



REVIEW ARTICLE

Pharmaceutical Salts

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Keyphrases □ Pharmaceutical salts—general pharmacy, physicochemical properties, bioavailability, pharmaceutical properties, toxicology, review □ Salts, pharmaceutical—general pharmacy, physicochemical properties, bioavailability, pharmaceutical properties, toxicology, review □ Physicochemical properties—dissolution, solubility, stability, and organoleptic properties of pharmaceutical salts, review □ Bioavailability—formulation effects, absorption alteration and pharmacokinetics of pharmaceutical salts, review □ Toxicology—pharmaceutical salts, review

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The chemical, biological, physical, and economic characteristics of medicinal agents can be manipulated and, hence, often optimized by conversion to a salt form. Choosing the appropriate salt, however, can be a very difficult task, since each salt imparts unique properties to the parent compound.

Salt-forming agents are often chosen empirically. Of the many salts synthesized, the preferred form is selected by pharmaceutical chemists primarily on a practical basis: cost of raw materials, ease of crystallization, and percent yield. Other basic considerations include stability, hygroscopicity, and flowability of the resulting bulk drug. Unfortunately, there is no reliable way of predicting the influence of a particular salt species on the behavior of the parent compound. Furthermore, even after many salts of the same basic agent have been prepared, no efficient screening techniques exist to facilitate selection of the salt most likely to exhibit the desired pharmacokinetic, solubility, and formulation profiles.

Some decision-making models have, however, been developed to help predict salt performance. For example, Walkling and Appino (1) described two techniques, "decision analysis" and "potential problem analysis," and applied them to the selection of the most suitable derivative of an organic acid for development as a tablet. The derivatives considered were the free acid and the potassium, sodium, and calcium salts. Both techniques are based on the chemical, physical, and biological properties of these specific derivatives and offer a promising avenue for developing optimal salt forms.

Information on salts is widely dispersed throughout the pharmaceutical literature, much of which addresses the use of salt formation to prolong the release of the active component, thereby eliminating various undesirable drug properties (2-6). This review surveys literature of the last 25 years, emphasizing comparisons between the properties of different salt forms of the same compound. Included also is a discussion of potentially useful salt forms. Our purpose is twofold: to present an overview of the many different salts from which new drug candidates can be chosen and

Table I—FDA-Approved Commercially Marketed Salts

Anion	Percent ^a	Anion	Percent ^a
Acetate	1.26	Iodide	2.02
Benzenesulfonate	0.25	Isethionate ⁱ	0.88
Benzoate	0.51	Lactate	0.76
Bicarbonate	0.13	Lactobionate	0.13
Bitartrate	0.63	Malate	0.13
Bromide	4.68	Maleate	3.03
Calcium edetate	0.25	Mandelate	0.38
Camsylate ^b	0.25	Mesylate	2.02
Carbonate	0.38	Methylbromide	0.76
Chloride	4.17	Methylnitrate	0.38
Citrate	3.03	Methylsulfate	0.88
Dihydrochloride	0.51	Mucate	0.13
Edetate	0.25	Napsylate	0.25
Edisylate ^c	0.38	Nitrate	0.64
Estolate ^d	0.13	Pamoate (Embonate)	1.01
Esylate ^e	0.13	Pantothenate	0.25
Fumarate	0.25	Phosphate/diphosphate	3.16
Glucaptate ^f	0.18	Polygalacturonate	0.13
Gluconate	0.51	Salicylate	0.88
Glutamate	0.25	Stearate	0.25
Glycollylarsanilate ^g	0.13	Subacetate	0.38
Hexylresorcinate	0.13	Succinate	0.38
Hydrabamine ^h	0.25	Sulfate	7.46
Hydrobromide	1.90	Tannate	0.88
Hydrochloride	42.98	Tartrate	3.54
Hydroxynaphthoate	0.25	Teoclate ^j	0.13
		Triethiodide	0.13
Cation	Percent ^a	Cation	Percent ^a
Organic:		Metallic:	
Benzathine ^k	0.66	Aluminum	0.66
Chloroprocaine	0.33	Calcium	10.49
Choline	0.33	Lithium	1.64
Diethanolamine	0.98	Magnesium	1.31
Ethylenediamine	0.66	Potassium	10.82
Meglumine ^l	2.29	Sodium	61.97
Procaine	0.66	Zinc	2.95

^a Percent is based on total number of anionic or cationic salts in use through 1974. ^b Camphorsulfonate. ^c 1,2-Ethanedisulfonate. ^d Lauryl sulfate. ^e Ethanesulfonate. ^f Glucoheptonate. ^g *p*-Glycollamidophenylarsionate. ^h *N,N'*-Di(dehydroabietyl)ethylenediamine. ⁱ 2-Hydroxyethanesulfonate. ^j 8-Chlorotheophyllinate. ^k *N,N'*-Dibenzylethylenediamine. ^l *N*-Methylglucamine.

to assemble data that will provide, for the student and practitioner alike, a rational basis for selecting a suitable salt form.

