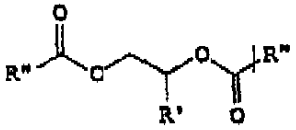
3. A pharmaceutical composition according to Claim 1 wherein the lipophilic solvent has the formula:



where the R" groups are the same or different and represent C_1-C_{12} alkyl and R''' is hydrogen or

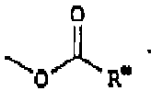


4. A pharmaceutical composition according to Claim 1 wherein the lipophilic solvent has the formula:



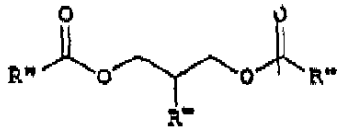
where the R" groups are the same or different and represent C_1-C_{12} alkyl and R' is C_1-C_6 alkyl.

5. A pharmaceutical composition according to Claim 3, where the R" groups are the same and represent C_1-C_4 alkyl and R''' is

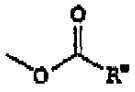


6. A pharmaceutical composition according to Claim 4, where the R" groups are the same or different and represent C_1-C_4 alkyl and R' is methyl.

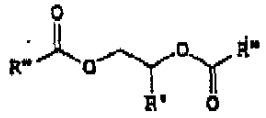
7. A pharmaceutical composition according to Claim 1, wherein the lipophilic solvent comprises a mixture of a alkylene glycol derivative of the formula:



where the R" groups are the same or different and represent C_1-C_{12} alkyl and R''' is hydrogen or

 and

a alkylene glycol derivative of the formula:



where the R" groups are the same or different and represent C_1-C_{12} alkyl and R' is C_1-C_6 alkyl.

8. A pharmaceutical composition of Claim 1 wherein at least one lipophilic solvent has no free hydroxyl groups.

9. A pharmaceutical composition comprising ketoprofen, naproxen, oxaprozin or ibuprofen solubilized up to 14% by weight in 1,2,3-propanetriol triacetate.

10. A pharmaceutical composition comprising ketoprofen, ibuprofen, oxaprozin or naproxen solubilized up to 5% by weight in propylene glycol dicaprylate/dicaprate.

11. The pharmaceutical composition of Claim 9, wherein the ketoprofen, naproxen, oxaprozin or ibuprofen is solubilized in a mixture of 1 to 50% by weight of propylene glycol dicaprylate/dicaprate and 50 to 99% by weight of 1,2,3-propanetriol triacetate.

12. A pharmaceutical composition comprising ketoprofen, oxaprozin, naproxen, oxaprozin or ibuprofen solubilized up to 22% by weight in a mixture of 40 to 98% by weight of propylene glycol dicaprylate/dicaprate, 1 to 55% by weight of 1,2,3-propanetriol triacetate, and 1 to 50% by weight of a surfactant.

13. A solution comprising from about 0.1 to about 30% by weight of ibuprofen, naproxen, oxaprozin or ketoprofen in a lipophilic solvent.

14. A solution according to Claim 13, comprising from about 5 to about 20% by weight of ibuprofen, naproxen, oxaprozin or ketoprofen in a lipophilic solvent.

15. A solution according to Claim 13, comprising from about 10 to about 15% by weight of ibuprofen, naproxen, oxaprozin or ketoprofen in a lipophilic solvent.

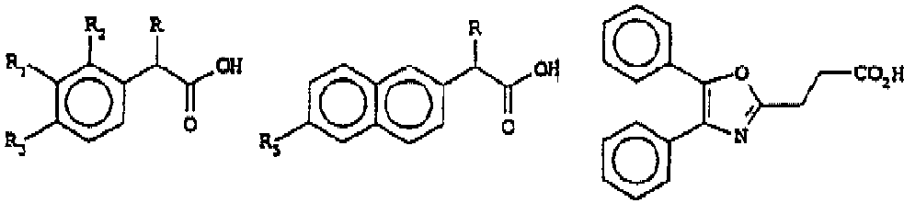
16. A soft gelatin capsule comprising a solution of ketoprofen, naproxen, or ibuprofen in a lipophilic solvent.

17. A soft gelatin capsule according to Claim 16, wherein the amount of ketoprofen, naproxen, oxaprozin or ibuprofen in the solution is from about 10 to 15% by weight of the solution.

18. A solution according to Claim 13, wherein the lipophilic solvent is suitable for encapsulation by a gelatin shell.

19. A pharmaceutical composition comprising an amount of ketoprofen, ibuprofen, oxaprozin or naproxen effective to produce analgesia in a patient, the ketoprofen, ibuprofen, oxaprozin or naproxen being present as a solution in a pharmaceutically acceptable lipophilic solvent.

20. A method for preparing a liquid mixture of a 2- or 3-aryl or 3-heteroaryl alkanoic acid suitable for encapsulation in a soft gelatin capsule comprising mixing a 2- or 3-aryl or 3-heteroaryl alkanoic acid of the formula:

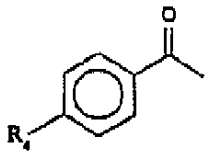


or pharmaceutically acceptable salts thereof,

wherein

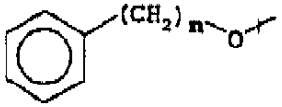
R represents a hydrogen atom or an alkyl group containing 1 to 4 carbon atoms;

R_1 represents hydrogen, halogen, C_1-C_6 alkyl, phenylalkyl where the alkyl is C_1-C_6 alkyl, a benzoyl group of the formula:



where R_4 represents hydrogen, C_1-C_6 alkyl, or an alkylthio group having 1 to 4 carbon atoms; or

R_1 represents a group of the formula:



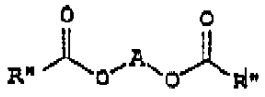
where n is 0, 1 or 2;

R_2 represents hydrogen, hydroxy or C_1-C_6 alkoxy;

R_3 represents hydrogen, C_1-C_6 alkyl or phenyl; and

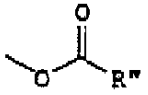
R_5 is C_1-C_6 alkoxy,

with an effective solubilizing amount of at least one lipophilic solvent of the formula:



wherein

A represents C_1-C_4 alkylene optionally substituted with alkyl or



; and

the R" groups are the same of different and represent C_1-C_{12} alkyl.

INTERNATIONAL SEARCH REPORT

Interna d Application No
PCT/US 95/06183

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K31/19 A61K47/14

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X Y	US,A,5 059 626 (PARK MOO W ET AL) 22 October 1991 see column 1, line 59 - line 60; example 1; table II	1-7,9, 10,13-20 8,11,12
X Y	WO,A,92 08445 (AFFINITY BIOTECH INC) 29 May 1992 see claims 1-3	1-6,9, 10,13-20 7,8,11, 12
X Y	US,A,4 727 109 (SCHMIDT PETER C ET AL) 23 February 1988 see claims 1-8; examples 4,7,8	1-7,9, 13-20 8,10-12
Y	WO,A,92 10996 (MERRELL DOW PHARMA) 9 July 1992 see page 7, paragraph 1; claims 1-3	7,10

-/--

[X] Further documents are listed in the continuation of box C. [X] Patent family members are listed in annex.

* Special categories of cited documents :

'A' document defining the general state of the art which is not considered to be of particular relevance
'E' earlier document but published on or after the international filing date
'L' document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
'O' document referring to an oral disclosure, use, exhibition or other means
'P' document published prior to the international filing date but later than the priority date claimed
'T' later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
'X' document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
'Y' document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
'&' document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
28 September 1995	27. 10. 95

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+ 31-70) 340-3016	Foerster, W

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INTERNATIONAL SEARCH REPORT

Interna il Application No
PCT/US 95/06183

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US,A,5 071 643 (YU MAN S ET AL) 10 December 1991 cited in the application see example IX; table 1 ---	1-20
A	WO,A,94 07488 (PFIZER ;AHMED IMRAN (US)) 14 April 1994 see the whole document -----	1-20

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Information on patent family members

Internat Application No
PCT/US 95/06183

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
US-A-5059626	22-10-91	US-A-	4918103	17-04-90
		US-A-	5011852	30-04-91
WO-A-9208445	29-05-92	US-A-	5110606	05-05-92
		AU-B-	648483	21-04-94
		AU-A-	9054191	11-06-92
		CA-A-	2095819	14-05-92
		EP-A-	0561874	29-09-93
		JP-T-	5509332	22-12-93
US-A-4727109	23-02-88	DE-A-	3500103	10-07-86
WO-A-9210996	09-07-92	AT-T-	117200	15-02-95
		AU-B-	647563	24-03-94
		AU-A-	9067891	22-07-92
		DE-D-	69106892	02-03-95
		DE-T-	69106892	18-05-95
		EP-A-	0563112	06-10-93
		ES-T-	2069987	16-05-95
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		NZ-A-	240961	25-03-94
US-A-5071643	10-12-91	AU-B-	606367	07-02-91
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		CA-A-	1316823	27-04-93
		DE-A-	3772760	10-10-91
		EP-A,B	0293406	07-12-88
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		KR-B-	9406270	14-07-94
		KR-B-	9408030	01-09-94
		KR-B-	9408031	01-09-94
		WO-A-	8802625	21-04-88
		US-A-	5360615	01-11-94
WO-A-9407488	14-04-94	AU-B-	4839293	26-04-94
		CN-A-	1089138	13-07-94
		EP-A-	0662831	19-07-95
		FI-A-	934387	08-04-94

Form PCT/ISA/210 (patent family annex) (July 1992)

INTERNATIONAL SEARCH REPORT

Information on patent family members

Interna tl Application No
PCT/US 95/06183

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO-A-9407488		HU-A-	68533	27-04-95
		NO-A-	951350	06-06-95
		PL-A-	308307	24-07-95

Form PCT/ISA/210 (patent family annex) (July 1992)

POTTER CLARKSON

To:	**European Patent Office** **80298 Munich**
Your Fax No:	00 49 89 2399 4465
From:	Charlotte Crowhurst
Date:	22 August 2014
Our Ref:	PABCX/P38814EP
Your Ref:	Application No. 06737018.9 -2123 Appeal No. T0826/12
Sheet 1 of 54	**Original by Post:** ✓

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POTTER CLARKSON

The European Patent Office
80298
Munich
Germany

22 August 2014

URGENT – ORAL PROCEEDINGS SCHEDULED FOR 16 SEPTEMBER 2014

Sent by Fax

Dear Sirs

European Patent Application No. 06737018.9 - 2123
Appeal No. T0826/12
BANNER PHARMACAPS, INC.
Our Ref: PABCX/P38814EP

In response to the Communication of the Board of Appeal dated 1 August 2014, we are now enclosing new Claim Requests to replace the Claim Requests currently on file. A new Main Request and seven new Auxiliary Requests are enclosed.

The new Main Request is based on previous Auxiliary Request 3. The 1st Auxiliary Request is based on previous Auxiliary Request 4 except the list of acids has been limited to organic acids. The 2nd Auxiliary Request is also based on previous Auxiliary Request 4 except that the list of acids has been limited to organic acids and citric acid has been deleted from the list of organic acids. The 3rd Auxiliary Request is based on previous Auxiliary Request 5.

The new Main Request and Auxiliary Requests 1 to 3 have been amended to contain just 1 independent composition claim (Claim1). This addresses the point raised by the Board in section 2 of the Communication of 1 August.

Auxiliary Requests 4 to 7 correspond to the Main, 1st, 2nd and 3rd Auxiliary Requests respectively except that Claim 1 is in product by process format (based on the independent claim deleted from the previous Requests when producing the new Main Request and the 1st to 3rd Auxiliary Requests). In other words, these Requests are based on the second independent claim deleted from each of the previous Requests discussed above.

For the avoidance of doubt, we confirm that the enclosed Claim Requests replace all Requests previously on file.

The new Claim Requests address several issues raised in the Communication of 1 August 2014.

The previous Main Request and Auxiliary Requests 7, 8 and 9 are no longer under consideration. Thus, the objections of added subject matter against these claims do not apply to the Claim Requests now on file.

As mentioned above, the Board's concern regarding a number of independent claims has also be addressed.

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POTTER CLARKSON

It is noted that in the Communication of 1 August 2014 the Board did not raise any issues of lack of novelty against the Claim Requests on which the new Claim Requests are based. Thus, it is our understanding that the Board considers that the subject matter claimed is novel and that the main issue to be considered at the Oral Proceedings is inventive step.

We also enclose a copy of WO95/31979.

We would like to bring the Board's attention to the discussion at page 3, line 17 to page 4, line 22 of WO95/31979. The authors of WO95/31979 describe how they tried to apply the teaching of US 5,071,643 (Yu et al) to the anti-inflammatory analgesic drug ketoprofen.

US 5,071,643 is a US patent in the same patent family as the document D1 cited in these proceedings.

Ketoprofen is a drug compound that has many similarities with the drug used in the present invention, Naproxen. Both compounds are non-steroidal anti-inflammatory drugs (NSAIDs) of the propionic acid class.

The authors of WO95/31979 conducted some experiments to try to apply the teaching of Yu to ketoprofen. It was surprisingly found that the resulting formulation was not sufficiently stable for soft gel encapsulation due to the undesirable formulation of ketoprofen esters. This led the authors of WO95/31979 to seek alternative ways of stabilising ketoprofen for use in soft drug capsules. This alternative involved the use of non-hydroxol containing solvents.

Given the similarities between ketoprofen and naproxen it is to be expected that naproxen containing formulations produced in accordance with the teaching of Yu would suffer the same problems. In other words Yu does not disclose a realistic way of stabilising naproxen for use in soft gel capsules.

Please note that I will be accompanied at the Oral Proceedings by Mr Will Cutchins. Mr Cutchins is a US patent agent and is responsible for managing the patent family of which this application forms a part.

Yours faithfully

Charlotte Crowhurst PhD rh
For and on behalf of Potter Clarkson LLP

Enc. Main Request
Auxiliary Requests 1 to 7
WO95/31979

MAIN REQUEST

CLAIMS

1. A softgel capsule comprising a fill material wherein the fill material comprises

(a) naproxen sodium;

(b) a deionizing agent in an amount of from 0.2 to 1.0 mole equivalents per mole of the naproxen sodium;

(c) polyethylene glycol; and

(d) water.

2. The capsule of claim 1 wherein the deionizing is selected from hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, fumaric acid, maleic acid, tartaric acid, methane-, ethane-, and benzene sulfonates, citric acid, malic acid, acetic acid, proprionic acid, pyruvic acid, butanoic acid, and lactic acid.

3. The capsule of claim 2 wherein the deionizing agent is hydrochloric acid, citric acid or lactic acid.

4. The capsule of claim 3 wherein the deionizing agent is lactic acid.

5. The capsule of any one of the preceding claims wherein polyethylene glycol is present in an amount from 10% to 80% by weight.

6. The capsule of any one of the preceding claims wherein the polyethylene glycol is one or more polyethylene glycols with a molecular weight between 300 and 1500.

7. The capsule of any one of the preceding claims wherein water is present in an amount from 1% to 18% by weight.

8. The capsule of any one of the preceding claims further comprising one or more excipients selected from the group consisting of plasticizers, crystallization inhibitors, wetting agents, bulk filling agents, solubilizers, bioavailability enhancers, solvents, dyes, preservatives, solvents, surfactants, and combinations thereof.

9. The capsule of claim 8 wherein the solubilizer is selected from the group consisting of glycerin, polyvinylpyrrolidone, propylene glycol and combinations thereof.

10. The capsule of claim 9 wherein the solubilizer is present in amount from 1% to 10% by weight.

11. The capsule of any one of the preceding claims wherein the fill material is liquid.

12. A capsule of any one of the preceding claims for use as a medicament.

13. A method of making the capsule of any of the preceding claims comprising

(a) mixing naproxen sodium, the polyethylene glycol and the deionizing agent and water; and

(b) encapsulating the mixture in a softgel capsule.

14. The method of claim 13, wherein step (a) is conducted at a temperature of from 50°C to 70°C.

15. The use of

(a) naproxen sodium;

(b) a deionizing agent in an amount of from 0.2 to 1.0 mole equivalents per mole of the naproxen sodium;

(c) polyethylene glycol; and

(d) water

in the manufacture of a medicament in the form of a capsule for administration of the naproxen sodium to a patient in need thereof.

1st AUXILIARY REQUEST

CLAIMS

1. A softgel capsule comprising a fill material wherein the fill material comprises

(a) naproxen sodium;

(b) fumaric acid, maleic acid, tartaric acid, citric acid, malic acid, acetic acid, proprionic acid, pyruvic acid, butanoic acid or lactic acid in an amount of from 0.2 to 1.0 mole equivalents per mole of the naproxen sodium;

(c) polyethylene glycol; and

(d) water.

2. The capsule of claim 1 wherein (b) is citric acid or lactic acid.

3. The capsule of claim 2 wherein (b) is lactic acid.

4. The capsule of any one of the preceding claims wherein polyethylene glycol is present in an amount from 10% to 80% by weight.

5. The capsule of any one of the preceding claims wherein the polyethylene glycol is one or more polyethylene glycols with a molecular weight between 300 and 1500.

6. The capsule of any one of the preceding claims wherein water is present in an amount from 1% to 18% by weight.

7. The capsule of any one of the preceding claims further comprising one or more excipients selected from the group consisting of plasticizers, crystallization inhibitors, wetting agents, bulk filling agents, solubilizers, bioavailability enhancers, solvents, dyes, preservatives, solvents, surfactants, and combinations thereof.

8. The capsule of claim 7 wherein the solubilizer is selected from the group consisting of glycerin, polyvinylpyrrolidone, propylene glycol and combinations thereof.

9. The capsule of claim 8 wherein the solubilizer is present in amount from 1% to 10% by weight.

10. The capsule of any one of the preceding claims wherein the fill material is liquid.

11. A capsule of any of the preceding claims for use as a medicament.

12. A method of making the capsule of claim 1 comprising

(a) mixing components (a), (b), (c) and (d) as defined in claim 1; and

(b) encapsulating the mixture in a softgel capsule.

13. The method of claim 12, wherein step (a) is conducted at a temperature of from 50°C to 70°C.

14. The use of

(a) naproxen sodium;

(b) fumaric acid, maleic acid, tartaric acid, citric acid, malic acid, acetic acid, proprionic acid, pyruvic acid, butanoic acid or lactic acid in an amount of from 0.2 to 1.0 mole equivalents per mole of the naproxen sodium;

(c) polyethylene glycol; and

(d) water

in the manufacture of a medicament in the form of a capsule for administration of the naproxen sodium to a patient in need thereof.

2nd AUXILIARY REQUEST

CLAIMS

1. A softgel capsule comprising a fill material wherein the fill material comprises

(a) naproxen sodium;

(b) fumaric acid, maleic acid, tartaric acid, malic acid, acetic acid, proprionic acid, pyruvic acid, butanoic acid or lactic acid in an amount of from 0.2 to 1.0 mole equivalents per mole of the naproxen sodium;

(c) polyethylene glycol; and

(d) water.

2. The capsule of claim 1 wherein (b) is lactic acid.

3. The capsule of any one of the preceding claims wherein polyethylene glycol is present in an amount from 10% to 80% by weight.

4. The capsule of any one of the preceding claims wherein the polyethylene glycol is one or more polyethylene glycols with a molecular weight between 300 and 1500.

5. The capsule of any one of the preceding claims wherein water is present in an amount from 1% to 18% by weight.

6. The capsule of any one of the preceding claims further comprising one or more excipients selected from the group consisting of plasticizers, crystallization inhibitors, wetting agents, bulk filling agents, solubilizers, bioavailability enhancers, solvents, dyes, preservatives, solvents, surfactants, and combinations thereof.

7. The capsule of claim 6 wherein the solubilizer is selected from the group consisting of glycerin, polyvinylpyrrolidone, propylene glycol and combinations thereof.

8. The capsule of claim 7 wherein the solubilizer is present in amount from 1% to 10% by weight.

9. The capsule of any one of the preceding claims wherein the fill material is liquid.

10. A capsule of any of the preceding claims for use as a medicament.

11. A method of making the capsule of claim 1 comprising

(a) mixing components (a), (b), (c) and (d) as defined in claim 1; and

(b) encapsulating the mixture in a softgel capsule.

12. The method of claim 11, wherein step (a) is conducted at a temperature of from 50°C to 70°C.

13. The use of

(a) naproxen sodium;

(b) fumaric acid, maleic acid, tartaric acid, malic acid, acetic acid, proprionic acid, pyruvic acid, butanoic acid or lactic acid in an amount of from 0.2 to 1.0 mole equivalents per mole of the naproxen sodium;

(c) polyethylene glycol; and

(d) water

in the manufacture of a medicament in the form of a capsule for administration of the naproxen sodium to a patient in need thereof.

3rd AUXILIARY REQUEST

CLAIMS

1. A softgel capsule comprising a fill material wherein the fill material comprises
   (a) naproxen sodium;
   (b) lactic acid in an amount of from 0.2 to 1.0 molo equivalents per mole of the naproxen sodium;
   (c) polyethylene glycol; and
   (d) water.

2. The capsule of claim 1 wherein polyethylene glycol is present in an amount from 10% to 80% by weight.

3. The capsule of claim 1 wherein the polyethylene glycol is one or more polyethylene glycols with a molecular weight between 300 and 1500.

4. The capsule of claim 1 wherein water is present in an amount from 1% to 18% by weight.

5. The capsule of claim 1 further comprising one or more excipients selected from the group consisting of plasticizers, crystallization inhibitors, wetting agents, bulk filling agents, solubilizers, bioavailability enhancers, solvents, dyes, preservatives, solvents, surfactants, and combinations thereof.

6. The capsule of claim 5 wherein the solubilizer is selected from the group consisting of glycerin, polyvinylpyrrolidone, propylene glycol and combinations thereof.

7. The capsule of claim 6 wherein the solubilizer is present in amount from 1% to 10% by weight.

8. The capsule of any one of the preceding claims wherein the fill material is liquid.

9. A capsule of any one of the preceding claims for use as a medicament.

10. A method of making the capsule of any one of the preceding claims comprising

(a) mixing naproxen sodium, the polyethylene glycol, the lactic acid and water; and

(b) encapsulating the mixture in a softgel capsule.

11. The method of claim 10, wherein step (a) is conducted at a temperature of from 50°C to 70°C.

12. The use of

(a) naproxen sodium;

(b) lactic acid in an amount of from 0.2 to 1.0 mole equivalents per mole of the naproxen sodium;

(c) polyethylene glycol; and

(d) water

in the manufacture of a medicament in the form of a capsule for administration of the naproxen sodium to a patient in need thereof.

4th AUXILIARY REQUEST

CLAIMS

1. A softgel capsule obtainable by a method which comprises

(I) producing a fill material by mixing

(a) naproxen sodium;

(b) a deionizing agent in an amount of from 0.2 to 1.0 mole equivalents per mole of the naproxen sodium;

(c) polyethylene glycol; and

(d) water

at a temperature of from 50°C to 70°C; and

(II) encapsulating the mixture in a softgel capsule.

2. The capsule of claim 1 wherein the deionizing is selected from hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, fumaric acid, maleic acid, tartaric acid, methane-, ethane-, and benzene sulfonates, citric acid, malic acid, acetic acid, proprionic acid, pyruvic acid, butanoic acid, and lactic acid.

3. The capsule of claim 2 wherein the deionizing agent is hydrochloric acid, citric acid or lactic acid.

4. The capsule of claim 3 wherein the deionizing agent is lactic acid.

5. The capsule of any one of the preceding claims wherein polyethylene glycol is used in an amount from 10% to 80% by weight.

6. The capsule of any one of the preceding claims wherein the polyethylene glycol is one or more polyethylene glycols with a molecular weight between 300 and 1500.

7. The capsule of any one of the preceding claims wherein water is used in an amount from 1% to 18% by weight.

8. The capsule of any one of the preceding claims further comprising one or more excipients selected from the group consisting of plasticizers, crystallization inhibitors, wetting

agents, bulk filling agents, solubilizers, bioavailability enhancers, solvents, dyes, preservatives, solvents, surfactants, and combinations thereof.

9. The capsule of claim 8 wherein the solubilizer is selected from the group consisting of glycerin, polyvinylpyrrolidone, propylene glycol and combinations thereof.

10. The capsule of claim 9 wherein the solubilizer is present in amount from 1% to 10% by weight.

11. The capsule of any one of the preceding claims wherein the fill material is liquid.

12. A capsule of any one of the preceding claims for use as a medicament.

13. A method of making the capsule of any of the preceding claims comprising

(a) mixing naproxen sodium, the polyethylene glycol and the deionizing agent and water at a temperature of from 50°C to 70°C; and

(b) encapsulating the mixture in a softgel capsule.

14. The use of

(a) naproxen sodium;

(b) a deionizing agent in an amount of from 0.2 to 1.0 mole equivalents per mole of the naproxen sodium;

(c) polyethylene glycol; and

(d) water

in the manufacture of a medicamont in the form of a capsule for administration of the naproxen sodium to a patient in need thereof.

5th AUXILIARY REQUEST

CLAIMS

1. A softgel capsule obtainable by a method which comprises

(I) producing a fill material by mixing

(a) naproxen sodium;

(b) fumaric acid, maleic acid, tartaric acid, citric acid, malic acid, acetic acid, proprionic acid, pyruvic acid, butanoic acid or lactic acid in an amount of from 0.2 to 1.0 mole equivalents per mole of the naproxen sodium;

(c) polyethylene glycol; and

(d) water

at a temperature of from 50°C to 70°C; and

(II) encapsulating the mixture in a softgel capsule.

2. The capsule of claim 1 wherein (b) is citric acid or lactic acid.

3. The capsule of claim 2 wherein (b) is lactic acid.

4. The capsule of any one of the preceding claims wherein polyethylene glycol is used in an amount from 10% to 80% by weight.

5. The capsule of any one of the preceding claims wherein the polyethylene glycol is one or more polyethylene glycols with a molecular weight between 300 and 1500.

6. The capsule of any one of the preceding claims wherein water is used in an amount from 1% to 18% by weight.

7. The capsule of any one of the preceding claims further comprising one or more excipients selected from the group consisting of plasticizers, crystallization inhibitors, wetting agents, bulk filling agents, solubilizers, bioavailability enhancers, solvents, dyes, preservatives, solvents, surfactants, and combinations thereof.

8. The capsule of claim 7 wherein the solubilizer is selected from the group consisting of glycerin, polyvinylpyrrolidone, propylene glycol and combinations thereof.

9. The capsule of claim 8 wherein the solubilizer is present in amount from 1% to 10% by weight.

10. The capsule of any one of the preceding claims wherein the fill material is liquid.

11. A capsule of any of the preceding claims for use as a medicament.

12. A method of making the capsule of claim 1 comprising

(a) mixing components (a), (b), (c) and (d) as defined in claim 1 at a temperature of from 50°C to 70°C; and

(b) encapsulating the mixture in a softgel capsule.

13. The use of

(a) naproxen sodium;

(b) fumaric acid, maleic acid, tartaric acid, citric acid, malic acid, acetic acid, proprionic acid, pyruvic acid, butanoic acid or lactic acid in an amount of from 0.2 to 1.0 mole equivalents per mole of the naproxen sodium;

(c) polyethylene glycol; and

(d) water

in the manufacture of a medicament in the form of a capsule for administration of the naproxen sodium to a patient in need thereof.

6th AUXILIARY REQUEST

CLAIMS

1. A softgel capsule obtainable by a method which comprises

(I) producing a fill material by mixing

(a) naproxen sodium;

(b) fumaric acid, maleic acid, tartaric acid, malic acid, acetic acid, proprionic acid, pyruvic acid, butanoic acid or lactic acid in an amount of from 0.2 to 1.0 mole equivalents per mole of the naproxen sodium;

(c) polyethylene glycol; and

(d) water

at a temperature of from 50°C to 70°C; and

(II) encapsulating the mixture in a softgel capsule.

2. The capsule of claim 1 wherein (b) is lactic acid.

3. The capsule of any one of the preceding claims wherein polyethylene glycol is used in an amount from 10% to 80% by weight.

4. The capsule of any one of the preceding claims wherein the polyethylene glycol is one or more polyethylene glycols with a molecular weight between 300 and 1500.

5. The capsule of any one of the preceding claims wherein water is used in an amount from 1% to 18% by weight.

6. The capsule of any one of the preceding claims further comprising one or more excipients selected from the group consisting of plasticizers, crystallization inhibitors, wetting agents, bulk filling agents, solubilizers, bioavailability enhancers, solvents, dyes, preservatives, solvents, surfactants, and combinations thereof.

7. The capsule of claim 6 wherein the solubilizer is selected from the group consisting of glycerin, polyvinylpyrrolidone, propylene glycol and combinations thereof.

8. The capsule of claim 7 wherein the solubilizer is present in amount from 1% to 10% by weight.

9. The capsule of any one of the preceding claims wherein the fill material is liquid.

10. A capsule of any of the preceding claims for use as a medicament.

11. A method of making the capsule of claim 1 comprising

(a) mixing components (a), (b), (c) and (d) as defined in claim 1 at a temperature of from 50°C to 70°C; and

(b) encapsulating the mixture in a softgel capsule.

12. The use of

(a) naproxen sodium;

(b) fumaric acid, maleic acid, tartaric acid, malic acid, acetic acid, proprionic acid, pyruvic acid, butanoic acid or lactic acid in an amount of from 0.2 to 1.0 mole equivalents per mole of the naproxen sodium;

(c) polyethylene glycol; and

(d) water

in the manufacture of a medicament in the form of a capsule for administration of the naproxen sodium to a patient in need thereof.

7th AUXILIARY REQUEST

CLAIMS

1. A softgel capsule obtainable by a method which comprises

(I) producing a fill material by mixing

(a) naproxen sodium;

(b) lactic acid in an amount of from 0.2 to 1.0 mole equivalents per mole of the naproxen sodium;

(c) polyethylene glycol; and

(d) water

at a temperature of from 50°C to 70°C; and

(II) encapsulating the mixture in a softgel capsule.

2. The capsule of claim 1 wherein polyethylene glycol is used in an amount from 10% to 80% by weight.

3. The capsule of claim 1 wherein the polyethylene glycol is one or more polyethylene glycols with a molecular weight between 300 and 1500.

4. The capsule of claim 1 wherein water is used in an amount from 1% to 18% by weight.

5. The capsule of claim 1 further comprising one or more excipients selected from the group consisting of plasticizers, crystallization inhibitors, wetting agents, bulk filling agents, solubilizers, bioavailability enhancers, solvents, dyes, preservatives, solvents, surfactants, and combinations thereof.

6. The capsule of claim 5 wherein the solubilizer is selected from the group consisting of glycerin, polyvinylpyrrolidone, propylene glycol and combinations thereof.

7. The capsule of claim 6 wherein the solubilizer is present in amount from 1% to 10% by weight.

8. The capsule of any one of the preceding claims wherein the fill material is liquid.

9. A capsule of any one of the preceding claims for use as a medicament.

10. A method of making the capsule of any one of the preceding claims comprising

(a) mixing naproxen sodium, the polyethylene glycol, the lactic acid and water at a temperature of from 50°C to 70°C; and

(b) encapsulating the mixture in a softgel capsule.

11. The use of

(a) naproxen sodium;

(b) lactic acid in an amount of from 0.2 to 1.0 mole equivalents per mole of the naproxen sodium;

(c) polyethylene glycol; and

(d) water

in the manufacture of a medicament in the form of a capsule for administration of the naproxen sodium to a patient in need thereof.

POTTER CLARKSON

The European Patent Office
80298
Munich
Germany

22 August 2014

URGENT – ORAL PROCEEDINGS SCHEDULED FOR 16 SEPTEMBER 2014

Sent by Fax

Dear Sirs

European Patent Application No. 06737018.9 - 2123
Appeal No. T0826/12
BANNER PHARMACAPS, INC.
Our Ref: PABCX/P38814EP

In response to the Communication of the Board of Appeal dated 1 August 2014, we are now enclosing new Claim Requests to replace the Claim Requests currently on file. A new Main Request and seven new Auxiliary Requests are enclosed.

The new Main Request is based on previous Auxiliary Request 3. The 1st Auxiliary Request is based on previous Auxiliary Request 4 except the list of acids has been limited to organic acids. The 2nd Auxiliary Request is also based on previous Auxiliary Request 4 except that the list of acids has been limited to organic acids and citric acid has been deleted from the list of organic acids. The 3rd Auxiliary Request is based on previous Auxiliary Request 6.

The new Main Request and Auxiliary Requests 1 to 3 have been amended to contain just 1 independent composition claim (Claim1). This addresses the point raised by the Board in section 2 of the Communication of 1 August.

Auxiliary Requests 4 to 7 correspond to the Main, 1st, 2nd and 3rd Auxiliary Requests respectively except that Claim 1 is in product by process format (based on the independent claim deleted from the previous Requests when producing the new Main Request and the 1st to 3rd Auxiliary Requests). In other words, these Requests are based on the second independent claim deleted from each of the previous Requests discussed above.

For the avoidance of doubt, we confirm that the enclosed Claim Requests replace all Requests previously on file.

The new Claim Requests address several issues raised in the Communication of 1 August 2014.

The previous Main Request and Auxiliary Requests 7, 8 and 9 are no longer under consideration. Thus, the objections of added subject matter against these claims do not apply to the Claim Requests now on file.

As mentioned above, the Board's concern regarding a number of independent claims has also be addressed.

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It is noted that in the Communication of 1 August 2014 the Board did not raise any issues of lack of novelty against the Claim Requests on which the new Claim Requests are based. Thus, it is our understanding that the Board considers that the subject matter claimed is novel and that the main issue to be considered at the Oral Proceedings is inventive step.

We also enclose a copy of WO95/31979.

We would like to bring the Board's attention to the discussion at page 3, line 17 to page 4, line 22 of WO95/31979. The authors of WO95/31979 describe how they tried to apply the teaching of US 5,071,643 (Yu et al) to the anti-inflammatory analgesic drug ketoprofen.

US 5,071,643 is a US patent in the same patent family as the document D1 cited in these proceedings.

Ketoprofen is a drug compound that has many similarities with the drug used in the present invention, Naproxen. Both compounds are non-steroidal anti-inflammatory drugs (NSAIDs) of the propionic acid class.

The authors of WO95/31979 conducted some experiments to try to apply the teaching of Yu to ketoprofen. It was surprisingly found that the resulting formulation was not sufficiently stable for soft gel encapsulation due to the undesirable formulation of ketoprofen esters. This led the authors of WO95/31979 to seek alternative ways of stabilising ketoprofen for use in soft drug capsules. This alternative involved the use of non-hydroxol containing solvents.

Given the similarities between ketoprofen and naproxen it is to be expected that naproxen containing formulations produced in accordance with the teaching of Yu would suffer the same problems. In other words Yu does not disclose a realistic way of stabilising naproxen for use in soft gel capsules.

Please note that I will be accompanied at the Oral Proceedings by Mr Will Cutchins. Mr Cutchins is a US patent agent and is responsible for managing the patent family of which this application forms a part.

Yours faithfully

Charlotte Crowhurst PhD rh
For and on behalf of Potter Clarkson LLP

Enc. Main Request
Auxiliary Requests 1 to 7
WO95/31979

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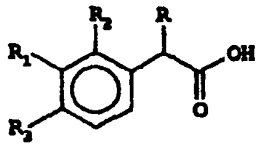
(54) Title: SOLUTIONS OF ARYL OR HETEROARYL SUBSTITUTED ALKANOIC ACIDS IN LIPOPHILIC SOLVENTS AND SOFT GELATIN CAPSULES CONTAINING SUCH SOLUTIONS

(57) Abstract

Methods and compositions are disclosed for preparing liquid mixtures of aryl or heteroaryl alkanoic acids suitable for encapsulation in soft gelatin capsules. The compositions comprise alkanoic acids of formulas (I), (Ia), (Ib) or pharmaceutically acceptable salts thereof, wherein R, R_1, R_2, R_3, and R_5 represent hydrogen or various organic substituents, and an effective solubilizing amount of at least one lipophilic solvent.



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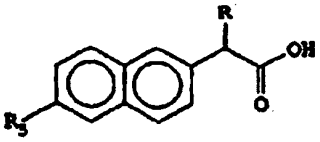

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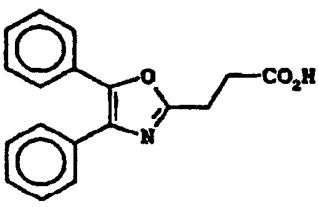

(Ib)

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SOLUTIONS OF ARYL OR HETEROARYL SUBSTITUTED ALKANOIC ACIDS IN LIPOPHILIC SOLVENTS AND SOFT GELATIN CAPSULES CONTAINING SUCH SOLUTIONS

BACKGROUND OF THE INVENTION

Field of the Invention

The present invention relates to solutions containing therapeutically useful substituted alkanoic acids in combination with at least one lipophilic solvent for encapsulation in soft gelatin capsules (softgel capsules).

Description of the Related Art

Hydrophilic softgels are well known for the oral administration of pharmaceutical agents. Typically, softgel capsules consist of an outer shell of gelatin containing a plasticizer and an inner filling of hydrophilic liquid containing a dissolved hydrophobic pharmaceutical agent. The plasticizer is chosen so that the solubility in the fill liquid is as low as possible. If the plasticizer is soluble in the fill liquid, it can migrate out of the shell over time into the fill, leaving the shell brittle and subject to rupture.

With respect to pharmaceutical agents of relatively low solubility and/or relatively high dosage amount, softgel capsules can pose problems for the pharmaceutical formulator. For example, if a given pharmaceutical agent has a relatively low solubility, it may need a relatively large volume of solution in order to deliver a pharmaceutically acceptable unit dose. While theoretically possible to encapsulate such a large volume of solution in a softgel capsule, for example, the practical

limitations on the size of capsules suitable for conventional oral administration to human patients could well preclude pharmaceutical use of the resulting softgel.

Similarly, if a pharmaceutical agent requires a relatively high dose, a large volume of solution may again be a necessity for delivery of the require dosage. Softgel encapsulation of such a large solution volume may be impractical because the size of the needed softgel would likely exceed the maximum limit for conventional oral administration to human patients.

As one approach to handling the problems of encapsulating low solubility or high dose pharmaceutical agents, U.S. Patent No. 5,071,643 (Yu et. al.) discloses the use of polyethylene glycol based solutions for acidic, basic and amphoteric pharmaceutical agents. These polyethylene glycol based solutions contain either an hydroxide species or a hydrogen ion species that causes the appropriate pharmaceutical agent to partially ionize, i.e., the pharmaceutical agent is present in both the free form and the salt form. The partial ionization described in Yu et al. results in enhanced solubility for the acidic, basic or amphoteric pharmaceutical agent. This enhanced solubility, in turn, may permit the preparation of a solution of pharmaceutical agent that is highly concentrated enough to be encapsulated in a capsule acceptably sized for oral administration to human patients. The Yu et al. patent discloses that enhanced solubility solutions can be prepared using polyethylene glycol and contemplated equivalents of polyethylene

glycol, such as polyethylene glycol ethers or various alcohols and copolymers of polyethylene glycol.

Softgel encapsulation is sometimes the preferred delivery system for many pharmaceutical agents that are administered orally to human patients. Generally, to be suitable for softgel encapsulation, a pharmaceutical formulation should be in the form of a clear, stable solution. The present inventors have discovered that the enhanced solubility solutions disclosed by the Yu et al. patent are not as effective with various substituted alkanoic acid pharmaceutical agents.

Therapeutically useful 2- or 3-aryl or 2- or 3-heteroaryl substituted alkanoic acids function as anti-inflammatory and analgesic agents and may be administered orally. They are also essentially insoluble in water. An example of such a useful alkanoic acid suitable for use in the present invention is ketoprofen which is 2-(3-benzoylphenyl) propionic acid.

Ketoprofen is an anti-inflammatory, analgesic agent that is principally indicated for the acute and long-term management of rheumatoid arthritis and osteoarthritis. Additionally it is a nonsteroidal compound and poorly water soluble. Some gastrointestinal irritation is ordinarily associated with oral dosage forms of ketoprofen. The properties of ketoprofen render it a good candidate for formulation with the enhanced solubility solutions disclosed in the Yu et al. patent. In a number of experiments, the present inventors applied the Yu et al. enhanced solubility solutions in formulations of ketoprofen for softgel encapsulation.

In one formulation, polyethylene glycol 400 and potassium hydroxide were used to solubilize the ketoprofen, with the mole ratio of potassium hydroxide to ketoprofen being in the range of 0.4 to 1. It was surprisingly found that the resulting formulation was not sufficiently stable for softgel encapsulation due to the undesirable formation of ketoprofen esters.

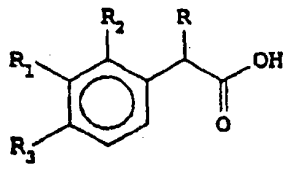
In an attempt to completely ionize the ketoprofen to prevent the formation of undesirable esters, the potassium hydroxide to ketoprofen mole ratio was adjusted to range from 1.1 to 1. With this second formulation, concerns arose that the ketoprofen salt thus formed and/or the high pH caused by the excess potassium hydroxide used could affect the physical stability of the softgel capsule when the formulation was encapsulated. Additionally, if an equilibrium amount of the ketoprofen free acid remained in the solution, it could form ketoprofen esters that could drive the reaction to form more ketoprofen free acid species, which could eventually result in a chemically unstable formulation.

The present inventors have discovered that non-hydroxyl containing solvents may be used to form pharmaceutically acceptable solutions of 2- or 3-aryl or 3-heteroaryl substituted alkanoic acids that are stable and suitable for softgel encapsulation.

SUMMARY OF THE INVENTION

The present invention provides enhanced solubility pharmaceutically acceptable solutions of therapeutically useful substituted alkanoic acids, preferably 2- or 3-aryl or 2- or 3-heteroaryl alkanoic acids, that can be encapsulated in softgel capsules of a size suitable for subsequent oral administration to human patients, having improved chemical stability compared with polyethylene glycol water miscible formulations of the alkanoic acids.

The therapeutically useful active agents, i.e., substituted alkanoic acids, preferred for use in the present invention have general formulas I, Ia or Ib:



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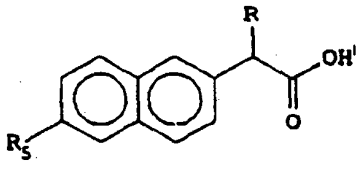
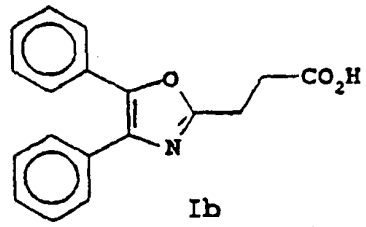


Ia

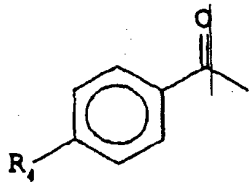


Ib

or pharmaceutically acceptable salts thereof, wherein

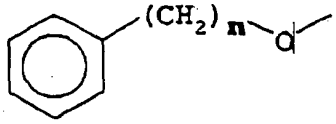
R represents a hydrogen atom or an alkyl group containing 1 to 4 carbon atoms;

R_1 represents hydrogen, halogen, C_1-C_6 alkyl, phenylalkyl where the alkyl is C_1-C_6 alkyl, a benzoyl group of the formula:



where R_4 represents hydrogen, C_1-C_6 alkyl, or an alkylthio group having 1 to 4 carbon atoms; or

R_1 represents a group of the formula:



where n is 0, 1 or 2;

R_2 represents hydrogen, hydroxy or C_1-C_6 alkoxy;

R_3 represents hydrogen, C_1-C_6 alkyl or phenyl; and

R_5 is C_1-C_6 alkoxy.

The enhanced solubility pharmaceutically acceptable solutions of therapeutically useful alkanoic acids can be encapsulated in softgel capsules of a size suitable for subsequent oral administration to human patients, which improves the physical stability of the softgel capsules used to encapsulate the pharmaceutical solutions compared with polyethylene glycol water miscible formulations of the alkanoic acids.

The present invention also provides enhanced solubility pharmaceutically acceptable solutions of alkanoic acids that unexpectedly can be encapsulated in a softgel capsule of a size smaller than what is required to encapsulate the same dose of the acid in polyethylene glycol water miscible formulations.

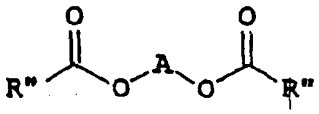
The enhanced solubility pharmaceutically acceptable solutions of 2- or 3-aryl or 3-heteroaryl alkanoic acids provided

by the present invention may reduce or eliminate the gastrointestinal irritation associated with oral dosage forms of these agents.

The lipophilic solvent and the hydroxyl containing softgel capsule plasticizers, such as glycerin, are immiscible, thereby improving both the chemical stability of the acid solution and improving the physical stability of the softgel capsule by greatly reducing the migration of capsule plasticizers into the encapsulated pharmaceutical formulation. Additionally, the use of the lipophilic solvent prevents the formation of esters which can decrease the chemical stability of the alkanoic acid solution.

Suitable lipophilic solvents are polyol esters of fatty acids. The polyol esters of fatty acids may be mono-, di-, tri-, etc, esters of the polyols. Thus, there may be free hydroxyl groups present in the polyol esters of fatty acids useful as lipophilic solvents of the invention.

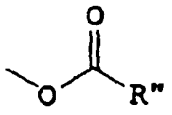
The lipophilic solvent preferred for use in the present invention is an alkylene glycol derivative of formula II:



II

wherein

A represents C_1-C_4 alkylene optionally substituted with alkyl or a group of the formula



; and

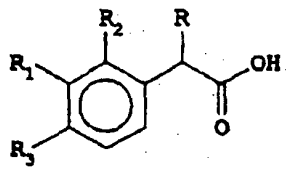
the R" groups are the same of different and represent C_1-C_{12} alkyl.

Further objects and embodiments of the present invention will be described in the following description of the preferred embodiments.

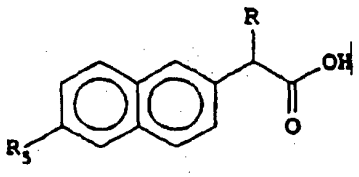
DESCRIPTION OF THE PREFERRED EMBODIMENTS

The present invention is useful for providing pharmaceutically acceptable solutions of substituted alkanoic acids dissolved in at least one lipophilic solvent, which are chemically stable and suitable for softgel encapsulation.

