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Editors

JAMES SWARBRICK
Vice President
Research and Development
AAI, Inc.
Wilmington, North Carolina

JAMES C. BOYLAN
Director
Pharmaceutical Technology
Hospital Products Division
Abbott Laboratories
Abbott Park, Illinois

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PRESERVATION OF PHARMACEUTICAL PRODUCTS TO SALT FORMS OF DRUGS AND ABSORPTION

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Salt Forms of Drugs and Absorption

Introduction

Salt formation is frequently performed on weak acidic or basic drugs because it is a relatively simple chemical manipulation which may alter the physicochemical, formulation, biopharmaceutical, and therapeutic properties of a drug without modifying the basic chemical structure. Salt selection has been largely semi-empirical, based on consideration of cost of raw materials, yield, ease of preparation and purification, etc. Although attempts have been made to apply "decision analysis" and "potential problem analysis" to select salts and help predict salt performance [1], the choice of which salt to use remains a difficult decision.

The ideal characteristics of a salt are that it is chemically stable, not hygroscopic, presents no processing problems, dissolves quickly from solid dosage forms (unless it is formed with the intent to delay dissolution), and exhibits good bioavailability.

The literature contains a large amount of information on salts; however, much of the early research addresses the use of salt formation to prolong the release of the active component, thereby eliminating various undesirable drug properties[2–6]. This article supplements an extensive review published in 1977 [7], providing a literature overview of approximately 40–45 years. Its objectives are to present potentially useful salts, their effect on the properties of the parent drug, and a decision tree for choosing the most desirable salt form(s) for development.

Potentially Useful Salts

Salt formation is one of the simplest chemical reactions, involving either a proton transfer or a neutralization reaction between an acid and a base. The relative strength of the acid or base, or the acidity and basicity constants of the species involved, significantly influences the occurrence of the reaction and provides a measure of the stability of the resulting salt. Theoretically, every compound possessing acidic and/or basic properties can participate in salt formation.

Salt forms that have been clinically evaluated in humans or were commercially marketed through 1993 are shown in Tables 1 and 2, compiled from the drug monographs listed in *Martindale, The Extra Pharmacopoeia*, 30th ed. [8]. Table 1 gives all anionic salt forms, Table 2 all cationic forms. The relative frequency (as a percentage) of use for each salt type was calculated based on the total number of anionic or cationic salts used through 1993.

The monoprotic hydrochlorides are by far the most frequent choice of an anionic salt-forming radical, probably for physiological reasons and simple availability. For similar reasons, sodium is the most predominate cation. These findings are identical to those reported in a similar survey [7] from 1977, even though they are based on twice the number of salts as the earlier study. Other comparisons between this and the previous review show an increase of approximately 40% in the types of anionic salts and approxi-

TABLE 1 Anionic Pharmaceutical Salt Forms Currently in Use

Anion	Percent[a]	Anion	Percent[a]	Anion	Percent[a]
Aceglumate	0.07	Formate	0.07	Nicotinate	0.13
Acephyllinate (7-Theophyllineacetate)	0.26	Fosfatex (Metaphosphate)	0.07	Nitrate	1.18
Acetamidobenzoate	0.07	Fumarate	0.92	Oleate	0.13
Acetate	2.09	Gluceptate (Glucoheptonate)	0.13	Orotate	0.26
Acetylasparaginate	0.07	Gluconate	0.52	Oxalate	0.26
Acetylaspartate	0.07	Glucuronate	0.13	Oxoglurate	0.13
Adipate	0.13	Glutamate	0.07	Pamoate (Embonate)	1.37
Aminosalicylate	0.13	Glycerophosphate	0.52	Pantothenate	0.07
Anhydromethylenecitrate	0.07	Glycinate	0.13	Pectinate	0.07
Ascorbate	0.13	Glycollylarsinilate (*p*-Glycollamidophenylarsonate)	0.07	Phenylethylbarbiturate	0.13
Aspartate	0.33	Glycyrrhizate	0.07	Phosphate	2.48
Benzoate	0.20	Hippurate	0.07	Picrate	0.07
Besylate (Benzenesulfonate)	0.26	Hemisulfate	0.13	Policrilix (Methacrylic acid polymer)	0.07
Bicarbonate	0.07	Hexylresorcinate	0.07	Polistirex[b]	0.85
Bisulfate	0.13	Hybenzate *o*-(4-Hydroxybenzyl)benzoate	0.20	Polygalacturonate	0.07
Bitartrate	0.52	Hydrobromide	1.37	Propionate	0.20
Borate	0.26	Hydrochloride	43.99	Pyridoxylphosphate	0.13
Bromide	3.79	Hydroiodide	0.07	Saccharinate	0.20
Butylbromide	0.07	Hydroxybenzenesulfonate	0.07	Salicylate	0.78
Camphorate	0.01	Hydroxybenzoate	0.07	Stearate	0.20
Camsylate (Camphorsulfonate)	0.59	Hydroxynaphthoate	0.07	Stearylsulfate	0.07

Carbonate	0.46	Iodide	1.11	Subacetate	0.07
Chloride	3.53	Isethionate (2-Hydroxyethanesulfonate)	0.52	Succinate	0.52
Chlorophenoxyacetate	0.07	Lactate	0.98	Sulfate	5.82
Citrate	2.81	Lactobionate	0.07	Sulfosalicylate	0.07
Closylate (4-Chlorobenzenesulfonate)	0.07	Lysine	0.65	Tannate	0.85
Cromesilate (6,7-Dihydroxycoumarin-4-methanesulfonate)	0.07	Malate	0.26	Tartrate	2.68
Cyclamate	0.13	Maleate	3.14	Teprosilate[c]	0.07
Dehydrocholate	0.07	Mandalate	0.13	Terephthalate	0.07
Dihydrochloride	1.37	Mesylate	3.20	Teoclate (8-Chlorotheophyllinate)	0.33
Dimalonate	0.07	Methylbromide	0.39	Thiocyanate	0.20
Edetate	0.07	Methyliodide	0.20	Tidiacicate (Thiazolidine-2,4-dicarboxylate)	0.07
Edisylate (1,2-Ethanedisulfonate)	0.20	Methylnitrate	0.13	Timonacicate (Thiazolidine-4-carboxylate)	0.07
Estolate (Lauryl sulfate)	0.13	Methylsulfate	0.98	Tosylate (Toluene-4-sulfonate)	0.39
Esylate (Ethanesulfonate)	0.13	Monophosadenine (Adenylic acid)	0.07	Triethiodide	0.07
Ethylbromide	0.07	Mucate	0.07	Undecanoate	0.13
Ethylsulfate	0.07	Napadisylate	0.13	Xinafoate (1-Hydroxyl-naphthoate)	0.07
Fendizoate (Hydroxyphenylbenzoylbenzoate)	0.07	Napsylate (1,5-Naphthalenedisulfonate)	0.20		

[a]Percent is based on total number of anionic salts in use through 1993.
[b]Sulfonated diethenylbenzene–ethenylbenzene copolymer complex.
[c]1,2,3,6-Tetrahydro-1,3-dimethyl-2,6-dioxopurine-7-propanesulfate.

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