POTENTIALLY USEFUL SALTS

Salt formation is an acid-base reaction involving either a proton-transfer or neutralization reaction and is therefore controlled by factors influencing such reactions. Theoretically, every compound that exhibits acid or base characteristics can participate in salt formation. Particularly important is the relative strength of the acid or base—the acidity and basicity constants of the chemical species involved. These factors determine whether or not formation occurs and are a measure of the stability of the resulting salt.

The number of salt forms available to a chemist is large; surveys of patent literature show numerous new salts being synthesized annually. Various salts of the same compound often behave quite differently because of the physical, chemical, and thermodynamic properties they impart to the parent compound. For example, a salt's hydrophobicity and high crystal lattice energy can affect dissolution rate and, hence, bioavailability. Ideally, it would be desirable if one could predict how a pharmaceutical agent's properties would be affected by salt formation.

Tables I and II list all salts that were commercially marketed through 1974. The list was compiled from all agents listed in "Martindale The Extra Pharmacopoeia,"

26th ed. (7). Table I categorizes all salt forms approved by the Food and Drug Administration (FDA), while Table II lists those not approved by the FDA but in use in other countries. (Only salts of organic compounds are considered because most drugs are organic substances.) The relative frequency with which each salt type has been used is calculated as a percentage, based on the total number of anionic or cationic salts in use through 1974. Because of simple availability and physiological reasons, the monoprotic hydrochlorides have been by far the most frequent choice of the available anionic salt-forming radicals, outnumbering the sulfates nearly six to one. For similar reasons, sodium has been the most predominant cation.

Knowledge that one salt form imparts greater water solubility, is less toxic, or slows dissolution rate would greatly benefit chemists and formulators. In some cases, such generalizations can be made. Miller and Heller (8) discussed some properties associated with specific classes of salt forms. They stated that, in general, salt combinations with monocarboxylic acids are insoluble in water and lend themselves to repository preparations, while those of dicarboxylic acids confer water solubility if one carboxylic group is left free. Pamoic acid, an aromatic dicarboxylic acid, is an exception since it is used as a means of obtaining prolonged action by forming slightly soluble salts with certain basic drugs. Saias *et al.* (9) reviewed the use of this salt form in preparing sustained-release preparations. More recently, latentiation of dihydrostreptomycin (10)

Table II—Salts

Anion	Percent ^a	Cation
Adipate		
Alginate		
Aminosalic		
Anhydrome		
Arecoline		
Aspartate		
Bisulfate		
Butylbromi		
Camphorate		
Digluconate		
Dihydrobro		
Disuccinate		
Glycerophos		
Hemisulfate		
Hydrofluori		
Hydroiodid		
Methyleneb		
Napadisylat		
Oxalate		
Pectinate		
Persulfate		
Phenylethyl		
Picrate		
Propionate		
Thiocyanate		
Tosylate		
Undecanoat		
Cation	Percent ^a	Cation
Organic:		
Benetharr		
Clemizole		
Diethylan		
Piperazin		
Trometha		
Metallic:		
Barium		
Bismuth		

^a Percent through 1974. ^b 1-*p*-Chloro-droxymethyl

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Adipate	
Alginate	
Aminosalicylate	
Anhydrometh	
Arecoline	
Aspartate	
Bisulfate	
Butylbromide	
Camphorate	
Digluconate	
Dihydrobrom	
Disuccinate	
Glycerophosp	
Hemisulfate	
Hydrofluorid	
Hydroiodide	
Methylenebis	
Napadisylate	
Oxalate	
Pectinate	
Persulfate	
Phenylethylt	
Picrate	
Propionate	
Thiocyanate	
Tosylate	
Undecanoate	
Cation	Percent ^a
Organic:	
Benethami	
Clemizole ^d	
Diethylam	
Piperazine	
Tromethar	
Metallic:	
Barium	
Bismuth	

^a Percent is based on total number of salts in use through 1974. ^b Camphorsulfonate. ^c 1,2-Ethanedisulfonate. ^d 1-*p*-Chlorodroxyethyl

using pamoic acid for prolonged action preparations.

Alginic acid is used in pharmaceutical preparations and shows various applications. A study that of pilsules dried to a solid preparation. While liquid ride salts that solid more effective. Solid dose because it which hold commonly immediate.

Málek *et al.* action through tribution of by merely molecules lymphatic.

