(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
6 July 2006 (06.07.2006)

PCT

(10) International Publication Number
WO 2006/069419 A1

(51) International Patent Classification:
A61K 9/51 (2006.01) *A61K 31/5513* (2006.01)
A61K 31/192 (2006.01) *A61P 15/10* (2006.01)
A61K 31/196 (2006.01) *A61P 25/18* (2006.01)
A61K 31/4985 (2006.01) *A61P 29/00* (2006.01)

(21) International Application Number:
PCT/AU2005/001977

(22) International Filing Date:
30 December 2005 (30.12.2005)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
2004907377 31 December 2004 (31.12.2004) AU

(71) Applicant *(for all designated States except US)*: **ICEUTICA PTY LTD** [AU/AU]; 52 Fairfield Street, Mouth Hawthorn, W.A. 6016 (AU).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: **PAYNE, Trevor** [AU/AU]; The University of Western Australia, Stirling Highway, Nedlands, W.A. 6907 (AU). **MEISER, Felix** [DE/AU]; The University of Melbourne, Grattan Street, Parkville, VIC 3052 (AU). **POSTMA, Almar** [NL/AU]; The University of Melbourne, Grattan Street, Parkville, VIC 3052 (AU). **CAMMARANO, Raffaele** [AU/AU]; 33 Montreal Street, Fremantle, W.A. 6160 (AU). **CARUSO, Frank** [AU/AU]; The University of Melbourne, Grattan Street, Parkville, VIC 3052 (AU). **WILLIAMS, James** [AU/AU]; 25 Second Avenue, Kensington, W.A. 6151 (AU). **MCCORMICK, Paul** [AU/AU]; The University of Western Australia, Stirling Highway, Nedlands, W.A. 6907 (AU). **DODD, Aaron** [AU/AU]; The University of Western Australia, Stirling Highway, Nedlands, W.A. 6907 (AU).

(74) Agent: **WRAY & ASSOCIATES**; Level 4, The Quadrant, 1 William Street, Perth, W.A. 6000 (AU).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: NANOPARTICLE COMPOSITION AND METHODS FOR SYNTHESIS THEREOF

(57) Abstract: The present invention relates to improved therapeutically active nanocomposite microstructure compositions, including nanoparticle compositions and nanoparticle preparations. Preferred embodiments include nanoparticle compositions comprising nanoparticles of a therapeutically active agent dispersed in a carrier matrix. The invention also relates to a method for preparing said compositions and preparations using solid-state mechanochemical synthesis. Further, it relates to therapeutic products produced using said compositions and to methods of treatment using the compositions.

WO 2006/069419 A1

Nanoparticle Compositions and Methods for Synthesis Thereof

Field of the Invention

The present invention relates to improved therapeutically active nanocomposite microstructure compositions, including nanoparticle compositions comprising nanoparticles of a therapeutically active agent dispersed in a carrier matrix and other nanoparticle preparations. The invention also relates to a method for preparing said compositions and preparations using solid-state mechanochemical synthesis. Further, it relates to therapeutic products produced using said compositions and to methods of treatment using the compositions.

Background

Poor bioavailability is a significant problem encountered in the development of therapeutic compositions, particularly those compounds containing an active agent that is poorly soluble in water. An active agent's bioavailability is the degree to which the active agent becomes available to the target tissue in the body after systemic administration through, for example, oral or intravenous means. Many factors may affect bioavailability, including the form of dosage and the solubility and dissolution rate of the active agent.

Poorly and slowly water soluble active agents tend to be eliminated from the gastrointestinal tract before being absorbed into the circulation. In addition, poorly soluble active agents tend to be disfavored or even unsafe for intravenous administration due to the risk of particles of agent blocking blood flow through capillaries.

It is known that the rate of dissolution of a particulate drug can increase with increasing surface area, that is, decreasing particle size. Consequently, methods of making finely divided or sized drugs have been studied and efforts have been made to control the size and size range of drug particles in pharmaceutical compositions. For example, dry milling techniques have been used to reduce particle size and hence influence drug absorption. However, in conventional dry milling the limit of fineness is reached generally in the region of about 100 microns

(100,000 nm), at which point material cakes on the milling chamber and prevents any further diminution of particle size. Alternatively, wet grinding may be employed to reduce particle size, but flocculation restricts the lower particle size limit to approximately 10 microns (10,000 nm). The wet milling process, however, is prone to contamination, thereby leading to a bias in the pharmaceutical art against wet milling. Another alternative milling technique, commercial airjet milling, has provided particles ranging in average size from as low as about 1 to about 50 microns (1,000-50,000 nm).