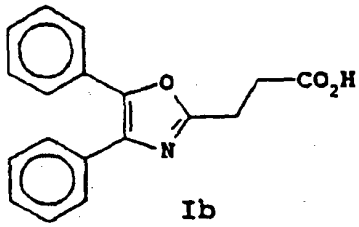
The therapeutically useful active agents, i.e., substituted alkanoic acids, preferred for use in the present invention have general formulas I, Ia or Ib:



I



Ia



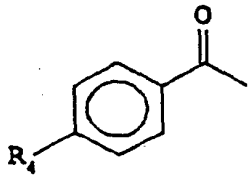
Ib

or pharmaceutically acceptable salts thereof,

wherein

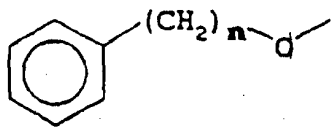
R represents a hydrogen atom or an alkyl group containing 1 to 4 carbon atoms;

R_1 represents hydrogen, halogen, C_1-C_6 alkyl, phenylalkyl where the alkyl is C_1-C_6 alkyl, a benzoyl group of the formula:



where R_4 represents hydrogen, C_1-C_6 alkyl, or an alkylthio group having 1 to 4 carbon atoms; or

R_1 represents a group of the formula:



where n is 0, 1 or 2;

R_2 represents hydrogen, hydroxy or C_1-C_6 alkoxy;

R_3 represents hydrogen, C_1-C_6 alkyl or phenyl; and

R_5 is C_1-C_6 alkoxy.

Suitable pharmaceutically acceptable, non-toxic salts include salts such as, for example, alkali metal, alkaline earth metal, ammonium and amine salts. Compounds of general formulas I, Ia, and Ib in which R represents an alkyl group can exist in optically active forms, including isomers and racemates thereof. Preferred alkanoic acids suitable for use in the present invention include ketoprofen (formula I where R is methyl, R_1 is benzoyl, and R_2 and R_3 are hydrogen, i.e., 2-(3-benzoylphenyl)propionic acid); ibuprofen (formula I where R is methyl, R_1 and R_2 are hydrogen, and R_3 is isobutyl, i.e., 2-(4-isobutylphenyl)propionic acid); naproxen (formula Ia where R is methyl and R_5 is methoxy, i.e., 2-(6-methoxy naphthyl)propionic acid); and oxaprozin, (formula Ib, i.e., 4,5-diphenyl-2-oxazolepropionic acid).

The enhanced solubility pharmaceutically acceptable solutions of therapeutically useful substituted alkanoic acids can be encapsulated in softgel capsules of a size suitable for

subsequent oral administration to human patients, which improves the physical stability of the softgel capsules used to encapsulate the pharmaceutical solutions compared with polyethylene glycol water miscible formulations of the alkanoic acids.

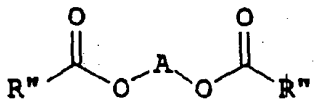
The present invention also provides enhanced solubility pharmaceutically acceptable solutions of ketoprofen that can be encapsulated in a softgel capsule of a size smaller than what is required to encapsulate the same dose of the acids in polyethylene glycol water miscible formulations.

The present invention provides pharmaceutically acceptable solutions containing from about 0.1 to 1000 mg, preferably about 5 to 200 mg, and most preferably about 10 to 100 mg, of an alkanoic acid dissolved in at least one lipophilic solvent, resulting in a clear solution suitable for softgel encapsulation. The lipophilic solvent and the hydroxyl containing softgel capsule plasticizers, such as glycerin, are immiscible, thereby improving both the chemical stability of the alkanoic acid solution and improving the physical stability of the softgel capsule by greatly reducing the migration of capsule plasticizers into the encapsulated pharmaceutical formulation. Additionally, the use of the lipophilic solvent prevents the formation of esters which can decrease the chemical stability of the alkanoic acid solution.

Suitable lipophilic solvents are polyol esters of fatty acids. The polyol esters of fatty acids may be mono-, di-, tri-, etc, esters of the polyols. Thus, there may be free hydroxyl

groups present in the polyol esters of fatty acids useful as lipophilic solvents of the invention.

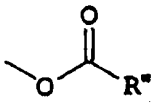
The lipophilic solvent preferred for use in the present invention is an alkylene glycol derivative of formula II:



II

wherein

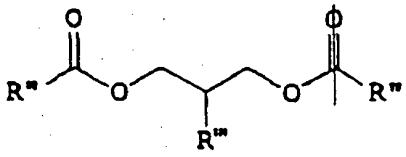
A represents C_1-C_4 alkylene optionally substituted with alkyl or



; and

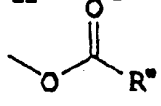
the R" groups are the same or different and represent C_1-C_{12} alkyl,

Suitable lipophilic solvents include those of formula III:



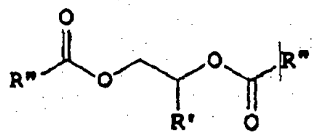
III

where the R" groups are the same or different and represent C_1-C_{12} alkyl and R''' is hydrogen or



.

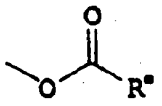
Suitable lipophilic solvents also include those of formula IV:



IV

where the R" groups are the same or different and represent C_1-C_{12} alkyl and R' is C_1-C_6 alkyl.

Other suitable lipophilic solvents are those of formula III where the R" groups are the same and represent C_1-C_4 alkyl and R''' is



Still other suitable lipophilic solvents are those of formula IV where the R" groups are the same or different and represent C_1-C_4 alkyl and R' is methyl.

Most preferred lipophilic solvents of formula III are those where R" is methyl. Most preferred lipophilic solvents of formula IV are those where the R" groups are the same or different and represent $CH_3(CH_2)_6$ or $CH_3(CH_2)_8$.

Particularly preferred solvents are selected from the group consisting of propylene glycol dicaprylate/dicaprate, 1,2,3-propanetriol triacetate and mixtures thereof. Most preferably the solvents suitable for use in the present invention include

propylene glycol dicaprylate/dicaprate, 1,2,3-propanetriol triacetate and mixtures thereof. Propylene glycol dicaprylate/dicaprate is available under the trade name Captex 200 from Karlshamn Lipid Specialties and 1,2,3-propanetriol triacetate is available under the trade name Triacetin from Eastman Chemicals.

The inventive solutions may also contain optional, additional ingredients to improve the dispersivity and dissolution of the substituted alkanoic acid. Suitable additional components include surfactants such as, for example, polyglyceryl esters of fatty acids, polyglycolyzed glycerides, propylene glycol esters, mono- and di-glycerides, sorbitan fatty acid esters, polyoxyethylene sorbitan fatty acid esters, polyoxyethylene sorbitol esters, polyoxyethylene acids, polyoxyethylene alcohols, and mixtures thereof. A preferred class of surfactants for use in combination with the lipophilic solvents is the polyoxyethylene sorbitan fatty acid esters. Suitable sorbitan esters are sold under the trade name Tween. A particularly useful Tween is polyoxyethylene (20) sorbitan mono-oleate (Tween 80).

The active substituted alkanoic acid pharmaceutical agent may be present in the solution in amounts ranging up to about 30% by weight of the solution. Preferred concentrations of the active agent are from about 5-20%, more preferably about 10-15%, by weight of the final solution. Combinations of lipophilic solvents may be used to obtain a desired final concentration.

For example, ketoprofen may be present in the solution in amounts ranging up to about 5% by weight of the solution when dissolved only in propylene glycol dicaprylate/dicaprate. Ketoprofen may be present in the solution in amounts ranging up to about 14% by weight of the solution when dissolved only in 1,2,3-propanetriol triacetate. When dissolved in a mixture of propylene glycol dicaprylate/dicaprate, 1,2,3-propanetriol triacetate and Tween, the ketoprofen pharmaceutical agent may be present in solution in amounts ranging up to about 22% by weight of solution.

In addition to the ketoprofen pharmaceutical agent and the lipophilic solvents, other adjuncts may optionally be present. Polyoxyethylene (20) sorbitan mono-oleate (Tween 80) may be included in the solution up to about 50% by weight of the solution.

Once the appropriate pharmaceutically acceptable solution of the substituted alkanoic acid is formulated, it can be encapsulated into conventional softgel capsules using any suitable encapsulation method, such as for example, the rotary die process.

All documents, e.g., patents and journal articles, cited above or below are hereby incorporated by reference in their entirety.

One skilled in the art will recognize that modifications may be made in the present invention without deviating from the spirit or scope of the invention. The invention is illustrated further by the following examples which are not to be construed

as limiting the invention or scope of the specific procedures described herein.

Example 1

Pharmaceutically acceptable solutions containing ketoprofen are prepared in the following manner. First, mix the following until homogeneous:

(1) about 92 mg of propylene glycol dicaprylate/dicaprate;

(2) about 92mg of 1,2,3-propanetriol acetate; and

(3) about 10 mg of polyoxyethylene (20) sorbitan mono-oleate.

Second, add about 25 mg of ketoprofen to the homogeneous mixture of propylene glycol dicaprylate, 1,2,3-propanetriol acetate and polyoxyethylene (20) sorbitan mono-oleate, and mix again. While mixing in the ketoprofen, heat the mixture and maintain the temperature between 110-125°F until the ketoprofen is dissolved. Once the ketoprofen is fully dissolved, the solution is then cooled and deaerated. After being cooled and deaerated, the ketoprofen solution can be encapsulated in suitable softgel capsules, such as 4 oval softgel. The filled softgel capsules are thereafter dry finished to the appropriate hardness.

Example 2

Pharmaceutically acceptable solutions containing ketoprofen are prepared in the following manner. First, mix the following until homogeneous:

(1) about 112 mg of propylene glycol dicaprylate/dicaprate;

(2) about 72 mg of 1,2,3-propanetriol acetate; and

(3) about 14 mg of polyoxyethylene (20) sorbitan mono-oleate.

Second, add about 25 mg of ketoprofen to the homogeneous mixture of propylene glycol dicaprylate, 1,2,3-propanetriol acetate and polyoxyethylene (20) sorbitan mono-oleate, and mix again. While mixing in the ketoprofen, heat the mixture and maintain the temperature between 110-125°F until the ketoprofen is dissolved. Once the ketoprofen is fully dissolved, the solution is then cooled and deaerated. After being cooled and deaerated, the ketoprofen solution can be encapsulated in suitable softgel capsules, such as 4 oval softgel. The filled softgel capsules are thereafter dry finished to the appropriate hardness.

Example 3

Pharmaceutically acceptable solutions containing up to about 22% ketoprofen by weight of solution are prepared in the following manner, which provides a self-emulsifying system. First, mix the following until homogeneous:

(1) propylene glycol dicaprylate/dicaprate in an amount ranging from about 40% to about 98% by weight;

(2) 1,2,3-propanetriol acetate in an amount ranging from about 1% to about 55% by weight; and

(3) polyoxyethylene (20) sorbitan mono-oleate in an amount ranging from about 1% to about 50% by weight.

Second, add ketoprofen to the homogeneous mixture of propylene glycol dicaprylate, 1,2,3-propanetriol triacetate and polyoxyethylene (20) sorbitan mono-oleate, and mix again. While mixing in the ketoprofen, heat the mixture and maintain the temperature between 110-125°F until the ketoprofen is dissolved. Once the ketoprofen is fully dissolved, the solution is then cooled and deaerated. After being cooled and deaerated, the ketoprofen solution can be encapsulated in suitable softgel capsules. The filled softgel capsules are thereafter dry finished to the appropriate hardness.

Example 4

Pharmaceutically acceptable solutions containing up to about 14% ketoprofen by weight of solution are prepared in the following manner. First, mix the following until homogeneous:

(1) propylene glycol dicaprylate/dicaprate in an amount ranging from about 1% to about 50% by weight; and

(2) 1,2,3-propanetriol acetate in an amount ranging from about 50% to about 99% by weight.

Second, add ketoprofen to the homogeneous mixture of propylene glycol dicaprylate and 1,2,3-propanetriol acetate and mix again. While mixing in the ketoprofen, heat the mixture and maintain the temperature between 110-125°F until the ketoprofen is dissolved. Once the ketoprofen is fully dissolved, the solution is then cooled and deaerated. After being cooled and deaerated, the ketoprofen solution can be encapsulated in suitable softgel

capsules. The filled softgel capsules are thereafter dry finished to the appropriate hardness.

Example 5

Pharmaceutically acceptable solutions containing up to about 5% ketoprofen by weight of solution are prepared by mixing the ketoprofen with propylene glycol dicaprylate/dicaprate while heating the mixture. The temperature of the mixture should be maintained between 110-125°F until the ketoprofen is dissolved. Once the ketoprofen is fully dissolved, the solution is then cooled and deaerated. After being cooled and deaerated, the ketoprofen solution can be encapsulated in suitable softgel capsules. The filled softgel capsules are thereafter dry finished to the appropriate hardness.

Example 6

Pharmaceutically acceptable solutions containing up to about 14% ketoprofen by weight of solution are prepared by mixing the ketoprofen with 1,2,3-propanetriol acetate while heating the mixture. The temperature of the mixture should be maintained between 110-125°F until the ketoprofen is dissolved. Once the ketoprofen is fully dissolved, the solution is then cooled and deaerated. After being cooled and deaerated, the ketoprofen solution can be encapsulated in suitable softgel capsules. The filled softgel capsules are thereafter dry finished to the appropriate hardness.

Example 7

The following formulations are prepared according to the invention using the procedure set forth above in Example 1.

Ingredient	A (mg)	B (mg)	C (mg)
Propylene glycol dicaprylate/dicaprate	92	184	276
1,2,3-Propanetriol triacetate	92	184	276
Polyoxyethylene (20) sorbitan mono-oleate	10	20	30
Ketoprofen	25	50	75
Final softgel size	4 oval	7.5 oval	12 oval

Example 8

The following comparative formulations are prepared essentially as in the procedure set forth above in Example 1 but do not include the lipophilic solvent according to the invention.

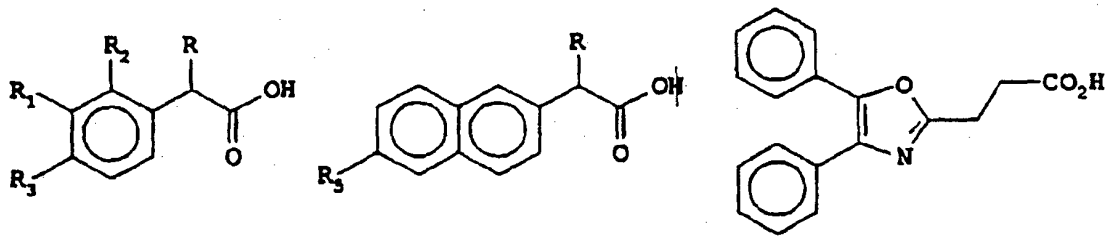
Ingredient	D (mg)	E (mg)	F (mg)
Water	5.46	10.92	16.38
Potassium hydroxide	6.06	12.12	18.18
Polyoxyethylene glycol 400	438.48	876.96	1315.44
Propylene glycol	25	50	75
Ketoprofen	25	50	75
Final softgel size	12 oval	20 oval	30 oval

Certain specific embodiments of the present invention have been discussed and disclosed in detail. Many other embodiments

that have not been disclosed or described are nevertheless the equivalent of and fall within the scope of the present invention and/or the following claims.

WE CLAIM:

1. A pharmaceutical composition comprising alkanoic acids selected from the group consisting of alkanoic acids of the formulas:

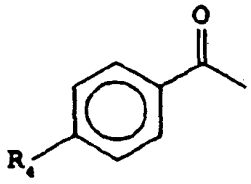


or pharmaceutically acceptable salts thereof,

wherein

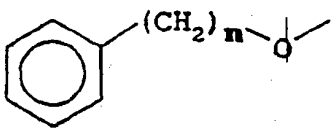
R represents a hydrogen atom or an alkyl group containing 1 to 4 carbon atoms;

R_1 represents hydrogen, halogen, C_1-C_6 alkyl, phenylalkyl where the alkyl is C_1-C_6 alkyl, a benzoyl group of the formula:



where R_4 represents hydrogen, C_1-C_6 alkyl, or an alkylthio group having 1 to 4 carbon atoms; or

R_1 represents a group of the formula:



where n is 0, 1 or 2;

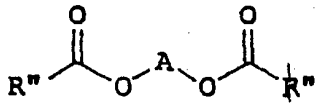
R_2 represents hydrogen, hydroxy or C_1-C_6 alkoxy;

R_3 represents hydrogen, C_1-C_6 alkyl or phenyl; and

R_5 is C_1-C_6 alkoxy.

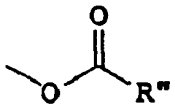
the 2-phenyl or naphthyl alkanoic acid being solubilized in a lipophilic solvent.

2. A pharmaceutical composition according to Claim 1 wherein the lipophilic solvent has the formula:



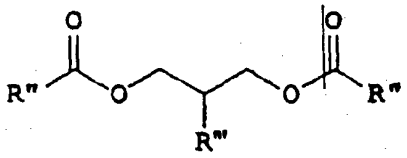
wherein

A represents C_1-C_4 alkylene optionally substituted with alkyl or

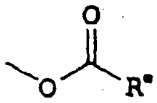
 ; and

the R" groups are the same of different and represent C_1-C_{12} alkyl.

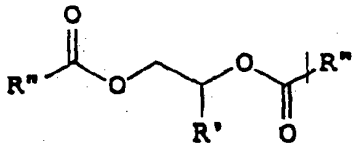
3. A pharmaceutical composition according to Claim 1 wherein the lipophilic solvent has the formula:



where the R" groups are the same or different and represent C_1-C_{12} alkyl and R''' is hydrogen or

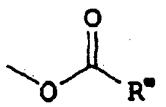


4. A pharmaceutical composition according to Claim 1 wherein the lipophilic solvent has the formula:



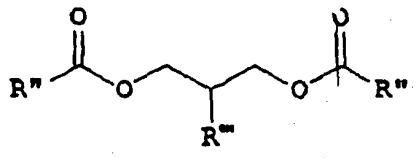
where the R" groups are the same or different and represent C_1-C_{12} alkyl and R' is C_1-C_6 alkyl.

5. A pharmaceutical composition according to Claim 3, where the R" groups are the same and represent C_1-C_4 alkyl and R''' is

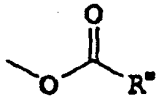


6. A pharmaceutical composition accoriding to Claim 4, where the R" groups are the same or different and represent C_1-C_4 alkyl and R' is methyl.

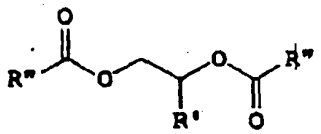
7. A pharmaceutical composition accoriding to Claim 1, wherein the lipophilic solvent comprises a mixture of a alkylene glycol derivative of the formula:



where the R" groups are the same or different and represent C_1-C_{12} alkyl and R''' is hydrogen or

 and

a alkylene glycol derivative of the formula:



where the R" groups are the same or different and represent C_1-C_{12} alkyl and R' is C_1-C_6 alkyl.

8. A pharmaceutical composition of Claim 1 wherein at least one lipophilic solvent has no free hydroxyl groups.

9. A pharmaceutical composition comprising ketoprofen, naproxen, oxaprozin or ibuprofen solubilized up to 14% by weight in 1,2,3-propanetriol triacetate.

10. A pharmaceutical composition comprising ketoprofen, ibuprofen, oxaprozin or naproxen solubilized up to 5% by weight in propylene glycol dicaprylate/dicaprate.

11. The pharmaceutical composition of Claim 9, wherein the ketoprofen, naproxen, oxaprozin or ibuprofen is solubilized in a mixture of 1 to 50% by weight of propylene glycol dicaprylate/dicaprate and 50 to 99% by weight of 1,2,3-propanetriol triacetate.

12. A pharmaceutical composition comprising ketoprofen, oxaprozin, naproxen, oxaprozin or ibuprofen solubilized up to 22% by weight in a mixture of 40 to 98% by weight of propylene glycol dicaprylate/dicaprate, 1 to 55% by weight of 1,2,3-propanetriol triacetate, and 1 to 50% by weight of a surfactant.

13. A solution comprising from about 0.1 to about 30% by weight of ibuprofen, naproxen, oxaprozin or ketoprofen in a lipophilic solvent.

14. A solution according to Claim 13, comprising from about 5 to about 20% by weight of ibuprofen, naproxen, oxaprozin or ketoprofen in a lipophilic solvent.

15. A solution according to Claim 13, comprising from about 10 to about 15% by weight of ibuprofen, naproxen, oxaprozin or ketoprofen in a lipophilic solvent.

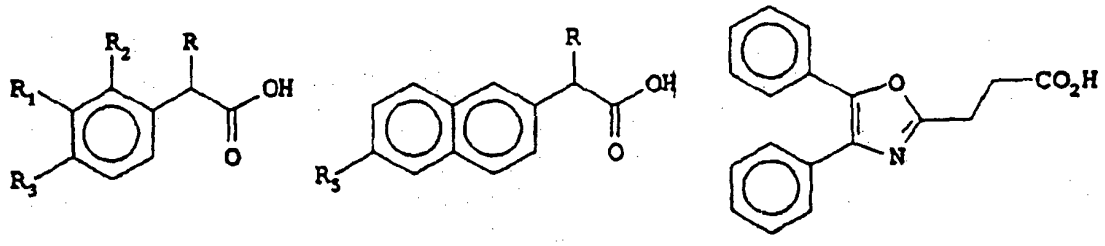
16. A soft gelatin capsule comprising a solution of ketoprofen, naproxen, or ibuprofen in a lipophilic solvent.

17. A soft gelatin capsule according to Claim 16, wherein the amount of ketoprofen, naproxen, oxaprozin or ibuprofen in the solution is from about 10 to 15% by weight of the solution.

18. A solution according to Claim 13, wherein the lipophilic solvent is suitable for encapsulation by a gelatin shell.

19. A pharmaceutical composition comprising an amount of ketoprofen, ibuprofen, oxaprozin or naproxen effective to produce analgesia in a patient, the ketoprofen, ibuprofen, oxaprozin or naproxen being present as a solution in a pharmaceutically acceptable lipophilic solvent.

20. A method for preparing a liquid mixture of a 2- or 3-aryl or 3-heteroaryl alkanoic acid suitable for encapsulation in a soft gelatin capsule comprising mixing a 2- or 3-aryl or 3-heteroaryl alkanoic acid of the formula:

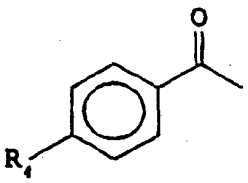


or pharmaceutically acceptable salts thereof,

wherein

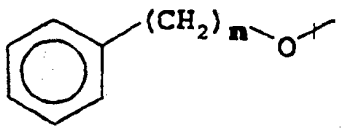
R represents a hydrogen atom or an alkyl group containing 1 to 4 carbon atoms;

R_1 represents hydrogen, halogen, C_1-C_6 alkyl, phenylalkyl where the alkyl is C_1-C_6 alkyl, a benzoyl group of the formula:



where R_4 represents hydrogen, C_1-C_6 alkyl, or an alkylthio group having 1 to 4 carbon atoms; or

R_1 represents a group of the formula:



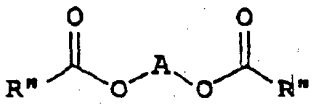
where n is 0, 1 or 2;

R_2 represents hydrogen, hydroxy or C_1-C_6 alkoxy;

R_3 represents hydrogen, C_1-C_6 alkyl or phenyl; and

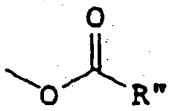
R_5 is C_1-C_6 alkoxy,

with an effective solubilizing amount of at least one lipophilic solvent of the formula:



wherein

A represents C_1-C_4 alkylene optionally substituted with alkyl or



; and

the R" groups are the same of different and represent C_1-C_{12} alkyl.

INTERNATIONAL SEARCH REPORT

Interna ıl Application No
PCT/US 95/06183

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K31/19 A61K47/14

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X Y	US,A,5 059 626 (PARK MOO W ET AL) 22 October 1991 see column 1, line 59 - line 60; example 1; table II	1-7,9, 10,13-20 8,11,12
X Y	WO,A,92 08445 (AFFINITY BIOTECH INC) 29 May 1992 see claims 1-3	1-6,9, 10,13-20 7,8,11, 12
X Y	US,A,4 727 109 (SCHMIDT PETER C ET AL) 23 February 1988 see claims 1-8; examples 4,7,8	1-7,9, 13-20 8,10-12
Y	WO,A,92 10996 (MERRELL DOW PHARMA) 9 July 1992 see page 7, paragraph 1; claims 1-3	7,10

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
28 September 1995	27. 10. 95

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl, Fax (+ 31-70) 340-3016	Foerster, W

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INTERNATIONAL SEARCH REPORT

Interna ıl Application No
PCT/US 95/06183

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US,A,5 071 643 (YU MAN S ET AL) 10 December 1991 cited in the application see example IX; table 1 ---	1-20
A	WO,A,94 07488 (PFIZER ;AHMED IMRAN (US)) 14 April 1994 see the whole document -----	1-20

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Information on patent family members

Internat Application No
PCT/US 95/06183

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
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		US-A-	5011852	30-04-91
WO-A-9208445	29-05-92	US-A-	5110606	05-05-92
		AU-B-	648483	21-04-94
		AU-A-	9054191	11-06-92
		CA-A-	2095819	14-05-92
		EP-A-	0561874	29-09-93
		JP-T-	5509332	22-12-93
US-A-4727109	23-02-88	DE-A-	3500103	10-07-86
WO-A-9210996	09-07-92	AT-T-	117200	15-02-95
		AU-B-	647563	24-03-94
		AU-A-	9067891	22-07-92
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		EP-A-	0662831	19-07-95
		FI-A-	934387	08-04-94

INTERNATIONAL SEARCH REPORT

Information on patent family members

Interna l Application No
PCT/US 95/06183

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO-A-9407488		HU-A-	68533	27-04-95
		NO-A-	951350	06-06-95
		PL-A-	308307	24-07-95

MAIN REQUEST

CLAIMS

1. A softgel capsule comprising a fill material wherein the fill material comprises

(a) naproxen sodium;

(b) a deionizing agent in an amount of from 0.2 to 1.0 mole equivalents per mole of the naproxen sodium;

(c) polyethylene glycol; and

(d) water.

2. The capsule of claim 1 wherein the deionizing is selected from hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, fumaric acid, maleic acid, tartaric acid, methane-, ethane-, and benzene sulfonates, citric acid, malic acid, acetic acid, proprionic acid, pyruvic acid, butanoic acid, and lactic acid.

3. The capsule of claim 2 wherein the deionizing agent is hydrochloric acid, citric acid or lactic acid.

4. The capsule of claim 3 wherein the deionizing agent is lactic acid.

5. The capsule of any one of the preceding claims wherein polyethylene glycol is present in an amount from 10% to 80% by weight.

6. The capsule of any one of the preceding claims wherein the polyethylene glycol is one or more polyethylene glycols with a molecular weight between 300 and 1500.

7. The capsule of any one of the preceding claims wherein water is present in an amount from 1% to 18% by weight.

8. The capsule of any one of the preceding claims further comprising one or more excipients selected from the group consisting of plasticizers, crystallization inhibitors, wetting agents, bulk filling agents, solubilizers, bioavailability enhancers, solvents, dyes, preservatives, solvents, surfactants, and combinations thereof.

9. The capsule of claim 8 wherein the solubilizer is selected from the group consisting of glycerin, polyvinylpyrrolidone, propylene glycol and combinations thereof.

10. The capsule of claim 9 wherein the solubilizer is present in amount from 1% to 10% by weight.

11. The capsule of any one of the preceding claims wherein the fill material is liquid.

12. A capsule of any one of the preceding claims for use as a medicament.

13. A method of making the capsule of any of the preceding claims comprising

(a) mixing naproxen sodium, the polyethylene glycol and the deionizing agent and water; and

(b) encapsulating the mixture in a softgel capsule.

14. The method of claim 13, wherein step (a) is conducted at a temperature of from 50°C to 70°C.

15. The use of

(a) naproxen sodium;

(b) a deionizing agent in an amount of from 0.2 to 1.0 mole equivalents per mole of the naproxen sodium;

(c) polyethylene glycol; and

(d) water

in the manufacture of a medicament in the form of a capsule for administration of the naproxen sodium to a patient in need thereof.

1st AUXILIARY REQUEST

CLAIMS

1. A softgel capsule comprising a fill material wherein the fill material comprises

(a) naproxen sodium;

(b) fumaric acid, maleic acid, tartaric acid, citric acid, malic acid, acetic acid, proprionic acid, pyruvic acid, butanoic acid or lactic acid in an amount of from 0.2 to 1.0 mole equivalents per mole of the naproxen sodium;

(c) polyethylene glycol; and

(d) water.

2. The capsule of claim 1 wherein (b) is citric acid or lactic acid.

3. The capsule of claim 2 wherein (b) is lactic acid.

4. The capsule of any one of the preceding claims wherein polyethylene glycol is present in an amount from 10% to 80% by weight.

5. The capsule of any one of the preceding claims wherein the polyethylene glycol is one or more polyethylene glycols with a molecular weight between 300 and 1500.

6. The capsule of any one of the preceding claims wherein water is present in an amount from 1% to 18% by weight.

7. The capsule of any one of the preceding claims further comprising one or more excipients selected from the group consisting of plasticizers, crystallization inhibitors, wetting agents, bulk filling agents, solubilizers, bioavailability enhancers, solvents, dyes, preservatives, solvents, surfactants, and combinations thereof.

8. The capsule of claim 7 wherein the solubilizer is selected from the group consisting of glycerin, polyvinylpyrrolidone, propylene glycol and combinations thereof.

9. The capsule of claim 8 wherein the solubilizer is present in amount from 1% to 10% by weight.

10. The capsule of any one of the preceding claims wherein the fill material is liquid.

11. A capsule of any of the preceding claims for use as a medicament.

12. A method of making the capsule of claim 1 comprising

(a) mixing components (a), (b), (c) and (d) as defined in claim 1; and

(b) encapsulating the mixture in a softgel capsule.

13. The method of claim 12, wherein step (a) is conducted at a temperature of from 50°C to 70°C.

14. The use of

(a) naproxen sodium;

(b) fumaric acid, maleic acid, tartaric acid, citric acid, malic acid, acetic acid, proprionic acid, pyruvic acid, butanoic acid or lactic acid in an amount of from 0.2 to 1.0 mole equivalents per mole of the naproxen sodium;

(c) polyethylene glycol; and

(d) water

in the manufacture of a medicament in the form of a capsule for administration of the naproxen sodium to a patient in need thereof.

2nd AUXILIARY REQUEST

CLAIMS

1. A softgel capsule comprising a fill material wherein the fill material comprises

(a) naproxen sodium;

(b) fumaric acid, maleic acid, tartaric acid, malic acid, acetic acid, proprionic acid, pyruvic acid, butanoic acid or lactic acid in an amount of from 0.2 to 1.0 mole equivalents per mole of the naproxen sodium;

(c) polyethylene glycol; and

(d) water.

2. The capsule of claim 1 wherein (b) is lactic acid.

3. The capsule of any one of the preceding claims wherein polyethylene glycol is present in an amount from 10% to 80% by weight.

4. The capsule of any one of the preceding claims wherein the polyethylene glycol is one or more polyethylene glycols with a molecular weight between 300 and 1500.

5. The capsule of any one of the preceding claims wherein water is present in an amount from 1% to 18% by weight.

6. The capsule of any one of the preceding claims further comprising one or more excipients selected from the group consisting of plasticizers, crystallization inhibitors, wetting agents, bulk filling agents, solubilizers, bioavailability enhancers, solvents, dyes, preservatives, solvents, surfactants, and combinations thereof.

7. The capsule of claim 6 wherein the solubilizer is selected from the group consisting of glycerin, polyvinylpyrrolidone, propylene glycol and combinations thereof.

8. The capsule of claim 7 wherein the solubilizer is present in amount from 1% to 10% by weight.

9. The capsule of any one of the preceding claims wherein the fill material is liquid.

10. A capsule of any of the preceding claims for use as a medicament.

11. A method of making the capsule of claim 1 comprising

(a) mixing components (a), (b), (c) and (d) as defined in claim 1; and

(b) encapsulating the mixture in a softgel capsule.

12. The method of claim 11, wherein step (a) is conducted at a temperature of from 50°C to 70°C.

13. The use of

(a) naproxen sodium;

(b) fumaric acid, maleic acid, tartaric acid, malic acid, acetic acid, proprionic acid, pyruvic acid, butanoic acid or lactic acid in an amount of from 0.2 to 1.0 mole equivalents per mole of the naproxen sodium;

(c) polyethylene glycol; and

(d) water

in the manufacture of a medicament in the form of a capsule for administration of the naproxen sodium to a patient in need thereof.

3rd AUXILIARY REQUEST

CLAIMS

1. A softgel capsule comprising a fill material wherein the fill material comprises

(a) naproxen sodium;

(b) lactic acid in an amount of from 0.2 to 1.0 mole equivalents per mole of the naproxen sodium;

(c) polyethylene glycol; and

(d) water.

2. The capsule of claim 1 wherein polyethylene glycol is present in an amount from 10% to 80% by weight.

3. The capsule of claim 1 wherein the polyethylene glycol is one or more polyethylene glycols with a molecular weight between 300 and 1500.

4. The capsule of claim 1 wherein water is present in an amount from 1% to 18% by weight.

5. The capsule of claim 1 further comprising one or more excipients selected from the group consisting of plasticizers, crystallization inhibitors, wetting agents, bulk filling agents, solubilizers, bioavailability enhancers, solvents, dyes, preservatives, solvents, surfactants, and combinations thereof.

6. The capsule of claim 5 wherein the solubilizer is selected from the group consisting of glycerin, polyvinylpyrrolidone, propylene glycol and combinations thereof.

7. The capsule of claim 6 wherein the solubilizer is present in amount from 1% to 10% by weight.

8. The capsule of any one of the preceding claims wherein the fill material is liquid.

9. A capsule of any one of the preceding claims for use as a medicament.

10. A method of making the capsule of any one of the preceding claims comprising

(a) mixing naproxen sodium, the polyethylene glycol, the lactic acid and water; and

(b) encapsulating the mixture in a softgel capsule.

11. The method of claim 10, wherein step (a) is conducted at a temperature of from 50°C to 70°C.

12. The use of

(a) naproxen sodium;

(b) lactic acid in an amount of from 0.2 to 1.0 mole equivalents per mole of the naproxen sodium;

(c) polyethylene glycol; and

(d) water

in the manufacture of a medicament in the form of a capsule for administration of the naproxen sodium to a patient in need thereof.

4th AUXILIARY REQUEST

CLAIMS

1. A softgel capsule obtainable by a method which comprises

(I) producing a fill material by mixing

(a) naproxen sodium;

(b) a deionizing agent in an amount of from 0.2 to 1.0 mole equivalents per mole of the naproxen sodium;

(c) polyethylene glycol; and

(d) water

at a temperature of from 50°C to 70°C; and

(II) encapsulating the mixture in a softgel capsule.

2. The capsule of claim 1 wherein the deionizing is selected from hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, fumaric acid, maleic acid, tartaric acid, methane-, ethane-, and benzene sulfonates, citric acid, malic acid, acetic acid, proprionic acid, pyruvic acid, butanoic acid, and lactic acid.

3. The capsule of claim 2 wherein the deionizing agent is hydrochloric acid, citric acid or lactic acid.

4. The capsule of claim 3 wherein the deionizing agent is lactic acid.

5. The capsule of any one of the preceding claims wherein polyethylene glycol is used in an amount from 10% to 80% by weight.

6. The capsule of any one of the preceding claims wherein the polyethylene glycol is one or more polyethylene glycols with a molecular weight between 300 and 1500.

7. The capsule of any one of the preceding claims wherein water is used in an amount from 1% to 18% by weight.

8. The capsule of any one of the preceding claims further comprising one or more excipients selected from the group consisting of plasticizers, crystallization inhibitors, wetting

agents, bulk filling agents, solubilizers, bioavailability enhancers, solvents, dyes, preservatives, solvents, surfactants, and combinations thereof.

9. The capsule of claim 8 wherein the solubilizer is selected from the group consisting of glycerin, polyvinylpyrrolidone, propylene glycol and combinations thereof.

10. The capsule of claim 9 wherein the solubilizer is present in amount from 1% to 10% by weight.

11. The capsule of any one of the preceding claims wherein the fill material is liquid.

12. A capsule of any one of the preceding claims for use as a medicament.

13. A method of making the capsule of any of the preceding claims comprising

(a) mixing naproxen sodium, the polyethylene glycol and the deionizing agent and water at a temperature of from 50°C to 70°C; and

(b) encapsulating the mixture in a softgel capsule.

14. The use of

(a) naproxen sodium;

(b) a deionizing agent in an amount of from 0.2 to 1.0 mole equivalents per mole of the naproxen sodium;

(c) polyethylene glycol; and

(d) water

in the manufacture of a medicament in the form of a capsule for administration of the naproxen sodium to a patient in need thereof.

5th AUXILIARY REQUEST

CLAIMS

1. A softgel capsule obtainable by a method which comprises

(I) producing a fill material by mixing

(a) naproxen sodium;

(b) fumaric acid, maleic acid, tartaric acid, citric acid, malic acid, acetic acid, proprionic acid, pyruvic acid, butanoic acid or lactic acid in an amount of from 0.2 to 1.0 mole equivalents per mole of the naproxen sodium;

(c) polyethylene glycol; and

(d) water

at a temperature of from 50°C to 70°C; and

(II) encapsulating the mixture in a softgel capsule.

2. The capsule of claim 1 wherein (b) is citric acid or lactic acid.

3. The capsule of claim 2 wherein (b) is lactic acid.

4. The capsule of any one of the preceding claims wherein polyethylene glycol is used in an amount from 10% to 80% by weight.

5. The capsule of any one of the preceding claims wherein the polyethylene glycol is one or more polyethylene glycols with a molecular weight between 300 and 1500.

6. The capsule of any one of the preceding claims wherein water is used in an amount from 1% to 18% by weight.

7. The capsule of any one of the preceding claims further comprising one or more excipients selected from the group consisting of plasticizers, crystallization inhibitors, wetting agents, bulk filling agents, solubilizers, bioavailability enhancers, solvents, dyes, preservatives, solvents, surfactants, and combinations thereof.

8. The capsule of claim 7 wherein the solubilizer is selected from the group consisting of glycerin, polyvinylpyrrolidone, propylene glycol and combinations thereof.

9. The capsule of claim 8 wherein the solubilizer is present in amount from 1% to 10% by weight.

10. The capsule of any one of the preceding claims wherein the fill material is liquid.

11. A capsule of any of the preceding claims for use as a medicament.

12. A method of making the capsule of claim 1 comprising

(a) mixing components (a), (b), (c) and (d) as defined in claim 1 at a temperature of from 50°C to 70°C; and

(b) encapsulating the mixture in a softgel capsule.

13. The use of

(a) naproxen sodium;

(b) fumaric acid, maleic acid, tartaric acid, citric acid, malic acid, acetic acid, proprionic acid, pyruvic acid, butanoic acid or lactic acid in an amount of from 0.2 to 1.0 mole equivalents per mole of the naproxen sodium;

(c) polyethylene glycol; and

(d) water

in the manufacture of a medicament in the form of a capsule for administration of the naproxen sodium to a patient in need thereof.

6th AUXILIARY REQUEST

CLAIMS

1. A softgel capsule obtainable by a method which comprises

(I) producing a fill material by mixing

(a) naproxen sodium;

(b) fumaric acid, maleic acid, tartaric acid, malic acid, acetic acid, proprionic acid, pyruvic acid, butanoic acid or lactic acid in an amount of from 0.2 to 1.0 mole equivalents per mole of the naproxen sodium;

(c) polyethylene glycol; and

(d) water

at a temperature of from 50°C to 70°C; and

(II) encapsulating the mixture in a softgel capsule.

2. The capsule of claim 1 wherein (b) is lactic acid.

3. The capsule of any one of the preceding claims wherein polyethylene glycol is used in an amount from 10% to 80% by weight.

4. The capsule of any one of the preceding claims wherein the polyethylene glycol is one or more polyethylene glycols with a molecular weight between 300 and 1500.

5. The capsule of any one of the preceding claims wherein water is used in an amount from 1% to 18% by weight.

6. The capsule of any one of the preceding claims further comprising one or more excipients selected from the group consisting of plasticizers, crystallization inhibitors, wetting agents, bulk filling agents, solubilizers, bioavailability enhancers, solvents, dyes, preservatives, solvents, surfactants, and combinations thereof.

7. The capsule of claim 6 wherein the solubilizer is selected from the group consisting of glycerin, polyvinylpyrrolidone, propylene glycol and combinations thereof.

8. The capsule of claim 7 wherein the solubilizer is present in amount from 1% to 10% by weight.

9. The capsule of any one of the preceding claims wherein the fill material is liquid.

10. A capsule of any of the preceding claims for use as a medicament.

11. A method of making the capsule of claim 1 comprising

(a) mixing components (a), (b), (c) and (d) as defined in claim 1 at a temperature of from 50°C to 70°C; and

(b) encapsulating the mixture in a softgel capsule.

12. The use of

(a) naproxen sodium;

(b) fumaric acid, maleic acid, tartaric acid, malic acid, acetic acid, proprionic acid, pyruvic acid, butanoic acid or lactic acid in an amount of from 0.2 to 1.0 mole equivalents per mole of the naproxen sodium;

(c) polyethylene glycol; and

(d) water

in the manufacture of a medicament in the form of a capsule for administration of the naproxen sodium to a patient in need thereof.

7th AUXILIARY REQUEST

CLAIMS

1. A softgel capsule obtainable by a method which comprises

(I) producing a fill material by mixing

(a) naproxen sodium;

(b) lactic acid in an amount of from 0.2 to 1.0 mole equivalents per mole of the naproxen sodium;

(c) polyethylene glycol; and

(d) water

at a temperature of from 50°C to 70°C; and

(II) encapsulating the mixture in a softgel capsule.

2. The capsule of claim 1 wherein polyethylene glycol is used in an amount from 10% to 80% by weight.

3. The capsule of claim 1 wherein the polyethylene glycol is one or more polyethylene glycols with a molecular weight between 300 and 1500.

4. The capsule of claim 1 wherein water is used in an amount from 1% to 18% by weight.

5. The capsule of claim 1 further comprising one or more excipients selected from the group consisting of plasticizers, crystallization inhibitors, wetting agents, bulk filling agents, solubilizers, bioavailability enhancers, solvents, dyes, preservatives, solvents, surfactants, and combinations thereof.

6. The capsule of claim 5 wherein the solubilizer is selected from the group consisting of glycerin, polyvinylpyrrolidone, propylene glycol and combinations thereof.

7. The capsule of claim 6 wherein the solubilizer is present in amount from 1% to 10% by weight.

8. The capsule of any one of the preceding claims wherein the fill material is liquid.

9. A capsule of any one of the preceding claims for use as a medicament.

10. A method of making the capsule of any one of the preceding claims comprising

(a) mixing naproxen sodium, the polyethylene glycol, the lactic acid and water at a temperature of from 50°C to 70°C; and

(b) encapsulating the mixture in a softgel capsule.

11. The use of

(a) naproxen sodium;

(b) lactic acid in an amount of from 0.2 to 1.0 mole equivalents per mole of the naproxen sodium;

(c) polyethylene glycol; and

(d) water

in the manufacture of a medicament in the form of a capsule for administration of the naproxen sodium to a patient in need thereof.

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Datum/Date
09.10.14

Zeichen/Reference/Référence	Anmeldung Nr./Application No./Demande n°//Patent Nr./Patent No./Brevet n°
PABCA/P38814EP APPR	06737018 / 1863458

Anmelder/Applicant/Demandeur//Patentinhaber/Proprietor/Titulaire
Banner Pharmacaps Inc.

Appeal number: T0826/12-3.3.07

Please find enclosed a copy of the minutes of the oral proceedings of 16.09.14.

The Registrar S. Fabiani
Tel.: 089 / 2399 - 3371

Annex(es):

Registered letter

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Appeal number T0826/12-3.3.07

Application No.: 06737018.9
Applicant: Banner Pharmacaps Inc.

Minutes of the oral proceedings

of 16 September 2014

Composition of the Board:

Chairman: J. Riolo
Members: D. Boulois
W. Ungler

Start of oral proceedings:	09.00 hours
End of oral proceedings:	10.25 hours

Documents presented: Claims 1 to 13 of an amended main request.

Present on behalf of the appellant: Ms C. Crowhurst
professional representative, identified by: ID-Card
accompanied by: Mr W. Cutchins

The Chairman declared the oral proceedings open.
He summarised the relevant facts as appearing from the file.

The appellant addressed the Board.
The matter was then discussed with the appellant.

After having discussed the main request filed with letter dated 22 August 2014 the appellant filed an amended version of the main request. The former main request and all auxiliary requests were withdrawn.

As regards claim 13 of the (amended) main request the appellant shared the view of the Board that this claim was directed to a

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Appeal number T0826/12-3.3.07

method of preparation of a medicament instead of claiming a second medical use.

The appellant requested that the decision under appeal be set aside and that a patent be granted on the basis of the claims of the main request filed during the oral proceedings of 16 September 2014.

The Chairman asked the appellant if they had any further comments or requests. There were none.

The Chairman then declared the debate closed.

After deliberation by the Board, the following decision was given:

1. The decision under appeal is set aside.
2. The case is remitted to the department of first instance with the order to grant a patent on the basis of the claims of the main request filed during the oral proceedings of 16 September 2014 and a description to be adapted thereto.

The Chairman then closed the oral proceedings.

The Minute Writer:

W. Ungler

The Chairman:

J. Riolo

Main

~~1st AUXILIARY~~ REQUEST

CLAIMS

1. A softgel capsule comprising a fill material wherein the fill material comprises

(a) naproxen sodium;

(b) fumaric acid, maleic acid, tartaric acid, citric acid, malic acid, acetic acid, proprionic acid, pyruvic acid, butanoic acid or lactic acid in an amount of from 0.2 to 1.0 mole equivalents per mole of the naproxen sodium;

(c) polyethylene glycol; ~~and~~

(d) water; and

(e) (A)

2. The capsule of claim 1 wherein (b) is citric acid or lactic acid.

3. The capsule of claim 2 wherein (b) is lactic acid.

4. The capsule of any one of the preceding claims wherein polyethylene glycol is present in an amount from 10% to 80% by weight.