Table II—Non-FDA-Approved Commercially Marketed Salts

Percent ^a	Anion	Percent ^a
2.02	Adipate	0.13
0.88	Alginate	0.13
0.76	Aminosalicylate	0.25
0.13	Anhydromethylenecitrate	0.13
0.13	Arecoline	0.13
3.03	Aspartate	0.25
0.38	Bisulfate	0.25
2.02	Butylbromide	0.13
0.76	Camphorate	0.13
0.38	Digluconate	0.13
0.88	Dihydrobromide	0.13
0.13	Disuccinate	0.13
0.13	Glycerophosphate	0.88
0.64	Hemisulfate	0.13
1.01	Hydrofluoride	0.13
0.25	Hydroiodide	0.25
3.16	Methylenebis(salicylate)	0.13
0.13	Napadisylate ^b	0.13
0.88	Oxalate	0.25
0.25	Pectinate	0.13
0.38	Persulfate	0.13
7.46	Phenylethylbarbiturate	0.13
0.88	Picrate	0.13
3.54	Propionate	0.13
0.13	Thiocyanate	0.13
0.13	Tosylate	0.13
Percent ^a	Undecanoate	0.13
Cation	Percent ^a	
0.66	Organic:	
10.49	Benethamine ^c	0.33
1.64	Clemizole ^d	0.33
1.31	Diethylamine	0.33
10.82	Piperazine	0.98
61.97	Tromethamine ^e	0.33
2.95	Metallic:	
Lauryl sulfate.	Barium	0.33
banesulfonate.	Bismuth	0.98

^a Percent is based on total number of anionic and cationic salts in use through 1974. ^b 1,5-Naphthalenedisulfonate. ^c *N*-Benzylphenethylamine. ^d 1-*p*-Chlorobenzyl-2-pyrrolidin-1'-ylmethylbenzimidazole. ^e Tris(hydroxymethyl)aminomethane.

using pamoic acid resulted in the formation of a delayed-action preparation. Numerous studies using pamoate salts are dispersed throughout the literature (11-15).

Alginate acid has been used to prepare long-acting pharmaceuticals. Streptomycin alginate was prepared (16) and shown to be effective in sustained-release preparations. A striking example of a long-acting alginate salt is that of pilocarpine. When dispersed in sterile water and dried to a solid gel, this compound was found useful in the preparation of long-acting ophthalmic dosage forms (17). While liquid preparations of the alginate and hydrochloride salts possess similar miotic activity, studies showed that solid pilocarpine alginate flakes constricted pupil size more effectively and increased the duration of miosis significantly when compared with the liquid preparations. Solid dose pilocarpine may be more uniformly available, because it diffuses more slowly through the gel matrix which holds the drug in reserve. In contrast, drops of the commonly employed solution dosage form release the dose immediately to the conjunctival fluid.

Málek *et al.* (18) devised a unique way of prolonging action through salt formation; they showed that the distribution of several antibiotics could be markedly altered by merely preparing macromolecular salts. Since macromolecules and colloidal particles have an affinity for the lymphatic system, streptomycin, neomycin, viomycin, and

streptothrycin were combined with high molecular weight compounds such as polyacrylic acids, sulfonic or phosphorylated polysaccharides, and polyuronic derivatives. Parenteral administration of these compounds produced low blood levels of the antibiotic for long periods, while lymph levels were high. (In comparison, streptomycin sulfate gave high blood levels but low lymph levels.) This alteration in distribution caused the streptomycin to prolong its passage through the body, since lymphatic circulation is quite slow.

The appropriate choice of a salt form has been found to reduce toxicity. It can be rationalized that any compound associated with the normal metabolism of food and drink must be essentially nontoxic. The approach of choosing organic radicals that are readily excreted or metabolized opened up a new class of substances from which to select a salt form. For example, certain salts of the strong base choline have proven to be considerably less toxic than their parent compound. The preparation and properties of choline salts of a series of theophylline derivatives were reported (19), and it was shown that choline theophyllinate possessed a greater LD₅₀ than theophylline or its other salts (20). It was postulated that this agent would be less irritating to the GI tract than aminophylline, because "its basic constituent, choline, is an almost completely nontoxic substance of actual importance to the physiologic economy." This evidence led to the preparation of choline salicylate (21) as an attempt to reduce the GI disturbances associated with salicylate administration. Clinical studies indicated that choline salicylate elicited a lower incidence of GI distress, was tolerated in higher doses, and was of greater benefit to the patient than was acetylsalicylic acid (aspirin).

Amino acids and acid vitamins also have been used as salt-forming agents. Based on the evidence that coadministration of amino acids with aminoglycoside antibiotics reduced their toxicity, a series of amino acid salts of dihydrostreptomycin was prepared (22). In all but one case, the acute toxicities of these salts were lower than the toxicity of the sulfate. The ascorbate and pantothenate also were synthesized and shown to be less toxic than the sulfate. Of the salts prepared, the ascorbate had the highest LD₅₀.