There are several approaches currently used to formulate poorly soluble active agents. One approach is to prepare the active agent as a soluble salt. Where this approach cannot be employed, alternate (usually physical) approaches are employed to improve the solubility of the active agent. Alternate approaches generally subject the active agent to physical conditions which change the agent's physical and or chemical properties to improve its solubility. These include process technologies such as micro-ionisation, modification of crystal or polymorphic structure, development of oil based solutions, use of co-solvents, surface stabilizers or complexing agents, micro-emulsions, super critical fluid and production of solid dispersions or solutions. More than one of these processes may be used in combination to improve formulation of a particular therapeutic compound.

These techniques for preparing such pharmaceutical compositions tend to be complex. By way of example, a principal technical difficulty encountered with emulsion polymerization is the removal of contaminants, such as unreacted monomers or initiators (which may have undesirable levels of toxicity), at the end of the manufacturing process.

Another method of providing reduced particle size is the formation of pharmaceutical drug microencapsules, which techniques include micronizing, polymerisation and co-dispersion. However, these techniques suffer from a number of disadvantages including at least the inability to produce sufficiently small particles such as those obtained by milling, and the presence of co-solvents and/or contaminants such as toxic monomers which are difficult to remove, leading to expensive manufacturing processes.

Over the last decade intense scientific investigation has been carried out to improving the solubility of active agents by converting the agents to ultra fine powders by methods such as milling and grinding. These techniques may be used to increase the dissolution rate of a particulate solid by increasing the overall surface area and decreasing the average particle size.

Some investigation of the applicability of mechanochemical synthesis ("MCS") techniques to active agents has been undertaken. However, these investigations have focused on providing an alternative manufacturing process that reduces the need for solvents and improves yields, rather than improving solubility by reducing particle size.

It is important to note the clear distinction between the MCS method, described more fully below in the Detailed Description of the Invention, which is one of building nanoparticles from chemical precursors, as compared to a particle size reduction methods.

Methods of making nanoparticulate compositions have been described as early as US Pat. No. 5,145,684. Methods of making nanoparticulate compositions are also described in U.S. Pat. Nos. 5,534,270; 5,510,118; 5,470,583; 5,591,456; 6,428,814; 6,811,767; and 6,908,626, all of which are specifically incorporated herein by reference. However, these patents do not teach MCS methods of forming nanoparticulate compositions. Rather, the techniques described therein are size reduction techniques. Additionally, these techniques do not result in nanoparticulate compositions with average particle sizes in the range of the present invention's particles, nor do they teach the matrix carrier feature of some embodiments of the present invention.

Accordingly the present invention seeks to provide improved therapeutically active nanocomposite microstructure compositions and nanoparticle preparations as well as methods for their preparation, which at least ameliorate some of the problems attendant with prior technologies.

Summary of the Invention

The present invention is directed to the surprising and unexpected discovery that improved nanocomposite microstructure compositions can be produced by mechanochemically synthesising therapeutically active nanoparticles in a carrier matrix using a solid-state chemical reaction. By mechanochemically synthesising the therapeutically active nanoparticles in a carrier matrix using mechanochemical procedures, applicant is able to control the size of the resultant nano particles in the composition. As a result, the improved nanocomposite microstructure compositions are expected to have several advantages, including improved drug bioavailability compared to unprocessed or conventional active agents.

Accordingly, the present invention relates to an improved nanocomposite microstructure composition comprising therapeutically active nanoparticles dispersed in a carrier matrix, wherein said composition is mechanochemically prepared using a solid-state chemical reaction. Preferably, the preparation is a solid solution or solid dispersion suitable for delivery to an animal.

The present invention also resides in a method for preparing an improved nanocomposite microstructure composition, said method comprising the step of: contacting a precursor compound with a co-reactant under mechanochemical synthesis conditions to generate a solid-state chemical reaction between the precursor compound and the co-reactant to produce therapeutically active nanoparticles dispersed in a carrier matrix. The carrier matrix produced by this method will preferably be non-toxic or alternatively should be separable from the therapeutically active nanoparticles.

The present invention also relates to the use of the composition of the invention in the manufacture of a medicament. Such a medicament may include the composition alone or more preferably the composition may be combined with one or more pharmaceutically acceptable carriers, as well as any desired excipients or other like agents commonly used in the preparation of pharmaceutically acceptable compositions.

DOCKET ALARM

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts

Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research

With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips

Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS
Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS
Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS
Sync your system to PACER to automate legal marketing.