5. The capsule of any one of the preceding claims wherein the polyethylene glycol is one or more polyethylene glycols with a molecular weight between 300 and 1500.

6. The capsule of any one of the preceding claims wherein water is present in an amount from 1% to 18% by weight.

7. The capsule of any one of the preceding claims further comprising one or more excipients selected from the group consisting of plasticizers, crystallization inhibitors, wetting agents, bulk filling agents, solubilizers, bioavailability enhancers, solvents, dyes, preservatives, solvents, surfactants, and combinations thereof.

(A) 8. ~~The capsule of claim 7 wherein the~~ a solubilizer ~~is~~ selected from the group consisting of glycerin, polyvinylpyrrolidone, propylene glycol and combinations thereof.

8. ~~8.~~ The capsule of ~~claim 7~~ any one of the preceding wherein the solubilizer is present in amount from 1% to 10% by weight.

16/9/14

9 ~~10~~. The capsule of any one of the preceding claims wherein the fill material is liquid.

10 ~~11~~. A capsule of any of the preceding claims for use as a medicament.

11 ~~12~~. A method of making the capsule of claim 1 comprising and (e) (A)

(a) mixing components (a), (b), (c) ~~and~~ (d) as defined in claim 1; and

(b) encapsulating the mixture in a softgel capsule.

12 ~~13~~. The method of claim ~~12~~ 11, wherein step (a) is conducted at a temperature of from 50°C to 70°C.

13 ~~14~~. The use of

(a) naproxen sodium;

(b) fumaric acid, maleic acid, tartaric acid, citric acid, malic acid, acetic acid, proprionic acid, pyruvic acid, butanoic acid or lactic acid in an amount of from 0.2 to 1.0 mole equivalents per mole of the naproxen sodium;

(c) polyethylene glycol; ~~and~~

(d) water; and

in the manufacture of a medicament in the form of a capsule for administration of the naproxen sodium to a patient in need thereof.

(e) (A)

Draft 16/91

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Datum/Date
06.11.14

Zeichen/Reference/Référence	Anmeldung Nr./Application No./Demande n°//Patent Nr./Patent No./Brevet n°
PABCA/P38814EP APPR	06737018 / 1863458

Anmelder/Applicant/Demandeur//Patentinhaber/Proprietor/Titulaire
Banner Pharmacaps Inc.

Appeal number: **T0826/12-3.3.07**

Please find enclosed a copy of the decision dated 16.09.14.

The Registrar S. Fabiani
Tel.: 089 / 2399 - 3371

Annex(es): ☑ Acknowledgement of receipt - EPO Form 3936
☐

Registered letter with advice of delivery

Internal distribution code:

(A) [-] Publication in OJ
(B) [-] To Chairmen and Members
(C) [-] To Chairmen
(D) [X] No distribution

Datasheet for the decision of 16 September 2014

Case Number: T 0826/12 - 3.3.07

Application Number: 06737018.9

Publication Number: 1863458

IPC: A61K9/48

Language of the proceedings: EN

Title of invention:
SOLVENT SYSTEM FOR ENHANCING THE SOLUBILITY OF PHARMACEUTICAL AGENTS

Applicant:
Banner Pharmacaps Inc.

Headword:
SOLVENT SYSTEM FOR ENHANCING THE SOLUBILITY OF PHARMACEUTICAL AGENTS/Banner Pharmacaps

Relevant legal provisions:
EPC Art. 54, 56

Keyword:
Novelty - (yes)
Inventive step - (yes)

Decisions cited:

Catchword:

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Case Number: T 0826/12 - 3.3.07

D E C I S I O N
of Technical Board of Appeal 3.3.07
of 16 September 2014

Appellant: (Applicant)	Banner Pharmacaps Inc. 4125 Premier Drive High Point, NC 27265-8144 (US)
Representative:	Potter Clarkson LLP The Belgrave Centre Talbot Street Nottingham, NG1 5GG (GB)
Decision under appeal:	**Decision of the Examining Division of the European Patent Office posted on 29 November 2011 refusing European patent application No. 06737018.9 pursuant to Article 97(2) EPC.**

Composition of the Board:

Chairman	J. Riolo
Members:	D. Boulois
	W. Ungler

Summary of Facts and Submissions

I. The appeal lies from the decision of the Examining Division refusing European patent application No. 06 737 018.9.

II. The decision was based on the sets of claims of the main request and auxiliary requests 1-5 filed with the letter of 16 September 2011 and the auxiliary request 6 filed with the letter of 4 October 2011.

Claim 1 of the main request read as follows:

"1. A pharmaceutical composition comprising
a) a salt of an acidic pharmaceutical agent;
b) a deionizing agent which is a hydrogen ion species in an amount to cause partial deionisation of the salt of from about 0.2 to 1.0 mole equivalents per mole of the pharmaceutically active agent;
c) polyethylene glycol; and optional
d) water."

The independent claims of subsequent requests differed from claim 1 of the main request mainly in the category of the claim ("A softgel capsule...", "A pharmaceutical composition obtainable by a method...", "A method of making a pharmaceutical composition, and the use of the composition). Only according to the sixth auxiliary request was the acidic pharmaceutical agent limited to naproxen sodium.

III. In the decision under appeal, the following documents were cited *inter alia*:
D1: US-A-5 360 615
D2: WO-A-95/31979
D3: US-A-2001/007668

IV. The decision under appeal, as far as relevant to the present decision, may be summarised as follows:

a) Claim 1 of the main request was not novel in view of D3, which disclosed a composition comprising naproxen sodium.

b) Inventive step of the main request was also assessed by the Examining Division despite the finding that claim 1 was not novel. The closest prior art was seen as being either D1 or D3. The distinguishing feature was the presence of the additional acid. The experimental data provided with the letter of 16 September 2011, when compared with the information provided in D2 regarding the instability of a formulation according to D1, did not provide evidence of a technical effect since there were too many differences between the formulations in question, and an effect could not be attributed to the distinguishing feature. The problem was consequently identified as the provision of a further composition. In order to solve the problem of providing an alternative, the addition of any compound to the composition, including an acid, was seen as obvious and in view of this, inventive step was denied.

c) Auxiliary requests 1-5 failed for the same reasons as those provided for the main request.

d) Claim 1 of auxiliary request 6 did not fulfill the requirements of Article 123(2) EPC. Novelty was also denied in view of D3.

V. The applicant (appellant) filed an appeal against that decision. With the statement setting out the grounds of appeal, the appellant filed a new main request and thirteen auxiliary requests, and submitted the following item of evidence:

D7: Annex to grounds of Appeal: Report on comparative studies.

VI. With the communication sent in preparation for oral proceedings, the Board expressed a preliminary view with respect to novelty, added subject-matter and inventive step, in particular stating that the experimental tests provided as D7 appeared to show less PEG ester formation using the compositions according to the application. The Board also noted that said tests appeared to demonstrate that the compositions alleged prepared according to the application, with the exception of samples 8 and 11, were characterised by phase separation and precipitation, and questioned whether they could be considered suitable for the intended purpose, i.e. encapsulation into softgel capsules.

VII. With the letter of 22 August 2014 the appellant submitted further arguments, a new main request and auxiliary requests 1-7 to replace all previous requests on file.

VIII. Oral proceedings were held on 16 September 2014 during which a new set of claims 1-13 was submitted as main and sole request, all previous requests being withdrawn.

Claims 1 and 13 of the main request read as follows:

"1. A softgel capsule comprising a fill material where the fill material comprises
(a) naproxen sodium
(b) fumaric acid, maleic acid, tartaric acid, citric acid, malic acid, acetic acid, proprionic acid, pyruvic acid, butanoic acid, or lactic acid in an amount of from 0.2 to 1.0 mole equivalents per mole of the naproxen sodium;
(c) polyethylene glycol;
(d) water; and
(e) a solubilizer selected from the group consisting of glycerin, polyvinylpyrrolidone, propylene glycol and combinations thereof."

"13. The use of
(a) naproxen sodium;
(b) fumaric acid, maleic acid, tartaric acid, citric acid, malic acid, acetic acid, proprionic acid, pyruvic acid, butanoic acid, or lactic acid in an amount of from 0.2 to 1.0 mole equivalents per mole of the naproxen sodium;
(c) polyethylene glycol;
(d) water; and
(e) a solubilizer selected from the group consisting of glycerin, polyvinylpyrrolidone, propylene glycol and combinations thereof in the manufacture of a medicament in the form of a capsule for administration of the naproxen sodium to a patient in need thereof.

IX. The appellant's arguments, as far as relevant to the present decision, can be summarised as follows:

Main request - inventive step

D1 is the closest prior art. The tests submitted as D7 demonstrated that when subjected to accelerated stress conditions, the amount of polyethylene glycol (PEG) esters present in the pharmaceutical compositions prepared in accordance with the application is lower than that present in the compositions prepared in accordance with the teaching of D1 under the same conditions.

Although samples 1-15 of D7 were, with the exception of samples 8 and 11, for the most part physically characterised by the formation of a phase separated precipitate which would not be suitable for encapsulation in a softgel capsule, the purpose of the tests had been merely to demonstrate the improvement over D1 with respect to the decreased production of PEG esters; the composition of said samples lacked the solubilizers required by claim 1, which would produce solutions suitable for encapsulation into softgel capsules. One such capsule according to the application had been produced according to the experimental report filed before the first instance with the letter of 16 September 2011. The capsules produced according to the application consequently provided unexpected advantages in that the fill material contains less PEG esters both initially and after stability studies, when compared with the corresponding formulations of D1. These advantages could not have been predicted starting from D1 as the closest prior art.

X. The appellant requested that the decision under appeal be set aside and that a patent be granted on the basis of the set of claims 1 to 13 of the main and sole

request, filed during oral proceedings before the Board on 16 September 2014.

Reasons for the Decision

Basis in the application as filed

1. Claim 1 originates from independent claim 19 of the application as filed with the limitation that the pharmaceutically active agent is the preferred agent naproxen sodium, employed in all 12 examples.

1.1 The "deionising agent" referred to in claim 19, ingredient (b) as originally filed, is limited to some of the acids chosen from the list disclosed on page 6, lines 17-21 of the application as filed. That said acid is present "in an amount of from 0.2 to 1.0 mole equivalents per mole of the naproxen sodium" is supported by claim 21 as originally filed, which depends on claim 19. The presence of further ingredients of the fill material in claim 1, namely PEG (component (c)) and water (component (d)) finds support in the application as filed in reference to the preparation of the fill material (page 8, lines 25-27; page 10, lines 14-16). Finally, the presence of a solubilizer according to claim 1, step (e) is supported by the passage in the description as filed on page 7, lines 13-15.

1.2 Since a capsule comprising the fill material according to claim 1 finds support in the application documents as filed, it follows that the use of said fill material in the manufacture of a medicament in the form of a capsule according to claim 13 is also supported.

1.3 It follows that the claims of the main request fulfill the requirements of Article 123(2) EPC.

Novelty - main request

2. Claim 1

2.1 D1 discloses a solvent system for enhancing the solubility of pharmaceutical agents suitable for encapsulation in softgels (column 2, lines 29-33). Example IV concerns the preparation of a concentrated solution of naproxen in which naproxen free acid is mixed with 0.50 mole equivalents of 50% aqueous potassium hydroxide (KOH) and PEG-600.

Claim 1 of the main request differs from example IV of D1 in that:

a) a softgel capsule is claimed; D1 merely discloses solutions (filling mixtures) suitable for filling softgels;
b) naproxen sodium is used instead of naproxen free acid;
c) an acid chosen from the list provided in claim 1, part (b) is added to the naproxen sodium, rather than adding KOH to naproxen free acid; and
d) a solubilizer is employed.

2.1.1 It follows that the subject-matter of claim 1 is novel over the disclosure of D1.

2.2 D3, specifically example 17 thereof, discloses a solution formulation consisting of 21.67 % naproxen sodium, 72.40 % PEG-300, 0.05 % KOH (as a solution of 6.8g KOH in 100 ml of water) and 5.88% sodium

propionate (as a solution of 500 g sodium propionate in 700 ml of water). The formulations of D3 are intended as concentrated solutions of pharmaceutical agents suitable for encapsulation into softgel capsules (paragraph [0013]).

2.2.1 The fill material of claim 1 of the main request differs from example 17 of D3 in that the latter:

a) does not employ an acid chosen from the list provided in claim 1, part (b) in the mole equivalent required; and
b) does not disclose the use of a solubilizer as required by claim 1, ingredient (e).

2.2.2 With respect to difference a), although sodium propionate in aqueous solution exists in equilibrium with propionic acid (denoted "proprionic acid" according to claim 1), the amount of the acid present at equilibrium in the formulation of example 17 of D3 can only be far below the lower limit of 0.2 mole equivalents required by claim 1. Furthermore, although D3 mentions that the pH of the propionate solution may be adjusted by the addition of propionic acid in an amount of 1-2 % by weight of the propionate solution (paragraph [0032]), such a minor proportion would not significantly affect the amount of acid present at equilibrium.

2.2.3 It follows that the subject-matter of claim 1 is novel over the disclosure of D3.

3. Claim 13

3.1 In order to assess novelty of claim 13, its subject-matter needs first to be defined, as discussed during

the oral proceedings. Said claim is drafted in a manner resembling the so-called Swiss-type second medical use claim as instituted by decision G5/83 (OJ EPO 1985, 64), a claim form which would still be permissible in the present application by virtue of the priority date thereof (decision G2/08, order, answer to question 3). A so-called Swiss-type claim may be construed as a purpose-limited process claim, and was introduced specifically to overcome the absence of a specific provision in EPC 1973 allowing purpose-limited product claims for further medical indications (the use-related product claim was allowable for the first medical indication according to Article 54(5) EPC 1973).

3.1.1 The subject-matter of claim 13 is thus not a Swiss-type claim defining a second medical use, but a mere process claim, deriving its novelty from the novelty of the composition of the fill material comprised therein, and not from a new therapeutic use of naproxen sodium. This is evident since the claim fails to identify a specific therapeutic indication for naproxen sodium. Not comprising such a use, the feature "for administration of the naproxen sodium to a patient in need thereof" remains *de facto* purely illustrative and does not limit the scope of the claim to that specific application.

Inventive step

4. Closest prior art

4.1 Both D1 and D3 were seen as suitable closest prior art documents according to the appealed decision, while the appellant has focused on D1 as the closest prior art in

relation to which comparative tests have been provided as D7.

4.2 D3, by virtue of the fact that it discloses in example 17 a formulation comprising naproxen sodium (see section 2.2, above), as well as the salt of an acid listed in claim 1, might appear at first sight to represent a more suitable starting point for the skilled person. However, the remaining 16 examples thereof concern different pharmaceutically active agents, none of which are employed in the salt form. The possibility of using a salt of the pharmaceutical agent is not mentioned at all in the description (D3, paragraphs [0035] and [0040]), and no explanation whatsoever is provided as to the purpose of the added KOH in example 17. Furthermore, D3 explains by way of mechanism that the purpose of the salt of the organic acid used (sodium propionate according to the examples) is to help ionise the medicament (paragraphs [0028] and [0041]). This proposed mechanism does not make logical sense in the context of example 17 in which the naproxen is added as the sodium salt, i.e. already fully ionised. Given this contradiction between on the one hand the use of naproxen sodium in example 17 and on the other hand, the teaching in the description with respect to the role of sodium propionate, coupled with the apparent lack of explanation regarding the use of KOH, example 17 represents an unrealistic starting point which the skilled person, on reading D3, would discard as being inconsistent with the teaching of the remainder of said document.

4.3 For these reasons, D1 is chosen as representing the closest prior art. Example IV of D1, the embodiment closest to the subject-matter of claim 1, does not disclose a softgel capsule comprising specifically the

sodium salt of naproxen, the addition of an acid thereto, nor the use of a solubilizer (see section 2.1, above).

Problem solved

5. According to the appellant, the problem to be solved is the provision of a stable solvent system for naproxen sodium which is suitable for encapsulation in a softgel capsule, wherein the formation of PEG esters is minimized.

5.1 As a solution to this problem, the appellant proposes a softgel capsule according to claim 1 of the main request comprising *inter alia* naproxen sodium and an organic acid chosen from a list in an amount of from 0.2 to 1.0 mole equivalents per mole of the naproxen sodium.

5.2 The experimental tests provided by the appellant as D7 compare the production of undesired PEG esters in samples 16-21 prepared according to D1 with samples 1-15 according to the application. Samples 7-15 correspond to compositions prepared in accordance with claim 1 of the main request with the exception that component (e) thereof is missing, while samples 1-6 employ HCl, an acid which does not fall under the alternatives listed in claim 1, part (b). After being subjected to accelerated stability testing at 60 °C for 7 days, no PEG ester formation was detected in samples 7-12 and 15, while minor amounts were observed in samples 13 and 14. In the solutions of samples 16-21, PEG ester formation was detected (D7, table on pages 6 and 7).

5.2.1 While samples 8 and 11 were physically characterised as clear solutions after the stability tests, samples 7, 9, 10 and 12-15, despite displaying no detectable PEG ester formation, were all physically characterised by either a phase separated precipitate or a semi-solid paste, physical states unfavourable for encapsulation into softgel capsules. The explanation provided by the appellant that the tests of D7 were carried out specifically for the purpose of demonstrating the reduction in PEG ester formation *vis à vis* the compositions prepared according to D1, rather than necessarily to produce clear solutions suitable for incorporation into a softgel capsule, is plausible. Addition of the solubilizer required by claim 1, step (e) to said samples would indeed be expected to provide the desired clear solutions.

5.2.2 It is also plausible that the effect of a reduction in PEG ester formation displayed by samples 7, 9, 10 and 12-15 would remain had the required solubilizer of claim 1, component (e) been included therein, thus producing a clear solution. Furthermore, said effect is credible not only for softgel capsule fill material prepared using lactic acid or citric acid according to comparative samples 7-15, but also for fill materials prepared using the alternative closely related organic acids listed in claim 1, component (b). The effect of a reduction in PEG ester formation is consequently recognised in respect of the whole scope of claim 1.

5.3 On the basis of the effect, the problem has been credibly solved by the subject-matter of claim 1.

Obviousness

6. Although D1 is also concerned with the preparation of a solvent system for enhancing the solubility of naproxen in order to produce concentrated solutions thereof suitable for encapsulation in a softgel, the problem of undesirable PEG ester formation is not recognised nor addressed therein.

6.1 Furthermore, according to D1 it is presumed that the increase in solubility is accomplished by increasing the number of species of naproxen (ionised and unionised) that are available to go into solution, thereby using both the hydrophobic and hydrophilic binding sites of PEG (D1, column 6, line 26 - column 7, line 26). D1 also suggests that the same effect can be achieved by simply adding in the appropriate ratio to PEG and water both the salt and the free acid, without the need for an ionising agent (column 10, lines 39-48).

6.2 Thus D1 teaches that in order to provide the concentrated solution of naproxen desired, the presence of both the free acid and the salt thereof is a prerequisite; how this mixture is obtained is less crucial. It follows that even if the skilled person were to recognise that the (partial) treatment of naproxen sodium with an acid would be a further method leading to the formation of the desired mixture of ionised and unionised naproxen, he would not expect the resultant solution to differ in any of its properties to that produced according to the options provided in D1. Consequently, there is nothing in D1 which would lead the skilled person looking to solve the above problem to the solution of claim 1 of the main request.

6.3 On that basis claim 1 of the main request involves an inventive step.

6.4 Since claim 1 directed to a capsule comprising a fill material involves an inventive step, the same conclusion applies to the use of said fill material in the manufacture of a medicament in the form of a capsule according to claim 13.

6.5 On that basis claim 13 of the main request involves an inventive step.

Conclusion

7. The subject-matter of independent claims 1 and 13 of the main and sole request fulfill the requirements of the EPC.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The case is remitted to the department of first instance with the order to grant a patent on the basis of the claims of the main request filed during the oral proceedings of 16 September 2014 and a description to be adapted thereto.

The Registrar: The Chairman:

S. Fabiani J. Riolo

Decision electronically authenticated

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Boards of Appeal

The Registry
Name: S Fabiani
Tel.: 089 / 2399 - 3371
Date: 06.11.14

Zeichen/Reference/Référence		Anmeldung Nr./Application No./Demande n°
PABCA/P36814EP	APPR	06737018 / 1863458
Anmelder/Applicant/Demandeur/Patentinhaber/Proprietor/Titulaire		
Banner Pharmacaps Inc.		

Appeal number: T0826/12-3.3.07

EPA/EPO/OEB Formblatt/Form/Formulaire: 3030

Empfangsbescheinigung über den Zugang des vorstehend bezeichneten Schriftstücks
Acknowledgement of receipt of the document specified above
Récépissé du document spécifié ci-dessus

Unter Bezugnahme auf die Mitteilung im ABl. EPA 7/2010, 377 wird gebeten, die Empfangsbescheinigung mit Empfangsdatum und Unterschrift zu versehen und **umgehend** an das EPA zurückzusenden:

With reference to the Notice in OJ EPO 7/2010, 377, you are requested to date and sign the acknowledgement of receipt and return it to the EPO **immediately:**

Conformément au communiqué paru au JO OEB 7/2010, 377, vous êtes prié d'indiquer sur le récépissé la date de réception du document, de signer le récépissé et de le renvoyer **sans délai** à l' OEB:

- **über die Online-Dienste des EPA** (als Anlage zu EPA Form 1038) / **through EPO Online Services** (as annex to EPO Form 1038) / **par les services en ligne de l'OEB** (en tant que pièce jointe au formulaire OEB 1038),
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T0826/12-3302

06737018.9

Addressee

Potter Clarkson LLP
The Belgrave Centre
Talbot Street
Nottingham, NG1 5GG
ROYAUME UNI

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EPO - Munich
58
12. Nov. 2014

POTTER CLARKSON

European Patent Office
80298 Munich
GERMANY

5 December 2014

Dear Sirs

Recordal of Transfer - EP Application No. 06737018.9
FROM: BANNER PHARMACAPS INC.
TO: BANNER LIFE SCIENCES LLC
Our ref: PABCX/P38814EP

There has been an assignment from Banner Pharmacaps Inc. to Banner Life Sciences LLC in respect of European patent application no. 06737018.9.

We enclose a copy of an assignment document by way of evidence.

Please record the transfer of European patent application no. 06737018.9 to Banner Life Sciences LLC.

Our Accounts Department is making arrangements to pay the transfer fee from our Deposit Account.

We look forward to receiving confirmation of recordal.

Yours faithfully

pp Caroline Marshall
For and on behalf of Potter Clarkson LLP

cxs/vc

Encs: Copy of assignment document

cc: PABAS/M18649

Potter Clarkson LLP
The Belgrave Centre
Talbot Street
Nottingham NG1 5GG
T:+44 (0)115 955 2211
F:+44 (0)115 955 2201
E:info@potterclarkson.com
W:www.potterclarkson.com

ASSIGNMENT

Banner Pharmacaps Inc., a corporation of the State of Delaware, having its principal place of business at 4125 Premier Drive, High Point, North Carolina, 27265 (hereinafter "Assignor") for good and valuable consideration from Banner Life Sciences LLC, a corporation of the State of Delaware, having its principal place of business at 4125 Premier Drive, High Point, North Carolina, 27265 (hereinafter "Assignee"), the receipt of which is hereby acknowledged, does hereby sell, assign and transfer unto Assignee, its successors and assigns, the entire interest for the United States of America, and its territories and all foreign countries and jurisdictions, including all rights of priority under the International Convention for the Protection of Industrial Property, in (1) certain inventions or improvements described in the applications and patents identified in Schedules A and B, attached hereto (collectively, the "Patents and Patent Applications"), (2) the Patents and Patent Applications, and (3) all Letters Patent of the United States and its territories and all foreign countries and jurisdictions which may or shall be granted on the inventions, or on the Patents and Patent Applications, or any provisional, divisional, continuation, reissue, or other applications based thereon. Assignor agrees, for itself and its successors and assigns, with Assignee and its successors and assigns, but at its or their expense or charges, hereafter to execute all applications, amended specifications, deeds or other instruments, and to do all acts necessary or proper to secure the grant of Letters Patent in the United States and its territories and in all other foreign countries and jurisdictions to Assignee, with specifications and claims in such form as shall be approved by the counsel of Assignee, and to vest and confirm in Assignee, its successors and assigns, the legal title to all such patents.

The effective date of this Assignment is November 1, 2014.

Assignor does hereby authorize and request the Commissioner of Patents and Trademarks of the United States to issue such Letters Patent as shall be granted upon said Patents and Patent Applications or other applications based thereon to Assignee, its successors and assigns.

Assignor does hereby authorize Assignee's attorney to correct any typographical errors on this form, if necessary, and to complete this form by the addition of the application number(s), application filing date(s), and attorney docket number(s), if necessary.

IN WITNESS WHEREOF, the Assignor has caused this instrument to be executed by its duly authorized representative this 21 day of November, 2014.

PHYLLIS E. HARDIN
Notary Public
Randolph County
My Commission Expires
07/29/2019
NORTH CAROLINA

BANNER PHARMACAPS INC.

Ageel Fatmi
Name

Ageel Fatmi
Signature

Executive VP, Global R&D
Title

State of North Carolina)
County of Randolph)

Then personally appeared the above named Ageel Fatmi and attested that he/she is authorized to execute documents on behalf of Banner Pharmacaps Inc., and acknowledged the foregoing instrument to be his/her free act and deed, before me this 21 day of November, 2014.

Phyllis E. Hardin
Notary Public

My Commission expires: 07/29/2019

ACCEPTANCE OF ASSIGNMENT

Banner Life Sciences LLC does hereby declare that it has accepted from Banner Pharmacaps Inc., the Assignment of rights in certain inventions or improvements described in the attached Schedules A and B including all rights of priority, and in all Letters Patent of the United States and its territories and all foreign countries and jurisdictions which may or shall be granted on the inventions, or any parts thereof, or any provisional, divisional, continuation, continuation-in-part, reissue, or other applications based in whole or in part thereon.

WITNESS my hand and seal this 24th day of November, 2014.

BANNER LIFE SCIENCES LLC

Name

Jason Conner

Signature

Corporate Secretary

Title

State of North Carolina)

County of Durham)

Then personally appeared the above named Jason Conner, and attested that he/she is authorized to execute documents on behalf of Banner Life Sciences LLC, and acknowledged the foregoing instrument to be his/her free act and deed, before me this 24th day of November, 2014.

Susan L. Christensen

Notary Public

SUSAN L. CHRISTENSEN
Notary Public, North Carolina
Franklin County
My Commission Expires
January 15, 2017

My Commission expires: 1-15-2017

SCHEDULE A

No.	PPG Docket No.	Country	Application Serial No.	Date Filed	Patent No.	Issue/ Grant Date	Status
1.	BAN 102	U.S.	11/367,238	March 3, 2006			Pending
2.	BAN 102 PCT	PCT	PCT/US2006/007788	March 6, 2006			National
3.	BAN 102 CA	Canada	2,600,023	March 6, 2006	2,600,023	Nov. 1, 2011	Registered
4.	BAN 102 CN	China	200680014012.3	March 6, 2006	ZL 200680014012.3	Jan. 9, 2013	Registered
5.	BAN 102 EP	Europe	06737018.9	March 6, 2006			Pending
6.	BAN 102 MX	Mexico	MX/a/2007/011039	March 6, 2006			Pending
7.	BAN 102 DIV CN	China	201210499255.8	Nov. 29, 2012			Pending
8.	BAN 105 CIP PCT	PCT	PCT/US2006/039045	Oct. 11, 2006			National
9.	BAN 105 CIP CA	Canada	2,625,554	Oct. 11, 2006	2,625,554	Aug. 9, 2011	Registered
10.	BAN 105 CIP EP	Europe	06816361.7	Oct. 11, 2006			Pending
11.	BAN 105 CIP MX	Mexico	MX/a/2008/004774	Oct. 11, 2006	283909	Feb. 10, 2011	Registered
12.	BAN 106 H	U.S.	11/553,356	Oct. 26, 2006	8,333,989	Dec. 18, 2012	Granted
13.	BAN 106 H PCT	PCT	PCT/US2006/042177	Oct. 26, 2006			National
14.	BAN 106 H CA	Canada	2,627,292	Oct. 26, 2006	2,627,292	April 17, 2012	Registered
15.	BAN 106 H CN	China	200680045727.5	Oct. 26, 2006	ZL 200680045727.5	April 17, 2013	Registered
16.	BAN 106 H EP	Europe	06826983.6	Oct. 26, 2006			Pending
17.	BAN 106 H JP	Japan	2008-538048	Oct. 26, 2006	5406530	Nov. 8, 2013	Registered
18.	BAN 106 H MX	Mexico	MX/a/2008/005474	Oct. 26, 2006	311280	July 9, 2013	Registered
19.	BAN 106 L	U.S.	11/553,349	Oct. 26, 2006	8,293,270	Oct. 23, 2012	Granted
20.	BAN 106 L PCT	PCT	PCT/US2006/041722	Oct. 26, 2006			National
21.	BAN 106 L CA	Canada	2,627,351	Oct. 26, 2006	2,627,351	May 1, 2012	Registered
22.	BAN 106 L CN	China	200680045615.X	Oct. 26, 2006	ZL 200680045615.X	July 3, 2013	Registered
23.	BAN 106 L EP	Europe	06826700.4	Oct. 26, 2006			Pending
24.	BAN 106 L JP	Japan	2008-537930	Oct. 26, 2006	5406529	Nov. 8, 2013	Registered
25.	BAN 106 L MX	Mexico	MX/a/2008/005470	Oct. 26, 2006	311282	July 9, 2013	Registered
26.	BAN 107 PCT	PCT	PCT/US2006/048029	Dec. 18, 2006			National
27.	BAN 107 CA	Canada	2,633,924	Dec. 18, 2006	2,633,924	Nov. 19, 2013	Registered
28.	BAN 107 EP	Europe	06845613.6	Dec. 18, 2006			Pending
29.	BAN 107 JP	Japan	2008-547361	Dec. 18, 2006	5627854	Oct. 10, 2014	Registered
30.	BAN 107 MX	Mexico	MX/a/2008/007874	Dec. 18, 2006			Pending
31.	BAN 107 DIV	U.S.	12/716,593	March 3, 2010			Pending
32.	BAN 107 DIV CA	Canada	2,798,511	Dec. 5, 2012			Allowed
33.	BAN 107 DIV EP	Europe	14150121.3	Jan. 3, 2014			Pending
34.	BAN 107 DIV JP	Japan	2013-119371	June 6, 2013			Pending
35.	BAN 107 DIV CON	U.S.	14/078,156	Nov. 12, 2013			Allowed

SCHEDULE A CONTINUED

No.	PPG Docket No.	Country	Application Serial No.	Date Filed	Patent No.	Issue/ Grant Date	Status
36.	BAN 107 DIV CON CON	U.S.	14/507,327	Oct. 6, 2014			Pending
37.	BAN 109	U.S.	12/638,212	Dec. 15, 2009	8,524,280	Sept. 3, 2013	Granted
38.	BAN 109 PCT	PCT	PCT/US2009/068017	Dec. 15, 2009			National
39.	BAN 109 CA	Canada	2,746,887	Dec. 15, 2009			Pending
40.	BAN 109 CN	China	200980156203.7	Dec. 15, 2009			Pending
41.	BAN 109 EP	Europe	09775053.3	Dec. 15, 2009			Pending
42.	BAN 109 JP	Japan	2011-540967	Dec. 15, 2009			Pending
43.	BAN 109 MX	Mexico	MX/a/2011-006307	Dec. 15, 2009	317377	Jan. 22, 2014	Registered
44.	BAN 109 CON	U.S.	13/956,571	Aug. 1, 2013			Allowed
45.	BAN 115	U.S.	12/574,215	Oct. 6, 2009	8,309,107	Nov. 13, 2012	Granted
46.	BAN 116	U.S.	12/752,629	April 1, 2010			Pending

SCHEDULE B

No.	PPG Docket No.	Country	Application Serial No.	Date Filed	Status
1.	BAN 100		60/621,260	Oct. 22, 2004	Lapse
2..	BAN 100 PCT	PCT	PCT/US2005/036210	Oct. 7, 2005	Lapse
3.	BAN 100	U.S.	11/083,869	March 18, 2005	Abandoned
4.	BAN 102	U.S.	60/659,679	March 8, 2005	Lapse
5.	BAN 105 CIP	U.S.	11/548,607	Oct. 11, 2006	Abandoned
6.	BAN 105	U.S.	11/247,389	Oct. 11, 2005	Abandoned
7.	BAN 106H	U.S.	60/730,406	Oct. 26, 2005	Lapse
8.	BAN 106H DIV JP	Japan	2013-133677	June 26, 2013	Abandoned
9.	BAN 106L	U.S.	60/730,514	Oct. 26, 2005	Lapse
10.	BAN 106L DIV JP	Japan	2013-133882	June 26, 2013	Abandoned
11.	BAN 107	U.S.	11/316,830	Dec. 22, 2005	Abandoned
12.	BAN 109	U.S.	61/122,497	Dec. 15, 2008	Lapse
13.	BAN 115	U.S.	61/103,062	Oct. 6, 2008	Lapse
14.	BAN 115 PCT	PCT	PCT/US2009/059676	Oct. 6, 2009	Expired
15.	BAN 116	U.S.	61/166,866	April 6, 2009	Lapse
16.	BAN 116 PCT	PCT	PCT/US2010/029625	April 1, 2010	Expired

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Fax: +49 89 2399 4465

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ROYAUME-UNI

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or call
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Substantive Examiner
Name: Büttner, Ulf
Tel: +49 89 2399 - 7841

Application No.	Ref.	Date
06 737 018.9 - 1464	PABCA/P38814EP	16.01.2015
Applicant: Banner Pharmacaps Inc.		

Communication pursuant to Article 94(3) EPC

The examination of the above-identified application has revealed that it does not meet the requirements of the European Patent Convention for the reasons enclosed herewith. If the deficiencies indicated are not rectified the application may be refused pursuant to Article 97(2) EPC.

You are invited to file your observations and insofar as the deficiencies are such as to be rectifiable, to correct the indicated deficiencies within a period

of 4 months

from the notification of this communication, this period being computed in accordance with Rules 126(2) and 131(2) and (4) EPC. One set of amendments to the description, claims and drawings is to be filed within the said period on separate sheets (R. 50(1) EPC).

If filing amendments, you must identify them and indicate the basis for them in the application as filed. Failure to meet either requirement may lead to a communication from the Examining Division requesting that you correct this deficiency (R. 137(4) EPC).

Failure to comply with this invitation in due time will result in the application being deemed to be withdrawn (Art. 94(4) EPC).

Registered letter
EPO Form 2001 12.10CSX

Büttner, Ulf
Primary Examiner
For the Examining Division

Enclosure(s): 1 page/s reasons (Form 2906)

Registered letter
EPO Form 2001 12.10CSX

The examination is being carried out on the **following application documents**

Description, Pages

1-15	as published	

Claims, Numbers

1-8	filed on	06-11-2014

The newly filed claims were considered to be allowable. The applicant is therefore requested to bring the description into conformity with these claims; care should be taken during revision, especially of the introductory portion including any statements of problem or advantage, not to add subject-matter which extends beyond the content of the application as originally filed (Article 123(2) EPC).

Europäisches Patentamt
European Patent Office
Office européen des brevets

European Patent Office
80298 MUNICH
GERMANY

Questions about this communication ?
Contact Customer Services at www.epo.org/contact

Potter Clarkson LLP
The Belgrave Centre
Talbot Street
Nottingham, NG1 5GG
ROYAUME UNI

Date
12.02.15

Reference	Application No./Patent No.
PABCA/P38814EP	06737018.9 - 1464 / 1863458
Applicant/Proprietor	
Banner Life Sciences LLC	

Communication

concerning the registration of amendments relating to

☑ a transfer (R. 22 and 85 EPC)

☐ entries pertaining to the applicant / the proprietor (R. 143(1)(f) EPC)

As requested, the entries pertaining to the applicant of the above-mentioned European patent application / to the proprietor of the above-mentioned European patent have been amended to the following:

AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HU IE IS IT LI LT LU LV MC NL PL PT RO SE SI SK TR
Banner Life Sciences LLC
4125 Premier Drive
High Point, North Carolina 27265/US

The registration of the changes has taken effect on 08.12.14.

In the case of a published application / a patent, the change will be recorded in the Register of European Patents and published in the European Patent Bulletin (Section I.12 / II.12).

Your attention is drawn to the fact that, in the case of the registration of a transfer, any automatic debit order only ceases to be effective from the date of its express revocation (cf. point 14(c) of the Arrangements for the automatic debiting procedure, Supplementary publication 4 - OJ EPO 2014).

Receiving Section / For the Examining Division / For the Opposition Division / For the Legal Division *)

Europäisches Patentamt • European Patent Office • Office européen des brevets

*) See note.

Note
This communication is issued by/for the department with whom responsibility lies. The Legal Division is responsible for the registration of transfers, changes of name (Articles 71, 72 and 74 EPC and Rules 22 and 85 EPC) as well as for the rectification of the designation of the inventor (Rule 21 EPC) (see Decision of the President of the EPO, OJ EPO 2013, 600). In all other cases, the Receiving Section, the Examining Division or the Opposition Division is responsible, depending on the stage in proceedings.

POTTER CLARKSON

EPO - Munich
58
08. Mai 2015

European Patent Office
80298 München
GERMANY

6 May 2015

Dear Sirs

European Patent Application No. 06737018.9 - 1464
BANNER LIFE SCIENCES LLC
Our ref: PABCX/P38814EP

This is a response to the communication pursuant to Article 94(3) EPC dated 16 January 2015.

Amendments

We enclose retyped description pages 1, 3 to 7, 11, 12 and 15 to replace pages 1, 3 to 7, 11, 12 and 15 currently on file. A copy of pages 3, 6, 7, 9 and 15 currently on file, showing in tracked changes the amendments made, is enclosed to assist the examiner.

The amendments made bring the description into conformity with the claims found allowable at the Oral Proceedings before the Board of Appeal on 16 September 2014. Amendments have also been made to bring the description into conformity with European Practice.

To assist the examiner, we also enclose a retyped copy of the claims as allowed by the Board of Appeal.

We submit that the application is in order for allowance.

Any amendment is not to be construed as abandonment of subject matter.

Should the examiner be inclined to refuse this application, we request, in order of preference, a telephone interview or a personal interview first. In any event, we request oral proceedings before the application is refused.

Yours faithfully

Charlotte Crowhurst PhD
For and on behalf of Potter Clarkson LLP

lr/lw

Enc: Pages 1, 3 to 7, 11, 12 and 15 (clean and tracked)
Retyped copy of claims

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SOLVENT SYSTEM FOR ENHANCING THE SOLUBILITY OF PHARMACEUTICAL AGENTS

FIELD OF THE INVENTION

This invention is in the field of fill materials encapsulated in soft gelatin capsules. ~~This application claims priority under 35 U.S.C. 119 to U.S.S.N. 60/659,679 filed March 8, 2005.~~

BACKGROUND OF THE INVENTION

Filled one-piece soft gelatin capsules ("softgels") have been widely used for years to encapsulate consumable materials such as vitamins and pharmaceuticals in a liquid vehicle or carrier. Because softgels have properties which are quite different from two-piece hardshell capsules, softgels are more capable of retaining a liquid fill material.

Not all liquids may be enclosed in a softgel capsule. Liquids containing more than about 20% water by weight are generally not enclosed in softgels, because the water tends to dissolve the gelatin shell. Other solvents such as propylene glycol, glycerin, low molecular weight alcohols, ketones, acids, amines, and esters all tend to degrade or dissolve the gelatin shell to some extent.

Softgels are also somewhat sensitive to pH, and generally require a pH in the encapsulated liquid from about 2.5 to about 7.5. Highly acidic liquids may hydrolyze the gelatin, resulting in leaks, while basic liquids may tan the gelatin, resulting in decreased solubility of the gelatin shell.

Pharmaceutical liquids are usually enclosed in softgels as either viscous solutions or suspensions. Suspensions are pharmaceutically less desirable because they can settle during manufacture, which leads to a less uniform product. In contrast, solutions provide the best liquid form for obtaining optimal "content uniformity" in a batch. Further, solutions typically provide a faster and more uniform absorption of an active agent than do suspensions.

Suitable softgel solutions, however, can be difficult to achieve. One constraint is size. Many pharmaceutical agents require volumes of solvent

The previously described methods all involve the conversion of the free pharmaceutical agent to the corresponding salt. In cases where the free pharmaceutical agent is acidic, the resulting anion can react with the polyethylene glycol in the fill to produce polyethylene glycol esters, thus reducing the amount of available pharmaceutical agent.

There is a need for a solvent system containing a medicament, which can be encapsulated in a softgel capsule, wherein the formation of PEG esters is minimized.

Therefore it is an object of the invention to provide a stable solvent system for pharmaceutical agents, which is suitable for encapsulation in a softgel capsule, wherein the formation of PEG esters is minimized.

BRIEF SUMMARY OF THE INVENTION

The present invention provides a softgel capsule according to Claim 1 and a use according to Claim 13. Liquid and semi-solid pharmaceutical compositions, which can be administered in liquid form or can be used for preparing capsules, are described herein. ~~The composition comprises the salt of one or more active agents, and 0.2-1.0 mole equivalents of a de-ionizing agent per mole of active agent. The pH of the composition is adjusted within the range of 2.5 - 7.5.~~ The acid present in the compositions of the invention~~de-ionizing agent~~ causes partial de-ionization (neutralization) of naproxen sodium~~the salt of the active agent~~ resulting in enhanced bioavailability ~~of salts of weakly acidic, basic or amphoteric active agents~~ as well as decreased amounts of polyethylene glycol (PEG) esters. Thus, hereinafter the acid maybe referred to as the deionizing agent.

DETAILED DESCRIPTION OF THE INVENTION

I. Composition

A. Fill Materials

1. Drugs to be Formulated

In the present invention the fill material comprises naproxen sodium. Other~~The~~ formulations described herein may ~~can~~ contain any therapeutic, diagnostic, prophylactic or nutraceutical agent. Exemplary agents include, but are not limited to, analeptic agents; analgesic agents; anesthetic agents; antiasthmatic agents; antiarthritic agents; anticancer agents; anticholinergic agents; anticonvulsant agents; antidepressant agents; antidiabetic agents; antidiarrheal agents; antiemetic agents; antihelminthic agents; antihistamines; antihyperlipidemic agents; antihypertensive agents; anti-infective agents; anti-inflammatory

agents; antimigraine agents; antineoplastic agents; antiparkinson drugs; antipruritic agents; antipsychotic agents; antipyretic agents; antispasmodic agents; antitubercular agents; antiulcer agents; antiviral agents; anxiolytic agents; appetite suppressants (anorexic agents); attention deficit disorder and attention deficit hyperactivity disorder drugs; cardiovascular agents including calcium channel blockers, antianginal agents, central nervous system ("CNS") agents, beta-blockers and antiarrhythmic agents; central nervous system stimulants; diuretics; genetic materials; hormonolytics; hypnotics; hypoglycemic agents; immunosuppressive agents; muscle relaxants; narcotic antagonists; nicotine; nutritional agents; parasympatholytics; peptide drugs; psychostimulants; sedatives; sialagogues, steroids; smoking cessation agents; sympathomimetics; tranquilizers; vasodilators; beta-agonist; and tocolytic agents.

~~A first class of drugs is selected based on inclusion in the molecule of a weakly acidic, basic or amphoteric group that can form a salt.~~ Any drug that bears an acidic or a basic functional group, for example, an amine, imine, imidazoyl, guanidine, piperidinyl, pyridinyl, quaternary ammonium, or other basic group, or a carboxylic, phosphoric, phenolic, sulfuric, sulfonic or other acidic group, can react with the de-ionizing agent.

Some other~~specific~~ drugs that bear acidic or basic functional groups and thus may be converted to the corresponding salt for use in the ~~described~~ formulations described herein include, but are not limited to, Acetaminophen, Acetylsalicylic acid, Alendronic acid, Alosetron, Amantadine, Amlopidine, Anagrelide, Argatroban, Atomoxetine, Atrovastatin, Azithromycin dehydrate, Balsalazide, Bromocriptan, Bupropion, Candesartan, Carboplatin, Ceftriaxone, Clavulonic acid, Clindamycin, Cimetadine, Dehydrocholic (acid), Dexmethylphenidate, Diclofenac, Dicyclomine, Diflunisal, Diltiazem, Donepezil, Doxorubicin, Doxepin, Epirubicin, Etodolic acid, Ethacrynic acid, Fenoprofen, Fluoxetine, Flurbiprofen, Furosemide, Gemfibrozil, Hydroxyzine, Ibuprofen, Imipramine, Indomethacin, Ketoprofen, Levothyroxine, Maprolitline, Meclizine, Methadone, Methylphenidate, Minocycline, Mitoxantone, Moxifloxacin, Mycophenolic

acid, ~~Naproxen,~~ Niflumic acid, Ofloxacin, Ondansetron, Pantoprazole, Paroxetine, Pergolide, Pramipexole, Phenytoin, Pravastain, Probenecid, Rabeprazole, Risedronic acid, Retinoic acid, Ropinirole, Selegiline, Sulindac, Tamsulosin, Telmisertan, Terbinafine, Theophyline, Tiludronic Acid, Tinzaparin, Ticarcillin, Tometin, Valproic acid, Salicylic acid, Sevelamer, Ziprasidone, Zoledronic acid, Acetophenazine, Albuterol, Almotriptan, Amitriptyline, Amphetamine, Atracurium, Beclomethasone, Benztropine, Biperiden, Bosentan, Bromodiphenhydramine, Brompheniramine carbinoxamine, Caffeine, Capecitabine, Carbergoline, Cetirizine, Chlocylizine, Chlorpheniramine, Chlorphenoxamine, Chlorpromazine, Citalopram, Clavunate potassium, Ciprofloxacin, Clemastine, Clomiphene, Clonidine, Clopidogrel, Codeine, Cyclizine, Cyclobenzaprine, Cyproheptadine, Delavirdine, Diethylpropion, Divalproex, Desipramine, Dexmethylphenidate, Dexbrompheniramine, Dexchlopheniramine, Dexchlor, Dextroamphetamine, Dexedrine, Dextromethorphan, Fiflunisal, Diphemanil methylsulphate, Diphenhydramine, Dolasetron, Doxylamine, Enoxaparin, Ergotamine, Ertepenem, Eprosartan, Escitalopram, Esomeprazole, Fenoldopam, Fentanyl, Fexofenadine, Flufenamic acid, Fluvastatin, Fluphenazine, Fluticasone, Fosinopril, Frovatriptan, Gabapentin, Galatamine, Gatifloxacin, Gemcitabine, Haloperidol, Hyalurondate, Hydrocodone, Hydroxychloroquine, Hyoscyamine, Imatinib, Imipenem, Ipatropin, Lisinopril, Leuprolide, Levopropoxyphene, Losartan, Meclofenamic acid, Mefanamic acid, Mesalamine, Mepenzolate, Meperidine, Mephentermine, Mesalimine, Mesoridazine, Metaproteranol, Metformin, Methdialazine, Methscopolamine, Methysergide, Metoprolol, Metronidazole, Mibefradil, Montelukast, Morphine, Mometasone, Naratriptan, Nelfinavir, Nortriptylene, Noscapine, Nylindrin, Omeprazole, Orphenadrine, Oseltamivir, Oxybutynin, Papaverine, Pentazocine, Phendimetrazine, Phentermine, Pioglitazone, Pilocarpine, Prochloroperazine, Pyrilamine, Quetapine, Ranitidine, Rivastigmine, Rosiglitazone, Salmetrol, Sertaline, Sotalol, Sumatriptan, Tazobactam, Tacrolimus, Tamoxifen, Ticlopidine, Topiramate, Tolterodine,

Triptorelin, Triplennamine, Triprolidine, Tramadol, Trovofloxacin, Ursodiol, Promazine, Propoxyphene, Propanolol, Pseudoephedrine, Pyrilamine, Quinidine, Oxybate sodium, Sermorelin, Tacrolimus, Tegaseroid, Teriparatide, Tolterodine, Triptorelin pamoate, Scoplolamine, Venlafaxine, Zamivir, Aminocaproic acid, Aminosalicylic acid, Hydromorphone, Isosuprine, Levorphanol, Melhalan, Nalidixic acid, and Para-aminosalicylic acid.

2. **Deionizing Agent**

The fill material of the present invention comprises fumaric acid, maleic acid, tartaric acid, citric acid, malic acid, acetic acid, proprionic acid, pyruvic acid, butanoic acid or lactic acid in an amount of from 0.2 to 1.0 mole equivalents per mole of the naproxen sodium. These acids act as deionizing agents.

The deionizing agent functions by causing partial deionization (neutralization) of the salt of the~~one or more~~ pharmaceutically active agent (in this invention naproxen sodium)~~s~~. As described herein ~~W~~when the active agent is the salt of a weak acid and a strong base, the deionizing agent is preferably a hydrogen ion species such as an acid as described above or ~~.~~ ~~W~~when the active agent is the salt of a weak base and a strong acid, the deionizing agent is preferably a hydroxide ion species such as a metal hydroxide such as sodium hydroxide, potassium hydroxide, ammonium hydroxide, calcium hydroxide, aluminum hydroxide, and magnesium hydroxide.

~~The deionizing agent is preferably present in an amount between 0.2 to 1.0 mole equivalents per mole of the pharmaceutically active agent.~~

~~Exemplary hydrogen ion species useful as de-ionizing agents described herein, include, but are not limited to, hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, fumaric acid, maleic acid, tartaric acid, methane-, ethane-, and benzene sulfonates, citric acid, malic acid, acetic acid, proprionic acid, pyruvic acid, butanoic acid, and lactic acid.~~

~~Exemplary hydroxide ion species useful as de-ionizing agents described herein, include, but are not limited to, metal hydroxides such as sodium hydroxide, potassium hydroxide, ammonium hydroxide, calcium hydroxide, aluminum hydroxide, and magnesium hydroxide.~~

Additional acid or base can be added to adjust the pH of the fill composition. In a preferred embodiment, the pH of the fill composition is from about 2.5 to about 7.5.

3. Excipients

Formulations may be prepared using a pharmaceutically acceptable carrier composed of materials that are considered safe and effective and may be administered to an individual without causing undesirable biological side

effects or unwanted interactions. The carrier is all components present in the pharmaceutical formulation other than the active ingredient or ingredients. As generally used herein "carrier" includes, but is not limited to, plasticizers, crystallization inhibitors, wetting agents, bulk filling agents, solubilizers, bioavailability enhancers, solvents, pH-adjusting agents and combinations thereof.

~~In a preferred embodiment, a~~A mixture of polyethylene glycol and water is used as a solvent for the naproxen sodium~~salt of the active agent~~ and the de-ionizing agent. Polyethylene glycol is present in an amount from about 10% to about 80% by weight. Water is present in an amount from about 1% to 18% by weight. The molecular weight of polyethylene glycol is between 300 and 1500. Other suitable solvents described herein include surfactants and copolymers of polyethylene glycol. The fill material of the present invention also comprises a solubilizer selected from the group consisting of~~Optionally,~~ glycerin, polyvinyl pyrrolidone (PVP) or propylene glycol (PPG) and combinations thereof ~~can be added to enhance the solubility of the drug agent~~.

B. Shell Composition

1. Gelatin

Gelatin is the product of the partial hydrolysis of collagen. Gelatin is classified as either Type A or Type B gelatin. Type A gelatin is derived from the acid hydrolysis of collagen while Type B gelatin is derived from alkaline hydrolysis of collagen. Traditionally, bovine bones and skins have been used as raw materials for manufacturing Type A and Type B gelatin while porcine skins have been used extensively for manufacturing Type A gelatin. In general acid-processed gelatins form stronger gels than lime- processed gelatins of the same average molecular weight.

2. Other Shell Additives

Other suitable shell additives include plasticizers, opacifiers, colorants, humectants, preservatives, flavorings, and buffering salts and acids.

Plasticizers are chemical agents added to gelatin to make the material softer and more flexible. Suitable plasticizers include glycerin, sorbitol

Example 2. Naproxen Sodium with Citric Acid as the Deionizing Agent

Fill Material:

Ingredients	% (by weight)
Naproxen Sodium	25.50
Citric Acid	4.75
PVP	1.85
PEG 400	60.50
Water	7.40

Reference Example 3. Naproxen Sodium with Hydrochloric Acid as the Deionizing Agent

Fill Material:

Ingredients	% (by weight)
Naproxen Sodium	25.50
Hydrochloric Acid	4.72
PVP	1.85
PEG 400	63.52
Water	7.40

Example 4. Naproxen Sodium with Acetic Acid as the Deionizing Agent

Fill Material:

Ingredients	% (by weight)
Naproxen Sodium	25.50
Acetic Acid	3.00
PVP	1.85
PEG 400	31.15
Water	7.40
PEG 600	31.15

Example 5. Naproxen Sodium with Citric Acid as the Deionizing Agent

Fill Material:

Ingredients	% (by weight)
Naproxen Sodium	25.50
Citric Acid	4075
PVP	1.85
PEG 400	30.25
Water	7.40
PEG 600	30.25

Reference Example 6. Naproxen Sodium with Hydrochloric Acid as the Deionizing Agent

Fill Material:

Ingredients	% (by weight)
Naproxen Sodium	25.50
Hydrochloric Acid	4072
PVP	1.85
PEG 400	30.25
Water	7.40
PEG 600	30.25

Example 7. Naproxen Sodium with Lactic Acid as the Deionizing Agent

Fill Material:

Ingredients	% (by weight)
Naproxen Sodium	27.50
Lactic Acid	5.27
Propylene Glycol	2.00
PEG 400	64.64
Water	0.60

for which they are cited are specifically incorporated ~~by reference~~. Nothing herein is to be construed as an admission that the invention is not entitled to antedate such disclosure by virtue of prior invention.

CLAIMS

1. A softgel capsule comprising a fill material wherein the fill material comprises

(a) naproxen sodium;

(b) fumaric acid, maleic acid, tartaric acid, citric acid, malic acid, acetic acid, proprionic acid, pyruvic acid, butanoic acid or lactic acid in an amount of from 0.2 to 1.0 mole equivalents per mole of the naproxen sodium;

(c) polyethylene glycol;

(d) water; and

(e) a solubilizer selected from the group consisting of glycerin, polyvinylpyrrolidone, propylene glycol and combinations thereof.

2. The capsule of claim 1 wherein (b) is citric acid or lactic acid.

3. The capsule of claim 2 wherein (b) is lactic acid.

4. The capsule of any one of the preceding claims wherein polyethylene glycol is present in an amount from 10% to 80% by weight.

5. The capsule of any one of the preceding claims wherein the polyethylene glycol is one or more polyethylene glycols with a molecular weight between 300 and 1500.

6. The capsule of any one of the preceding claims wherein water is present in an amount from 1% to 18% by weight.

7. The capsule of any one of the preceding claims further comprising one or more excipients selected from the group consisting of plasticizers, crystallization inhibitors, wetting agents, bulk filling agents, solubilizers, bioavailability enhancers, solvents, dyes, preservatives, solvents, surfactants, and combinations thereof.

8. The capsule of any one of the preceding claims wherein the solubilizer is present in amount from 1% to 10% by weight.

9. The capsule of any one of the preceding claims wherein the fill material is liquid.

10. A capsule of any of the preceding claims for use as a medicament.

11. A method of making the capsule of claim 1 comprising

(a) mixing components (a), (b), (c), (d) and (e) as defined in claim 1; and

(b) encapsulating the mixture in a softgel capsule.

12. The method of claim 11, wherein step (a) is conducted at a temperature of from 50°C to 70°C.

13. The use of

(a) naproxen sodium;

(b) fumaric acid, maleic acid, tartaric acid, citric acid, malic acid, acetic acid, proprionic acid, pyruvic acid, butanoic acid or lactic acid in an amount of from 0.2 to 1.0 mole equivalents per mole of the naproxen sodium;

(c) polyethylene glycol;

(d) water; and

(e) a solubilizer selected from the group consisting of glycerin, polyvinylpyrrolidone, propylene glycol and combinations thereof,

in the manufacture of a medicament in the form of a capsule for administration of the naproxen sodium to a patient in need thereof.

SOLVENT SYSTEM FOR ENHANCING THE SOLUBILITY OF PHARMACEUTICAL AGENTS

FIELD OF THE INVENTION

This invention is in the field of fill materials encapsulated in soft gelatin capsules.

BACKGROUND OF THE INVENTION

Filled one-piece soft gelatin capsules ("softgels") have been widely used for years to encapsulate consumable materials such as vitamins and pharmaceuticals in a liquid vehicle or carrier. Because softgels have properties which are quite different from two-piece hardshell capsules, softgels are more capable of retaining a liquid fill material.

Not all liquids may be enclosed in a softgel capsule. Liquids containing more than about 20% water by weight are generally not enclosed in softgels, because the water tends to dissolve the gelatin shell. Other solvents such as propylene glycol, glycerin, low molecular weight alcohols, ketones, acids, amines, and esters all tend to degrade or dissolve the gelatin shell to some extent.

Softgels are also somewhat sensitive to pH, and generally require a pH in the encapsulated liquid from about 2.5 to about 7.5. Highly acidic liquids may hydrolyze the gelatin, resulting in leaks, while basic liquids may tan the gelatin, resulting in decreased solubility of the gelatin shell.

Pharmaceutical liquids are usually enclosed in softgels as either viscous solutions or suspensions. Suspensions are pharmaceutically less desirable because they can settle during manufacture, which leads to a less uniform product. In contrast, solutions provide the best liquid form for obtaining optimal "content uniformity" in a batch. Further, solutions typically provide a faster and more uniform absorption of an active agent than do suspensions.

Suitable softgel solutions, however, can be difficult to achieve. One constraint is size. Many pharmaceutical agents require volumes of solvent

The previously described methods all involve the conversion of the free pharmaceutical agent to the corresponding salt. In cases where the free pharmaceutical agent is acidic, the resulting anion can react with the polyethylene glycol in the fill to produce polyethylene glycol esters, thus reducing the amount of available pharmaceutical agent.

There is a need for a solvent system containing a medicament, which can be encapsulated in a softgel capsule, wherein the formation of PEG esters is minimized.

Therefore it is an object of the invention to provide a stable solvent system for pharmaceutical agents, which is suitable for encapsulation in a softgel capsule, wherein the formation of PEG esters is minimized.

BRIEF SUMMARY OF THE INVENTION

The present invention provides a softgel capsule according to Claim 1 and a use according to Claim 13. Liquid and semi-solid pharmaceutical compositions, which can be administered in liquid form or can be used for preparing capsules, are described herein. The acid present in the compositions of the invention causes partial de-ionization (neutralization) of naproxen sodium resulting in enhanced bioavailability as well as decreased amounts of polyethylene glycol (PEG) esters. Thus, hereinafter the acid maybe referred to as the deionizing agent.

DETAILED DESCRIPTION OF THE INVENTION

I. Composition

A. Fill Materials

1. Drugs to be Formulated

In the present invention the fill material comprises naproxen sodium. Other formulations described herein may contain any therapeutic, diagnostic, prophylactic or nutraceutical agent. Exemplary agents include, but are not limited to, analeptic agents; analgesic agents; anesthetic agents; antiasthmatic agents; antiarthritic agents; anticancer agents; anticholinergic agents; anticonvulsant agents; antidepressant agents; antidiabetic agents; antidiarrheal agents; antiemetic agents; antihelminthic agents; antihistamines; antihyperlipidemic agents; antihypertensive agents; anti-infective agents; anti-inflammatory

agents; antimigraine agents; antineoplastic agents; antiparkinson drugs; antipruritic agents; antipsychotic agents; antipyretic agents; antispasmodic agents; antitubercular agents; antiulcer agents; antiviral agents; anxiolytic agents; appetite suppressants (anorexic agents); attention deficit disorder and attention deficit hyperactivity disorder drugs; cardiovascular agents including calcium channel blockers, antianginal agents, central nervous system ("CNS") agents, beta-blockers and antiarrhythmic agents; central nervous system stimulants; diuretics; genetic materials; hormonolytics; hypnotics; hypoglycemic agents; immunosuppressive agents; muscle relaxants; narcotic antagonists; nicotine; nutritional agents; parasympatholytics; peptide drugs; psychostimulants; sedatives; sialagogues, steroids; smoking cessation agents; sympathomimetics; tranquilizers; vasodilators; beta-agonist; and tocolytic agents.

Any drug that bears an acidic or a basic functional group, for example, an amine, imine, imidazoyl, guanidine, piperidinyl, pyridinyl, quaternary ammonium, or other basic group, or a carboxylic, phosphoric, phenolic, sulfuric, sulfonic or other acidic group, can react with the de-ionizing agent.

Some other drugs that bear acidic or basic functional groups and thus may be converted to the corresponding salt for use in the formulations described herein include, but are not limited to, Acetaminophen, Acetylsalicylic acid, Alendronic acid, Alosetron, Amantadine, Amlopidine, Anagrelide, Argatroban, Atomoxetine, Atrovastatin, Azithromycin dehydrate, Balsalazide, Bromocriptan, Bupropion, Candesartan, Carboplatin, Ceftriaxone, Clavulonic acid, Clindamycin, Cimetadine, Dehydrocholic (acid), Dexmethylphenidate, Diclofenac, Dicyclomine, Diflunisal, Diltiazem, Donepezil, Doxorubicin, Doxepin, Epirubicin, Etodolic acid, Ethacrynic acid, Fenoprofen, Fluoxetine, Flurbiprofen, Furosemide, Gemfibrozil, Hydroxyzine, Ibuprofen, Imipramine, Indomethacin, Ketoprofen, Levothyroxine, Maprolitline, Meclizine, Methadone, Methylphenidate, Minocycline, Mitoxantone, Moxifloxacin, Mycophenolic

acid, Niflumic acid, Ofloxacin, Ondansetron, Pantoprazole, Paroxetine, Pergolide, Pramipexole, Phenytoin, Pravastain, Probenecid, Rabeprazole, Risedronic acid, Retinoic acid, Ropinirole, Selegiline, Sulindac, Tamsulosin, Telmisertan, Terbinafine, Theophyline, Tiludronic Acid, Tinzaparin, Ticarcillin, Tometin, Valproic acid, Salicylic acid, Sevelamer, Ziprasidone, Zoledronic acid, Acetophenazine, Albuterol, Almotriptan, Amitriptyline, Amphetamine, Atracurium, Beclomethasone, Benztropine, Biperiden, Bosentan, Bromodiphenhydramine, Brompheniramine carbinoxamine, Caffeine, Capecitabine, Carbergoline, Cetirizine, Chlocylizine, Chlorpheniramine, Chlorphenoxamine, Chlorpromazine, Citalopram, Clavunate potassium, Ciprofloxacin, Clemastine, Clomiphene, Clonidine, Clopidogrel, Codeine, Cyclizine, Cyclobenzaprine, Cyproheptadine, Delavirdine, Diethylpropion, Divalproex, Desipramine, Dexmethylphenidate, Dexbrompheniramine, Dexchlopheniramine, Dexchlor, Dextroamphetamine, Dexedrine, Dextromethorphan, Fiflunisal, Diphemanil methylsulphate, Diphenhydramine, Dolasetron, Doxylamine, Enoxaparin, Ergotamine, Ertepenem, Eprosartan, Escitalopram, Esomeprazole, Fenoldopam, Fentanyl, Fexofenadine, Flufenamic acid, Fluvastatin, Fluphenazine, Fluticasone, Fosinopril, Frovatriptan, Gabapentin, Galatamine, Gatifloxacin, Gemcitabine, Haloperidol, Hyalurondate, Hydrocodone, Hydroxychloroquine, Hyoscyamine, Imatinib, Imipenem, Ipatropin, Lisinopril, Leuprolide, Levopropoxyphene, Losartan, Meclofenamic acid, Mefanamic acid, Mesalamine, Mepenzolate, Meperidine, Mephentermine, Mesalimine, Mesoridazine, Metaproteranol, Metformin, Methdialazine, Methscopolamine, Methysergide, Metoprolol, Metronidazole, Mibefradil, Montelukast, Morphine, Mometasone, Naratriptan, Nelfinavir, Nortriptylene, Noscapine, Nylindrin, Omeprazole, Orphenadrine, Oseltamivir, Oxybutynin, Papaverine, Pentazocine, Phendimetrazine, Phentermine, Pioglitazone, Pilocarpine, Prochloroperazine, Pyrilamine, Quetapine, Ranitidine, Rivastigmine, Rosiglitazone, Salmetrol, Sertaline, Sotalol, Sumatriptan, Tazobactam, Tacrolimus, Tamoxifen, Ticlopidine, Topiramate, Tolterodine,

Triptorelin, Triplennamine, Triprolidine, Tramadol, Trovofloxacin, Ursodiol, Promazine, Propoxyphene, Propanolol, Pseudoephedrine, Pyrilamine, Quinidine, Oxybate sodium, Sermorelin, Tacrolimus, Tegaseroid, Teriparatide, Tolterodine, Triptorelin pamoate, Scoplolamine, Venlafaxine, Zamivir, Aminocaproic acid, Aminosalicylic acid, Hydromorphone, Isosuprine, Levorphanol, Melhalan, Nalidixic acid, and Para-aminosalicylic acid.

2. Deionizing Agent

The fill material of the present invention comprises fumaric acid, maleic acid, tartaric acid, citric acid, malic acid, acetic acid, proprionic acid, pyruvic acid, butanoic acid or lactic acid in an amount of from 0.2 to 1.0 mole equivalents per mole of the naproxen sodium. These acids act as deionizing agents.

The deionizing agent functions by causing partial deionization (neutralization) of the salt of the pharmaceutically active agent (in this invention naproxen sodium). As described herein when the active agent is the salt of a weak acid and a strong base, the deionizing agent is preferably a hydrogen ion species such as an acid as described above or when the active agent is the salt of a weak base and a strong acid, the deionizing agent is preferably a hydroxide ion species such as a metal hydroxide such as sodium hydroxide, potassium hydroxide, ammonium hydroxide, calcium hydroxide, aluminum hydroxide, and magnesium hydroxide.

Additional acid or base can be added to adjust the pH of the fill composition. In a preferred embodiment, the pH of the fill composition is from about 2.5 to about 7.5.

3. Excipients

Formulations may be prepared using a pharmaceutically acceptable carrier composed of materials that are considered safe and effective and may be administered to an individual without causing undesirable biological side

effects or unwanted interactions. The carrier is all components present in the pharmaceutical formulation other than the active ingredient or ingredients. As generally used herein "carrier" includes, but is not limited to, plasticizers, crystallization inhibitors, wetting agents, bulk filling agents, solubilizers, bioavailability enhancers, solvents, pH-adjusting agents and combinations thereof.

A mixture of polyethylene glycol and water is used as a solvent for the naproxen sodium and the de-ionizing agent. Polyethylene glycol is present in an amount from about 10% to about 80% by weight. Water is present in an amount from about 1% to 18% by weight. The molecular weight of polyethylene glycol is between 300 and 1500. Other suitable solvents described herein include surfactants and copolymers of polyethylene glycol. The fill material of the present invention also comprises a solubilizer selected from the group consisting of glycerin, polyvinyl pyrrolidone (PVP) or propylene glycol (PPG) and combinations thereof.

B. Shell Composition

1. Gelatin

Gelatin is the product of the partial hydrolysis of collagen. Gelatin is classified as either Type A or Type B gelatin. Type A gelatin is derived from the acid hydrolysis of collagen while Type B gelatin is derived from alkaline hydrolysis of collagen. Traditionally, bovine bones and skins have been used as raw materials for manufacturing Type A and Type B gelatin while porcine skins have been used extensively for manufacturing Type A gelatin. In general acid-processed gelatins form stronger gels than lime- processed gelatins of the same average molecular weight.

2. Other Shell Additives

Other suitable shell additives include plasticizers, opacifiers, colorants, humectants, preservatives, flavorings, and buffering salts and acids.

Plasticizers are chemical agents added to gelatin to make the material softer and more flexible. Suitable plasticizers include glycerin, sorbitol

Example 2. Naproxen Sodium with Citric Acid as the Deionizing Agent

Fill Material:

Ingredients	% (by weight)
Naproxen Sodium	25.50
Citric Acid	4.75
PVP	1.85
PEG 400	60.50
Water	7.40

Reference Example 3. Naproxen Sodium with Hydrochloric Acid as the Deionizing Agent

Fill Material:

Ingredients	% (by weight)
Naproxen Sodium	25.50
Hydrochloric Acid	4.72
PVP	1.85
PEG 400	63.52
Water	7.40

Example 4. Naproxen Sodium with Acetic Acid as the Deionizing Agent

Fill Material:

Ingredients	% (by weight)
Naproxen Sodium	25.50
Acetic Acid	3.00
PVP	1.85
PEG 400	31.15
Water	7.40
PEG 600	31.15

Example 5. Naproxen Sodium with Citric Acid as the Deionizing Agent

Fill Material:

Ingredients	% (by weight)
Naproxen Sodium	25.50
Citric Acid	4075
PVP	1.85
PEG 400	30.25
Water	7.40
PEG 600	30.25

Reference Example 6. Naproxen Sodium with Hydrochloric Acid as the Deionizing Agent

Fill Material:

Ingredients	% (by weight)
Naproxen Sodium	25.50
Hydrochloric Acid	4072
PVP	1.85
PEG 400	30.25
Water	7.40
PEG 600	30.25

Example 7. Naproxen Sodium with Lactic Acid as the Deionizing Agent

Fill Material:

Ingredients	% (by weight)
Naproxen Sodium	27.50
Lactic Acid	5.27
Propylene Glycol	2.00
PEG 400	64.64
Water	0.60

for which they are cited are specifically incorporated. Nothing herein is to be construed as an admission that the invention is not entitled to antedate such disclosure by virtue of prior invention.

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Application No.	Ref.	Date
06 737 018.9 - 1464	PABCA/P38814EP	18.11.2015
Applicant: Banner Life Sciences LLC		

Communication under Rule 71(3) EPC

1. Intention to grant

You are informed that the examining division intends to grant a European patent on the basis of the above application, with the text and drawings and the related bibliographic data as indicated below.

A copy of the relevant documents is enclosed.

1.1 In the text for the Contracting States:
AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HU IE IS IT LI LT LU LV MC NL PL PT RO SE SI SK TR

Description, Pages

2, 8-10, 13, 14	as published			
1, 3-7, 11, 12, 15	received on	08-05-2015	with letter of	08-05-2015

Claims, Numbers

1-13	received on	08-05-2015	with letter of	08-05-2015

With the following amendments to the above-mentioned documents proposed by the division

Description, Pages 14, 15

Comments

DESCRIPTION
Page 14: Guidelines F. III. 8
Page 15: Guidelines F. III. 8

Registered letter
EPO Form 2004C 07.15CSXP

1.2 Bibliographic data

The title of the invention in the three official languages of the European Patent Office, the international patent classification, the designated contracting states, the registered name(s) of the applicant(s) and the other bibliographic data are shown on **EPO Form 2056** (enclosed).

2. Invitation

You are invited, **within a non-extendable period of four months** of notification of this communication,

2.1 to EITHER approve the text communicated above and verify the bibliographic data (Rule 71(5) EPC)

(1) by filing a translation of the claim(s) in the other two official languages of the EPO

		Fee code	EUR
(2a)	by paying the fee for grant including the fee for printing (Art. 2(2) RFees):	**007**	915.00
	minus any amount already paid (Rule 71a(5) EPC):		0.00
(2b)	by paying the printing fee (Art. 2(2) RFees) for the 36th and each subsequent page; number of pages payable: 0	**008**	0.00
	minus any amount already paid (Rule 71a(5) EPC):		0.00
		Total amount:	915.00
(3)	by paying additional claims fees under Rule 71(4) EPC; number of claims fees payable: 0	**016**	0.00
	minus any amount already paid (Rule 71a(5) EPC):		0.00
		Total amount:	0.00

Important: If the translations of the claims and fees have already been filed and paid respectively in reply to a previous communication under Rule 71(3) EPC, e.g. in the case of resumption of examination after approval (see Guidelines C-V, 6), **agreement as to the text to be granted** (Rule 71a(1) EPC) must be expressed within the same time limit (e.g. by approving the text and verifying the bibliographic data, by confirming that grant proceedings can go ahead with the documents on file and/or by stating which translations of the claims already on file are to be used).

Note 1: See "Important notes concerning fee payments" below.
Note 2: Any overpaid "minus" amounts will be refunded when the decision to grant (EPO Form 2006A) has been issued.
Note 3: For the calculation of the grant fee under Article 2(2), No. 7, RFees (old fee structure), the number of pages is determined on the basis of a clean copy of the application documents, in which text deleted as a result of any amendments by the examining division is not shown. Such clean copy is made available via on-line file inspection only.

2.2 OR, in the case of disapproval, to request reasoned amendments or corrections to the text communicated above or keep to the latest text submitted by you (Rule 71(6) EPC).

In this case the translations of the claims and fee payments mentioned under point 2.1 above are NOT due.

The terms "amendment(s)" and "correction(s)" refer only to amendments or corrections of the application documents and not of other documents (e.g. bibliographic data, the designation of the inventor, etc.).

If filing amendments, you must identify them and indicate the basis for them in the application as filed. Failure to meet either requirement may lead to a communication from the examining division requesting that you correct this deficiency (Rule 137(4) EPC).

2.3 Bibliographic data

Where you request a change or correction of bibliographic data in response to the Rule 71(3) communication, this will **not** cause the sending of a further communication under Rule 71(3) EPC. You will still have to pay the fees and file translations in reply to the Rule 71(3) communication in the case of 2.1 above, unless you also file a reasoned request for amendments or corrections in response to the Rule 71(3) communication (see case 2.2 above).

3. Loss of rights

If neither of the two possible actions above (see points 2.1 or 2.2) is performed in due time, the European patent application will be deemed to be withdrawn (Rule 71(7) EPC).

4. Further procedure

4.1 In the case of point 2.1 above

4.1.1 The decision to grant the European patent will be issued, and the **mention of the grant** of the patent will be published in the European Patent Bulletin, if the requirements concerning the translation of the claims and the payment of all fees are fulfilled and there is agreement as to the text to be granted (Rule 71a(1) EPC).

Note on payment of the renewal fee:
If a renewal fee becomes due before the next possible date for publication of the mention of the grant of the European patent, publication will be effected only after the renewal fee and any additional fee have been paid (Rule 71a(4) EPC).

Under Article 86(2) EPC, the obligation to pay renewal fees to the European Patent Office terminates with the payment of the renewal fee due in respect of the year in which the mention of the grant of the European patent is published.

Note on payment of the designation fee(s):
If the designation fee(s) become(s) due after the communication under Rule 71(3) EPC, the mention of the grant of the European patent will not be published until these fees have been paid (Rule 71a(3) EPC).

4.1.2 After publication, the **European patent specification** can be downloaded free of charge from the EPO publication server https://data.epo.org/publication-server or ordered from the Vienna sub-office upon payment of a fee (OJ EPO 2005, 126).

4.1.3 Filing of translations in the contracting states

As regards translation requirements prescribed by the contracting states under Article 65(1) EPC, please consult the website of the European Patent Office
www.epo.org ➞Law & practice ➞Legal texts, National law relating to the EPC
www.epo.org ➞Law & practice ➞All Legal texts ➞London Agreement

In the case of a valid extension or validation

As regards translation requirements prescribed by the extension or validation states, please consult the website of the European Patent Office
www.epo.org ➞Law & practice ➞Legal texts, National law relating to the EPC

Failure to supply a prescribed translation in a contracting state, or in an extension or validation state may result in the patent being deemed to be void *ab initio* in the state concerned (Art. 65(3) EPC).

4.2 In the case of 2.2 above

If the present communication under Rule 71(3) EPC is based on an auxiliary request and, within the time limit, you maintain the main request or a higher ranking request which is not allowable, the application will be refused (Art. 97(2) EPC).

If the examining division gives its consent to the requested amendments or corrections, it will issue a new communication under Rule 71(3) EPC; otherwise, it shall resume the examination proceedings (Rule 71(6) EPC).

5. Filing of a divisional application

Any divisional application relating to this European patent application must be filed directly with the European Patent Office in Munich, The Hague or Berlin and will be in the language of the proceedings for the present application, or if the latter was not in an official language of the EPO, the divisional application may be filed in the language of the present application as filed (see Article 76(1) and Rule 36(2) EPC). Any such divisional application must be filed while the present application is still pending (Rule 36(1) EPC; Guidelines A-IV, 1.1.1).

6. Important notes concerning fee payments

6.1 For all payments, please refer to the relevant **fee code(s).**

6.2 Automatic debiting procedure

The fee for grant, including the fee for printing (Art. 2(2) RFees), and any additional claims fees due under Rule 71(4) EPC will be debited automatically on the date of filing of the translations of the claims, or on the last day of the period of this communication. However, if the designation fee(s) become(s) due as set out in Rule 71a(3) EPC and/or a renewal fee becomes due as set out in Rule 71a(4) EPC, these should be paid separately by another permitted way of payment in order not to delay the publication of the mention of the grant. The same applies in these circumstances to the payment of extension and validation fees. For further details see the Arrangements for the automatic debiting procedure (AAD) and accompanying information from the EPO concerning the automatic debiting procedure (Annexes A.1 and A.2 to the Arrangements for deposit accounts (ADA) in Supplementary publication - OJ EPO 3/2015).

Note: If a waiver is expressed in response to a Rule 71(3) communication (see OJ EPO 2015, A52), the fee for grant, including the fee for publication/printing, and any additional claims fees will not be debited automatically. These fees must be paid separately by another means of payment allowed under the Rules relating to Fees.

6.3 Important information relating to fee amounts

Following any amendment to the Rules relating to Fees, the amount(s) mentioned in this communication may be different from the amount(s) **actually due on the date of payment.** The latest version of the Schedule of fees and expenses, published as a Supplement to the Official Journal of the EPO, is also available on the EPO website (www.epo.org) and can be found under www.epo.org/schedule-of-fees, which allows the viewing, downloading and searching for individual fee amounts, both current and previous.
Please note that procedural fees are usually adjusted every two years, on even years, with effect from 1 April.

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Enclosures: Text intended for grant

EPO Form 2056

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EPO Form 2004C 07.15CSXP

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European Patent Office
Office européen des brevets

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Application No.: 06 737 018.9

IV.2. Patent classification

The classification indicated on the published patent application remains unchanged. It is as follows:

INV. A61K9/48

IV.3. Title of the invention

The title indicated on the published patent application remains unchanged. It reads as follows:

LÖSUNGSMITTELSYSTEM ZUR ERHÖHUNG DER LÖSLICHKEIT PHARMAZEUTISCHER WIRKSTOFFE

SOLVENT SYSTEM FOR ENHANCING THE SOLUBILITY OF PHARMACEUTICAL AGENTS

SYSTEME DE SOLVANT DESTINE A AMELIORER LA SOLUBILITE DES AGENTS PHARMACEUTIQUES

IV.4. Documentation

26.10.15
Date

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Chairman

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1st examiner

Paul Soto, Raquel
2nd examiner

Enclosure(s):

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European Patent Office
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Annex to EPO Form 2004, Communication pursuant to Rule 71(3) EPC

Bibliographical data of European patent application No. 06 737 018.9

For the intended grant of the European patent, the bibliographical data are set out below, for information:

Title of invention:
- LÖSUNGSMITTELSYSTEM ZUR ERHÖHUNG DER LÖSLICHKEIT PHARMAZEUTISCHER WIRKSTOFFE
- SOLVENT SYSTEM FOR ENHANCING THE SOLUBILITY OF PHARMACEUTICAL AGENTS
- SYSTEME DE SOLVANT DESTINE A AMELIORER LA SOLUBILITE DES AGENTS PHARMACEUTIQUES

Classification: INV. A61K9/48

Date of filing: 06.03.2006

Priority claimed: US / 08.03.2005 / USP659679

Contracting States* for which fees have been paid: AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HU IE IS IT LI LT LU LV MC NL PL PT RO SE SI SK TR

Extension States* for which fees have been paid:

Validation States* for which fees have been paid:

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*) If the time limit for the payment of designation fees according to Rule 39(1) EPC has not yet expired and the applicant has not withdrawn any designation, **all Contracting States/Extension States/Validation States** are currently still deemed to be designated.

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See also Rule 71a(3) EPC and, if applicable, the above Note to users of the automatic debiting procedure.

**) If two or more applicants have designated different Contracting States, this is indicated here.

SOLVENT SYSTEM FOR ENHANCING THE SOLUBILITY OF PHARMACEUTICAL AGENTS

FIELD OF THE INVENTION

This invention is in the field of fill materials encapsulated in soft gelatin capsules.

BACKGROUND OF THE INVENTION

Filled one-piece soft gelatin capsules ("softgels") have been widely used for years to encapsulate consumable materials such as vitamins and pharmaceuticals in a liquid vehicle or carrier. Because softgels have properties which are quite different from two-piece hardshell capsules, softgels are more capable of retaining a liquid fill material.

Not all liquids may be enclosed in a softgel capsule. Liquids containing more than about 20% water by weight are generally not enclosed in softgels, because the water tends to dissolve the gelatin shell. Other solvents such as propylene glycol, glycerin, low molecular weight alcohols, ketones, acids, amines, and esters all tend to degrade or dissolve the gelatin shell to some extent.

Softgels are also somewhat sensitive to pH, and generally require a pH in the encapsulated liquid from about 2.5 to about 7.5. Highly acidic liquids may hydrolyze the gelatin, resulting in leaks, while basic liquids may tan the gelatin, resulting in decreased solubility of the gelatin shell.

Pharmaceutical liquids are usually enclosed in softgels as either viscous solutions or suspensions. Suspensions are pharmaceutically less desirable because they can settle during manufacture, which leads to a less uniform product. In contrast, solutions provide the best liquid form for obtaining optimal "content uniformity" in a batch. Further, solutions typically provide a faster and more uniform absorption of an active agent than do suspensions.

Suitable softgel solutions, however, can be difficult to achieve. One constraint is size. Many pharmaceutical agents require volumes of solvent

too large to produce a softgel capsule small enough to be taken by patients. The solvent must also have sufficient solvating power to dissolve a large amount of the pharmaceutical agent to produce a concentrated solution and yet not dissolve, hydrolyze or tan the gelatin shell.

Concentrated solutions of pharmaceutical agents for use in softgel capsules have been described. Most of these systems involve ionizing the free pharmaceutical agent *in situ* to the corresponding salt. For example, U.S. Patent No. 5,360,615 to Yu *et al.* discloses a solvent system for enhancing the solubility of acidic, basic, or amphoteric pharmaceutical agents. The solvent system comprises polyethylene glycol, an ionizing agent, and water. The ionizing agent functions by causing the partial ionization of the free pharmaceutical agent. U.S. Patent No. 6,383,515, U.S. Patent Application Publication No. 2002/0187195, and U.S. Patent Application Publication No. 2001/0007668 to Sawyer *et al.* discloses pharmaceutically acceptable solutions containing a medicament suitable for filling softgel capsules comprising a polymer such as polyethylene glycol and an acid salt of a compound having three or more carbon atoms, such as sodium propionate. The salt helps to ionize the medicament without relying on the use of strong acids or bases. U.S. Patent No. 6,689,382 to Berthel *et al.* describes a pharmaceutical formulation suitable for filling softgel capsules comprising (a) a therapeutically effective amount of a non-steroidal anti-inflammatory drug (NSAID); and (b) a solvent system comprising 40% to 60% by weight a polyoxyethylene ether, 15% to 35% by weight of glycerin and 15% to 35% by weight water. In cases where the NSAID has a carboxyl or an acidic functional group, the solvent system also includes hydroxide ions. U.S. Patent No. 5,505,961 to Shelley *et al.* describes a method for increasing the solubility of acetaminophen alone or in combination with other pharmaceutically active agents to form a clear solution for encapsulation into a softgel capsule. The method comprises solubilizing acetaminophen in a mixture of propylene glycol, polyethylene glycol, water, polyvinylpyrrolidone and sodium or potassium acetate.

The previously described methods all involve the conversion of the free pharmaceutical agent to the corresponding salt. In cases where the free pharmaceutical agent is acidic, the resulting anion can react with the polyethylene glycol in the fill to produce polyethylene glycol esters, thus reducing the amount of available pharmaceutical agent.

There is a need for a solvent system containing a medicament, which can be encapsulated in a softgel capsule, wherein the formation of PEG esters is minimized.

Therefore it is an object of the invention to provide a stable solvent system for pharmaceutical agents, which is suitable for encapsulation in a softgel capsule, wherein the formation of PEG esters is minimized.

BRIEF SUMMARY OF THE INVENTION

The present invention provides a softgel capsule according to Claim 1 and a use according to Claim 13. Liquid and semi-solid pharmaceutical compositions, which can be administered in liquid form or can be used for preparing capsules, are described herein. The acid present in the compositions of the invention causes partial de-ionization (neutralization) of naproxen sodium resulting in enhanced bioavailability as well as decreased amounts of polyethylene glycol (PEG) esters. Thus, hereinafter the acid maybe referred to as the deionizing agent.

DETAILED DESCRIPTION OF THE INVENTION

I. Composition

A. Fill Materials

1. Drugs to be Formulated

In the present invention the fill material comprises naproxen sodium. Other formulations described herein may contain any therapeutic, diagnostic, prophylactic or nutraceutical agent. Exemplary agents include, but are not limited to, analeptic agents; analgesic agents; anesthetic agents; antiasthmatic agents; antiarthritic agents; anticancer agents; anticholinergic agents; anticonvulsant agents; antidepressant agents; antidiabetic agents; antidiarrheal agents; antiemetic agents; antihelminthic agents; antihistamines; antihyperlipidemic agents; antihypertensive agents; anti-infective agents; anti-inflammatory

agents; antimigraine agents; antineoplastic agents; antiparkinson drugs; antipruritic agents; antipsychotic agents; antipyretic agents; antispasmodic agents; antitubercular agents; antiulcer agents; antiviral agents; anxiolytic agents; appetite suppressants (anorexic agents); attention deficit disorder and attention deficit hyperactivity disorder drugs; cardiovascular agents including calcium channel blockers, antianginal agents, central nervous system ("CNS") agents, beta-blockers and antiarrhythmic agents; central nervous system stimulants; diuretics; genetic materials; hormonolytics; hypnotics; hypoglycemic agents; immunosuppressive agents; muscle relaxants; narcotic antagonists; nicotine; nutritional agents; parasympatholytics; peptide drugs; psychostimulants; sedatives; sialagogues, steroids; smoking cessation agents; sympathomimetics; tranquilizers; vasodilators; beta-agonist; and tocolytic agents.

Any drug that bears an acidic or a basic functional group, for example, an amine, imine, imidazoyl, guanidine, piperidinyl, pyridinyl, quaternary ammonium, or other basic group, or a carboxylic, phosphoric, phenolic, sulfuric, sulfonic or other acidic group, can react with the de-ionizing agent.

Some other drugs that bear acidic or basic functional groups and thus may be converted to the corresponding salt for use in the formulations described herein include, but are not limited to, Acetaminophen, Acetylsalicylic acid, Alendronic acid, Alosetron, Amantadine, Amlopidine, Anagrelide, Argatroban, Atomoxetine, Atrovastatin, Azithromycin dehydrate, Balsalazide, Bromocriptan, Bupropion, Candesartan, Carboplatin, Ceftriaxone, Clavulonic acid, Clindamycin, Cimetadine, Dehydrocholic (acid), Dexmethylphenidate, Diclofenac, Dicyclomine, Diflunisal, Diltiazem, Donepezil, Doxorubicin, Doxepin, Epirubicin, Etodolic acid, Ethacrynic acid, Fenoprofen, Fluoxetine, Flurbiprofen, Furosemide, Gemfibrozil, Hydroxyzine, Ibuprofen, Imipramine, Indomethacin, Ketoprofen, Levothyroxine, Maprolitline, Meclizine, Methadone, Methylphenidate, Minocycline, Mitoxantone, Moxifloxacin, Mycophenolic

acid, Niflumic acid, Ofloxacin, Ondansetron, Pantoprazole, Paroxetine, Pergolide, Pramipexole, Phenytoin, Pravastain, Probenecid, Rabeprazole, Risedronic acid, Retinoic acid, Ropinirole, Selegiline, Sulindac, Tamsulosin, Telmisertan, Terbinafine, Theophyline, Tiludronic Acid, Tinzaparin, Ticarcillin, Tometin, Valproic acid, Salicylic acid, Sevelamer, Ziprasidone, Zoledronic acid, Acetophenazine, Albuterol, Almotriptan, Amitriptyline, Amphetamine, Atracurium, Beclomethasone, Benztropine, Biperiden, Bosentan, Bromodiphenhydramine, Brompheniramine carbinoxamine, Caffeine, Capecitabine, Carbergoline, Cetirizine, Chlocylizine, Chlorpheniramine, Chlorphenoxamine, Chlorpromazine, Citalopram, Clavunate potassium, Ciprofloxacin, Clemastine, Clomiphene, Clonidine, Clopidogrel, Codeine, Cyclizine, Cyclobenzaprine, Cyproheptadine, Delavirdine, Diethylpropion, Divalproex, Desipramine, Dexmethylphenidate, Dexbrompheniramine, Dexchlopheniramine, Dexchlor, Dextroamphetamine, Dexedrine, Dextromethorphan, Fiflunisal, Diphemanil methylsulphate, Diphenhydramine, Dolasetron, Doxylamine, Enoxaparin, Ergotamine, Ertepenem, Eprosartan, Escitalopram, Esomeprazole, Fenoldopam, Fentanyl, Fexofenadine, Flufenamic acid, Fluvastatin, Fluphenazine, Fluticasone, Fosinopril, Frovatriptan, Gabapentin, Galatamine, Gatifloxacin, Gemcitabine, Haloperidol, Hyalurondate, Hydrocodone, Hydroxychloroquine, Hyoscyamine, Imatinib, Imipenem, Ipatropin, Lisinopril, Leuprolide, Levopropoxyphene, Losartan, Meclofenamic acid, Mefanamic acid, Mesalamine, Mepenzolate, Meperidine, Mephentermine, Mesalimine, Mesoridazine, Metaproteranol, Metformin, Methdialazine, Methscopolamine, Methysergide, Metoprolol, Metronidazole, Mibefradil, Montelukast, Morphine, Mometasone, Naratriptan, Nelfinavir, Nortriptylene, Noscapine, Nylindrin, Omeprazole, Orphenadrine, Oseltamivir, Oxybutynin, Papaverine, Pentazocine, Phendimetrazine, Phentermine, Pioglitazone, Pilocarpine, Prochloroperazine, Pyrilamine, Quetapine, Ranitidine, Rivastigmine, Rosiglitazone, Salmetrol, Sertaline, Sotalol, Sumatriptan, Tazobactam, Tacrolimus, Tamoxifen, Ticlopidine, Topiramate, Tolterodine,

Triptorelin, Triplennamine, Triprolidine, Tramadol, Trovofloxacin, Ursodiol, Promazine, Propoxyphene, Propanolol, Pseudoephedrine, Pyrilamine, Quinidine, Oxybate sodium, Sermorelin, Tacrolimus, Tegaseroid, Teriparatide, Tolterodine, Triptorelin pamoate, Scoplolamine, Venlafaxine, Zamivir, Aminocaproic acid, Aminosalicylic acid, Hydromorphone, Isosuprine, Levorphanol, Melhalan, Nalidixic acid, and Para-aminosalicylic acid.

2. Deionizing Agent

The fill material of the present invention comprises fumaric acid, maleic acid, tartaric acid, citric acid, malic acid, acetic acid, proprionic acid, pyruvic acid, butanoic acid or lactic acid in an amount of from 0.2 to 1.0 mole equivalents per mole of the naproxen sodium. These acids act as deionizing agents.

The deionizing agent functions by causing partial deionization (neutralization) of the salt of the pharmaceutically active agent (in this invention naproxen sodium). As described herein when the active agent is the salt of a weak acid and a strong base, the deionizing agent is preferably a hydrogen ion species such as an acid as described above or when the active agent is the salt of a weak base and a strong acid, the deionizing agent is preferably a hydroxide ion species such as a metal hydroxide such as sodium hydroxide, potassium hydroxide, ammonium hydroxide, calcium hydroxide, aluminum hydroxide, and magnesium hydroxide.

Additional acid or base can be added to adjust the pH of the fill composition. In a preferred embodiment, the pH of the fill composition is from about 2.5 to about 7.5.

3. Excipients

Formulations may be prepared using a pharmaceutically acceptable carrier composed of materials that are considered safe and effective and may be administered to an individual without causing undesirable biological side

effects or unwanted interactions. The carrier is all components present in the pharmaceutical formulation other than the active ingredient or ingredients. As generally used herein "carrier" includes, but is not limited to, plasticizers, crystallization inhibitors, wetting agents, bulk filling agents, solubilizers, bioavailability enhancers, solvents, pH-adjusting agents and combinations thereof.

A mixture of polyethylene glycol and water is used as a solvent for the naproxen sodium and the de-ionizing agent. Polyethylene glycol is present in an amount from about 10% to about 80% by weight. Water is present in an amount from about 1% to 18% by weight. The molecular weight of polyethylene glycol is between 300 and 1500. Other suitable solvents described herein include surfactants and copolymers of polyethylene glycol. The fill material of the present invention also comprises a solubilizer selected from the group consisting of glycerin, polyvinyl pyrrolidone (PVP) or propylene glycol (PPG) and combinations thereof.

B. Shell Composition

1. Gelatin

Gelatin is the product of the partial hydrolysis of collagen. Gelatin is classified as either Type A or Type B gelatin. Type A gelatin is derived from the acid hydrolysis of collagen while Type B gelatin is derived from alkaline hydrolysis of collagen. Traditionally, bovine bones and skins have been used as raw materials for manufacturing Type A and Type B gelatin while porcine skins have been used extensively for manufacturing Type A gelatin. In general acid-processed gelatins form stronger gels than lime- processed gelatins of the same average molecular weight.

2. Other Shell Additives

Other suitable shell additives include plasticizers, opacifiers, colorants, humectants, preservatives, flavorings, and buffering salts and acids.

Plasticizers are chemical agents added to gelatin to make the material softer and more flexible. Suitable plasticizers include glycerin, sorbitol

solutions which are mixtures of sorbitol and sorbitan, and other polyhydric alcohols such as propylene glycol and maltitol or combinations thereof.

Opacifiers are used to opacify the capsule shell when the encapsulated active agents are light sensitive. Suitable opacifiers include titanium dioxide, zinc oxide, calcium carbonate and combinations thereof.

Colorants can be used to for marketing and product identification/differentiation purposes. Suitable colorants include synthetic and natural dyes and combinations thereof.

Humectants can be used to suppress the water activity of the softgel. Suitable humectants include glycerin and sorbitol, which are often components of the plasticizer composition. Due to the low water activity of dried, properly stored softgels, the greatest risk from microorganisms comes from molds and yeasts. For this reason, preservatives can be incorporated into the capsule shell. Suitable preservatives include alkyl esters of p-hydroxy benzoic acid such as methyl, ethyl, propyl, butyl and heptyl (collectively known as "parabens") or combinations thereof.

Flavorings can be used to mask unpleasant odors and tastes of fill formulations. Suitable flavorings include synthetic and natural flavorings. The use of flavorings can be problematic due to the presence of aldehydes which can cross-link gelatin. As a result, buffering salts and acids can be used in conjunction with flavorings that contain aldehydes in order to inhibit cross-linking of the gelatin.

II. Method of Making

A. Fill Material

The fill material is prepared by mixing the agent (such as a salt of the drug), the deionizing agent, water, and polyethylene glycol at a temperature of 50°C to 70°C. The resulting solution is encapsulated using the appropriate gel mass. The pharmaceutical agent is present in an amount from about 10% to about 50% by weight. The deionizing agent is present in an amount from about 0.2 to 1.0 mole per mole of the pharmaceutical agent. Water is present in an amount from about 1% to about 20% by weight and polyethylene glycol is present in amount from about 10% to about 80% by weight.

Optionally, propylene glycol and/or polyvinyl pyrrolidone are present in an amount from about 1% to about 10%.

B. Gel Mass

The main ingredients of the softgel capsule shell are gelatin, plasticizer, and purified water. Typical gel formulations contain (w/w) 40-50% gelatin, 20-30% plasticizer, and 30-40% purified water. Most of the water is subsequently lost during capsule drying. The ingredients are combined to form a molten gelatin mass using either a cold melt or a hot melt process. The prepared gel masses are transferred to preheated, temperature-controlled, jacketed holding tanks where the gel mass is aged at 50-60°C until used for encapsulation.

1. Cold Melt Process

The cold melt process involves mixing gelatin with plasticizer and chilled water and then transferring the mixture to a jacket-heated tank. Typically, gelatin is added to the plasticizer at ambient temperature (18-22°C). The mixture is cooked (57-95°C) under vacuum for 15-30 minutes to a homogeneous, deaerated gel mass. Additional shell additives can be added to the gel mass at any point during the gel manufacturing process or they may be incorporated into the finished gel mass using a high torque mixer.

2. Hot Melt Process

The hot melt process involves adding, under mild agitation, the gelatin to a preheated (60-80°C) mixture of plasticizer and water and stirring the blend until complete melting is achieved. While the hot melt process is faster than the cold melt process, it is less accurately controlled and more susceptible to foaming and dusting.

C. Softgel Capsule

Softgel capsules are typically produced using a rotary die encapsulation process. The gel mass is fed either by gravity or through positive displacement pumping to two heated (48-65°C) metering devices. The metering devices control the flow of gel into cooled (10-18°C), rotating casting drums. Ribbons are formed as the cast gel masses set on contact with the surface of the drums.

The ribbons are fed through a series of guide rolls and between injection wedges and the capsule-forming dies. A food-grade lubricant oil is applied onto the ribbons to reduce their tackiness and facilitate their transfer. Suitable lubricants include mineral oil, medium chain triglycerides, and soybean oil. Fill formulations are fed into the encapsulation machine by gravity. In the preferred embodiment, the softgels contain printing on the surface, optionally identifying the encapsulated agent and/or dosage.

III. Method of Use

The softgels may be used to encapsulate a wide range of pharmaceutically active agents, nutritional agents and personal care products. Softgel capsules may be administered orally to a patient to deliver a pharmaceutically active agent.

Examples

In the following examples, the fill material can be prepared by mixing the salt of one or more pharmaceutically active agents, the deionizing agent, water and polyethylene glycol at a temperature of 50°C to 70°C. The resulting solution can be encapsulated in a softgel capsule using the appropriate gel mass.

Example 1. Naproxen Sodium with Acetic Acid as the Deionizing Agent

Fill Material:

Ingredients	**% (by weight)**
Naproxen Sodium	25.50
Acetic Acid	3.00
PVP	1.85
PEG 400	62.30
Water	7.40

Example 2. Naproxen Sodium with Citric Acid as the Deionizing Agent

Fill Material:

Ingredients	% (by weight)
Naproxen Sodium	25.50
Citric Acid	4.75
PVP	1.85
PEG 400	60.50
Water	7.40

Reference Example 3. Naproxen Sodium with Hydrochloric Acid as the Deionizing Agent

Fill Material:

Ingredients	% (by weight)
Naproxen Sodium	25.50
Hydrochloric Acid	4.72
PVP	1.85
PEG 400	63.52
Water	7.40

Example 4. Naproxen Sodium with Acetic Acid as the Deionizing Agent

Fill Material:

Ingredients	% (by weight)
Naproxen Sodium	25.50
Acetic Acid	3.00
PVP	1.85
PEG 400	31.15
Water	7.40
PEG 600	31.15

Example 5. Naproxen Sodium with Citric Acid as the Deionizing Agent

Fill Material:

Ingredients	% (by weight)
Naproxen Sodium	25.50
Citric Acid	4075
PVP	1.85
PEG 400	30.25
Water	7.40
PEG 600	30.25

Reference Example 6. Naproxen Sodium with Hydrochloric Acid as the Deionizing Agent

Fill Material:

Ingredients	% (by weight)
Naproxen Sodium	25.50
Hydrochloric Acid	4072
PVP	1.85
PEG 400	30.25
Water	7.40
PEG 600	30.25

Example 7. Naproxen Sodium with Lactic Acid as the Deionizing Agent

Fill Material:

Ingredients	% (by weight)
Naproxen Sodium	27.50
Lactic Acid	5.27
Propylene Glycol	2.00
PEG 400	64.64
Water	0.60

Example 8. Naproxen Sodium with Lactic Acid as the Deionizing Agent

Fill Material:

Ingredients	% (by weight)
Naproxen Sodium	25.00
Lactic Acid	0.24-0.35 M
Propylene glycol	2.00
PEG 600.	q.s.

Example 9. Naproxen Sodium with Lactic Acid as the Deionizing Agent

Fill Material:

Ingredients	% (by weight)
Naproxen Sodium	25.00
Lactic Acid	5.00
Propylene glycol	2.00
PEG 600	61.2
PEG 1000	6.80

Example 10. Naproxen Sodium with Lactic Acid as the Deionizing Agent

Fill Material:

Ingredients	% (by weight)
Naproxen Sodium	25.00
Lactic acid	5.00
Propylene glycol	2.00
PEG 600	51.00
PEG 1000	17.00

Example 11. Naproxen Sodium with Lactic Acid as the Deionizing Agent

Fill Material:

Ingredients	% (by weight)
Naproxen Sodium	25.00
Lactic Acid	5.00
Propylene glycol	2.00
PEG 600	34.00
PEG 1000	34.00

Example 12. Naproxen Sodium with Lactic Acid as the Deionizing Agent

Fill Material:

Ingredients	% (by weight)
Naproxen Sodium	25.00
Lactic acid	5.00
Propylene glycol	2.00
PEG 600	17.00
PEG 1000	51.00

It is understood that the disclosed invention is not limited to the particular methodology, protocols, and reagents described as these may vary. It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments only, and is not intended to limit the scope of the present invention which will be limited only by the appended claims.

Unless defined otherwise, all technical and scientific terms used herein have the same meanings as commonly understood by one of skill in the art to which the disclosed invention belongs. Although any methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present invention, the preferred methods, devices, and materials are as described.

Nothing herein is to be construed as an admission that the invention is not entitled to antedate such disclosure by virtue of prior invention.

CLAIMS

1. A softgel capsule comprising a fill material wherein the fill material comprises

(a) naproxen sodium;

(b) fumaric acid, maleic acid, tartaric acid, citric acid, malic acid, acetic acid, proprionic acid, pyruvic acid, butanoic acid or lactic acid in an amount of from 0.2 to 1.0 mole equivalents per mole of the naproxen sodium;

(c) polyethylene glycol;

(d) water; and

(e) a solubilizer selected from the group consisting of glycerin, polyvinylpyrrolidone, propylene glycol and combinations thereof.

2. The capsule of claim 1 wherein (b) is citric acid or lactic acid.

3. The capsule of claim 2 wherein (b) is lactic acid.

4. The capsule of any one of the preceding claims wherein polyethylene glycol is present in an amount from 10% to 80% by weight.

5. The capsule of any one of the preceding claims wherein the polyethylene glycol is one or more polyethylene glycols with a molecular weight between 300 and 1500.

6. The capsule of any one of the preceding claims wherein water is present in an amount from 1% to 18% by weight.

7. The capsule of any one of the preceding claims further comprising one or more excipients selected from the group consisting of plasticizers, crystallization inhibitors, wetting agents, bulk filling agents, solubilizers, bioavailability enhancers, solvents, dyes, preservatives, solvents, surfactants, and combinations thereof.

8. The capsule of any one of the preceding claims wherein the solubilizer is present in amount from 1% to 10% by weight.

9. The capsule of any one of the preceding claims wherein the fill material is liquid.

10. A capsule of any of the preceding claims for use as a medicament.

11. A method of making the capsule of claim 1 comprising

(a) mixing components (a), (b), (c), (d) and (e) as defined in claim 1; and

(b) encapsulating the mixture in a softgel capsule.

12. The method of claim 11, wherein step (a) is conducted at a temperature of from 50°C to 70°C.

13. The use of

(a) naproxen sodium;

(b) fumaric acid, maleic acid, tartaric acid, citric acid, malic acid, acetic acid, proprionic acid, pyruvic acid, butanoic acid or lactic acid in an amount of from 0.2 to 1.0 mole equivalents per mole of the naproxen sodium;

(c) polyethylene glycol;

(d) water; and

(e) a solubilizer selected from the group consisting of glycerin, polyvinylpyrrolidone, propylene glycol and combinations thereof,

in the manufacture of a medicament in the form of a capsule for administration of the naproxen sodium to a patient in need thereof.

SOLVENT SYSTEM FOR ENHANCING THE SOLUBILITY OF PHARMACEUTICAL AGENTS

FIELD OF THE INVENTION

This invention is in the field of fill materials encapsulated in soft gelatin capsules.

BACKGROUND OF THE INVENTION

Filled one-piece soft gelatin capsules ("softgels") have been widely used for years to encapsulate consumable materials such as vitamins and pharmaceuticals in a liquid vehicle or carrier. Because softgels have properties which are quite different from two-piece hardshell capsules, softgels are more capable of retaining a liquid fill material.

Not all liquids may be enclosed in a softgel capsule. Liquids containing more than about 20% water by weight are generally not enclosed in softgels, because the water tends to dissolve the gelatin shell. Other solvents such as propylene glycol, glycerin, low molecular weight alcohols, ketones, acids, amines, and esters all tend to degrade or dissolve the gelatin shell to some extent.

Softgels are also somewhat sensitive to pH, and generally require a pH in the encapsulated liquid from about 2.5 to about 7.5. Highly acidic liquids may hydrolyze the gelatin, resulting in leaks, while basic liquids may tan the gelatin, resulting in decreased solubility of the gelatin shell.

Pharmaceutical liquids are usually enclosed in softgels as either viscous solutions or suspensions. Suspensions are pharmaceutically less desirable because they can settle during manufacture, which leads to a less uniform product. In contrast, solutions provide the best liquid form for obtaining optimal "content uniformity" in a batch. Further, solutions typically provide a faster and more uniform absorption of an active agent than do suspensions.

Suitable softgel solutions, however, can be difficult to achieve. One constraint is size. Many pharmaceutical agents require volumes of solvent

too large to produce a softgel capsule small enough to be taken by patients. The solvent must also have sufficient solvating power to dissolve a large amount of the pharmaceutical agent to produce a concentrated solution and yet not dissolve, hydrolyze or tan the gelatin shell.

Concentrated solutions of pharmaceutical agents for use in softgel capsules have been described. Most of these systems involve ionizing the free pharmaceutical agent *in situ* to the corresponding salt. For example, U.S. Patent No. 5,360,615 to Yu *et al.* discloses a solvent system for enhancing the solubility of acidic, basic, or amphoteric pharmaceutical agents. The solvent system comprises polyethylene glycol, an ionizing agent, and water. The ionizing agent functions by causing the partial ionization of the free pharmaceutical agent. U.S. Patent No. 6,383,515, U.S. Patent Application Publication No. 2002/0187195, and U.S. Patent Application Publication No. 2001/0007668 to Sawyer *et al.* discloses pharmaceutically acceptable solutions containing a medicament suitable for filling softgel capsules comprising a polymer such as polyethylene glycol and an acid salt of a compound having three or more carbon atoms, such as sodium propionate. The salt helps to ionize the medicament without relying on the use of strong acids or bases. U.S. Patent No. 6,689,382 to Berthel *et al.* describes a pharmaceutical formulation suitable for filling softgel capsules comprising (a) a therapeutically effective amount of a non-steroidal anti-inflammatory drug (NSAID); and (b) a solvent system comprising 40% to 60% by weight a polyoxyethylene ether, 15% to 35% by weight of glycerin and 15% to 35% by weight water. In cases where the NSAID has a carboxyl or an acidic functional group, the solvent system also includes hydroxide ions. U.S. Patent No. 5,505,961 to Shelley *et al.* describes a method for increasing the solubility of acetaminophen alone or in combination with other pharmaceutically active agents to form a clear solution for encapsulation into a softgel capsule. The method comprises solubilizing acetaminophen in a mixture of propylene glycol, polyethylene glycol, water, polyvinylpyrrolidone and sodium or potassium acetate.

The previously described methods all involve the conversion of the free pharmaceutical agent to the corresponding salt. In cases where the free pharmaceutical agent is acidic, the resulting anion can react with the polyethylene glycol in the fill to produce polyethylene glycol esters, thus reducing the amount of available pharmaceutical agent.

There is a need for a solvent system containing a medicament, which can be encapsulated in a softgel capsule, wherein the formation of PEG esters is minimized.

Therefore it is an object of the invention to provide a stable solvent system for pharmaceutical agents, which is suitable for encapsulation in a softgel capsule, wherein the formation of PEG esters is minimized.

BRIEF SUMMARY OF THE INVENTION

The present invention provides a softgel capsule according to Claim 1 and a use according to Claim 13. Liquid and semi-solid pharmaceutical compositions, which can be administered in liquid form or can be used for preparing capsules, are described herein. The acid present in the compositions of the invention causes partial de-ionization (neutralization) of naproxen sodium resulting in enhanced bioavailability as well as decreased amounts of polyethylene glycol (PEG) esters. Thus, hereinafter the acid maybe referred to as the deionizing agent.

DETAILED DESCRIPTION OF THE INVENTION

I. Composition

A. Fill Materials

1. Drugs to be Formulated

In the present invention the fill material comprises naproxen sodium. Other formulations described herein may contain any therapeutic, diagnostic, prophylactic or nutraceutical agent. Exemplary agents include, but are not limited to, analeptic agents; analgesic agents; anesthetic agents; antiasthmatic agents; antiarthritic agents; anticancer agents; anticholinergic agents; anticonvulsant agents; antidepressant agents; antidiabetic agents; antidiarrheal agents; antiemetic agents; antihelminthic agents; antihistamines; antihyperlipidemic agents; antihypertensive agents; anti-infective agents; anti-inflammatory

agents; antimigraine agents; antineoplastic agents; antiparkinson drugs; antipruritic agents; antipsychotic agents; antipyretic agents; antispasmodic agents; antitubercular agents; antiulcer agents; antiviral agents; anxiolytic agents; appetite suppressants (anorexic agents); attention deficit disorder and attention deficit hyperactivity disorder drugs; cardiovascular agents including calcium channel blockers, antianginal agents, central nervous system ("CNS") agents, beta-blockers and antiarrhythmic agents; central nervous system stimulants; diuretics; genetic materials; hormonolytics; hypnotics; hypoglycemic agents; immunosuppressive agents; muscle relaxants; narcotic antagonists; nicotine; nutritional agents; parasympatholytics; peptide drugs; psychostimulants; sedatives; sialagogues, steroids; smoking cessation agents; sympathomimetics; tranquilizers; vasodilators; beta-agonist; and tocolytic agents.

Any drug that bears an acidic or a basic functional group, for example, an amine, imine, imidazoyl, guanidine, piperidinyl, pyridinyl, quaternary ammonium, or other basic group, or a carboxylic, phosphoric, phenolic, sulfuric, sulfonic or other acidic group, can react with the de-ionizing agent.

Some other drugs that bear acidic or basic functional groups and thus may be converted to the corresponding salt for use in the formulations described herein include, but are not limited to, Acetaminophen, Acetylsalicylic acid, Alendronic acid, Alosetron, Amantadine, Amlopidine, Anagrelide, Argatroban, Atomoxetine, Atrovastatin, Azithromycin dehydrate, Balsalazide, Bromocriptan, Bupropion, Candesartan, Carboplatin, Ceftriaxone, Clavulonic acid, Clindamycin, Cimetadine, Dehydrocholic (acid), Dexmethylphenidate, Diclofenac, Dicyclomine, Diflunisal, Diltiazem, Donepezil, Doxorubicin, Doxepin, Epirubicin, Etodolic acid, Ethacrynic acid, Fenoprofen, Fluoxetine, Flurbiprofen, Furosemide, Gemfibrozil, Hydroxyzine, Ibuprofen, Imipramine, Indomethacin, Ketoprofen, Levothyroxine, Maprolitline, Meclizine, Methadone, Methylphenidate, Minocycline, Mitoxantone, Moxifloxacin, Mycophenolic

acid, Niflumic acid, Ofloxacin, Ondansetron, Pantoprazole, Paroxetine, Pergolide, Pramipexole, Phenytoin, Pravastain, Probenecid, Rabeprazole, Risedronic acid, Retinoic acid, Ropinirole, Selegiline, Sulindac, Tamsulosin, Telmisertan, Terbinafine, Theophyline, Tiludronic Acid, Tinzaparin, Ticarcillin, Tometin, Valproic acid, Salicylic acid, Sevelamer, Ziprasidone, Zoledronic acid, Acetophenazine, Albuterol, Almotriptan, Amitriptyline, Amphetamine, Atracurium, Beclomethasone, Benztropine, Biperiden, Bosentan, Bromodiphenhydramine, Brompheniramine carbinoxamine, Caffeine, Capecitabine, Carbergoline, Cetirizine, Chlocylizine, Chlorpheniramine, Chlorphenoxamine, Chlorpromazine, Citalopram, Clavunate potassium, Ciprofloxacin, Clemastine, Clomiphene, Clonidine, Clopidogrel, Codeine, Cyclizine, Cyclobenzaprine, Cyproheptadine, Delavirdine, Diethylpropion, Divalproex, Desipramine, Dexmethylphenidate, Dexbrompheniramine, Dexchlopheniramine, Dexchlor, Dextroamphetamine, Dexedrine, Dextromethorphan, Fiflunisal, Diphemanil methylsulphate, Diphenhydramine, Dolasetron, Doxylamine, Enoxaparin, Ergotamine, Ertepenem, Eprosartan, Escitalopram, Esomeprazole, Fenoldopam, Fentanyl, Fexofenadine, Flufenamic acid, Fluvastatin, Fluphenazine, Fluticasone, Fosinopril, Frovatriptan, Gabapentin, Galatamine, Gatifloxacin, Gemcitabine, Haloperidol, Hyalurondate, Hydrocodone, Hydroxychloroquine, Hyoscyamine, Imatinib, Imipenem, Ipatropin, Lisinopril, Leuprolide, Levopropoxyphene, Losartan, Meclofenamic acid, Mefanamic acid, Mesalamine, Mepenzolate, Meperidine, Mephentermine, Mesalimine, Mesoridazine, Metaproteranol, Metformin, Methdialazine, Methscopolamine, Methysergide, Metoprolol, Metronidazole, Mibefradil, Montelukast, Morphine, Mometasone, Naratriptan, Nelfinavir, Nortriptylene, Noscapine, Nylindrin, Omeprazole, Orphenadrine, Oseltamivir, Oxybutynin, Papaverine, Pentazocine, Phendimetrazine, Phentermine, Pioglitazone, Pilocarpine, Prochloroperazine, Pyrilamine, Quetapine, Ranitidine, Rivastigmine, Rosiglitazone, Salmetrol, Sertaline, Sotalol, Sumatriptan, Tazobactam, Tacrolimus, Tamoxifen, Ticlopidine, Topiramate, Tolterodine,

Triptorelin, Triplennamine, Triprolidine, Tramadol, Trovofloxacin, Ursodiol, Promazine, Propoxyphene, Propanolol, Pseudoephedrine, Pyrilamine, Quinidine, Oxybate sodium, Sermorelin, Tacrolimus, Tegaseroid, Teriparatide, Tolterodine, Triptorelin pamoate, Scoplolamine, Venlafaxine, Zamivir, Aminocaproic acid, Aminosalicylic acid, Hydromorphone, Isosuprine, Levorphanol, Melhalan, Nalidixic acid, and Para-aminosalicylic acid.

2. Deionizing Agent

The fill material of the present invention comprises fumaric acid, maleic acid, tartaric acid, citric acid, malic acid, acetic acid, proprionic acid, pyruvic acid, butanoic acid or lactic acid in an amount of from 0.2 to 1.0 mole equivalents per mole of the naproxen sodium. These acids act as deionizing agents.

The deionizing agent functions by causing partial deionization (neutralization) of the salt of the pharmaceutically active agent (in this invention naproxen sodium). As described herein when the active agent is the salt of a weak acid and a strong base, the deionizing agent is preferably a hydrogen ion species such as an acid as described above or when the active agent is the salt of a weak base and a strong acid, the deionizing agent is preferably a hydroxide ion species such as a metal hydroxide such as sodium hydroxide, potassium hydroxide, ammonium hydroxide, calcium hydroxide, aluminum hydroxide, and magnesium hydroxide.

Additional acid or base can be added to adjust the pH of the fill composition. In a preferred embodiment, the pH of the fill composition is from about 2.5 to about 7.5.

3. Excipients

Formulations may be prepared using a pharmaceutically acceptable carrier composed of materials that are considered safe and effective and may be administered to an individual without causing undesirable biological side

effects or unwanted interactions. The carrier is all components present in the pharmaceutical formulation other than the active ingredient or ingredients. As generally used herein "carrier" includes, but is not limited to, plasticizers, crystallization inhibitors, wetting agents, bulk filling agents, solubilizers, bioavailability enhancers, solvents, pH-adjusting agents and combinations thereof.

A mixture of polyethylene glycol and water is used as a solvent for the naproxen sodium and the de-ionizing agent. Polyethylene glycol is present in an amount from about 10% to about 80% by weight. Water is present in an amount from about 1% to 18% by weight. The molecular weight of polyethylene glycol is between 300 and 1500. Other suitable solvents described herein include surfactants and copolymers of polyethylene glycol. The fill material of the present invention also comprises a solubilizer selected from the group consisting of glycerin, polyvinyl pyrrolidone (PVP) or propylene glycol (PPG) and combinations thereof.

B. Shell Composition

1. Gelatin

Gelatin is the product of the partial hydrolysis of collagen. Gelatin is classified as either Type A or Type B gelatin. Type A gelatin is derived from the acid hydrolysis of collagen while Type B gelatin is derived from alkaline hydrolysis of collagen. Traditionally, bovine bones and skins have been used as raw materials for manufacturing Type A and Type B gelatin while porcine skins have been used extensively for manufacturing Type A gelatin. In general acid-processed gelatins form stronger gels than lime- processed gelatins of the same average molecular weight.

2. Other Shell Additives

Other suitable shell additives include plasticizers, opacifiers, colorants, humectants, preservatives, flavorings, and buffering salts and acids.

Plasticizers are chemical agents added to gelatin to make the material softer and more flexible. Suitable plasticizers include glycerin, sorbitol

solutions which are mixtures of sorbitol and sorbitan, and other polyhydric alcohols such as propylene glycol and maltitol or combinations thereof.

Opacifiers are used to opacify the capsule shell when the encapsulated active agents are light sensitive. Suitable opacifiers include titanium dioxide, zinc oxide, calcium carbonate and combinations thereof.

Colorants can be used to for marketing and product identification/differentiation purposes. Suitable colorants include synthetic and natural dyes and combinations thereof.

Humectants can be used to suppress the water activity of the softgel. Suitable humectants include glycerin and sorbitol, which are often components of the plasticizer composition. Due to the low water activity of dried, properly stored softgels, the greatest risk from microorganisms comes from molds and yeasts. For this reason, preservatives can be incorporated into the capsule shell. Suitable preservatives include alkyl esters of p-hydroxy benzoic acid such as methyl, ethyl, propyl, butyl and heptyl (collectively known as "parabens") or combinations thereof.

Flavorings can be used to mask unpleasant odors and tastes of fill formulations. Suitable flavorings include synthetic and natural flavorings. The use of flavorings can be problematic due to the presence of aldehydes which can cross-link gelatin. As a result, buffering salts and acids can be used in conjunction with flavorings that contain aldehydes in order to inhibit cross-linking of the gelatin.

II. Method of Making

A. Fill Material

The fill material is prepared by mixing the agent (such as a salt of the drug), the deionizing agent, water, and polyethylene glycol at a temperature of 50°C to 70°C. The resulting solution is encapsulated using the appropriate gel mass. The pharmaceutical agent is present in an amount from about 10% to about 50% by weight. The deionizing agent is present in an amount from about 0.2 to 1.0 mole per mole of the pharmaceutical agent. Water is present in an amount from about 1% to about 20% by weight and polyethylene glycol is present in amount from about 10% to about 80% by weight.

Optionally, propylene glycol and/or polyvinyl pyrrolidone are present in an amount from about 1% to about 10%.

B. Gel Mass

The main ingredients of the softgel capsule shell are gelatin, plasticizer, and purified water. Typical gel formulations contain (w/w) 40-50% gelatin, 20-30% plasticizer, and 30-40% purified water. Most of the water is subsequently lost during capsule drying. The ingredients are combined to form a molten gelatin mass using either a cold melt or a hot melt process. The prepared gel masses are transferred to preheated, temperature-controlled, jacketed holding tanks where the gel mass is aged at 50-60°C until used for encapsulation.

1. Cold Melt Process

The cold melt process involves mixing gelatin with plasticizer and chilled water and then transferring the mixture to a jacket-heated tank. Typically, gelatin is added to the plasticizer at ambient temperature (18-22°C). The mixture is cooked (57-95°C) under vacuum for 15-30 minutes to a homogeneous, deaerated gel mass. Additional shell additives can be added to the gel mass at any point during the gel manufacturing process or they may be incorporated into the finished gel mass using a high torque mixer.

2. Hot Melt Process

The hot melt process involves adding, under mild agitation, the gelatin to a preheated (60-80°C) mixture of plasticizer and water and stirring the blend until complete melting is achieved. While the hot melt process is faster than the cold melt process, it is less accurately controlled and more susceptible to foaming and dusting.

C. Softgel Capsule

Softgel capsules are typically produced using a rotary die encapsulation process. The gel mass is fed either by gravity or through positive displacement pumping to two heated (48-65°C) metering devices. The metering devices control the flow of gel into cooled (10-18°C), rotating casting drums. Ribbons are formed as the cast gel masses set on contact with the surface of the drums.

The ribbons are fed through a series of guide rolls and between injection wedges and the capsule-forming dies. A food-grade lubricant oil is applied onto the ribbons to reduce their tackiness and facilitate their transfer. Suitable lubricants include mineral oil, medium chain triglycerides, and soybean oil. Fill formulations are fed into the encapsulation machine by gravity. In the preferred embodiment, the softgels contain printing on the surface, optionally identifying the encapsulated agent and/or dosage.

III. Method of Use

The softgels may be used to encapsulate a wide range of pharmaceutically active agents, nutritional agents and personal care products. Softgel capsules may be administered orally to a patient to deliver a pharmaceutically active agent.

Examples

In the following examples, the fill material can be prepared by mixing the salt of one or more pharmaceutically active agents, the deionizing agent, water and polyethylene glycol at a temperature of 50°C to 70°C. The resulting solution can be encapsulated in a softgel capsule using the appropriate gel mass.

Example 1. Naproxen Sodium with Acetic Acid as the Deionizing Agent

Fill Material:

Ingredients	% (by weight)
Naproxen Sodium	25.50
Acetic Acid	3.00
PVP	1.85
PEG 400	62.30
Water	7.40

Example 2. Naproxen Sodium with Citric Acid as the Deionizing Agent

Fill Material:

Ingredients	% (by weight)
Naproxen Sodium	25.50
Citric Acid	4.75
PVP	1.85
PEG 400	60.50
Water	7.40

Reference Example 3. Naproxen Sodium with Hydrochloric Acid as the Deionizing Agent

Fill Material:

Ingredients	% (by weight)
Naproxen Sodium	25.50
Hydrochloric Acid	4.72
PVP	1.85
PEG 400	63.52
Water	7.40

Example 4. Naproxen Sodium with Acetic Acid as the Deionizing Agent

Fill Material:

Ingredients	% (by weight)
Naproxen Sodium	25.50
Acetic Acid	3.00
PVP	1.85
PEG 400	31.15
Water	7.40
PEG 600	31.15

Example 5. Naproxen Sodium with Citric Acid as the Deionizing Agent

Fill Material:

Ingredients	% (by weight)
Naproxen Sodium	25.50
Citric Acid	4075
PVP	1.85
PEG 400	30.25
Water	7.40
PEG 600	30.25

Reference Example 6. Naproxen Sodium with Hydrochloric Acid as the Deionizing Agent

Fill Material:

Ingredients	% (by weight)
Naproxen Sodium	25.50
Hydrochloric Acid	4072
PVP	1.85
PEG 400	30.25
Water	7.40
PEG 600	30.25

Example 7. Naproxen Sodium with Lactic Acid as the Deionizing Agent

Fill Material:

Ingredients	% (by weight)
Naproxen Sodium	27.50
Lactic Acid	5.27
Propylene Glycol	2.00
PEG 400	64.64
Water	0.60

Example 8. Naproxen Sodium with Lactic Acid as the Deionizing Agent

Fill Material:

Ingredients	% (by weight)
Naproxen Sodium	25.00
Lactic Acid	0.24-0.35 M
Propylene glycol	2.00
PEG 600.	q.s.

Example 9. Naproxen Sodium with Lactic Acid as the Deionizing Agent

Fill Material:

Ingredients	% (by weight)
Naproxen Sodium	25.00
Lactic Acid	5.00
Propylene glycol	2.00
PEG 600	61.2
PEG 1000	6.80

Example 10. Naproxen Sodium with Lactic Acid as the Deionizing Agent

Fill Material:

Ingredients	% (by weight)
Naproxen Sodium	25.00
Lactic acid	5.00
Propylene glycol	2.00
PEG 600	51.00
PEG 1000	17.00

Example 11. Naproxen Sodium with Lactic Acid as the Deionizing Agent

Fill Material:

Ingredients	% (by weight)
Naproxen Sodium	25.00
Lactic Acid	5.00
Propylene glycol	2.00
PEG 600	34.00
PEG 1000	34.00

Example 12. Naproxen Sodium with Lactic Acid as the Deionizing Agent

Fill Material:

Ingredients	% (by weight)
Naproxen Sodium	25.00
Lactic acid	5.00
Propylene glycol	2.00
PEG 600	17.00
PEG 1000	51.00

It is understood that the disclosed invention is not limited to the particular methodology, protocols, and reagents described as these may vary. It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments only, and is not intended to limit the scope of the present invention which will be limited only by the appended claims.

Unless defined otherwise, all technical and scientific terms used herein have the same meanings as commonly understood by one of skill in the art to which the disclosed invention belongs. Although any methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present invention, the preferred methods, devices, and materials are as described. ~~Publications cited herein and the materials~~

Nothing herein is to be construed as an admission that the invention is not entitled to antedate such disclosure by virtue of prior invention.

CLAIMS

1. A softgel capsule comprising a fill material wherein the fill material comprises

(a) naproxen sodium;

(b) fumaric acid, maleic acid, tartaric acid, citric acid, malic acid, acetic acid, proprionic acid, pyruvic acid, butanoic acid or lactic acid in an amount of from 0.2 to 1.0 mole equivalents per mole of the naproxen sodium;

(c) polyethylene glycol;

(d) water; and

(e) a solubilizer selected from the group consisting of glycerin, polyvinylpyrrolidone, propylene glycol and combinations thereof.

2. The capsule of claim 1 wherein (b) is citric acid or lactic acid.

3. The capsule of claim 2 wherein (b) is lactic acid.

4. The capsule of any one of the preceding claims wherein polyethylene glycol is present in an amount from 10% to 80% by weight.

5. The capsule of any one of the preceding claims wherein the polyethylene glycol is one or more polyethylene glycols with a molecular weight between 300 and 1500.

6. The capsule of any one of the preceding claims wherein water is present in an amount from 1% to 18% by weight.

7. The capsule of any one of the preceding claims further comprising one or more excipients selected from the group consisting of plasticizers, crystallization inhibitors, wetting agents, bulk filling agents, solubilizers, bioavailability enhancers, solvents, dyes, preservatives, solvents, surfactants, and combinations thereof.

8. The capsule of any one of the preceding claims wherein the solubilizer is present in amount from 1% to 10% by weight.

9. The capsule of any one of the preceding claims wherein the fill material is liquid.

10. A capsule of any of the preceding claims for use as a medicament.

11. A method of making the capsule of claim 1 comprising

(a) mixing components (a), (b), (c), (d) and (e) as defined in claim 1; and

(b) encapsulating the mixture in a softgel capsule.

12. The method of claim 11, wherein step (a) is conducted at a temperature of from 50°C to 70°C.

13. The use of

(a) naproxen sodium;

(b) fumaric acid, maleic acid, tartaric acid, citric acid, malic acid, acetic acid, proprionic acid, pyruvic acid, butanoic acid or lactic acid in an amount of from 0.2 to 1.0 mole equivalents per mole of the naproxen sodium;

(c) polyethylene glycol;

(d) water; and

(e) a solubilizer selected from the group consisting of glycerin, polyvinylpyrrolidone, propylene glycol and combinations thereof,

in the manufacture of a medicament in the form of a capsule for administration of the naproxen sodium to a patient in need thereof.

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Letter accompanying subsequently filed items

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The document(s) listed below is (are) subsequently filed documents pertaining to the following application:

Application number	06737018.9
Applicant's or representative's reference	PABQ/P38814EP

	Description of document	Original file name	Assigned file name
1	Reply to the communication under rule 71(3) EPC	P38814EP Reply to 71(3).pdf	IGRA-1.pdf
2	German translations of the claims	P38814EP DE Claims.pdf	CLMSTRAN-DE-1.pdf
3	French translations of the claims	P38814EP FR Claims.pdf	CLMSTRAN-FR-1.pdf
4	Amended claims (clean copy)	Amended claims.pdf	CLMS-1.pdf

	Fees	Factor applied	Fee schedule	Amount to be paid
15-1	007 Fee for grant and printing (not more than 35 pages) or fee for grant including fee for publication	1	915.00	915.00
	Total:		**EUR**	**915.00**

	Payment	
1	Mode of payment	Debit from deposit account
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	The European Patent Office is hereby authorised, to debit from the deposit account with the EPO any fees and costs indicated on the fees page.	
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	Account holder:	Potter Clarkson LLP
2	Refund/Reimburserment	
	Reimbursement (if any) to be made to EPO deposit account:	28050040
	Account holder:	Potter Clarkson LLP

Signatures

Place: **Nottingham, United Kingdom**

Date: **17 March 2016**

Signed by:	/Crowhurst, Charlotte Waveney/
Association:	Potter Clarkson LLP
Representative name:	Crowhurst, Charlotte Waveney
Capacity:	(Representative)

CLAIMS

1. A softgel capsule comprising a fill material wherein the fill material comprises

(a) naproxen sodium;

(b) fumaric acid, maleic acid, tartaric acid, citric acid, malic acid, acetic acid, proprionic acid, pyruvic acid, butanoic acid or lactic acid in an amount of from 0.2 to 1.0 mole equivalents per mole of the naproxen sodium;

(c) polyethylene glycol;

(d) water; and

(e) a solubilizer selected from the group consisting of glycerin, polyvinylpyrrolidone, propylene glycol and combinations thereof.

2. The capsule of claim 1 wherein (b) is citric acid or lactic acid.

3. The capsule of claim 2 wherein (b) is lactic acid.

4. The capsule of any one of the preceding claims wherein polyethylene glycol is present in an amount from 10% to 80% by weight.

5. The capsule of any one of the preceding claims wherein the polyethylene glycol is one or more polyethylene glycols with a molecular weight between 300 and 1500.

6. The capsule of any one of the preceding claims wherein water is present in an amount from 1% to 18% by weight.

7. The capsule of any one of the preceding claims further comprising one or more excipients selected from the group consisting of plasticizers, crystallization inhibitors, wetting agents, bulk filling agents, solubilizers, bioavailability enhancers, solvents, dyes, preservatives, surfactants, and combinations thereof.

8. The capsule of any one of the preceding claims wherein the solubilizer is present in amount from 1% to 10% by weight.

9. The capsule of any one of the preceding claims wherein the fill material is liquid.

10. A capsule of any of the preceding claims for use as a medicament.

PATENTANSPRÜCHE

1. Weichkapsel, umfassend ein Füllmaterial, wobei das Füllmaterial Folgendes umfasst:
   (a) Naproxennatrium;
   (b) Fumarsäure, Maleinsäure, Weinsäure, Citronensäure, Äpfelsäure, Essigsäure, Propionsäure, Brenztraubensäure, Buttersäure oder Milchsäure in einer Menge von 0,2 bis 1,0 Moläquivalenten pro Mol Naproxennatrium;
   (c) Polyethylenglycol;
   (d) Wasser; und
   (e) einen Lösungsvermittler aus der Gruppe, bestehend aus Glycerin, Polyvinylpyrrolidon, Propylenglycol und Kombinationen daraus.

2. Kapsel nach Anspruch 1, wobei (b) Citronensäure oder Milchsäure ist.

3. Kapsel nach Anspruch 2, wobei (b) Milchsäure ist.

4. Kapsel nach einem der vorhergehenden Ansprüche, wobei das Polyethylenglycol in einer Menge von 10 Gew.-% bis 80 Gew.-% vorliegt.

5. Kapsel nach einem der vorhergehenden Ansprüche, wobei das Polyethylenglycol ein oder mehrere Polyethylenglycole mit einer Molekülmasse zwischen 300 und 1500 ist.

6. Kapsel nach einem der vorhergehenden Ansprüche, wobei Wasser in einer Menge von 1 Gew.-% bis 18 Gew.-% vorhanden ist.

7. Kapsel nach einem der vorhergehenden Ansprüche, ferner umfassend ein oder mehrere Hilfsstoffe, ausgewählt aus der Gruppe, bestehend aus Weichmachern, Kristallisationshemmern, Benetzungsmitteln, Massenfüllmitteln, Lösungsvermittlern, Bioverfügbarkeitsverstärkern, Lösungsmitteln, Farbstoffen, Konservierungsmitteln, Tensiden und Kombinationen daraus.

8. Kapsel nach einem der vorhergehenden Ansprüche, wobei der Lösungsvermittler in einer Menge von 1 Gew.-% bis 10 Gew.-% vorhanden ist.

9. Kapsel nach einem der vorhergehenden Ansprüche, wobei das Füllmaterial flüssig ist.

10. Kapsel nach einem der vorhergehenden Ansprüche zur Verwendung als ein Medikament.

11. Verfahren zum Herstellen der Kapsel nach Anspruch 1, Folgendes umfassend:

(a) Mischen der Komponenten (a), (b), (c), (d) und (e) nach Anspruch 1; und

(b) Einkapseln der Mischung in eine Weichkapsel.

12. Verfahren nach Anspruch 11, wobei Schritt (a) bei einer Temperatur von 50 °C bis 70 °C durchgeführt wird.

13. Gebrauch von

(a) Naproxennatrium;

(b) Fumarsäure, Maleinsäure, Weinsäure, Citronensäure, Äpfelsäure, Essigsäure, Propionsäure, Brenztraubensäure, Buttersäure oder Milchsäure in einer Menge von 0,2 bis 1,0 Moläquivalenten pro Mol Naproxennatrium;

(c) Polyethylenglycol;

(d) Wasser; und

(e) einem Lösungsvermittler aus der Gruppe, bestehend aus Glycerin, Polyvinylpyrrolidon, Propylenglycol und Kombinationen daraus,

bei der Herstellung eines Medikaments in der Form einer Kapsel zum Verabreichen von Naproxennatrium an einen Patienten, der dies benötigt.

REVENDICATIONS

1. Capsule molle comprenant un matériau de remplissage dans laquelle le matériau de remplissage comprend :

(a) du naproxène sodique ;

(b) de l'acide fumarique, de l'acide maléique, de l'acide tartrique, de l'acide citrique, de l'acide malique, de l'acide acétique, de l'acide proprionique, de l'acide pyruvique, de l'acide butanoïque ou de l'acide lactique dans une quantité comprise entre 0,2 et 1,0 équivalent molaire par mole de naproxène sodique ;

(c) du polyéthylène glycol ;

(d) de l'eau ; et

(e) un solubilisant choisi dans le groupe constitué par la glycérine, la polyvinylpyrrolidone, le propylène glycol et des combinaisons de ceux-ci.

2. Capsule selon la revendication 1, dans laquelle (b) est de l'acide citrique ou de l'acide lactique.

3. Capsule selon la revendication 2, dans laquelle (b) est de l'acide lactique.

4. Capsule selon l'une quelconque des revendications précédentes, dans laquelle le polyéthylène glycol est présent dans une quantité comprise entre 10 % et 80 % en poids.

5. Capsule selon l'une quelconque des revendications précédentes, dans laquelle le polyéthylène glycol est un ou plusieurs polyéthylènes glycols ayant un poids moléculaire compris entre 300 et 1 500.

6. Capsule selon l'une quelconque des revendications précédentes, dans laquelle l'eau est présente dans une quantité comprise entre 1 % et 18 % en poids.

7. Capsule selon l'une quelconque des revendications précédentes, comprenant en outre un ou plusieurs excipients choisis dans le groupe constitué par les plastifiants, les inhibiteurs de cristallisation, les agents mouillants, les agents de remplissage en vrac, les solubilisants, les amplificateurs de biodisponibilité, les solvants, les colorants, les conservateurs, les tensioactifs et des combinaisons de ceux-ci.

8. Capsule selon l'une quelconque des revendications précédentes, dans laquelle le solubilisant est présent dans une quantité comprise entre 1 % et 10 % en poids.

9. Capsule selon l'une quelconque des revendications précédentes, dans laquelle le matériau de remplissage est liquide.

10. Capsule selon l'une quelconque des revendications précédentes, pour une utilisation en tant que médicament.

11. Procédé de fabrication de la capsule selon la revendication 1, comprenant les étapes consistant à :

(a) mélanger les composants (a), (b), (c), (d) et (e) tels que définis dans la revendication 1 ; et

(b) encapsuler le mélange dans une capsule molle.

12. Procédé capsule selon la revendication 11, dans lequel l'étape (a) est effectuée à une température comprise entre 50 °C et 70 °C.

13. Utilisation

(a) de naproxène sodique ;

(b) d'acide fumarique, d'acide maléique, d'acide tartrique, d'acide citrique, d'acide malique, d'acide acétique, d'acide proprionique, d'acide pyruvique, d'acide butanoïque ou d'acide lactique dans une quantité comprise entre 0,2 et 1,0 équivalent molaire par mole de naproxène sodique ;

(c) de polyéthylène glycol ;

(d) d'eau ; et

(e) d'un solubilisant choisi dans le groupe constitué par la glycérine, la polyvinylpyrrolidone, le propylène glycol et des combinaisons de ceux-ci,

dans la fabrication d'un médicament sous la forme d'une capsule pour l'administration du naproxène sodique à un patient en ayant besoin.

POTTER CLARKSON

European Patent Office
80298 München
GERMANY

17 March 2016

Dear Sirs

European Patent Application No. 06737018.9
Publication No. 1863458
Banner Life Sciences LLC
Our Reference: PABQ/P38814EP

In response to the communication under Rule 71(3) EPC, we enclose translations of the claims into French and German.

The text of the specification is approved for grant as specified in the Communication under Rule 71(3) subject to the following amendment.

We have corrected an error in claim 7. In this claim "solvents" was listed twice. We have corrected the error by deleting the second occurrence of "solvents".

We hereby waive the right to receive a further communication under Rule 71(3) EPC in the event that the Examination Division consents to these amendments.

Please update the address for the inventor Nachiappan Chidambaram. His new address is stated below:

8410 Handcart Circle
Sandy
Utah 84070
United States of America.

The fee for grant, printing fees and excess claims fees, if any, should be taken from our deposit account.

Yours faithfully

Charlotte Crowhurst
For and on behalf of Potter Clarkson LLP

Enc: French and German claims

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Europäisches Patentamt
European Patent Office
Office européen des brevets

Acknowledgement of receipt

We hereby acknowledge receipt of the following subsequently filed document(s):

Submission number	4202986
Application number	EP06737018.9
Date of receipt	17 March 2016
Receiving Office	European Patent Office, The Hague
Your reference	PABQ/P38814EP
Applicant	All applicants as on file
Documents submitted	package-data.xml epf1038.pdf (2 p.) CLMSTRAN-DE-1.pdf\P38814EP DE Claims.pdf (2 p.) CLMS-1.pdf\Amended claims.pdf (1 p.) ep-sfd-request.xml IGRA-1.pdf\P38814EP Reply to 71(3).pdf (1 p.) CLMSTRAN-FR-1.pdf\P38814EP FR Claims.pdf (2 p.)
Submitted by	CN=Roberta Morbioli 47887
Method of submission	Online
Date and time receipt generated	17 March 2016, 16:09 (CET)
Message Digest	50:C3:0C:38:3E:4E:91:71:94:E7:D6:D0:1C:C0:06:F6:37:99:7B:BC

Correction by the EPO of errors in debit instructions filed by eOLF
Errors in debit instructions filed by eOLF that are caused by the editing of Form 1038E entries or the continued use of outdated software (all forms) may be corrected automatically by the EPO, leaving the payment date unchanged (see decision T 152/82, OJ EPO 1984, 301 and point 6.3 ff ADA, Supplement to OJ EPO 10/2007).

/European Patent Office/

Europäisches Patentamt
European Patent Office
Office européen des brevets

European Patent Office
80298 MUNICH
GERMANY

Questions about this communication ?
Contact Customer Services at www.epo.org/contact

Potter Clarkson LLP
The Belgrave Centre
Talbot Street
Nottingham NG1 5GG
ROYAUME UNI

Date
05.04.2016

Reference	Application No./Patent No.
PABCA/P38814EP	06737018.9 - 1466 / 1863458
Applicant/Proprietor	
Banner Life Sciences LLC	

BRIEF COMMUNICATION

Subject:
- [X] Your letter of 17.03.2016
- [ ] Our telephone conversation of
- [ ] Communication of
- [ ]

Enclosure(s):
- [ ] Letter from the proprietor of the patent of
- [X] Copy (copies) EPO Form 2056
- [ ] Communication:

Following your request dated 17.03.2016 the address of the inventor CHIDAMBARAM, Nachiappan has be updated as indicated on attached EPO Form 2056.

Please take note.

For the Legal Division

Europäisches Patentamt • European Patent Office • Office européen des brevets

☐ **Registered letter**

Europäisches Patentamt
European Patent Office
Office européen des brevets

Annex to EPO Form 2004, Communication pursuant to Rule 71(3) EPC

Bibliographical data of European patent application No. 06737018.9.

For the intended grant of the European patent, the bibliographic data are set out below, for information:

Title of invention:
- LÖSUNGSMITTELSYSTEM ZUR ERHÖHUNG DER LÖSLICHKEIT PHARMAZEUTISCHER WIRKSTOFFE
- SOLVENT SYSTEM FOR ENHANCING THE SOLUBILITY OF PHARMACEUTICAL AGENTS
- SYSTEME DE SOLVANT DESTINE A AMELIORER LA SOLUBILITE DES AGENTS PHARMACEUTIQUES

Classification: A61K9/48

Date of filing: 06.03.06

Priority claimed: US / 08.03.05 / USP 659679

Contracting States* for which fees have been paid: AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HU IE IS IT LI LT LU LV MC NL PL PT RO SE SI SK TR

Extension States* for which fees have been paid:

Validation States* for which fees have been paid:

Applicant(s) **:
Banner Life Sciences LLC
4125 Premier Drive
High Point, North Carolina 27265/US

Inventor(s):
CHIDAMBARAM, Nachiappan
8410 Handcart Circle
Sandy, Utah 84070/US

FATMI, Aqeel
3809 Camden Falls Court
Greensboro, North Carolina 27410/US

*) If the time limit for the payment of designation fees according to Rule 39(1) EPC has not yet expired and the applicant has not withdrawn any designation, **all Contracting States/Extension States/Validation States** are currently still deemed to be designated. See also Rule 71a(3) EPC and, if applicable, the above Note to users of the automatic debiting procedure.

**) If two or more applicants have designated different Contracting States, this is indicated here.

Europäisches Patentamt
European Patent Office
Office européen des brevets

European patent application No. 06737018.9

After communication under Rule 71(3) EPC (IGRA) but before decision to grant (EPO Form 2006A)

☒ **Request for amendments/corrections of documents (IGRE coded) dated** 17.03.2016

☒ **WAIVER** of right to receive a new communication under Rule 71(3) EPC (IGRE03 coded)

Note 1: If the request is treated when the decision to grant (EPO Form 2006A) has already been handed over to the EPO postal service, it is to be submitted to the examining division with EPO Form 2051.
Note 2: If the request concerns only the title(s) and/or classification, it is to be submitted to the examining division with EPO Form 2034.

● ☐ **Third-party observations under Article 115 EPC (TIPA coded) dated** ..... *Continue with point 2.*

Note: If the observations are treated when the decision to grant (EPO Form 2006A) has already been handed over to the EPO postal service, they must no longer be submitted to the examining division.

1. Finding

☒ The request was received **within** the IGRA period.

☐ The request was received **after** expiry of the IGRA period. The applicant failed to reply in time (ADWI situation) but further processing has been requested.

☐ The request was received **after having already paid fees and submitted translations of claims** in due time. The decision to grant (EPO Form 2006A) has not yet been handed over to the EPO postal service.

2. To the examining division

● Please decide below whether the requested amendments/corrections are allowable or whether the third-party observations are relevant.

Date: 29.03.2016 Formalities Officer: Striese-Kiepe, Christine

3. To the formalities officer

3.1 ☒ **Consent** is given to the amendments/corrections requested.

☐ Non-waiver case: A new communication under Rule 71(3) EPC (IGRA) is to be issued (IGRA06=blank).

☐ **WAIVER case, but** the examining division **does not completely agree** to the request of the applicant (IGRA06=No). A new communication under Rule 71(3) EPC (IGRA) is to be issued.

☒ **WAIVER case:** The examining division **completely agrees** to the request of the applicant (IGRA06=Yes). Consent is given to the waiver if the formal requirements concerning payment of fees and filing of claims translations are also fulfilled. If this is not the case, a new communication under Rule 71(3) EPC (IGRA) is to be issued.

3.2 ☐ Following a telephone conversation **agreement** has been reached. A new communication under Rule 71(3) EPC (IGRA) is to be issued. Attached EPO Form 2036 (telephone consultation) is to be enclosed with it.

3.3 ☐ **Not all or none** of the amendments/corrections can be allowed. Examination proceedings are to be resumed.

☐ Attached **communication** is to be despatched with EPO Form 2001 (EXRE) / 2909 (INBA).

☐ Attached EPO Form 2036 (**telephone consultation**) is to be despatched with EPO Form 2049 (EXRE).

☐ Attached **summons to oral proceedings** is to be despatched with EPO Form 2008 (ORAL).
(Note for examiner: At least one communication under Rule 71(1)(2) EPC must have been sent before summons to oral proceedings can be sent.)

☐ Attached reasoned **refusal** is to be despatched with EPO Form 2007 (REFU).
(Note for examiner: At least one communication under Rule 71(1)(2) EPC must have been sent and the applicant's rights according to Articles 113(1) and 116 EPC must have been met before a refusal can be sent.)

☐ The communication under Rule 71(3) EPC was based upon an auxiliary request. Since the applicant maintains the main or higher ranking request which is not allowable, the application is to be refused (Art. 97(2) EPC).

☐ The applicant has expressed disapproval. Since there is no text on which to base a decision, the application is to be refused (Art. 113(2) EPC; see T 237/96 and Guidelines C-V, 4.9)
(Note for examiner: Standard clause N17C will be used.)

☐ The applicant has not overcome the objections raised in the communication under Rule 71(3) EPC. The reasons for non-compliance with the EPC have already been communicated to him. The application is to be refused.

3.4 ☐ **Observations by a third party (Art. 115 EPC)**

☐ The observations under Article 115 EPC give no cause for amendment of the documents.
Note: TIPA04 is to be coded (to release RPUB).

☐ Examination proceedings are to be resumed. Attached communication is to be despatched.
Note: A fictitious IGRE is to be coded. If necessary, an explanation is to be sent to the applicant.

Date: 6/4/16 Examining Division

Chairman	Second Examiner	Primary Examiner	Legal Member

Europäisches Patentamt
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Office européen des brevets

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Nottingham NG1 5GG
ROYAUME-UNI

Formalities Officer
Name: Brell, Eva
Tel: +49 89 2399 - 6724
or call
+31 (0)70 340 45 00

Application No.	Ref.	Date
06 737 018.9 - 1466	PABCA/P38814EP	23.05.2016
Applicant: Banner Life Sciences LLC		

Communication under Rule 71(3) EPC

1. Intention to grant

You are informed that the examining division intends to grant a European patent on the basis of the above application, with the text and drawings and the related bibliographic data as indicated below.

A copy of the relevant documents is enclosed.

1.1 In the text for the Contracting States:
AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HU IE IS IT LI LT LU LV MC NL PL PT RO SE SI SK TR

Description, Pages

2, 8-10, 13, 14	as published			
1, 3-7, 11, 12, 15	received on	06-05-2015	with letter of	06-05-2015

Claims, Numbers

11-13	received on	06-05-2015	with letter of	06-05-2015
1-10	filed in electronic form on			17-03-2016

With the following amendments to the above-mentioned documents proposed by the division

Description, Pages 14, 15

Comments

DESCRIPTION
Pages 14, 15: Guidelines F. III. 8

Registered letter
EPO Form 2004C 07.15CSXP

1.2 Bibliographic data

The title of the invention in the three official languages of the European Patent Office, the international patent classification, the designated contracting states, the registered name(s) of the applicant(s) and the other bibliographic data are shown on **EPO Form 2056** (enclosed).

2. Invitation

You are invited, **within a non-extendable period of four months** of notification of this communication,

2.1 to EITHER approve the text communicated above and verify the bibliographic data (Rule 71(5) EPC)

(1) by filing a translation of the claim(s) in the other two official languages of the EPO

		Fee code	EUR
(2a)	by paying the fee for grant including the fee for printing (Art. 2(2) RFees):	**007**	925.00
	minus any amount already paid (Rule 71a(5) EPC):		915.00
(2b)	by paying the printing fee (Art. 2(2) RFees) for the 36th and each subsequent page; number of pages payable: 0	**008**	0.00
	minus any amount already paid (Rule 71a(5) EPC):		0.00
		Total amount:	10.00
(3)	by paying additional claims fees under Rule 71(4) EPC; number of claims fees payable: 0	**016**	0.00
	minus any amount already paid (Rule 71a(5) EPC):		0.00
		Total amount:	0.00

Important: If the translations of the claims and fees have already been filed and paid respectively in reply to a previous communication under Rule 71(3) EPC, e.g. in the case of resumption of examination after approval (see Guidelines C-V, 6), **agreement as to the text to be granted** (Rule 71a(1) EPC) must be expressed within the same time limit (e.g. by approving the text and verifying the bibliographic data, by confirming that grant proceedings can go ahead with the documents on file and/or by stating which translations of the claims already on file are to be used).

Note 1: See "Important notes concerning fee payments" below.
Note 2: Any overpaid "minus" amounts will be refunded when the decision to grant (EPO Form 2006A) has been issued.
Note 3: For the calculation of the grant fee under Article 2(2), No. 7, RFees (old fee structure), the number of pages is determined on the basis of a clean copy of the application documents, in which text deleted as a result of any amendments by the examining division is not shown. Such clean copy is made available via on-line file inspection only.

2.2 OR, in the case of disapproval, to request reasoned amendments or corrections to the text communicated above or keep to the latest text submitted by you (Rule 71(6) EPC).

In this case the translations of the claims and fee payments mentioned under point 2.1 above are NOT due.

The terms "amendment(s)" and "correction(s)" refer only to amendments or corrections of the application documents and not of other documents (e.g. bibliographic data, the designation of the inventor, etc.).

If filing amendments, you must identify them and indicate the basis for them in the application as filed. Failure to meet either requirement may lead to a communication from the examining division requesting that you correct this deficiency (Rule 137(4) EPC).

2.3 Bibliographic data

Where you request a change or correction of bibliographic data in response to the Rule 71(3) communication, this will **not** cause the sending of a further communication under Rule 71(3) EPC. You will still have to pay the fees and file translations in reply to the Rule 71(3) communication in the case of 2.1 above, unless you also file a reasoned request for amendments or corrections in response to the Rule 71(3) communication (see case 2.2 above).

3. Loss of rights

If neither of the two possible actions above (see points 2.1 or 2.2) is performed in due time, the European patent application will be deemed to be withdrawn (Rule 71(7) EPC).

4. Further procedure

4.1 In the case of point 2.1 above

4.1.1 The decision to grant the European patent will be issued, and the **mention of the grant** of the patent will be published in the European Patent Bulletin, if the requirements concerning the translation of the claims and the payment of all fees are fulfilled and there is agreement as to the text to be granted (Rule 71a(1) EPC).

Note on payment of the renewal fee:
If a renewal fee becomes due before the next possible date for publication of the mention of the grant of the European patent, publication will be effected only after the renewal fee and any additional fee have been paid (Rule 71a(4) EPC).

Under Article 86(2) EPC, the obligation to pay renewal fees to the European Patent Office terminates with the payment of the renewal fee due in respect of the year in which the mention of the grant of the European patent is published.

Note on payment of the designation fee(s):
If the designation fee(s) become(s) due after the communication under Rule 71(3) EPC, the mention of the grant of the European patent will not be published until these fees have been paid (Rule 71a(3) EPC).

4.1.2 After publication, the **European patent specification** can be downloaded free of charge from the EPO publication server https://data.epo.org/publication-server or ordered from the Vienna sub-office upon payment of a fee (OJ EPO 2005, 126).

4.1.3 Filing of translations in the contracting states

As regards translation requirements prescribed by the contracting states under Article 65(1) EPC, please consult the website of the European Patent Office
www.epo.org ➞Law & practice ➞Legal texts, National law relating to the EPC
www.epo.org ➞Law & practice ➞All Legal texts ➞London Agreement

In the case of a valid extension or validation

As regards translation requirements prescribed by the extension or validation states, please consult the website of the European Patent Office
www.epo.org ➞Law & practice ➞Legal texts, National law relating to the EPC

Failure to supply a prescribed translation in a contracting state, or in an extension or validation state may result in the patent being deemed to be void *ab initio* in the state concerned (Art. 65(3) EPC).

4.2 In the case of 2.2 above

If the present communication under Rule 71(3) EPC is based on an auxiliary request and, within the time limit, you maintain the main request or a higher ranking request which is not allowable, the application will be refused (Art. 97(2) EPC).

If the examining division gives its consent to the requested amendments or corrections, it will issue a new communication under Rule 71(3) EPC; otherwise, it shall resume the examination proceedings (Rule 71(6) EPC).

5. Filing of a divisional application

Any divisional application relating to this European patent application must be filed directly with the European Patent Office in Munich, The Hague or Berlin and will be in the language of the proceedings for the present application, or if the latter was not in an official language of the EPO, the divisional application may be filed in the language of the present application as filed (see Article 76(1) and Rule 36(2) EPC). Any such divisional application must be filed while the present application is still pending (Rule 36(1) EPC; Guidelines A-IV, 1.1.1).

6. Important notes concerning fee payments

6.1 For all payments, please refer to the relevant **fee code(s).**

6.2 Automatic debiting procedure

The fee for grant, including the fee for printing (Art. 2(2) RFees), and any additional claims fees due under Rule 71(4) EPC will be debited automatically on the date of filing of the translations of the claims, or on the last day of the period of this communication. However, if the designation fee(s) become(s) due as set out in Rule 71a(3) EPC and/or a renewal fee becomes due as set out in Rule 71a(4) EPC, these should be paid separately by another permitted way of payment in order not to delay the publication of the mention of the grant. The same applies in these circumstances to the payment of extension and validation fees. For further details see the Arrangements for the automatic debiting procedure (AAD) and accompanying information from the EPO concerning the automatic debiting procedure (Annexes A.1 and A.2 to the Arrangements for deposit accounts (ADA) in Supplementary publication - OJ EPO 3/2015).

Note: If a waiver is expressed in response to a Rule 71(3) communication (see OJ EPO 2015, A52), the fee for grant, including the fee for publication/printing, and any additional claims fees will not be debited automatically. These fees must be paid separately by another means of payment allowed under the Rules relating to Fees.

6.3 Important information relating to fee amounts

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Please note that procedural fees are usually adjusted every two years, on even years, with effect from 1 April.

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Application No.: 06 737 018.9

IV.2. Patent classification

The classification indicated on the published patent application remains unchanged. It is as follows:

INV. A61K9/48

IV.3. Title of the invention

The title indicated on the published patent application remains unchanged. It reads as follows:

LÖSUNGSMITTELSYSTEM ZUR ERHÖHUNG DER LÖSLICHKEIT PHARMAZEUTISCHER WIRKSTOFFE

SOLVENT SYSTEM FOR ENHANCING THE SOLUBILITY OF PHARMACEUTICAL AGENTS

SYSTEME DE SOLVANT DESTINE A AMELIORER LA SOLUBILITE DES AGENTS PHARMACEUTIQUES

IV.4. Documentation

6/4/16
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Enclosure(s):

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Annex to EPO Form 2004, Communication pursuant to Rule 71(3) EPC

Bibliographical data of European patent application No. 06 737 018.9

For the intended grant of the European patent, the bibliographical data are set out below, for information:

Title of invention:
- LÖSUNGSMITTELSYSTEM ZUR ERHÖHUNG DER LÖSLICHKEIT PHARMAZEUTISCHER WIRKSTOFFE
- SOLVENT SYSTEM FOR ENHANCING THE SOLUBILITY OF PHARMACEUTICAL AGENTS
- SYSTEME DE SOLVANT DESTINE A AMELIORER LA SOLUBILITE DES AGENTS PHARMACEUTIQUES

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*) If the time limit for the payment of designation fees according to Rule 39(1) EPC has not yet expired and the applicant has not withdrawn any designation, **all Contracting States/Extension States/Validation States** are currently still deemed to be designated.

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**)	If two or more applicants have designated different Contracting States, this is indicated here.

SOLVENT SYSTEM FOR ENHANCING THE SOLUBILITY OF PHARMACEUTICAL AGENTS

FIELD OF THE INVENTION

This invention is in the field of fill materials encapsulated in soft gelatin capsules.

BACKGROUND OF THE INVENTION

Filled one-piece soft gelatin capsules ("softgels") have been widely used for years to encapsulate consumable materials such as vitamins and pharmaceuticals in a liquid vehicle or carrier. Because softgels have properties which are quite different from two-piece hardshell capsules, softgels are more capable of retaining a liquid fill material.

Not all liquids may be enclosed in a softgel capsule. Liquids containing more than about 20% water by weight are generally not enclosed in softgels, because the water tends to dissolve the gelatin shell. Other solvents such as propylene glycol, glycerin, low molecular weight alcohols, ketones, acids, amines, and esters all tend to degrade or dissolve the gelatin shell to some extent.

Softgels are also somewhat sensitive to pH, and generally require a pH in the encapsulated liquid from about 2.5 to about 7.5. Highly acidic liquids may hydrolyze the gelatin, resulting in leaks, while basic liquids may tan the gelatin, resulting in decreased solubility of the gelatin shell.

Pharmaceutical liquids are usually enclosed in softgels as either viscous solutions or suspensions. Suspensions are pharmaceutically less desirable because they can settle during manufacture, which leads to a less uniform product. In contrast, solutions provide the best liquid form for obtaining optimal "content uniformity" in a batch. Further, solutions typically provide a faster and more uniform absorption of an active agent than do suspensions.

Suitable softgel solutions, however, can be difficult to achieve. One constraint is size. Many pharmaceutical agents require volumes of solvent

too large to produce a softgel capsule small enough to be taken by patients. The solvent must also have sufficient solvating power to dissolve a large amount of the pharmaceutical agent to produce a concentrated solution and yet not dissolve, hydrolyze or tan the gelatin shell.

Concentrated solutions of pharmaceutical agents for use in softgel capsules have been described. Most of these systems involve ionizing the free pharmaceutical agent *in situ* to the corresponding salt. For example, U.S. Patent No. 5,360,615 to Yu *et al.* discloses a solvent system for enhancing the solubility of acidic, basic, or amphoteric pharmaceutical agents. The solvent system comprises polyethylene glycol, an ionizing agent, and water. The ionizing agent functions by causing the partial ionization of the free pharmaceutical agent. U.S. Patent No. 6,383,515, U.S. Patent Application Publication No. 2002/0187195, and U.S. Patent Application Publication No. 2001/0007668 to Sawyer *et al.* discloses pharmaceutically acceptable solutions containing a medicament suitable for filling softgel capsules comprising a polymer such as polyethylene glycol and an acid salt of a compound having three or more carbon atoms, such as sodium propionate. The salt helps to ionize the medicament without relying on the use of strong acids or bases. U.S. Patent No. 6,689,382 to Berthel *et al.* describes a pharmaceutical formulation suitable for filling softgel capsules comprising (a) a therapeutically effective amount of a non-steroidal anti-inflammatory drug (NSAID); and (b) a solvent system comprising 40% to 60% by weight a polyoxyethylene ether, 15% to 35% by weight of glycerin and 15% to 35% by weight water. In cases where the NSAID has a carboxyl or an acidic functional group, the solvent system also includes hydroxide ions. U.S. Patent No. 5,505,961 to Shelley *et al.* describes a method for increasing the solubility of acetaminophen alone or in combination with other pharmaceutically active agents to form a clear solution for encapsulation into a softgel capsule. The method comprises solubilizing acetaminophen in a mixture of propylene glycol, polyethylene glycol, water, polyvinylpyrrolidone and sodium or potassium acetate.

The previously described methods all involve the conversion of the free pharmaceutical agent to the corresponding salt. In cases where the free pharmaceutical agent is acidic, the resulting anion can react with the polyethylene glycol in the fill to produce polyethylene glycol esters, thus reducing the amount of available pharmaceutical agent.

There is a need for a solvent system containing a medicament, which can be encapsulated in a softgel capsule, wherein the formation of PEG esters is minimized.

Therefore it is an object of the invention to provide a stable solvent system for pharmaceutical agents, which is suitable for encapsulation in a softgel capsule, wherein the formation of PEG esters is minimized.

BRIEF SUMMARY OF THE INVENTION

The present invention provides a softgel capsule according to Claim 1 and a use according to Claim 13. Liquid and semi-solid pharmaceutical compositions, which can be administered in liquid form or can be used for preparing capsules, are described herein. The acid present in the compositions of the invention causes partial de-ionization (neutralization) of naproxen sodium resulting in enhanced bioavailability as well as decreased amounts of polyethylene glycol (PEG) esters. Thus, hereinafter the acid maybe referred to as the deionizing agent.

DETAILED DESCRIPTION OF THE INVENTION

I. Composition

A. Fill Materials

1. Drugs to be Formulated

In the present invention the fill material comprises naproxen sodium. Other formulations described herein may contain any therapeutic, diagnostic, prophylactic or nutraceutical agent. Exemplary agents include, but are not limited to, analeptic agents; analgesic agents; anesthetic agents; antiasthmatic agents; antiarthritic agents; anticancer agents; anticholinergic agents; anticonvulsant agents; antidepressant agents; antidiabetic agents; antidiarrheal agents; antiemetic agents; antihelminthic agents; antihistamines; antihyperlipidemic agents; antihypertensive agents; anti-infective agents; anti-inflammatory

agents; antimigraine agents; antineoplastic agents; antiparkinson drugs; antipruritic agents; antipsychotic agents; antipyretic agents; antispasmodic agents; antitubercular agents; antiulcer agents; antiviral agents; anxiolytic agents; appetite suppressants (anorexic agents); attention deficit disorder and attention deficit hyperactivity disorder drugs; cardiovascular agents including calcium channel blockers, antianginal agents, central nervous system ("CNS") agents, beta-blockers and antiarrhythmic agents; central nervous system stimulants; diuretics; genetic materials; hormonolytics; hypnotics; hypoglycemic agents; immunosuppressive agents; muscle relaxants; narcotic antagonists; nicotine; nutritional agents; parasympatholytics; peptide drugs; psychostimulants; sedatives; sialagogues, steroids; smoking cessation agents; sympathomimetics; tranquilizers; vasodilators; beta-agonist; and tocolytic agents.

Any drug that bears an acidic or a basic functional group, for example, an amine, imine, imidazoyl, guanidine, piperidinyl, pyridinyl, quaternary ammonium, or other basic group, or a carboxylic, phosphoric, phenolic, sulfuric, sulfonic or other acidic group, can react with the de-ionizing agent.

Some other drugs that bear acidic or basic functional groups and thus may be converted to the corresponding salt for use in the formulations described herein include, but are not limited to, Acetaminophen, Acetylsalicylic acid, Alendronic acid, Alosetron, Amantadine, Amlopidine, Anagrelide, Argatroban, Atomoxetine, Atrovastatin, Azithromycin dehydrate, Balsalazide, Bromocriptan, Bupropion, Candesartan, Carboplatin, Ceftriaxone, Clavulonic acid, Clindamycin, Cimetadine, Dehydrocholic (acid), Dexmethylphenidate, Diclofenac, Dicyclomine, Diflunisal, Diltiazem, Donepezil, Doxorubicin, Doxepin, Epirubicin, Etodolic acid, Ethacrynic acid, Fenoprofen, Fluoxetine, Flurbiprofen, Furosemide, Gemfibrozil, Hydroxyzine, Ibuprofen, Imipramine, Indomethacin, Ketoprofen, Levothyroxine, Maprolitline, Meclizine, Methadone, Methylphenidate, Minocycline, Mitoxantone, Moxifloxacin, Mycophenolic

acid, Niflumic acid, Ofloxacin, Ondansetron, Pantoprazole, Paroxetine, Pergolide, Pramipexole, Phenytoin, Pravastain, Probenecid, Rabeprazole, Risedronic acid, Retinoic acid, Ropinirole, Selegiline, Sulindac, Tamsulosin, Telmisertan, Terbinafine, Theophyline, Tiludronic Acid, Tinzaparin, Ticarcillin, Tometin, Valproic acid, Salicylic acid, Sevelamer, Ziprasidone, Zoledronic acid, Acetophenazine, Albuterol, Almotriptan, Amitriptyline, Amphetamine, Atracurium, Beclomethasone, Benztropine, Biperiden, Bosentan, Bromodiphenhydramine, Brompheniramine carbinoxamine, Caffeine, Capecitabine, Carbergoline, Cetirizine, Chlocylizine, Chlorpheniramine, Chlorphenoxamine, Chlorpromazine, Citalopram, Clavunate potassium, Ciprofloxacin, Clemastine, Clomiphene, Clonidine, Clopidogrel, Codeine, Cyclizine, Cyclobenzaprine, Cyproheptadine, Delavirdine, Diethylpropion, Divalproex, Desipramine, Dexmethylphenidate, Dexbrompheniramine, Dexchlopheniramine, Dexchlor, Dextroamphetamine, Dexedrine, Dextromethorphan, Fiflunisal, Diphemanil methylsulphate, Diphenhydramine, Dolasetron, Doxylamine, Enoxaparin, Ergotamine, Ertepenem, Eprosartan, Escitalopram, Esomeprazole, Fenoldopam, Fentanyl, Fexofenadine, Flufenamic acid, Fluvastatin, Fluphenazine, Fluticasone, Fosinopril, Frovatriptan, Gabapentin, Galatamine, Gatifloxacin, Gemcitabine, Haloperidol, Hyalurondate, Hydrocodone, Hydroxychloroquine, Hyoscyamine, Imatinib, Imipenem, Ipatropin, Lisinopril, Leuprolide, Levopropoxyphene, Losartan, Meclofenamic acid, Mefanamic acid, Mesalamine, Mepenzolate, Meperidine, Mephentermine, Mesalimine, Mesoridazine, Metaproteranol, Metformin, Methdialazine, Methscopolamine, Methysergide, Metoprolol, Metronidazole, Mibefradil, Montelukast, Morphine, Mometasone, Naratriptan, Nelfinavir, Nortriptylene, Noscapine, Nylindrin, Omeprazole, Orphenadrine, Oseltamivir, Oxybutynin, Papaverine, Pentazocine, Phendimetrazine, Phentermine, Pioglitazone, Pilocarpine, Prochloroperazine, Pyrilamine, Quetapine, Ranitidine, Rivastigmine, Rosiglitazone, Salmetrol, Sertaline, Sotalol, Sumatriptan, Tazobactam, Tacrolimus, Tamoxifen, Ticlopidine, Topiramate, Tolterodine,

Triptorelin, Triplennamine, Triprolidine, Tramadol, Trovofloxacin, Ursodiol, Promazine, Propoxyphene, Propanolol, Pseudoephedrine, Pyrilamine, Quinidine, Oxybate sodium, Sermorelin, Tacrolimus, Tegaseroid, Teriparatide, Tolterodine, Triptorelin pamoate, Scoplolamine, Venlafaxine, Zamivir, Aminocaproic acid, Aminosalicylic acid, Hydromorphone, Isosuprine, Levorphanol, Melhalan, Nalidixic acid, and Para-aminosalicylic acid.

2. Deionizing Agent

The fill material of the present invention comprises fumaric acid, maleic acid, tartaric acid, citric acid, malic acid, acetic acid, proprionic acid, pyruvic acid, butanoic acid or lactic acid in an amount of from 0.2 to 1.0 mole equivalents per mole of the naproxen sodium. These acids act as deionizing agents.

The deionizing agent functions by causing partial deionization (neutralization) of the salt of the pharmaceutically active agent (in this invention naproxen sodium). As described herein when the active agent is the salt of a weak acid and a strong base, the deionizing agent is preferably a hydrogen ion species such as an acid as described above or when the active agent is the salt of a weak base and a strong acid, the deionizing agent is preferably a hydroxide ion species such as a metal hydroxide such as sodium hydroxide, potassium hydroxide, ammonium hydroxide, calcium hydroxide, aluminum hydroxide, and magnesium hydroxide.

Additional acid or base can be added to adjust the pH of the fill composition. In a preferred embodiment, the pH of the fill composition is from about 2.5 to about 7.5.

3. Excipients

Formulations may be prepared using a pharmaceutically acceptable carrier composed of materials that are considered safe and effective and may be administered to an individual without causing undesirable biological side

effects or unwanted interactions. The carrier is all components present in the pharmaceutical formulation other than the active ingredient or ingredients. As generally used herein "carrier" includes, but is not limited to, plasticizers, crystallization inhibitors, wetting agents, bulk filling agents, solubilizers, bioavailability enhancers, solvents, pH-adjusting agents and combinations thereof.

A mixture of polyethylene glycol and water is used as a solvent for the naproxen sodium and the de-ionizing agent. Polyethylene glycol is present in an amount from about 10% to about 80% by weight. Water is present in an amount from about 1% to 18% by weight. The molecular weight of polyethylene glycol is between 300 and 1500. Other suitable solvents described herein include surfactants and copolymers of polyethylene glycol. The fill material of the present invention also comprises a solubilizer selected from the group consisting of glycerin, polyvinyl pyrrolidone (PVP) or propylene glycol (PPG) and combinations thereof.

B. Shell Composition

1. Gelatin

Gelatin is the product of the partial hydrolysis of collagen. Gelatin is classified as either Type A or Type B gelatin. Type A gelatin is derived from the acid hydrolysis of collagen while Type B gelatin is derived from alkaline hydrolysis of collagen. Traditionally, bovine bones and skins have been used as raw materials for manufacturing Type A and Type B gelatin while porcine skins have been used extensively for manufacturing Type A gelatin. In general acid-processed gelatins form stronger gels than lime- processed gelatins of the same average molecular weight.

2. Other Shell Additives

Other suitable shell additives include plasticizers, opacifiers, colorants, humectants, preservatives, flavorings, and buffering salts and acids.

Plasticizers are chemical agents added to gelatin to make the material softer and more flexible. Suitable plasticizers include glycerin, sorbitol

solutions which are mixtures of sorbitol and sorbitan, and other polyhydric alcohols such as propylene glycol and maltitol or combinations thereof.

Opacifiers are used to opacify the capsule shell when the encapsulated active agents are light sensitive. Suitable opacifiers include titanium dioxide, zinc oxide, calcium carbonate and combinations thereof.

Colorants can be used to for marketing and product identification/differentiation purposes. Suitable colorants include synthetic and natural dyes and combinations thereof.

Humectants can be used to suppress the water activity of the softgel. Suitable humectants include glycerin and sorbitol, which are often components of the plasticizer composition. Due to the low water activity of dried, properly stored softgels, the greatest risk from microorganisms comes from molds and yeasts. For this reason, preservatives can be incorporated into the capsule shell. Suitable preservatives include alkyl esters of p-hydroxy benzoic acid such as methyl, ethyl, propyl, butyl and heptyl (collectively known as "parabens") or combinations thereof.

Flavorings can be used to mask unpleasant odors and tastes of fill formulations. Suitable flavorings include synthetic and natural flavorings. The use of flavorings can be problematic due to the presence of aldehydes which can cross-link gelatin. As a result, buffering salts and acids can be used in conjunction with flavorings that contain aldehydes in order to inhibit cross-linking of the gelatin.

II. Method of Making

A. Fill Material

The fill material is prepared by mixing the agent (such as a salt of the drug), the deionizing agent, water, and polyethylene glycol at a temperature of 50°C to 70°C. The resulting solution is encapsulated using the appropriate gel mass. The pharmaceutical agent is present in an amount from about 10% to about 50% by weight. The deionizing agent is present in an amount from about 0.2 to 1.0 mole per mole of the pharmaceutical agent. Water is present in an amount from about 1% to about 20% by weight and polyethylene glycol is present in amount from about 10% to about 80% by weight.

Optionally, propylene glycol and/or polyvinyl pyrrolidone are present in an amount from about 1% to about 10%.

B. Gel Mass

The main ingredients of the softgel capsule shell are gelatin, plasticizer, and purified water. Typical gel formulations contain (w/w) 40-50% gelatin, 20-30% plasticizer, and 30-40% purified water. Most of the water is subsequently lost during capsule drying. The ingredients are combined to form a molten gelatin mass using either a cold melt or a hot melt process. The prepared gel masses are transferred to preheated, temperature-controlled, jacketed holding tanks where the gel mass is aged at 50-60°C until used for encapsulation.

1. Cold Melt Process

The cold melt process involves mixing gelatin with plasticizer and chilled water and then transferring the mixture to a jacket-heated tank. Typically, gelatin is added to the plasticizer at ambient temperature (18-22°C). The mixture is cooked (57-95°C) under vacuum for 15-30 minutes to a homogeneous, deaerated gel mass. Additional shell additives can be added to the gel mass at any point during the gel manufacturing process or they may be incorporated into the finished gel mass using a high torque mixer.

2. Hot Melt Process

The hot melt process involves adding, under mild agitation, the gelatin to a preheated (60-80°C) mixture of plasticizer and water and stirring the blend until complete melting is achieved. While the hot melt process is faster than the cold melt process, it is less accurately controlled and more susceptible to foaming and dusting.

C. Softgel Capsule

Softgel capsules are typically produced using a rotary die encapsulation process. The gel mass is fed either by gravity or through positive displacement pumping to two heated (48-65°C) metering devices. The metering devices control the flow of gel into cooled (10-18°C), rotating casting drums. Ribbons are formed as the cast gel masses set on contact with the surface of the drums.

The ribbons are fed through a series of guide rolls and between injection wedges and the capsule-forming dies. A food-grade lubricant oil is applied onto the ribbons to reduce their tackiness and facilitate their transfer. Suitable lubricants include mineral oil, medium chain triglycerides, and soybean oil. Fill formulations are fed into the encapsulation machine by gravity. In the preferred embodiment, the softgels contain printing on the surface, optionally identifying the encapsulated agent and/or dosage.

III. Method of Use

The softgels may be used to encapsulate a wide range of pharmaceutically active agents, nutritional agents and personal care products. Softgel capsules may be administered orally to a patient to deliver a pharmaceutically active agent.

Examples

In the following examples, the fill material can be prepared by mixing the salt of one or more pharmaceutically active agents, the deionizing agent, water and polyethylene glycol at a temperature of 50°C to 70°C. The resulting solution can be encapsulated in a softgel capsule using the appropriate gel mass.

Example 1. Naproxen Sodium with Acetic Acid as the Deionizing Agent

Fill Material:

Ingredients	% (by weight)
Naproxen Sodium	25.50
Acetic Acid	3.00
PVP	1.85
PEG 400	62.30
Water	7.40

Example 2. Naproxen Sodium with Citric Acid as the Deionizing Agent

Fill Material:

Ingredients	% (by weight)
Naproxen Sodium	25.50
Citric Acid	4.75
PVP	1.85
PEG 400	60.50
Water	7.40

Reference Example 3. Naproxen Sodium with Hydrochloric Acid as the Deionizing Agent

Fill Material:

Ingredients	% (by weight)
Naproxen Sodium	25.50
Hydrochloric Acid	4.72
PVP	1.85
PEG 400	63.52
Water	7.40

Example 4. Naproxen Sodium with Acetic Acid as the Deionizing Agent

Fill Material:

Ingredients	% (by weight)
Naproxen Sodium	25.50
Acetic Acid	3.00
PVP	1.85
PEG 400	31.15
Water	7.40
PEG 600	31.15

Example 5. Naproxen Sodium with Citric Acid as the Deionizing Agent

Fill Material:

Ingredients	% (by weight)
Naproxen Sodium	25.50
Citric Acid	4075
PVP	1.85
PEG 400	30.25
Water	7.40
PEG 600	30.25

Reference Example 6. Naproxen Sodium with Hydrochloric Acid as the Deionizing Agent

Fill Material:

Ingredients	% (by weight)
Naproxen Sodium	25.50
Hydrochloric Acid	4072
PVP	1.85
PEG 400	30.25
Water	7.40
PEG 600	30.25

Example 7. Naproxen Sodium with Lactic Acid as the Deionizing Agent

Fill Material:

Ingredients	% (by weight)
Naproxen Sodium	27.50
Lactic Acid	5.27
Propylene Glycol	2.00
PEG 400	64.64
Water	0.60

Example 8. Naproxen Sodium with Lactic Acid as the Deionizing Agent

Fill Material:

Ingredients	% (by weight)
Naproxen Sodium	25.00
Lactic Acid	0.24-0.35 M
Propylene glycol	2.00
PEG 600.	q.s.

Example 9. Naproxen Sodium with Lactic Acid as the Deionizing Agent

Fill Material:

Ingredients	% (by weight)
Naproxen Sodium	25.00
Lactic Acid	5.00
Propylene glycol	2.00
PEG 600	61.2
PEG 1000	6.80

Example 10. Naproxen Sodium with Lactic Acid as the Deionizing Agent

Fill Material:

Ingredients	% (by weight)
Naproxen Sodium	25.00
Lactic acid	5.00
Propylene glycol	2.00
PEG 600	51.00
PEG 1000	17.00

Example 11. Naproxen Sodium with Lactic Acid as the Deionizing Agent

Fill Material:

Ingredients	% (by weight)
Naproxen Sodium	25.00
Lactic Acid	5.00
Propylene glycol	2.00
PEG 600	34.00
PEG 1000	34.00

Example 12. Naproxen Sodium with Lactic Acid as the Deionizing Agent

Fill Material:

Ingredients	% (by weight)
Naproxen Sodium	25.00
Lactic acid	5.00
Propylene glycol	2.00
PEG 600	17.00
PEG 1000	51.00

It is understood that the disclosed invention is not limited to the particular methodology, protocols, and reagents described as these may vary. It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments only, and is not intended to limit the scope of the present invention which will be limited only by the appended claims.

Unless defined otherwise, all technical and scientific terms used herein have the same meanings as commonly understood by one of skill in the art to which the disclosed invention belongs. Although any methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present invention, the preferred methods, devices, and materials are as described.

Nothing herein is to be construed as an admission that the invention is not entitled to antedate such disclosure by virtue of prior invention.

CLAIMS

1. A softgel capsule comprising a fill material wherein the fill material comprises

(a) naproxen sodium;

(b) fumaric acid, maleic acid, tartaric acid, citric acid, malic acid, acetic acid, proprionic acid, pyruvic acid, butanoic acid or lactic acid in an amount of from 0.2 to 1.0 mole equivalents per mole of the naproxen sodium;

(c) polyethylene glycol;

(d) water; and

(e) a solubilizer selected from the group consisting of glycerin, polyvinylpyrrolidone, propylene glycol and combinations thereof.

2. The capsule of claim 1 wherein (b) is citric acid or lactic acid.

3. The capsule of claim 2 wherein (b) is lactic acid.

4. The capsule of any one of the preceding claims wherein polyethylene glycol is present in an amount from 10% to 80% by weight.

5. The capsule of any one of the preceding claims wherein the polyethylene glycol is one or more polyethylene glycols with a molecular weight between 300 and 1500.

6. The capsule of any one of the preceding claims wherein water is present in an amount from 1% to 18% by weight.

7. The capsule of any one of the preceding claims further comprising one or more excipients selected from the group consisting of plasticizers, crystallization inhibitors, wetting agents, bulk filling agents, solubilizers, bioavailability enhancers, solvents, dyes, preservatives, surfactants, and combinations thereof.

8. The capsule of any one of the preceding claims wherein the solubilizer is present in amount from 1% to 10% by weight.

9. The capsule of any one of the preceding claims wherein the fill material is liquid.

10. A capsule of any of the preceding claims for use as a medicament.

11. A method of making the capsule of claim 1 comprising

(a) mixing components (a), (b), (c), (d) and (e) as defined in claim 1; and

(b) encapsulating the mixture in a softgel capsule.

12. The method of claim 11, wherein step (a) is conducted at a temperature of from 50°C to 70°C.

13. The use of

(a) naproxen sodium;

(b) fumaric acid, maleic acid, tartaric acid, citric acid, malic acid, acetic acid, proprionic acid, pyruvic acid, butanoic acid or lactic acid in an amount of from 0.2 to 1.0 mole equivalents per mole of the naproxen sodium;

(c) polyethylene glycol;

(d) water; and

(e) a solubilizer selected from the group consisting of glycerin, polyvinylpyrrolidone, propylene glycol and combinations thereof,

in the manufacture of a medicament in the form of a capsule for administration of the naproxen sodium to a patient in need thereof.

SOLVENT SYSTEM FOR ENHANCING THE SOLUBILITY OF PHARMACEUTICAL AGENTS

FIELD OF THE INVENTION

This invention is in the field of fill materials encapsulated in soft gelatin capsules.

BACKGROUND OF THE INVENTION

Filled one-piece soft gelatin capsules ("softgels") have been widely used for years to encapsulate consumable materials such as vitamins and pharmaceuticals in a liquid vehicle or carrier. Because softgels have properties which are quite different from two-piece hardshell capsules, softgels are more capable of retaining a liquid fill material.

Not all liquids may be enclosed in a softgel capsule. Liquids containing more than about 20% water by weight are generally not enclosed in softgels, because the water tends to dissolve the gelatin shell. Other solvents such as propylene glycol, glycerin, low molecular weight alcohols, ketones, acids, amines, and esters all tend to degrade or dissolve the gelatin shell to some extent.

Softgels are also somewhat sensitive to pH, and generally require a pH in the encapsulated liquid from about 2.5 to about 7.5. Highly acidic liquids may hydrolyze the gelatin, resulting in leaks, while basic liquids may tan the gelatin, resulting in decreased solubility of the gelatin shell.

Pharmaceutical liquids are usually enclosed in softgels as either viscous solutions or suspensions. Suspensions are pharmaceutically less desirable because they can settle during manufacture, which leads to a less uniform product. In contrast, solutions provide the best liquid form for obtaining optimal "content uniformity" in a batch. Further, solutions typically provide a faster and more uniform absorption of an active agent than do suspensions.

Suitable softgel solutions, however, can be difficult to achieve. One constraint is size. Many pharmaceutical agents require volumes of solvent

too large to produce a softgel capsule small enough to be taken by patients. The solvent must also have sufficient solvating power to dissolve a large amount of the pharmaceutical agent to produce a concentrated solution and yet not dissolve, hydrolyze or tan the gelatin shell.

Concentrated solutions of pharmaceutical agents for use in softgel capsules have been described. Most of these systems involve ionizing the free pharmaceutical agent *in situ* to the corresponding salt. For example, U.S. Patent No. 5,360,615 to Yu *et al.* discloses a solvent system for enhancing the solubility of acidic, basic, or amphoteric pharmaceutical agents. The solvent system comprises polyethylene glycol, an ionizing agent, and water. The ionizing agent functions by causing the partial ionization of the free pharmaceutical agent. U.S. Patent No. 6,383,515, U.S. Patent Application Publication No. 2002/0187195, and U.S. Patent Application Publication No. 2001/0007668 to Sawyer *et al.* discloses pharmaceutically acceptable solutions containing a medicament suitable for filling softgel capsules comprising a polymer such as polyethylene glycol and an acid salt of a compound having three or more carbon atoms, such as sodium propionate. The salt helps to ionize the medicament without relying on the use of strong acids or bases. U.S. Patent No. 6,689,382 to Berthel *et al.* describes a pharmaceutical formulation suitable for filling softgel capsules comprising (a) a therapeutically effective amount of a non-steroidal anti-inflammatory drug (NSAID); and (b) a solvent system comprising 40% to 60% by weight a polyoxyethylene ether, 15% to 35% by weight of glycerin and 15% to 35% by weight water. In cases where the NSAID has a carboxyl or an acidic functional group, the solvent system also includes hydroxide ions. U.S. Patent No. 5,505,961 to Shelley *et al.* describes a method for increasing the solubility of acetaminophen alone or in combination with other pharmaceutically active agents to form a clear solution for encapsulation into a softgel capsule. The method comprises solubilizing acetaminophen in a mixture of propylene glycol, polyethylene glycol, water, polyvinylpyrrolidone and sodium or potassium acetate.

The previously described methods all involve the conversion of the free pharmaceutical agent to the corresponding salt. In cases where the free pharmaceutical agent is acidic, the resulting anion can react with the polyethylene glycol in the fill to produce polyethylene glycol esters, thus reducing the amount of available pharmaceutical agent.

There is a need for a solvent system containing a medicament, which can be encapsulated in a softgel capsule, wherein the formation of PEG esters is minimized.

Therefore it is an object of the invention to provide a stable solvent system for pharmaceutical agents, which is suitable for encapsulation in a softgel capsule, wherein the formation of PEG esters is minimized.

BRIEF SUMMARY OF THE INVENTION

The present invention provides a softgel capsule according to Claim 1 and a use according to Claim 13. Liquid and semi-solid pharmaceutical compositions, which can be administered in liquid form or can be used for preparing capsules, are described herein. The acid present in the compositions of the invention causes partial de-ionization (neutralization) of naproxen sodium resulting in enhanced bioavailability as well as decreased amounts of polyethylene glycol (PEG) esters. Thus, hereinafter the acid maybe referred to as the deionizing agent.

DETAILED DESCRIPTION OF THE INVENTION

I. Composition

A. Fill Materials

1. Drugs to be Formulated

In the present invention the fill material comprises naproxen sodium. Other formulations described herein may contain any therapeutic, diagnostic, prophylactic or nutraceutical agent. Exemplary agents include, but are not limited to, analeptic agents; analgesic agents; anesthetic agents; antiasthmatic agents; antiarthritic agents; anticancer agents; anticholinergic agents; anticonvulsant agents; antidepressant agents; antidiabetic agents; antidiarrheal agents; antiemetic agents; antihelminthic agents; antihistamines; antihyperlipidemic agents; antihypertensive agents; anti-infective agents; anti-inflammatory

agents; antimigraine agents; antineoplastic agents; antiparkinson drugs; antipruritic agents; antipsychotic agents; antipyretic agents; antispasmodic agents; antitubercular agents; antiulcer agents; antiviral agents; anxiolytic agents; appetite suppressants (anorexic agents); attention deficit disorder and attention deficit hyperactivity disorder drugs; cardiovascular agents including calcium channel blockers, antianginal agents, central nervous system ("CNS") agents, beta-blockers and antiarrhythmic agents; central nervous system stimulants; diuretics; genetic materials; hormonolytics; hypnotics; hypoglycemic agents; immunosuppressive agents; muscle relaxants; narcotic antagonists; nicotine; nutritional agents; parasympatholytics; peptide drugs; psychostimulants; sedatives; sialagogues, steroids; smoking cessation agents; sympathomimetics; tranquilizers; vasodilators; beta-agonist; and tocolytic agents.

Any drug that bears an acidic or a basic functional group, for example, an amine, imine, imidazoyl, guanidine, piperidinyl, pyridinyl, quaternary ammonium, or other basic group, or a carboxylic, phosphoric, phenolic, sulfuric, sulfonic or other acidic group, can react with the de-ionizing agent.

Some other drugs that bear acidic or basic functional groups and thus may be converted to the corresponding salt for use in the formulations described herein include, but are not limited to, Acetaminophen, Acetylsalicylic acid, Alendronic acid, Alosetron, Amantadine, Amlopidine, Anagrelide, Argatroban, Atomoxetine, Atrovastatin, Azithromycin dehydrate, Balsalazide, Bromocriptan, Bupropion, Candesartan, Carboplatin, Ceftriaxone, Clavulonic acid, Clindamycin, Cimetadine, Dehydrocholic (acid), Dexmethylphenidate, Diclofenac, Dicyclomine, Diflunisal, Diltiazem, Donepezil, Doxorubicin, Doxepin, Epirubicin, Etodolic acid, Ethacrynic acid, Fenoprofen, Fluoxetine, Flurbiprofen, Furosemide, Gemfibrozil, Hydroxyzine, Ibuprofen, Imipramine, Indomethacin, Ketoprofen, Levothyroxine, Maprolitline, Meclizine, Methadone, Methylphenidate, Minocycline, Mitoxantone, Moxifloxacin, Mycophenolic

acid, Niflumic acid, Ofloxacin, Ondansetron, Pantoprazole, Paroxetine, Pergolide, Pramipexole, Phenytoin, Pravastain, Probenecid, Rabeprazole, Risedronic acid, Retinoic acid, Ropinirole, Selegiline, Sulindac, Tamsulosin, Telmisertan, Terbinafine, Theophyline, Tiludronic Acid, Tinzaparin, Ticarcillin, Tometin, Valproic acid, Salicylic acid, Sevelamer, Ziprasidone, Zoledronic acid, Acetophenazine, Albuterol, Almotriptan, Amitriptyline, Amphetamine, Atracurium, Beclomethasone, Benztropine, Biperiden, Bosentan, Bromodiphenhydramine, Brompheniramine carbinoxamine, Caffeine, Capecitabine, Carbergoline, Cetirizine, Chlocylizine, Chlorpheniramine, Chlorphenoxamine, Chlorpromazine, Citalopram, Clavunate potassium, Ciprofloxacin, Clemastine, Clomiphene, Clonidine, Clopidogrel, Codeine, Cyclizine, Cyclobenzaprine, Cyproheptadine, Delavirdine, Diethylpropion, Divalproex, Desipramine, Dexmethylphenidate, Dexbrompheniramine, Dexchlopheniramine, Dexchlor, Dextroamphetamine, Dexedrine, Dextromethorphan, Fiflunisal, Diphemanil methylsulphate, Diphenhydramine, Dolasetron, Doxylamine, Enoxaparin, Ergotamine, Ertepenem, Eprosartan, Escitalopram, Esomeprazole, Fenoldopam, Fentanyl, Fexofenadine, Flufenamic acid, Fluvastatin, Fluphenazine, Fluticasone, Fosinopril, Frovatriptan, Gabapentin, Galatamine, Gatifloxacin, Gemcitabine, Haloperidol, Hyalurondate, Hydrocodone, Hydroxychloroquine, Hyoscyamine, Imatinib, Imipenem, Ipatropin, Lisinopril, Leuprolide, Levopropoxyphene, Losartan, Meclofenamic acid, Mefanamic acid, Mesalamine, Mepenzolate, Meperidine, Mephentermine, Mesalimine, Mesoridazine, Metaproteranol, Metformin, Methdialazine, Methscopolamine, Methysergide, Metoprolol, Metronidazole, Mibefradil, Montelukast, Morphine, Mometasone, Naratriptan, Nelfinavir, Nortriptylene, Noscapine, Nylindrin, Omeprazole, Orphenadrine, Oseltamivir, Oxybutynin, Papaverine, Pentazocine, Phendimetrazine, Phentermine, Pioglitazone, Pilocarpine, Prochloroperazine, Pyrilamine, Quetapine, Ranitidine, Rivastigmine, Rosiglitazone, Salmetrol, Sertaline, Sotalol, Sumatriptan, Tazobactam, Tacrolimus, Tamoxifen, Ticlopidine, Topiramate, Tolterodine,

Triptorelin, Triplennamine, Triprolidine, Tramadol, Trovofloxacin, Ursodiol, Promazine, Propoxyphene, Propanolol, Pseudoephedrine, Pyrilamine, Quinidine, Oxybate sodium, Sermorelin, Tacrolimus, Tegaseroid, Teriparatide, Tolterodine, Triptorelin pamoate, Scoplolamine, Venlafaxine, Zamivir, Aminocaproic acid, Aminosalicylic acid, Hydromorphone, Isosuprine, Levorphanol, Melhalan, Nalidixic acid, and Para-aminosalicylic acid.

2. Deionizing Agent

The fill material of the present invention comprises fumaric acid, maleic acid, tartaric acid, citric acid, malic acid, acetic acid, proprionic acid, pyruvic acid, butanoic acid or lactic acid in an amount of from 0.2 to 1.0 mole equivalents per mole of the naproxen sodium. These acids act as deionizing agents.

The deionizing agent functions by causing partial deionization (neutralization) of the salt of the pharmaceutically active agent (in this invention naproxen sodium). As described herein when the active agent is the salt of a weak acid and a strong base, the deionizing agent is preferably a hydrogen ion species such as an acid as described above or when the active agent is the salt of a weak base and a strong acid, the deionizing agent is preferably a hydroxide ion species such as a metal hydroxide such as sodium hydroxide, potassium hydroxide, ammonium hydroxide, calcium hydroxide, aluminum hydroxide, and magnesium hydroxide.

Additional acid or base can be added to adjust the pH of the fill composition. In a preferred embodiment, the pH of the fill composition is from about 2.5 to about 7.5.

3. Excipients

Formulations may be prepared using a pharmaceutically acceptable carrier composed of materials that are considered safe and effective and may be administered to an individual without causing undesirable biological side

effects or unwanted interactions. The carrier is all components present in the pharmaceutical formulation other than the active ingredient or ingredients. As generally used herein "carrier" includes, but is not limited to, plasticizers, crystallization inhibitors, wetting agents, bulk filling agents, solubilizers, bioavailability enhancers, solvents, pH-adjusting agents and combinations thereof.

A mixture of polyethylene glycol and water is used as a solvent for the naproxen sodium and the de-ionizing agent. Polyethylene glycol is present in an amount from about 10% to about 80% by weight. Water is present in an amount from about 1% to 18% by weight. The molecular weight of polyethylene glycol is between 300 and 1500. Other suitable solvents described herein include surfactants and copolymers of polyethylene glycol. The fill material of the present invention also comprises a solubilizer selected from the group consisting of glycerin, polyvinyl pyrrolidone (PVP) or propylene glycol (PPG) and combinations thereof.

B. Shell Composition

1. Gelatin

Gelatin is the product of the partial hydrolysis of collagen. Gelatin is classified as either Type A or Type B gelatin. Type A gelatin is derived from the acid hydrolysis of collagen while Type B gelatin is derived from alkaline hydrolysis of collagen. Traditionally, bovine bones and skins have been used as raw materials for manufacturing Type A and Type B gelatin while porcine skins have been used extensively for manufacturing Type A gelatin. In general acid-processed gelatins form stronger gels than lime- processed gelatins of the same average molecular weight.

2. Other Shell Additives

Other suitable shell additives include plasticizers, opacifiers, colorants, humectants, preservatives, flavorings, and buffering salts and acids.

Plasticizers are chemical agents added to gelatin to make the material softer and more flexible. Suitable plasticizers include glycerin, sorbitol

solutions which are mixtures of sorbitol and sorbitan, and other polyhydric alcohols such as propylene glycol and maltitol or combinations thereof.

Opacifiers are used to opacify the capsule shell when the encapsulated active agents are light sensitive. Suitable opacifiers include titanium dioxide, zinc oxide, calcium carbonate and combinations thereof.

Colorants can be used to for marketing and product identification/differentiation purposes. Suitable colorants include synthetic and natural dyes and combinations thereof.

Humectants can be used to suppress the water activity of the softgel. Suitable humectants include glycerin and sorbitol, which are often components of the plasticizer composition. Due to the low water activity of dried, properly stored softgels, the greatest risk from microorganisms comes from molds and yeasts. For this reason, preservatives can be incorporated into the capsule shell. Suitable preservatives include alkyl esters of p-hydroxy benzoic acid such as methyl, ethyl, propyl, butyl and heptyl (collectively known as "parabens") or combinations thereof.

Flavorings can be used to mask unpleasant odors and tastes of fill formulations. Suitable flavorings include synthetic and natural flavorings. The use of flavorings can be problematic due to the presence of aldehydes which can cross-link gelatin. As a result, buffering salts and acids can be used in conjunction with flavorings that contain aldehydes in order to inhibit cross-linking of the gelatin.

II. Method of Making

A. Fill Material

The fill material is prepared by mixing the agent (such as a salt of the drug), the deionizing agent, water, and polyethylene glycol at a temperature of 50°C to 70°C. The resulting solution is encapsulated using the appropriate gel mass. The pharmaceutical agent is present in an amount from about 10% to about 50% by weight. The deionizing agent is present in an amount from about 0.2 to 1.0 mole per mole of the pharmaceutical agent. Water is present in an amount from about 1% to about 20% by weight and polyethylene glycol is present in amount from about 10% to about 80% by weight.

Optionally, propylene glycol and/or polyvinyl pyrrolidone are present in an amount from about 1% to about 10%.

B. Gel Mass

The main ingredients of the softgel capsule shell are gelatin, plasticizer, and purified water. Typical gel formulations contain (w/w) 40-50% gelatin, 20-30% plasticizer, and 30-40% purified water. Most of the water is subsequently lost during capsule drying. The ingredients are combined to form a molten gelatin mass using either a cold melt or a hot melt process. The prepared gel masses are transferred to preheated, temperature-controlled, jacketed holding tanks where the gel mass is aged at 50-60°C until used for encapsulation.

1. Cold Melt Process

The cold melt process involves mixing gelatin with plasticizer and chilled water and then transferring the mixture to a jacket-heated tank. Typically, gelatin is added to the plasticizer at ambient temperature (18-22°C). The mixture is cooked (57-95°C) under vacuum for 15-30 minutes to a homogeneous, deaerated gel mass. Additional shell additives can be added to the gel mass at any point during the gel manufacturing process or they may be incorporated into the finished gel mass using a high torque mixer.

2. Hot Melt Process

The hot melt process involves adding, under mild agitation, the gelatin to a preheated (60-80°C) mixture of plasticizer and water and stirring the blend until complete melting is achieved. While the hot melt process is faster than the cold melt process, it is less accurately controlled and more susceptible to foaming and dusting.

C. Softgel Capsule

Softgel capsules are typically produced using a rotary die encapsulation process. The gel mass is fed either by gravity or through positive displacement pumping to two heated (48-65°C) metering devices. The metering devices control the flow of gel into cooled (10-18°C), rotating casting drums. Ribbons are formed as the cast gel masses set on contact with the surface of the drums.

The ribbons are fed through a series of guide rolls and between injection wedges and the capsule-forming dies. A food-grade lubricant oil is applied onto the ribbons to reduce their tackiness and facilitate their transfer. Suitable lubricants include mineral oil, medium chain triglycerides, and soybean oil. Fill formulations are fed into the encapsulation machine by gravity. In the preferred embodiment, the softgels contain printing on the surface, optionally identifying the encapsulated agent and/or dosage.

III. Method of Use

The softgels may be used to encapsulate a wide range of pharmaceutically active agents, nutritional agents and personal care products. Softgel capsules may be administered orally to a patient to deliver a pharmaceutically active agent.

Examples

In the following examples, the fill material can be prepared by mixing the salt of one or more pharmaceutically active agents, the deionizing agent, water and polyethylene glycol at a temperature of 50°C to 70°C. The resulting solution can be encapsulated in a softgel capsule using the appropriate gel mass.

Example 1. Naproxen Sodium with Acetic Acid as the Deionizing Agent

Fill Material:

Ingredients	**% (by weight)**
Naproxen Sodium	25.50
Acetic Acid	3.00
PVP	1.85
PEG 400	62.30
Water	7.40

Example 2. Naproxen Sodium with Citric Acid as the Deionizing Agent

Fill Material:

Ingredients	% (by weight)
Naproxen Sodium	25.50
Citric Acid	4.75
PVP	1.85
PEG 400	60.50
Water	7.40

Reference Example 3. Naproxen Sodium with Hydrochloric Acid as the Deionizing Agent

Fill Material:

Ingredients	% (by weight)
Naproxen Sodium	25.50
Hydrochloric Acid	4.72
PVP	1.85
PEG 400	63.52
Water	7.40

Example 4. Naproxen Sodium with Acetic Acid as the Deionizing Agent

Fill Material:

Ingredients	% (by weight)
Naproxen Sodium	25.50
Acetic Acid	3.00
PVP	1.85
PEG 400	31.15
Water	7.40
PEG 600	31.15

Example 5. Naproxen Sodium with Citric Acid as the Deionizing Agent

Fill Material:

Ingredients	% (by weight)
Naproxen Sodium	25.50
Citric Acid	4075
PVP	1.85
PEG 400	30.25
Water	7.40
PEG 600	30.25

Reference Example 6. Naproxen Sodium with Hydrochloric Acid as the Deionizing Agent

Fill Material:

Ingredients	% (by weight)
Naproxen Sodium	25.50
Hydrochloric Acid	4072
PVP	1.85
PEG 400	30.25
Water	7.40
PEG 600	30.25

Example 7. Naproxen Sodium with Lactic Acid as the Deionizing Agent

Fill Material:

Ingredients	% (by weight)
Naproxen Sodium	27.50
Lactic Acid	5.27
Propylene Glycol	2.00
PEG 400	64.64
Water	0.60

Example 8. Naproxen Sodium with Lactic Acid as the Deionizing Agent

Fill Material:

Ingredients	% (by weight)
Naproxen Sodium	25.00
Lactic Acid	0.24-0.35 M
Propylene glycol	2.00
PEG 600.	q.s.

Example 9. Naproxen Sodium with Lactic Acid as the Deionizing Agent

Fill Material:

Ingredients	% (by weight)
Naproxen Sodium	25.00
Lactic Acid	5.00
Propylene glycol	2.00
PEG 600	61.2
PEG 1000	6.80

Example 10. Naproxen Sodium with Lactic Acid as the Deionizing Agent

Fill Material:

Ingredients	% (by weight)
Naproxen Sodium	25.00
Lactic acid	5.00
Propylene glycol	2.00
PEG 600	51.00
PEG 1000	17.00

Example 11. Naproxen Sodium with Lactic Acid as the Deionizing Agent

Fill Material:

Ingredients	% (by weight)
Naproxen Sodium	25.00
Lactic Acid	5.00
Propylene glycol	2.00
PEG 600	34.00
PEG 1000	34.00

Example 12. Naproxen Sodium with Lactic Acid as the Deionizing Agent

Fill Material:

Ingredients	% (by weight)
Naproxen Sodium	25.00
Lactic acid	5.00
Propylene glycol	2.00
PEG 600	17.00
PEG 1000	51.00

It is understood that the disclosed invention is not limited to the particular methodology, protocols, and reagents described as these may vary. It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments only, and is not intended to limit the scope of the present invention which will be limited only by the appended claims.

Unless defined otherwise, all technical and scientific terms used herein have the same meanings as commonly understood by one of skill in the art to which the disclosed invention belongs. Although any methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present invention, the preferred methods, devices, and materials are as described. ~~Publications cited herein and the materials~~

Nothing herein is to be construed as an admission that the invention is not entitled to antedate such disclosure by virtue of prior invention.

CLAIMS

1. A softgel capsule comprising a fill material wherein the fill material comprises

(a) naproxen sodium;

(b) fumaric acid, maleic acid, tartaric acid, citric acid, malic acid, acetic acid, proprionic acid, pyruvic acid, butanoic acid or lactic acid in an amount of from 0.2 to 1.0 mole equivalents per mole of the naproxen sodium;

(c) polyethylene glycol;

(d) water; and

(e) a solubilizer selected from the group consisting of glycerin, polyvinylpyrrolidone, propylene glycol and combinations thereof.

2. The capsule of claim 1 wherein (b) is citric acid or lactic acid.

3. The capsule of claim 2 wherein (b) is lactic acid.

4. The capsule of any one of the preceding claims wherein polyethylene glycol is present in an amount from 10% to 80% by weight.

5. The capsule of any one of the preceding claims wherein the polyethylene glycol is one or more polyethylene glycols with a molecular weight between 300 and 1500.

6. The capsule of any one of the preceding claims wherein water is present in an amount from 1% to 18% by weight.

7. The capsule of any one of the preceding claims further comprising one or more excipients selected from the group consisting of plasticizers, crystallization inhibitors, wetting agents, bulk filling agents, solubilizers, bioavailability enhancers, solvents, dyes, preservatives, surfactants, and combinations thereof.

8. The capsule of any one of the preceding claims wherein the solubilizer is present in amount from 1% to 10% by weight.

9. The capsule of any one of the preceding claims wherein the fill material is liquid.

10. A capsule of any of the preceding claims for use as a medicament.

11. A method of making the capsule of claim 1 comprising

(a) mixing components (a), (b), (c), (d) and (e) as defined in claim 1; and

(b) encapsulating the mixture in a softgel capsule.

12. The method of claim 11, wherein step (a) is conducted at a temperature of from 50°C to 70°C.

13. The use of

(a) naproxen sodium;

(b) fumaric acid, maleic acid, tartaric acid, citric acid, malic acid, acetic acid, proprionic acid, pyruvic acid, butanoic acid or lactic acid in an amount of from 0.2 to 1.0 mole equivalents per mole of the naproxen sodium;

(c) polyethylene glycol;

(d) water; and

(e) a solubilizer selected from the group consisting of glycerin, polyvinylpyrrolidone, propylene glycol and combinations thereof,

in the manufacture of a medicament in the form of a capsule for administration of the naproxen sodium to a patient in need thereof.

Europäisches Patentamt
European Patent Office
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Letter accompanying subsequently filed items

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The document(s) listed below is (are) subsequently filed documents pertaining to the following application:

Application number	06737018.9
Applicant's or representative's reference	BRIQ/P38814EP

	Description of document	Original file name	Assigned file name
1	Reply to the communication under rule 71(3) EPC	P38814EP EPO Covering letter.pdf	IGRA-1.pdf
2	Request for correction/amendment of the text proposed for grant sent from 01.04.2012	P38814EP Amendment schedule.pdf	IGRE-1.pdf
3	Amended description (clean copy)	P38814EP Amended page (clean).pdf	DESC-1.pdf
4	Amended description with annotations	P38814EP Amended page (tracked).pdf	DESC-HWA-1.pdf

	Fees	Factor applied	Fee schedule	Amount to be paid
15-1	007 Fee for grant and printing (not more than 35 pages) or fee for grant including fee for publication	1	10.00	10.00
	Total:		**EUR**	**10.00**

	Payment	
1	Mode of payment	Debit from deposit account
	Currency:	EUR
	The European Patent Office is hereby authorised, to debit from the deposit account with the EPO any fees and costs indicated on the fees page.	
	Deposit account number:	28050040
	Account holder:	Potter Clarkson LLP
2	Refund/Reimburserment	
	Reimbursement (if any) to be made to EPO deposit account:	28050040
	Account holder:	Potter Clarkson LLP

Signatures

Place:	**Nottingham, United Kingdom**
Date:	**30 June 2016**
Signed by:	**/Crowhurst, Charlotte Waveney/**
Association:	**Potter Clarkson LLP**
Representative name:	**Crowhurst, Charlotte Waveney**
Capacity:	**(Representative)**

Example 11. Naproxen Sodium with Lactic Acid as the Deionizing Agent

Fill Material:

Ingredients	% (by weight)
Naproxen Sodium	25.00
Lactic Acid	5.00
Propylene glycol	2.00
PEG 600	34.00
PEG 1000	34.00

Example 12. Naproxen Sodium with Lactic Acid as the Deionizing Agent

Fill Material:

Ingredients	% (by weight)
Naproxen Sodium	25.00
Lactic acid	5.00
Propylene glycol	2.00
PEG 600	17.00
PEG 1000	51.00

It is understood that the disclosed invention is not limited to the particular methodology, protocols, and reagents described as these may vary. It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments only, and is not intended to limit the scope of the present invention which will be limited only by the appended claims.

Unless defined otherwise, all technical and scientific terms used herein have the same meanings as commonly understood by one of skill in the art to which the disclosed invention belongs. Although any methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present invention, the preferred methods, devices, and materials are as described.

Example 11. Naproxen Sodium with Lactic Acid as the Deionizing Agent

Fill Material:

Ingredients	% (by weight)
Naproxen Sodium	25.00
Lactic Acid	5.00
Propylene glycol	2.00
PEG 600	34.00
PEG 1000	34.00

Example 12. Naproxen Sodium with Lactic Acid as the Deionizing Agent

Fill Material:

Ingredients	% (by weight)
Naproxen Sodium	25.00
Lactic acid	5.00
Propylene glycol	2.00
PEG 600	17.00
PEG 1000	51.00

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~~for which they are cited are specifically incorporated. Nothing herein is to be construed as an admission that the invention is not entitled to antedate such disclosure by virtue of prior invention.~~

POTTER CLARKSON

European Patent Office
80298 München
GERMANY

30 June 2016

Dear Sirs

European Patent Application No. 06737018.9
Publication No. 1863458
Banner Life Sciences LLC
Our Reference: BRIQ/P38814EP

In response to the further communication under Rule 71(3) EPC dated 23 May 2016, we hereby pay an additional amount of 10.00 Euros to cover the increase in the fee for grant. The additional amount for the increase in the fee for grant should be taken from our deposit account.

The text of the specification is approved for grant subject to the amendment in the attached schedule.

We hereby waive the right to receive a further communication under Rule 71(3) EPC in the event that the Examination Division consents to this amendment.

Translations of the claims into French and German have already been filed on 17 March 2016 (Submission number: 4202986).

Yours faithfully

Charlotte Crowhurst
For and on behalf of Potter Clarkson LLP

Enc: Amendment schedule
Amended page (clean and tracked)

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Schedule of Amendments made to Application

Page / line	**Reason / basis**
Page 14, line 20	Confirming deletion of text deleted by the examiner.
Page 15, lines 1 to 3	Deletion of remaining text on page 15, resulting in deletion of page 15. This text is not necessary in view of the amendment made by the examiner.

Europäisches Patentamt
European Patent Office
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Acknowledgement of receipt

We hereby acknowledge receipt of the following subsequently filed document(s):

Submission number	4459887
Application number	EP06737018.9
Date of receipt	30 June 2016
Receiving Office	European Patent Office, The Hague
Your reference	BRIQ/P38814EP
Applicant	All applicants as on file
Documents submitted	package-data.xml epf1038.pdf (2 p.) IGRE-1.pdf\P38814EP Amendment schedule.pdf (1 p.) DESC-HWA-1.pdf\P38814EP Amended page (tracked).pdf (2 p.) ep-sfd-request.xml IGRA-1.pdf\P38814EP EPO Covering letter.pdf (1 p.) DESC-1.pdf\P38814EP Amended page (clean).pdf (1 p.)
Submitted by	CN=Roberta Morbioli 47887
Method of submission	Online
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Correction by the EPO of errors in debit instructions filed by eOLF
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INFORMATION
according to applicant's waiver of right to
receive a further communication under Rule 71(3) EPC

Application No.	Ref.	Date
06 737 018.9 - 1466	PABCA/P38814EP	05.08.2016
Applicant Banner Life Sciences, LLC		

Information under Rule 71(3) EPC

1. Intention to grant

The examining division intends to grant a European patent on the basis of the above application, with the text and drawings and the related bibliographic data as indicated below.

A copy of the relevant documents is enclosed.

1.1 In the text for the Contracting States:
AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HU IE IS IT LI LT LU LV MC NL PL PT RO SE SI SK TR

Description, Pages

2, 8-10, 13	as published			
1, 3-7, 11, 12	received on	08-05-2015	with letter of	08-05-2015
14	filed in electronic form on			30-06-2016

Claims, Numbers

11-13	received on	08-05-2015	with letter of	08-05-2015
1-10	filed in electronic form on			17-03-2016

With the following amendments to the above-mentioned documents according to your request dated 30-06-2016: (2)

Description, Pages

Delete Previous: 15

Comments

DESCRIPTION

Page 15: (PAGE DELETED) - text deleted by applicant

1.2 Bibliographic data

The title of the invention in the three official languages of the European Patent Office, the international patent classification, the designated contracting states, the registered name(s) of the applicant(s) and the other bibliographic data are shown on **EPO Form 2056** (enclosed).

2. Consent to the applicant's waiver of the right to receive a further communication under Rule 71(3) EPC

Following the communication under Rule 71(3) EPC of 23.05.2016, the applicant indicated to the EPO that he wished to waive his right to receive a further communication under Rule 71(3) EPC.

By indicating this wish and by fulfilling the requirements concerning the payment of the fees under Rule 71(3) EPC and, where applicable, Rule 71(4) EPC, as well as the filing of the translations of the claims under Rule 71(3) EPC, the applicant is deemed to have approved the grant of the patent as amended or corrected and to have verified the bibliographic data (see Notice from the EPO dated 8 June 2015, OJ EPO 2015, A52).

The examining division gives its consent to the amendments or corrections requested by the applicant on 30.06.2016 and, since there is agreement as to the text to be granted and all the formal requirements mentioned above have been met, to the waiver indicated by the applicant.

Once the patent has been granted, no errors remaining in the text of the patent as approved can be corrected under Rule 140 EPC.

3. Further procedure

3.1 Since the conditions for consent to the waiver have been met, the decision to grant the European patent will be issued and the **mention of the grant** of the patent published in the European Patent Bulletin.

Note on payment of the renewal fee

If a renewal fee becomes due before the next possible date for publication of the mention of the grant of the European patent, publication will be effected only after the renewal fee and any additional fee have been paid (Rule 71a(4) EPC).

Under Article 86(2) EPC, the obligation to pay renewal fees to the European Patent Office terminates with the payment of the renewal fee due in respect of the year in which the mention of the grant of the European patent is published.

Note on payment of the designation fee(s)

If the designation fee(s) become(s) due after the information under Rule 71(3) EPC has been published, the mention of the grant of the European patent will not be published until these fees have been paid (Rule 71a(3) EPC).

3.2 After publication, the **European patent specification** can be downloaded free of charge from the EPO publication server https://data.epo.org/publication-server or ordered from the Vienna sub-office upon payment of a fee (OJ EPO 2005, 126).

Examining Division:

Chairman:	Borst, Markus
2nd Examiner:	Paul Soto, Raquel
1st Examiner:	Büttner, Ulf

Stark, Saskia
For the Examining Division
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Enclosures: Text intended for grant

EPO Form 2056

Europäisches Patentamt
European Patent Office
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Application No.: 06 737 018.9

IV.2. Patent classification

The classification indicated on the published patent application remains unchanged. It is as follows:

INV. A61K9/48

IV.3. Title of the invention

The title indicated on the published patent application remains unchanged. It reads as follows:

LÖSUNGSMITTELSYSTEM ZUR ERHÖHUNG DER LÖSLICHKEIT PHARMAZEUTISCHER WIRKSTOFFE

SOLVENT SYSTEM FOR ENHANCING THE SOLUBILITY OF PHARMACEUTICAL AGENTS

SYSTEME DE SOLVANT DESTINE A AMELIORER LA SOLUBILITE DES AGENTS PHARMACEUTIQUES

IV.4. Documentation

7/8/16
Date

Borst, Markus
Chairman

Büttner, Ulf
1st examiner

Paul Soto, Raquel
2nd examiner

Enclosure(s):

Europäisches Patentamt
European Patent Office
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Annex to EPO Form 2004, Communication pursuant to Rule 71(3) EPC

Bibliographical data of European patent application No. 06 737 018.9

For the intended grant of the European patent, the bibliographical data are set out below, for information:

Title of invention:
- LÖSUNGSMITTELSYSTEM ZUR ERHÖHUNG DER LÖSLICHKEIT PHARMAZEUTISCHER WIRKSTOFFE
- SOLVENT SYSTEM FOR ENHANCING THE SOLUBILITY OF PHARMACEUTICAL AGENTS
- SYSTEME DE SOLVANT DESTINE A AMELIORER LA SOLUBILITE DES AGENTS PHARMACEUTIQUES

Classification: INV. A61K9/48

Date of filing: 06.03.2006

Priority claimed: US / 08.03.2005 / USP659679

Contracting States* for which fees have been paid: AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HU IE IS IT LI LT LU LV MC NL PL PT RO SE SI SK TR

Extension States* for which fees have been paid:

Validation States* for which fees have been paid:

Applicant(s):**

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Greensboro, North Carolina 27410
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*) If the time limit for the payment of designation fees according to Rule 39(1) EPC has not yet expired and the applicant has not withdrawn any designation, **all Contracting States/Extension States/Validation States** are currently still deemed to be designated.

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	See also Rule 71a(3) EPC and, if applicable, the above Note to users of the automatic debiting procedure.
**)	If two or more applicants have designated different Contracting States, this is indicated here.

Europäisches Patentamt
European Patent Office
Office européen des brevets

European patent application No. 06737018.9

After communication under Rule 71(3) EPC (IGRA) but before decision to grant (EPO Form 2006A)

☒ **Request for amendments/corrections of documents (IGRE coded) dated** 30.06.2016

☒ **WAIVER** of right to receive a new communication under Rule 71(3) EPC (IGRE03 coded)

Note 1: If the request is treated when the decision to grant (EPO Form 2006A) has already been handed over to the EPO postal service, it is to be submitted to the examining division with EPO Form 2051.
Note 2: If the request concerns only the title(s) and/or classification, it is to be submitted to the examining division with EPO Form 2034.

● **Third-party observations under Article 115 EPC (TIPA coded) dated** ..... *Continue with point 2.*

Note: If the observations are treated when the decision to grant (EPO Form 2006A) has already been handed over to the EPO postal service, they must no longer be submitted to the examining division.

1. Finding

☒ The request was received **within** the IGRA period.

☐ The request was received **after** expiry of the IGRA period. The applicant failed to reply in time (ADWI situation) but further processing has been requested.

☐ The request was received **after having already paid fees and submitted translations of claims** in due time. The decision to grant (EPO Form 2006A) has not yet been handed over to the EPO postal service.

2. To the examining division

● Please decide below whether the requested amendments/corrections are allowable or whether the third-party observations are relevant.

Date: 01.07.2016 Formalities Officer: Brell, Eva

3. To the formalities officer

3.1 ☒ **Consent** is given to the amendments/corrections requested.

☐ Non-waiver case: A new communication under Rule 71(3) EPC (IGRA) is to be issued (IGRA06=blank).

☐ **WAIVER case, but** the examining division **does not completely agree** to the request of the applicant (IGRA06=No). A new communication under Rule 71(3) EPC (IGRA) is to be issued.

☒ **WAIVER case:** The examining division **completely agrees** to the request of the applicant (IGRA06=Yes). Consent is given to the waiver if the formal requirements concerning payment of fees and filing of claims translations are also fulfilled. If this is not the case, a new communication under Rule 71(3) EPC (IGRA) is to be issued.

3.2 ☐ Following a telephone conversation **agreement** has been reached. A new communication under Rule 71(3) EPC (IGRA) is to be issued. Attached EPO Form 2036 (telephone consultation) is to be enclosed with it.

3.3 ☐ **Not all or none** of the amendments/corrections can be allowed. Examination proceedings are to be resumed.

☐ Attached **communication** is to be despatched with EPO Form 2001 (EXRE) / 2909 (INBA).

☐ Attached EPO Form 2036 (**telephone consultation**) is to be despatched with EPO Form 2049 (EXRE).

☐ Attached **summons to oral proceedings** is to be despatched with EPO Form 2008 (ORAL).
(Note for examiner: At least one communication under Rule 71(1)(2) EPC must have been sent before summons to oral proceedings can be sent.)

☐ Attached reasoned **refusal** is to be despatched with EPO Form 2007 (REFU).
(Note for examiner: At least one communication under Rule 71(1)(2) EPC must have been sent and the applicant's rights according to Articles 113(1) and 116 EPC must have been met before a refusal can be sent.)

☐ The communication under Rule 71(3) EPC was based upon an auxiliary request. Since the applicant maintains the main or higher ranking request which is not allowable, the application is to be refused (Art. 97(2) EPC).

☐ The applicant has expressed disapproval. Since there is no text on which to base a decision, the application is to be refused (Art. 113(2) EPC; see T 237/96 and Guidelines C-V, 4.9)
(Note for examiner: Standard clause N17C will be used.)

☐ The applicant has not overcome the objections raised in the communication under Rule 71(3) EPC. The reasons for non-compliance with the EPC have already been communicated to him. The application is to be refused.

3.4 ☐ **Observations by a third party (Art. 115 EPC)**

☐ The observations under Article 115 EPC give no cause for amendment of the documents.
Note: TIPA04 is to be coded (to release RPUB).

☐ Examination proceedings are to be resumed. Attached communication is to be despatched.
Note: A fictitious IGRE is to be coded. If necessary, an explanation is to be sent to the applicant.

Date: 8.12.16 Examining Division

Chairman | Second Examiner | Primary Examiner | Legal Member

SOLVENT SYSTEM FOR ENHANCING THE SOLUBILITY OF PHARMACEUTICAL AGENTS

FIELD OF THE INVENTION

This invention is in the field of fill materials encapsulated in soft gelatin capsules.

BACKGROUND OF THE INVENTION

Filled one-piece soft gelatin capsules ("softgels") have been widely used for years to encapsulate consumable materials such as vitamins and pharmaceuticals in a liquid vehicle or carrier. Because softgels have properties which are quite different from two-piece hardshell capsules, softgels are more capable of retaining a liquid fill material.

Not all liquids may be enclosed in a softgel capsule. Liquids containing more than about 20% water by weight are generally not enclosed in softgels, because the water tends to dissolve the gelatin shell. Other solvents such as propylene glycol, glycerin, low molecular weight alcohols, ketones, acids, amines, and esters all tend to degrade or dissolve the gelatin shell to some extent.

Softgels are also somewhat sensitive to pH, and generally require a pH in the encapsulated liquid from about 2.5 to about 7.5. Highly acidic liquids may hydrolyze the gelatin, resulting in leaks, while basic liquids may tan the gelatin, resulting in decreased solubility of the gelatin shell.

Pharmaceutical liquids are usually enclosed in softgels as either viscous solutions or suspensions. Suspensions are pharmaceutically less desirable because they can settle during manufacture, which leads to a less uniform product. In contrast, solutions provide the best liquid form for obtaining optimal "content uniformity" in a batch. Further, solutions typically provide a faster and more uniform absorption of an active agent than do suspensions.

Suitable softgel solutions, however, can be difficult to achieve. One constraint is size. Many pharmaceutical agents require volumes of solvent

too large to produce a softgel capsule small enough to be taken by patients. The solvent must also have sufficient solvating power to dissolve a large amount of the pharmaceutical agent to produce a concentrated solution and yet not dissolve, hydrolyze or tan the gelatin shell.

Concentrated solutions of pharmaceutical agents for use in softgel capsules have been described. Most of these systems involve ionizing the free pharmaceutical agent *in situ* to the corresponding salt. For example, U.S. Patent No. 5,360,615 to Yu *et al.* discloses a solvent system for enhancing the solubility of acidic, basic, or amphoteric pharmaceutical agents. The solvent system comprises polyethylene glycol, an ionizing agent, and water. The ionizing agent functions by causing the partial ionization of the free pharmaceutical agent. U.S. Patent No. 6,383,515, U.S. Patent Application Publication No. 2002/0187195, and U.S. Patent Application Publication No. 2001/0007668 to Sawyer *et al.* discloses pharmaceutically acceptable solutions containing a medicament suitable for filling softgel capsules comprising a polymer such as polyethylene glycol and an acid salt of a compound having three or more carbon atoms, such as sodium propionate. The salt helps to ionize the medicament without relying on the use of strong acids or bases. U.S. Patent No. 6,689,382 to Berthel *et al.* describes a pharmaceutical formulation suitable for filling softgel capsules comprising (a) a therapeutically effective amount of a non-steroidal anti-inflammatory drug (NSAID); and (b) a solvent system comprising 40% to 60% by weight a polyoxyethylene ether, 15% to 35% by weight of glycerin and 15% to 35% by weight water. In cases where the NSAID has a carboxyl or an acidic functional group, the solvent system also includes hydroxide ions. U.S. Patent No. 5,505,961 to Shelley *et al.* describes a method for increasing the solubility of acetaminophen alone or in combination with other pharmaceutically active agents to form a clear solution for encapsulation into a softgel capsule. The method comprises solubilizing acetaminophen in a mixture of propylene glycol, polyethylene glycol, water, polyvinylpyrrolidone and sodium or potassium acetate.

The previously described methods all involve the conversion of the free pharmaceutical agent to the corresponding salt. In cases where the free pharmaceutical agent is acidic, the resulting anion can react with the polyethylene glycol in the fill to produce polyethylene glycol esters, thus reducing the amount of available pharmaceutical agent.

There is a need for a solvent system containing a medicament, which can be encapsulated in a softgel capsule, wherein the formation of PEG esters is minimized.

Therefore it is an object of the invention to provide a stable solvent system for pharmaceutical agents, which is suitable for encapsulation in a softgel capsule, wherein the formation of PEG esters is minimized.

BRIEF SUMMARY OF THE INVENTION

The present invention provides a softgel capsule according to Claim 1 and a use according to Claim 13. Liquid and semi-solid pharmaceutical compositions, which can be administered in liquid form or can be used for preparing capsules, are described herein. The acid present in the compositions of the invention causes partial de-ionization (neutralization) of naproxen sodium resulting in enhanced bioavailability as well as decreased amounts of polyethylene glycol (PEG) esters. Thus, hereinafter the acid maybe referred to as the deionizing agent.

DETAILED DESCRIPTION OF THE INVENTION

I. Composition

A. Fill Materials

1. Drugs to be Formulated

In the present invention the fill material comprises naproxen sodium. Other formulations described herein may contain any therapeutic, diagnostic, prophylactic or nutraceutical agent. Exemplary agents include, but are not limited to, analeptic agents; analgesic agents; anesthetic agents; antiasthmatic agents; antiarthritic agents; anticancer agents; anticholinergic agents; anticonvulsant agents; antidepressant agents; antidiabetic agents; antidiarrheal agents; antiemetic agents; antihelminthic agents; antihistamines; antihyperlipidemic agents; antihypertensive agents; anti-infective agents; anti-inflammatory

agents; antimigraine agents; antineoplastic agents; antiparkinson drugs; antipruritic agents; antipsychotic agents; antipyretic agents; antispasmodic agents; antitubercular agents; antiulcer agents; antiviral agents; anxiolytic agents; appetite suppressants (anorexic agents); attention deficit disorder and attention deficit hyperactivity disorder drugs; cardiovascular agents including calcium channel blockers, antianginal agents, central nervous system ("CNS") agents, beta-blockers and antiarrhythmic agents; central nervous system stimulants; diuretics; genetic materials; hormonolytics; hypnotics; hypoglycemic agents; immunosuppressive agents; muscle relaxants; narcotic antagonists; nicotine; nutritional agents; parasympatholytics; peptide drugs; psychostimulants; sedatives; sialagogues, steroids; smoking cessation agents; sympathomimetics; tranquilizers; vasodilators; beta-agonist; and tocolytic agents.

Any drug that bears an acidic or a basic functional group, for example, an amine, imine, imidazoyl, guanidine, piperidinyl, pyridinyl, quaternary ammonium, or other basic group, or a carboxylic, phosphoric, phenolic, sulfuric, sulfonic or other acidic group, can react with the de-ionizing agent.

Some other drugs that bear acidic or basic functional groups and thus may be converted to the corresponding salt for use in the formulations described herein include, but are not limited to, Acetaminophen, Acetylsalicylic acid, Alendronic acid, Alosetron, Amantadine, Amlopidine, Anagrelide, Argatroban, Atomoxetine, Atrovastatin, Azithromycin dehydrate, Balsalazide, Bromocriptan, Bupropion, Candesartan, Carboplatin, Ceftriaxone, Clavulonic acid, Clindamycin, Cimetadine, Dehydrocholic (acid), Dexmethylphenidate, Diclofenac, Dicyclomine, Diflunisal, Diltiazem, Donepezil, Doxorubicin, Doxepin, Epirubicin, Etodolic acid, Ethacrynic acid, Fenoprofen, Fluoxetine, Flurbiprofen, Furosemide, Gemfibrozil, Hydroxyzine, Ibuprofen, Imipramine, Indomethacin, Ketoprofen, Levothyroxine, Maprolitline, Meclizine, Methadone, Methylphenidate, Minocycline, Mitoxantone, Moxifloxacin, Mycophenolic

acid, Niflumic acid, Ofloxacin, Ondansetron, Pantoprazole, Paroxetine, Pergolide, Pramipexole, Phenytoin, Pravastain, Probenecid, Rabeprazole, Risedronic acid, Retinoic acid, Ropinirole, Selegiline, Sulindac, Tamsulosin, Telmisertan, Terbinafine, Theophyline, Tiludronic Acid, Tinzaparin, Ticarcillin, Tometin, Valproic acid, Salicylic acid, Sevelamer, Ziprasidone, Zoledronic acid, Acetophenazine, Albuterol, Almotriptan, Amitriptyline, Amphetamine, Atracurium, Beclomethasone, Benztropine, Biperiden, Bosentan, Bromodiphenhydramine, Brompheniramine carbinoxamine, Caffeine, Capecitabine, Carbergoline, Cetirizine, Chlocylizine, Chlorpheniramine, Chlorphenoxamine, Chlorpromazine, Citalopram, Clavunate potassium, Ciprofloxacin, Clemastine, Clomiphene, Clonidine, Clopidogrel, Codeine, Cyclizine, Cyclobenzaprine, Cyproheptadine, Delavirdine, Diethylpropion, Divalproex, Desipramine, Dexmethylphenidate, Dexbrompheniramine, Dexchlopheniramine, Dexchlor, Dextroamphetamine, Dexedrine, Dextromethorphan, Fiflunisal, Diphemanil methylsulphate, Diphenhydramine, Dolasetron, Doxylamine, Enoxaparin, Ergotamine, Ertepenem, Eprosartan, Escitalopram, Esomeprazole, Fenoldopam, Fentanyl, Fexofenadine, Flufenamic acid, Fluvastatin, Fluphenazine, Fluticasone, Fosinopril, Frovatriptan, Gabapentin, Galatamine, Gatifloxacin, Gemcitabine, Haloperidol, Hyalurondate, Hydrocodone, Hydroxychloroquine, Hyoscyamine, Imatinib, Imipenem, Ipatropin, Lisinopril, Leuprolide, Levopropoxyphene, Losartan, Meclofenamic acid, Mefanamic acid, Mesalamine, Mepenzolate, Meperidine, Mephentermine, Mesalimine, Mesoridazine, Metaproteranol, Metformin, Methdialazine, Methscopolamine, Methysergide, Metoprolol, Metronidazole, Mibefradil, Montelukast, Morphine, Mometasone, Naratriptan, Nelfinavir, Nortriptylene, Noscapine, Nylindrin, Omeprazole, Orphenadrine, Oseltamivir, Oxybutynin, Papaverine, Pentazocine, Phendimetrazine, Phentermine, Pioglitazone, Pilocarpine, Prochloroperazine, Pyrilamine, Quetapine, Ranitidine, Rivastigmine, Rosiglitazone, Salmetrol, Sertaline, Sotalol, Sumatriptan, Tazobactam, Tacrolimus, Tamoxifen, Ticlopidine, Topiramate, Tolterodine,

Triptorelin, Triplennamine, Triprolidine, Tramadol, Trovofloxacin, Ursodiol, Promazine, Propoxyphene, Propanolol, Pseudoephedrine, Pyrilamine, Quinidine, Oxybate sodium, Sermorelin, Tacrolimus, Tegaseroid, Teriparatide, Tolterodine, Triptorelin pamoate, Scoplolamine, Venlafaxine, Zamivir, Aminocaproic acid, Aminosalicylic acid, Hydromorphone, Isosuprine, Levorphanol, Melhalan, Nalidixic acid, and Para-aminosalicylic acid.

2. Deionizing Agent

The fill material of the present invention comprises fumaric acid, maleic acid, tartaric acid, citric acid, malic acid, acetic acid, proprionic acid, pyruvic acid, butanoic acid or lactic acid in an amount of from 0.2 to 1.0 mole equivalents per mole of the naproxen sodium. These acids act as deionizing agents.

The deionizing agent functions by causing partial deionization (neutralization) of the salt of the pharmaceutically active agent (in this invention naproxen sodium). As described herein when the active agent is the salt of a weak acid and a strong base, the deionizing agent is preferably a hydrogen ion species such as an acid as described above or when the active agent is the salt of a weak base and a strong acid, the deionizing agent is preferably a hydroxide ion species such as a metal hydroxide such as sodium hydroxide, potassium hydroxide, ammonium hydroxide, calcium hydroxide, aluminum hydroxide, and magnesium hydroxide.

Additional acid or base can be added to adjust the pH of the fill composition. In a preferred embodiment, the pH of the fill composition is from about 2.5 to about 7.5.

3. Excipients

Formulations may be prepared using a pharmaceutically acceptable carrier composed of materials that are considered safe and effective and may be administered to an individual without causing undesirable biological side

effects or unwanted interactions. The carrier is all components present in the pharmaceutical formulation other than the active ingredient or ingredients. As generally used herein "carrier" includes, but is not limited to, plasticizers, crystallization inhibitors, wetting agents, bulk filling agents, solubilizers, bioavailability enhancers, solvents, pH-adjusting agents and combinations thereof.

A mixture of polyethylene glycol and water is used as a solvent for the naproxen sodium and the de-ionizing agent. Polyethylene glycol is present in an amount from about 10% to about 80% by weight. Water is present in an amount from about 1% to 18% by weight. The molecular weight of polyethylene glycol is between 300 and 1500. Other suitable solvents described herein include surfactants and copolymers of polyethylene glycol. The fill material of the present invention also comprises a solubilizer selected from the group consisting of glycerin, polyvinyl pyrrolidone (PVP) or propylene glycol (PPG) and combinations thereof.

B. Shell Composition

1. Gelatin

Gelatin is the product of the partial hydrolysis of collagen. Gelatin is classified as either Type A or Type B gelatin. Type A gelatin is derived from the acid hydrolysis of collagen while Type B gelatin is derived from alkaline hydrolysis of collagen. Traditionally, bovine bones and skins have been used as raw materials for manufacturing Type A and Type B gelatin while porcine skins have been used extensively for manufacturing Type A gelatin. In general acid-processed gelatins form stronger gels than lime- processed gelatins of the same average molecular weight.

2. Other Shell Additives

Other suitable shell additives include plasticizers, opacifiers, colorants, humectants, preservatives, flavorings, and buffering salts and acids.

Plasticizers are chemical agents added to gelatin to make the material softer and more flexible. Suitable plasticizers include glycerin, sorbitol

solutions which are mixtures of sorbitol and sorbitan, and other polyhydric alcohols such as propylene glycol and maltitol or combinations thereof.

Opacifiers are used to opacify the capsule shell when the encapsulated active agents are light sensitive. Suitable opacifiers include titanium dioxide, zinc oxide, calcium carbonate and combinations thereof.

Colorants can be used to for marketing and product identification/differentiation purposes. Suitable colorants include synthetic and natural dyes and combinations thereof.

Humectants can be used to suppress the water activity of the softgel. Suitable humectants include glycerin and sorbitol, which are often components of the plasticizer composition. Due to the low water activity of dried, properly stored softgels, the greatest risk from microorganisms comes from molds and yeasts. For this reason, preservatives can be incorporated into the capsule shell. Suitable preservatives include alkyl esters of p-hydroxy benzoic acid such as methyl, ethyl, propyl, butyl and heptyl (collectively known as "parabens") or combinations thereof.

Flavorings can be used to mask unpleasant odors and tastes of fill formulations. Suitable flavorings include synthetic and natural flavorings. The use of flavorings can be problematic due to the presence of aldehydes which can cross-link gelatin. As a result, buffering salts and acids can be used in conjunction with flavorings that contain aldehydes in order to inhibit cross-linking of the gelatin.

II. Method of Making

A. Fill Material

The fill material is prepared by mixing the agent (such as a salt of the drug), the deionizing agent, water, and polyethylene glycol at a temperature of 50°C to 70°C. The resulting solution is encapsulated using the appropriate gel mass. The pharmaceutical agent is present in an amount from about 10% to about 50% by weight. The deionizing agent is present in an amount from about 0.2 to 1.0 mole per mole of the pharmaceutical agent. Water is present in an amount from about 1% to about 20% by weight and polyethylene glycol is present in amount from about 10% to about 80% by weight.

Optionally, propylene glycol and/or polyvinyl pyrrolidone are present in an amount from about 1% to about 10%.

B. Gel Mass

The main ingredients of the softgel capsule shell are gelatin, plasticizer, and purified water. Typical gel formulations contain (w/w) 40-50% gelatin, 20-30% plasticizer, and 30-40% purified water. Most of the water is subsequently lost during capsule drying. The ingredients are combined to form a molten gelatin mass using either a cold melt or a hot melt process. The prepared gel masses are transferred to preheated, temperature-controlled, jacketed holding tanks where the gel mass is aged at 50-60°C until used for encapsulation.

1. Cold Melt Process

The cold melt process involves mixing gelatin with plasticizer and chilled water and then transferring the mixture to a jacket-heated tank. Typically, gelatin is added to the plasticizer at ambient temperature (18-22°C). The mixture is cooked (57-95°C) under vacuum for 15-30 minutes to a homogeneous, deaerated gel mass. Additional shell additives can be added to the gel mass at any point during the gel manufacturing process or they may be incorporated into the finished gel mass using a high torque mixer.

2. Hot Melt Process

The hot melt process involves adding, under mild agitation, the gelatin to a preheated (60-80°C) mixture of plasticizer and water and stirring the blend until complete melting is achieved. While the hot melt process is faster than the cold melt process, it is less accurately controlled and more susceptible to foaming and dusting.

C. Softgel Capsule

Softgel capsules are typically produced using a rotary die encapsulation process. The gel mass is fed either by gravity or through positive displacement pumping to two heated (48-65°C) metering devices. The metering devices control the flow of gel into cooled (10-18°C), rotating casting drums. Ribbons are formed as the cast gel masses set on contact with the surface of the drums.

The ribbons are fed through a series of guide rolls and between injection wedges and the capsule-forming dies. A food-grade lubricant oil is applied onto the ribbons to reduce their tackiness and facilitate their transfer. Suitable lubricants include mineral oil, medium chain triglycerides, and soybean oil. Fill formulations are fed into the encapsulation machine by gravity. In the preferred embodiment, the softgels contain printing on the surface, optionally identifying the encapsulated agent and/or dosage.

III. Method of Use

The softgels may be used to encapsulate a wide range of pharmaceutically active agents, nutritional agents and personal care products. Softgel capsules may be administered orally to a patient to deliver a pharmaceutically active agent.

Examples

In the following examples, the fill material can be prepared by mixing the salt of one or more pharmaceutically active agents, the deionizing agent, water and polyethylene glycol at a temperature of 50°C to 70°C. The resulting solution can be encapsulated in a softgel capsule using the appropriate gel mass.

Example 1. Naproxen Sodium with Acetic Acid as the Deionizing Agent

Fill Material:

Ingredients	% (by weight)
Naproxen Sodium	25.50
Acetic Acid	3.00
PVP	1.85
PEG 400	62.30
Water	7.40

Example 2. Naproxen Sodium with Citric Acid as the Deionizing Agent

Fill Material:

Ingredients	% (by weight)
Naproxen Sodium	25.50
Citric Acid	4.75
PVP	1.85
PEG 400	60.50
Water	7.40

Reference Example 3. Naproxen Sodium with Hydrochloric Acid as the Deionizing Agent

Fill Material:

Ingredients	% (by weight)
Naproxen Sodium	25.50
Hydrochloric Acid	4.72
PVP	1.85
PEG 400	63.52
Water	7.40

Example 4. Naproxen Sodium with Acetic Acid as the Deionizing Agent

Fill Material:

Ingredients	% (by weight)
Naproxen Sodium	25.50
Acetic Acid	3.00
PVP	1.85
PEG 400	31.15
Water	7.40
PEG 600	31.15

Example 5. Naproxen Sodium with Citric Acid as the Deionizing Agent

Fill Material:

Ingredients	% (by weight)
Naproxen Sodium	25.50
Citric Acid	4075
PVP	1.85
PEG 400	30.25
Water	7.40
PEG 600	30.25

Reference Example 6. Naproxen Sodium with Hydrochloric Acid as the Deionizing Agent

Fill Material:

Ingredients	% (by weight)
Naproxen Sodium	25.50
Hydrochloric Acid	4072
PVP	1.85
PEG 400	30.25
Water	7.40
PEG 600	30.25

Example 7. Naproxen Sodium with Lactic Acid as the Deionizing Agent

Fill Material:

Ingredients	% (by weight)
Naproxen Sodium	27.50
Lactic Acid	5.27
Propylene Glycol	2.00
PEG 400	64.64
Water	0.60

Example 8. Naproxen Sodium with Lactic Acid as the Deionizing Agent

Fill Material:

Ingredients	% (by weight)
Naproxen Sodium	25.00
Lactic Acid	0.24-0.35 M
Propylene glycol	2.00
PEG 600.	q.s.

Example 9. Naproxen Sodium with Lactic Acid as the Deionizing Agent

Fill Material:

Ingredients	% (by weight)
Naproxen Sodium	25.00
Lactic Acid	5.00
Propylene glycol	2.00
PEG 600	61.2
PEG 1000	6.80

Example 10. Naproxen Sodium with Lactic Acid as the Deionizing Agent

Fill Material:

Ingredients	% (by weight)
Naproxen Sodium	25.00
Lactic acid	5.00
Propylene glycol	2.00
PEG 600	51.00
PEG 1000	17.00

Example 11. Naproxen Sodium with Lactic Acid as the Deionizing Agent

Fill Material:

Ingredients	% (by weight)
Naproxen Sodium	25.00
Lactic Acid	5.00
Propylene glycol	2.00
PEG 600	34.00
PEG 1000	34.00

Example 12. Naproxen Sodium with Lactic Acid as the Deionizing Agent

Fill Material:

Ingredients	% (by weight)
Naproxen Sodium	25.00
Lactic acid	5.00
Propylene glycol	2.00
PEG 600	17.00
PEG 1000	51.00

It is understood that the disclosed invention is not limited to the particular methodology, protocols, and reagents described as these may vary. It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments only, and is not intended to limit the scope of the present invention which will be limited only by the appended claims.

Unless defined otherwise, all technical and scientific terms used herein have the same meanings as commonly understood by one of skill in the art to which the disclosed invention belongs. Although any methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present invention, the preferred methods, devices, and materials are as described.

CLAIMS

1. A softgel capsule comprising a fill material wherein the fill material comprises

(a) naproxen sodium;

(b) fumaric acid, maleic acid, tartaric acid, citric acid, malic acid, acetic acid, proprionic acid, pyruvic acid, butanoic acid or lactic acid in an amount of from 0.2 to 1.0 mole equivalents per mole of the naproxen sodium;

(c) polyethylene glycol;

(d) water; and

(e) a solubilizer selected from the group consisting of glycerin, polyvinylpyrrolidone, propylene glycol and combinations thereof.

2. The capsule of claim 1 wherein (b) is citric acid or lactic acid.

3. The capsule of claim 2 wherein (b) is lactic acid.

4. The capsule of any one of the preceding claims wherein polyethylene glycol is present in an amount from 10% to 80% by weight.

5. The capsule of any one of the preceding claims wherein the polyethylene glycol is one or more polyethylene glycols with a molecular weight between 300 and 1500.

6. The capsule of any one of the preceding claims wherein water is present in an amount from 1% to 18% by weight.

7. The capsule of any one of the preceding claims further comprising one or more excipients selected from the group consisting of plasticizers, crystallization inhibitors, wetting agents, bulk filling agents, solubilizers, bioavailability enhancers, solvents, dyes, preservatives, surfactants, and combinations thereof.

8. The capsule of any one of the preceding claims wherein the solubilizer is present in amount from 1% to 10% by weight.

9. The capsule of any one of the preceding claims wherein the fill material is liquid.

10. A capsule of any of the preceding claims for use as a medicament.

11. A method of making the capsule of claim 1 comprising

(a) mixing components (a), (b), (c), (d) and (e) as defined in claim 1; and

(b) encapsulating the mixture in a softgel capsule.

12. The method of claim 11, wherein step (a) is conducted at a temperature of from 50°C to 70°C.

13. The use of

(a) naproxen sodium;

(b) fumaric acid, maleic acid, tartaric acid, citric acid, malic acid, acetic acid, proprionic acid, pyruvic acid, butanoic acid or lactic acid in an amount of from 0.2 to 1.0 mole equivalents per mole of the naproxen sodium;

(c) polyethylene glycol;

(d) water; and

(e) a solubilizer selected from the group consisting of glycerin, polyvinylpyrrolidone, propylene glycol and combinations thereof,

in the manufacture of a medicament in the form of a capsule for administration of the naproxen sodium to a patient in need thereof.

SOLVENT SYSTEM FOR ENHANCING THE SOLUBILITY OF PHARMACEUTICAL AGENTS

FIELD OF THE INVENTION

This invention is in the field of fill materials encapsulated in soft gelatin capsules.

BACKGROUND OF THE INVENTION

Filled one-piece soft gelatin capsules ("softgels") have been widely used for years to encapsulate consumable materials such as vitamins and pharmaceuticals in a liquid vehicle or carrier. Because softgels have properties which are quite different from two-piece hardshell capsules, softgels are more capable of retaining a liquid fill material.

Not all liquids may be enclosed in a softgel capsule. Liquids containing more than about 20% water by weight are generally not enclosed in softgels, because the water tends to dissolve the gelatin shell. Other solvents such as propylene glycol, glycerin, low molecular weight alcohols, ketones, acids, amines, and esters all tend to degrade or dissolve the gelatin shell to some extent.

Softgels are also somewhat sensitive to pH, and generally require a pH in the encapsulated liquid from about 2.5 to about 7.5. Highly acidic liquids may hydrolyze the gelatin, resulting in leaks, while basic liquids may tan the gelatin, resulting in decreased solubility of the gelatin shell.

Pharmaceutical liquids are usually enclosed in softgels as either viscous solutions or suspensions. Suspensions are pharmaceutically less desirable because they can settle during manufacture, which leads to a less uniform product. In contrast, solutions provide the best liquid form for obtaining optimal "content uniformity" in a batch. Further, solutions typically provide a faster and more uniform absorption of an active agent than do suspensions.

Suitable softgel solutions, however, can be difficult to achieve. One constraint is size. Many pharmaceutical agents require volumes of solvent

too large to produce a softgel capsule small enough to be taken by patients. The solvent must also have sufficient solvating power to dissolve a large amount of the pharmaceutical agent to produce a concentrated solution and yet not dissolve, hydrolyze or tan the gelatin shell.

Concentrated solutions of pharmaceutical agents for use in softgel capsules have been described. Most of these systems involve ionizing the free pharmaceutical agent *in situ* to the corresponding salt. For example, U.S. Patent No. 5,360,615 to Yu *et al.* discloses a solvent system for enhancing the solubility of acidic, basic, or amphoteric pharmaceutical agents. The solvent system comprises polyethylene glycol, an ionizing agent, and water. The ionizing agent functions by causing the partial ionization of the free pharmaceutical agent. U.S. Patent No. 6,383,515, U.S. Patent Application Publication No. 2002/0187195, and U.S. Patent Application Publication No. 2001/0007668 to Sawyer *et al.* discloses pharmaceutically acceptable solutions containing a medicament suitable for filling softgel capsules comprising a polymer such as polyethylene glycol and an acid salt of a compound having three or more carbon atoms, such as sodium propionate. The salt helps to ionize the medicament without relying on the use of strong acids or bases. U.S. Patent No. 6,689,382 to Berthel *et al.* describes a pharmaceutical formulation suitable for filling softgel capsules comprising (a) a therapeutically effective amount of a non-steroidal anti-inflammatory drug (NSAID); and (b) a solvent system comprising 40% to 60% by weight a polyoxyethylene ether, 15% to 35% by weight of glycerin and 15% to 35% by weight water. In cases where the NSAID has a carboxyl or an acidic functional group, the solvent system also includes hydroxide ions. U.S. Patent No. 5,505,961 to Shelley *et al.* describes a method for increasing the solubility of acetaminophen alone or in combination with other pharmaceutically active agents to form a clear solution for encapsulation into a softgel capsule. The method comprises solubilizing acetaminophen in a mixture of propylene glycol, polyethylene glycol, water, polyvinylpyrrolidone and sodium or potassium acetate.

The previously described methods all involve the conversion of the free pharmaceutical agent to the corresponding salt. In cases where the free pharmaceutical agent is acidic, the resulting anion can react with the polyethylene glycol in the fill to produce polyethylene glycol esters, thus reducing the amount of available pharmaceutical agent.

There is a need for a solvent system containing a medicament, which can be encapsulated in a softgel capsule, wherein the formation of PEG esters is minimized.

Therefore it is an object of the invention to provide a stable solvent system for pharmaceutical agents, which is suitable for encapsulation in a softgel capsule, wherein the formation of PEG esters is minimized.

BRIEF SUMMARY OF THE INVENTION

The present invention provides a softgel capsule according to Claim 1 and a use according to Claim 13. Liquid and semi-solid pharmaceutical compositions, which can be administered in liquid form or can be used for preparing capsules, are described herein. The acid present in the compositions of the invention causes partial de-ionization (neutralization) of naproxen sodium resulting in enhanced bioavailability as well as decreased amounts of polyethylene glycol (PEG) esters. Thus, hereinafter the acid maybe referred to as the deionizing agent.

DETAILED DESCRIPTION OF THE INVENTION

I. Composition

A. Fill Materials

1. Drugs to be Formulated

In the present invention the fill material comprises naproxen sodium. Other formulations described herein may contain any therapeutic, diagnostic, prophylactic or nutraceutical agent. Exemplary agents include, but are not limited to, analeptic agents; analgesic agents; anesthetic agents; antiasthmatic agents; antiarthritic agents; anticancer agents; anticholinergic agents; anticonvulsant agents; antidepressant agents; antidiabetic agents; antidiarrheal agents; antiemetic agents; antihelminthic agents; antihistamines; antihyperlipidemic agents; antihypertensive agents; anti-infective agents; anti-inflammatory

agents; antimigraine agents; antineoplastic agents; antiparkinson drugs; antipruritic agents; antipsychotic agents; antipyretic agents; antispasmodic agents; antitubercular agents; antiulcer agents; antiviral agents; anxiolytic agents; appetite suppressants (anorexic agents); attention deficit disorder and attention deficit hyperactivity disorder drugs; cardiovascular agents including calcium channel blockers, antianginal agents, central nervous system ("CNS") agents, beta-blockers and antiarrhythmic agents; central nervous system stimulants; diuretics; genetic materials; hormonolytics; hypnotics; hypoglycemic agents; immunosuppressive agents; muscle relaxants; narcotic antagonists; nicotine; nutritional agents; parasympatholytics; peptide drugs; psychostimulants; sedatives; sialagogues, steroids; smoking cessation agents; sympathomimetics; tranquilizers; vasodilators; beta-agonist; and tocolytic agents.

Any drug that bears an acidic or a basic functional group, for example, an amine, imine, imidazoyl, guanidine, piperidinyl, pyridinyl, quaternary ammonium, or other basic group, or a carboxylic, phosphoric, phenolic, sulfuric, sulfonic or other acidic group, can react with the de-ionizing agent.

Some other drugs that bear acidic or basic functional groups and thus may be converted to the corresponding salt for use in the formulations described herein include, but are not limited to, Acetaminophen, Acetylsalicylic acid, Alendronic acid, Alosetron, Amantadine, Amlopidine, Anagrelide, Argatroban, Atomoxetine, Atrovastatin, Azithromycin dehydrate, Balsalazide, Bromocriptan, Bupropion, Candesartan, Carboplatin, Ceftriaxone, Clavulonic acid, Clindamycin, Cimetadine, Dehydrocholic (acid), Dexmethylphenidate, Diclofenac, Dicyclomine, Diflunisal, Diltiazem, Donepezil, Doxorubicin, Doxepin, Epirubicin, Etodolic acid, Ethacrynic acid, Fenoprofen, Fluoxetine, Flurbiprofen, Furosemide, Gemfibrozil, Hydroxyzine, Ibuprofen, Imipramine, Indomethacin, Ketoprofen, Levothyroxine, Maprolitline, Meclizine, Methadone, Methylphenidate, Minocycline, Mitoxantone, Moxifloxacin, Mycophenolic

acid, Niflumic acid, Ofloxacin, Ondansetron, Pantoprazole, Paroxetine, Pergolide, Pramipexole, Phenytoin, Pravastain, Probenecid, Rabeprazole, Risedronic acid, Retinoic acid, Ropinirole, Selegiline, Sulindac, Tamsulosin, Telmisertan, Terbinafine, Theophyline, Tiludronic Acid, Tinzaparin, Ticarcillin, Tometin, Valproic acid, Salicylic acid, Sevelamer, Ziprasidone, Zoledronic acid, Acetophenazine, Albuterol, Almotriptan, Amitriptyline, Amphetamine, Atracurium, Beclomethasone, Benztropine, Biperiden, Bosentan, Bromodiphenhydramine, Brompheniramine carbinoxamine, Caffeine, Capecitabine, Carbergoline, Cetirizine, Chlocylizine, Chlorpheniramine, Chlorphenoxamine, Chlorpromazine, Citalopram, Clavunate potassium, Ciprofloxacin, Clemastine, Clomiphene, Clonidine, Clopidogrel, Codeine, Cyclizine, Cyclobenzaprine, Cyproheptadine, Delavirdine, Diethylpropion, Divalproex, Desipramine, Dexmethylphenidate, Dexbrompheniramine, Dexchlopheniramine, Dexchlor, Dextroamphetamine, Dexedrine, Dextromethorphan, Fiflunisal, Diphemanil methylsulphate, Diphenhydramine, Dolasetron, Doxylamine, Enoxaparin, Ergotamine, Ertepenem, Eprosartan, Escitalopram, Esomeprazole, Fenoldopam, Fentanyl, Fexofenadine, Flufenamic acid, Fluvastatin, Fluphenazine, Fluticasone, Fosinopril, Frovatriptan, Gabapentin, Galatamine, Gatifloxacin, Gemcitabine, Haloperidol, Hyalurondate, Hydrocodone, Hydroxychloroquine, Hyoscyamine, Imatinib, Imipenem, Ipatropin, Lisinopril, Leuprolide, Levopropoxyphene, Losartan, Meclofenamic acid, Mefanamic acid, Mesalamine, Mepenzolate, Meperidine, Mephentermine, Mesalimine, Mesoridazine, Metaproteranol, Metformin, Methdialazine, Methscopolamine, Methysergide, Metoprolol, Metronidazole, Mibefradil, Montelukast, Morphine, Mometasone, Naratriptan, Nelfinavir, Nortriptylene, Noscapine, Nylindrin, Omeprazole, Orphenadrine, Oseltamivir, Oxybutynin, Papaverine, Pentazocine, Phendimetrazine, Phentermine, Pioglitazone, Pilocarpine, Prochloroperazine, Pyrilamine, Quetapine, Ranitidine, Rivastigmine, Rosiglitazone, Salmetrol, Sertaline, Sotalol, Sumatriptan, Tazobactam, Tacrolimus, Tamoxifen, Ticlopidine, Topiramate, Tolterodine,

Triptorelin, Triplennamine, Triprolidine, Tramadol, Trovofloxacin, Ursodiol, Promazine, Propoxyphene, Propanolol, Pseudoephedrine, Pyrilamine, Quinidine, Oxybate sodium, Sermorelin, Tacrolimus, Tegaseroid, Teriparatide, Tolterodine, Triptorelin pamoate, Scoplolamine, Venlafaxine, Zamivir, Aminocaproic acid, Aminosalicylic acid, Hydromorphone, Isosuprine, Levorphanol, Melhalan, Nalidixic acid, and Para-aminosalicylic acid.

2. Deionizing Agent

The fill material of the present invention comprises fumaric acid, maleic acid, tartaric acid, citric acid, malic acid, acetic acid, proprionic acid, pyruvic acid, butanoic acid or lactic acid in an amount of from 0.2 to 1.0 mole equivalents per mole of the naproxen sodium. These acids act as deionizing agents.

The deionizing agent functions by causing partial deionization (neutralization) of the salt of the pharmaceutically active agent (in this invention naproxen sodium). As described herein when the active agent is the salt of a weak acid and a strong base, the deionizing agent is preferably a hydrogen ion species such as an acid as described above or when the active agent is the salt of a weak base and a strong acid, the deionizing agent is preferably a hydroxide ion species such as a metal hydroxide such as sodium hydroxide, potassium hydroxide, ammonium hydroxide, calcium hydroxide, aluminum hydroxide, and magnesium hydroxide.

Additional acid or base can be added to adjust the pH of the fill composition. In a preferred embodiment, the pH of the fill composition is from about 2.5 to about 7.5.

3. Excipients

Formulations may be prepared using a pharmaceutically acceptable carrier composed of materials that are considered safe and effective and may be administered to an individual without causing undesirable biological side

effects or unwanted interactions. The carrier is all components present in the pharmaceutical formulation other than the active ingredient or ingredients. As generally used herein "carrier" includes, but is not limited to, plasticizers, crystallization inhibitors, wetting agents, bulk filling agents, solubilizers, bioavailability enhancers, solvents, pH-adjusting agents and combinations thereof.

A mixture of polyethylene glycol and water is used as a solvent for the naproxen sodium and the de-ionizing agent. Polyethylene glycol is present in an amount from about 10% to about 80% by weight. Water is present in an amount from about 1% to 18% by weight. The molecular weight of polyethylene glycol is between 300 and 1500. Other suitable solvents described herein include surfactants and copolymers of polyethylene glycol. The fill material of the present invention also comprises a solubilizer selected from the group consisting of glycerin, polyvinyl pyrrolidone (PVP) or propylene glycol (PPG) and combinations thereof.

B. Shell Composition

1. Gelatin

Gelatin is the product of the partial hydrolysis of collagen. Gelatin is classified as either Type A or Type B gelatin. Type A gelatin is derived from the acid hydrolysis of collagen while Type B gelatin is derived from alkaline hydrolysis of collagen. Traditionally, bovine bones and skins have been used as raw materials for manufacturing Type A and Type B gelatin while porcine skins have been used extensively for manufacturing Type A gelatin. In general acid-processed gelatins form stronger gels than lime- processed gelatins of the same average molecular weight.

2. Other Shell Additives

Other suitable shell additives include plasticizers, opacifiers, colorants, humectants, preservatives, flavorings, and buffering salts and acids.

Plasticizers are chemical agents added to gelatin to make the material softer and more flexible. Suitable plasticizers include glycerin, sorbitol

solutions which are mixtures of sorbitol and sorbitan, and other polyhydric alcohols such as propylene glycol and maltitol or combinations thereof.

Opacifiers are used to opacify the capsule shell when the encapsulated active agents are light sensitive. Suitable opacifiers include titanium dioxide, zinc oxide, calcium carbonate and combinations thereof.

Colorants can be used to for marketing and product identification/differentiation purposes. Suitable colorants include synthetic and natural dyes and combinations thereof.

Humectants can be used to suppress the water activity of the softgel. Suitable humectants include glycerin and sorbitol, which are often components of the plasticizer composition. Due to the low water activity of dried, properly stored softgels, the greatest risk from microorganisms comes from molds and yeasts. For this reason, preservatives can be incorporated into the capsule shell. Suitable preservatives include alkyl esters of p-hydroxy benzoic acid such as methyl, ethyl, propyl, butyl and heptyl (collectively known as "parabens") or combinations thereof.

Flavorings can be used to mask unpleasant odors and tastes of fill formulations. Suitable flavorings include synthetic and natural flavorings. The use of flavorings can be problematic due to the presence of aldehydes which can cross-link gelatin. As a result, buffering salts and acids can be used in conjunction with flavorings that contain aldehydes in order to inhibit cross-linking of the gelatin.

II. Method of Making

A. Fill Material

The fill material is prepared by mixing the agent (such as a salt of the drug), the deionizing agent, water, and polyethylene glycol at a temperature of 50°C to 70°C. The resulting solution is encapsulated using the appropriate gel mass. The pharmaceutical agent is present in an amount from about 10% to about 50% by weight. The deionizing agent is present in an amount from about 0.2 to 1.0 mole per mole of the pharmaceutical agent. Water is present in an amount from about 1% to about 20% by weight and polyethylene glycol is present in amount from about 10% to about 80% by weight.

Optionally, propylene glycol and/or polyvinyl pyrrolidone are present in an amount from about 1% to about 10%.

B. Gel Mass

The main ingredients of the softgel capsule shell are gelatin, plasticizer, and purified water. Typical gel formulations contain (w/w) 40-50% gelatin, 20-30% plasticizer, and 30-40% purified water. Most of the water is subsequently lost during capsule drying. The ingredients are combined to form a molten gelatin mass using either a cold melt or a hot melt process. The prepared gel masses are transferred to preheated, temperature-controlled, jacketed holding tanks where the gel mass is aged at 50-60°C until used for encapsulation.

1. Cold Melt Process

The cold melt process involves mixing gelatin with plasticizer and chilled water and then transferring the mixture to a jacket-heated tank. Typically, gelatin is added to the plasticizer at ambient temperature (18-22°C). The mixture is cooked (57-95°C) under vacuum for 15-30 minutes to a homogeneous, deaerated gel mass. Additional shell additives can be added to the gel mass at any point during the gel manufacturing process or they may be incorporated into the finished gel mass using a high torque mixer.

2. Hot Melt Process

The hot melt process involves adding, under mild agitation, the gelatin to a preheated (60-80°C) mixture of plasticizer and water and stirring the blend until complete melting is achieved. While the hot melt process is faster than the cold melt process, it is less accurately controlled and more susceptible to foaming and dusting.

C. Softgel Capsule

Softgel capsules are typically produced using a rotary die encapsulation process. The gel mass is fed either by gravity or through positive displacement pumping to two heated (48-65°C) metering devices. The metering devices control the flow of gel into cooled (10-18°C), rotating casting drums. Ribbons are formed as the cast gel masses set on contact with the surface of the drums.

The ribbons are fed through a series of guide rolls and between injection wedges and the capsule-forming dies. A food-grade lubricant oil is applied onto the ribbons to reduce their tackiness and facilitate their transfer. Suitable lubricants include mineral oil, medium chain triglycerides, and soybean oil. Fill formulations are fed into the encapsulation machine by gravity. In the preferred embodiment, the softgels contain printing on the surface, optionally identifying the encapsulated agent and/or dosage.

III. Method of Use

The softgels may be used to encapsulate a wide range of pharmaceutically active agents, nutritional agents and personal care products. Softgel capsules may be administered orally to a patient to deliver a pharmaceutically active agent.

Examples

In the following examples, the fill material can be prepared by mixing the salt of one or more pharmaceutically active agents, the deionizing agent, water and polyethylene glycol at a temperature of 50°C to 70°C. The resulting solution can be encapsulated in a softgel capsule using the appropriate gel mass.

Example 1. Naproxen Sodium with Acetic Acid as the Deionizing Agent

Fill Material:

Ingredients	**% (by weight)**
Naproxen Sodium	25.50
Acetic Acid	3.00
PVP	1.85
PEG 400	62.30
Water	7.40

Example 2. Naproxen Sodium with Citric Acid as the Deionizing Agent

Fill Material:

Ingredients	% (by weight)
Naproxen Sodium	25.50
Citric Acid	4.75
PVP	1.85
PEG 400	60.50
Water	7.40

Reference Example 3. Naproxen Sodium with Hydrochloric Acid as the Deionizing Agent

Fill Material:

Ingredients	% (by weight)
Naproxen Sodium	25.50
Hydrochloric Acid	4.72
PVP	1.85
PEG 400	63.52
Water	7.40

Example 4. Naproxen Sodium with Acetic Acid as the Deionizing Agent

Fill Material:

Ingredients	% (by weight)
Naproxen Sodium	25.50
Acetic Acid	3.00
PVP	1.85
PEG 400	31.15
Water	7.40
PEG 600	31.15

Example 5. Naproxen Sodium with Citric Acid as the Deionizing Agent

Fill Material:

Ingredients	% (by weight)
Naproxen Sodium	25.50
Citric Acid	4075
PVP	1.85
PEG 400	30.25
Water	7.40
PEG 600	30.25

Reference Example 6. Naproxen Sodium with Hydrochloric Acid as the Deionizing Agent

Fill Material:

Ingredients	% (by weight)
Naproxen Sodium	25.50
Hydrochloric Acid	4072
PVP	1.85
PEG 400	30.25
Water	7.40
PEG 600	30.25

Example 7. Naproxen Sodium with Lactic Acid as the Deionizing Agent

Fill Material:

Ingredients	% (by weight)
Naproxen Sodium	27.50
Lactic Acid	5.27
Propylene Glycol	2.00
PEG 400	64.64
Water	0.60

Example 8. Naproxen Sodium with Lactic Acid as the Deionizing Agent

Fill Material:

Ingredients	% (by weight)
Naproxen Sodium	25.00
Lactic Acid	0.24-0.35 M
Propylene glycol	2.00
PEG 600.	q.s.

Example 9. Naproxen Sodium with Lactic Acid as the Deionizing Agent

Fill Material:

Ingredients	% (by weight)
Naproxen Sodium	25.00
Lactic Acid	5.00
Propylene glycol	2.00
PEG 600	61.2
PEG 1000	6.80

Example 10. Naproxen Sodium with Lactic Acid as the Deionizing Agent

Fill Material:

Ingredients	% (by weight)
Naproxen Sodium	25.00
Lactic acid	5.00
Propylene glycol	2.00
PEG 600	51.00
PEG 1000	17.00

Example 11. Naproxen Sodium with Lactic Acid as the Deionizing Agent

Fill Material:

Ingredients	% (by weight)
Naproxen Sodium	25.00
Lactic Acid	5.00
Propylene glycol	2.00
PEG 600	34.00
PEG 1000	34.00

Example 12. Naproxen Sodium with Lactic Acid as the Deionizing Agent

Fill Material:

Ingredients	% (by weight)
Naproxen Sodium	25.00
Lactic acid	5.00
Propylene glycol	2.00
PEG 600	17.00
PEG 1000	51.00

It is understood that the disclosed invention is not limited to the particular methodology, protocols, and reagents described as these may vary. It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments only, and is not intended to limit the scope of the present invention which will be limited only by the appended claims.

Unless defined otherwise, all technical and scientific terms used herein have the same meanings as commonly understood by one of skill in the art to which the disclosed invention belongs. Although any methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present invention, the preferred methods, devices, and materials are as described.

CLAIMS

1. A softgel capsule comprising a fill material wherein the fill material comprises

(a) naproxen sodium;

(b) fumaric acid, maleic acid, tartaric acid, citric acid, malic acid, acetic acid, proprionic acid, pyruvic acid, butanoic acid or lactic acid in an amount of from 0.2 to 1.0 mole equivalents per mole of the naproxen sodium;

(c) polyethylene glycol;

(d) water; and

(e) a solubilizer selected from the group consisting of glycerin, polyvinylpyrrolidone, propylene glycol and combinations thereof.

2. The capsule of claim 1 wherein (b) is citric acid or lactic acid.

3. The capsule of claim 2 wherein (b) is lactic acid.

4. The capsule of any one of the preceding claims wherein polyethylene glycol is present in an amount from 10% to 80% by weight.

5. The capsule of any one of the preceding claims wherein the polyethylene glycol is one or more polyethylene glycols with a molecular weight between 300 and 1500.

6. The capsule of any one of the preceding claims wherein water is present in an amount from 1% to 18% by weight.

7. The capsule of any one of the preceding claims further comprising one or more excipients selected from the group consisting of plasticizers, crystallization inhibitors, wetting agents, bulk filling agents, solubilizers, bioavailability enhancers, solvents, dyes, preservatives, surfactants, and combinations thereof.

8. The capsule of any one of the preceding claims wherein the solubilizer is present in amount from 1% to 10% by weight.

9. The capsule of any one of the preceding claims wherein the fill material is liquid.

10. A capsule of any of the preceding claims for use as a medicament.

11. A method of making the capsule of claim 1 comprising

(a) mixing components (a), (b), (c), (d) and (e) as defined in claim 1; and

(b) encapsulating the mixture in a softgel capsule.

12. The method of claim 11, wherein step (a) is conducted at a temperature of from 50°C to 70°C.

13. The use of

(a) naproxen sodium;

(b) fumaric acid, maleic acid, tartaric acid, citric acid, malic acid, acetic acid, proprionic acid, pyruvic acid, butanoic acid or lactic acid in an amount of from 0.2 to 1.0 mole equivalents per mole of the naproxen sodium;

(c) polyethylene glycol;

(d) water; and

(e) a solubilizer selected from the group consisting of glycerin, polyvinylpyrrolidone, propylene glycol and combinations thereof,

in the manufacture of a medicament in the form of a capsule for administration of the naproxen sodium to a patient in need thereof.

Europäisches Patentamt
European Patent Office
Office européen des brevets

European Patent Office
80298 MUNICH
GERMANY

Questions about this communication ?
Contact Customer Services at www.epo.org/contact

Potter Clarkson LLP
The Belgrave Centre
Talbot Street
Nottingham NG1 5GG
ROYAUME UNI

Date
19.08.16

Reference	Application No./Patent No.
PABCA/P38814EP	06737018.9 - 1466 / 1863458
Applicant/Proprietor	
Banner Life Sciences, LLC	

Decision to grant a European patent pursuant to Article 97(1) EPC

Following examination of European patent application No. 06737018.9 a European patent with the title and the supporting documents indicated in the communication pursuant to Rule 71(3) EPC (EPO Form 2004C) or in the information (EPO Form 2004W, cf. Notice from the EPO dated 8 June 2015, OJ EPO 2015, A52) dated 05.08.16 is hereby granted in respect of the designated Contracting States.

Patent No. : 1863458
Date of filing : 06.03.06
Priority claimed : 08.03.05/USP 659679

Designated Contracting States and Proprietor(s) : AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HU IE IS IT LI LT LU LV MC NL PL PT RO SE SI SK TR
Banner Life Sciences, LLC
4125 Premier Drive
High Point, North Carolina 27265/US

This decision will take effect on the date on which the European Patent Bulletin mentions the grant (Art. 97(3) EPC).

The mention of the grant will be published in European Patent Bulletin 16/37 of 14.09.16.

Examining Division

Büttner U Paúl Soto R Borst M

Europäisches Patentamt · European Patent Office · Office européen des brevets

Registered letter
EPO Form 2006A 07.15 (11/08/16)

to EPO postal service: 12.08.16

ANMERKUNG ZUR ENTSCHEIDUNG ÜBER DIE ERTEILUNG
EINES EUROPÄISCHEN PATENTS (EPA Form 2006)

1. **EPA Informationsbroschüre "Nationales Recht zum EPÜ"**
Diese Broschüre enthält nützliche Informationen zu den formalen Erfordernissen und den Handlungen, die vor den Patentbehörden der Vertragsstaaten vorzunehmen sind, um Rechte in diesen Staaten zu erlangen. Da diese Handlungen einem ständigen Wandel unterworfen sind, sollte immer nur die neueste Ausgabe der Broschüre benutzt werden. Nachträgliche Informationen werden im Amtsblatt veröffentlicht.

2. **Übersetzung der europäischen Patentschrift nach Artikel 65 (1) des Europäischen Patentübereinkommens**
Sie werden erneut darauf hingewiesen, dass bestimmte Vertragsstaaten nach Artikel 65 (1) EPÜ eine Übersetzung der europäischen Patentschrift verlangen; hierauf wird in der Mitteilung gemäß Regel 71 (5) EPÜ verwiesen. Die Nichteinreichung dieser Übersetzung kann zur Folge haben, dass das Patent in dem betreffenden Staat/in den betreffenden Staaten als von Anfang an nicht eingetreten gilt. Weitere Einzelheiten entnehmen Sie bitte der oben genannten Broschüre.

3. **Zahlung von Jahresgebühren für europäische Patente**
Nach Artikel 141 EPÜ können "nationale" Jahresgebühren für das europäische Patent für die Jahre erhoben werden, die an das Jahr anschließen, in dem der Hinweis auf die Erteilung des europäischen Patents im "Europäischen Patentblatt" bekanntgemacht wird. Weitere Einzelheiten entnehmen Sie bitte der oben genannten Broschüre.

NOTE RELATING TO THE DECISION TO GRANT A
EUROPEAN PATENT (EPO Form 2006)

1. **EPO Information Brochure "National law relating to the EPC"**
This brochure provides useful information regarding formal requirements and the steps to be taken before the patent authorities of the Contracting States in order to acquire rights in those states. Since the necessary steps are subject to change the latest edition of the brochure should always be used. Subsequent information is published in the Official Journal.

2. **Translation of the European patent application under Article 65(1) of the European Patent Convention**
Your attention is again drawn to the requirements regarding translation of the European patent specification laid down by a number of Contracting States under Article 65(1) EPC, to which reference is made in the communication under Rule 71(5) EPC. Failure to supply such translation(s) may result in the patent being deemed to be void "ab initio" in the State(s) in question. For further details you are recommended to consult the above-mentioned brochure.

3. **Payment of renewal fees for European patents**
Under Article 141 EPC "national" renewal fees in respect of a European patent may be imposed for the years which follow that in which the mention of the grant of the European patent is published in the "European Patent Bulletin". For further details you are recommended to consult the above-mentioned brochure.

REMARQUE RELATIVE A LA DECISION DE DELIVRANCE
D'UN BREVET EUROPEEN (OEB Form 2006)

1. **Brochure d'information de l'OEB "Droit national relatif à la CBE"**
Cette brochure fournit d'utiles renseignements sur les conditions de forme requises et sur les actes à accomplir auprès des offices de brevet des Etats contractants aux fins d'obtenir des droits dans les Etats contractants. Etant donné que les actes indispensables sont susceptibles de modifications, il serait bon de toujours consulter la dernière édition de la brochure. Toute information ultérieure est publiée au Journal Officiel.

2. **Traduction du fascicule du brevet européen en vertu de l'article 65(1) de la Convention sur le brevet européen**
Votre attention est de nouveau attirée sur l'obligation faite par certains Etats contractants, en vertu de l'article 65(1) CBE, de fournir une traduction du fascicule du brevet européen, à laquelle il est fait référence dans la notification établie conformément à la règle 71(5) CBE. Si la(les) traduction(s) n'est(ne sont) pas fournie(s), le brevet européen peut, dès l'origine, être réputé sans effet dans cet(ces) Etat(s). Pour plus de détails, nous vous renvoyons à la brochure susmentionnée.

3. **Paiement des taxes annuelles pour le brevet européen**
Conformément à l'article 141 CBE des taxes annuelles "nationales" dues au titre du brevet européen peuvent être perçues pour les années suivant celle au cours de laquelle la mention de la délivrance du brevet européen est publiée au "Bulletin européen des brevets. Pour plus de détails, nous vous renvoyons à la brochure susmentionnée.

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Reference	Application No./Patent No.
PABCA/P38814EP	06737018.9 - 1466 / 1863458
Applicant/Proprietor	
Banner Life Sciences, LLC	

Transmission of the certificate for a European patent pursuant to Rule 74 EPC

The certificate for a European patent is herewith transmitted.

The European patent specification can be downloaded from the EPO publication server **https://data.epo.org/publication-server/** (see OJ EPO 2005, 126).

Note:
A corrected title page of the European patent specification will be published, if the bibliographic data have been changed after completion of the technical preparations.

For the Examining Division

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