The vitamins most commonly used for forming salts exhibiting reduced toxicity are ascorbic and pantothenic acids. Keller *et al.* (23) were the first to use pantothenic acid as a means of "detoxifying" the basic streptomycins antibiotics. Parenteral administration of the pantothenates of streptomycin and dihydrostreptomycin had a significantly reduced incidence of acute neurotoxicity in cats as compared with the sulfates. Subsequent studies (24-28) supported this finding and showed that the pantothenates of neomycin and viomycin also are less toxic. The ascorbate of oleandomycin was synthesized and its pharmacological properties were reported (29). Upon intramuscular injection in rats, it produced less irritation than the phosphate.

p-Acetamidobenzoic acid, an innocuous metabolite of folic acid present in normal blood and urine, has been used in preparing salts. In particular, it yields stable salts with amines that otherwise tend to form hygroscopic products with conventional acid components (30).

Often the salt form is chosen by determining a salt

component that will pharmacologically antagonize an unfavorable property or properties exhibited by the basic agent. Salts of *N*-cyclohexylsulfamic acid are an example of the practical application of this approach. *N*-Cyclohexylsulfamic acid salts, better known as cyclamates, have a characteristic sweet, pleasing taste. Although presently under investigation by the FDA for potentially carcinogenic properties, salts incorporating this compound can render unpleasant or bitter-tasting drugs acceptable. For example, the cyclamates of dextromethorphan and chlorpheniramine exhibit greatly improved bitterness thresholds compared to commonly occurring salts (31). Furthermore, their stability in aqueous solution was described as good when maintained at a pH not greater than 4.

N-Cyclohexylsulfamic acid salts of thiamine hydrochloride and lincomycin also have been synthesized. Thiamine *N*-cyclohexylsulfamate hydrochloride was reported to have a more pleasant taste than other thiamine salts while having an equal or greater stability (32). Lincomycin cyclamate, shown to possess an enhanced thermal stability over its hydrochloride, was prepared (33) to test the hypothesis that reduced lincomycin absorption in the presence of small quantities of cyclamates was due to a simple metathetic reaction. However, this assumption was found not to be true. An extensive study of the preparation and characterization of cyclamic acid salts of several widely used classes of drugs including antihistamines, antibiotics, antitussives, myospasmolytics, and local anesthetics was reported (34, 35).

Various salts of penicillin and basic amine compounds have been formulated in an effort to produce a long-acting, nonallergenic form of penicillin. Since antihistamines appear to mitigate the symptomatology of penicillin reactions in some patients, coadministration of the two has been advocated. The preparation of the benzhydrallamine salt of penicillin was an attempt to produce a repository form of penicillin with antiallergic properties (36). Blood levels achieved with this salt were comparable to those of penicillin G potassium; however, its antiallergic properties were not evaluated. In fact, the investigators noted that antihistamines can actually cause sensitization at times and stated that "despite their occasionally favorable influence on the symptoms of penicillin sensitivity, they contribute directly to the potential of drug sensitivity when co-administered with penicillin."

Silver salts of sulfanilamide, penicillin, and other antibiotics have been prepared and represent cases where the species (ions) are complementary. When aqueous solutions of the salts were applied topically to burned tissue, they yielded the combined benefits of the oligodynamic action of silver and the advantages of the antibacterial agents (37).

The use of 8-substituted xanthines, particularly the 8-substituted theophyllines, as salt-forming agents was first reported in the preparation of a series of antihistamine salts (38-41). Synthesis of these xanthine salts was an attempt to find a drug to counteract the drowsiness caused by the antihistamines with the stimulant properties of the xanthines. When an electronegative group is introduced into the xanthine molecule at the 8-position, the electron-drawing capacity of the substituent results in the creation of an acidic hydrogen at position 7. Thus, these

moderately strong acidic compounds can undergo salt formation with various organic bases.

The 8-halothephyllines were the first group of xanthines studied as potential salt-forming agents. Since the report on the preparation of the 8-chlorothephylline salt of diphenhydramine (42), synthesis of the 8-halothephyllinates of a number of organic bases has been attempted. The 8-chlorothephylline salts of quinine, ephedrine, and strychnine were prepared and characterized (43). These salts were less water soluble than the corresponding free alkaloidal bases. In a similar report, the 8-chlorothephyllinates of three synthetic narcotics, meperidine, levorphanol, and metopon, were prepared (44).

Pharmacological and clinical studies involving the 8-bromothephylline pyrilamine salt revealed the unusual diuretic properties associated with the 8-halothephylline portion of the compound (45, 46). This finding initiated an investigation into the preparation of a soluble 8-bromothephylline salt of high diuretic activity. With readily available amines, over 30 salts were synthesized and screened for diuretic activity (47). When tested against theophylline salts of the same amines, the 8-bromothephyllinates showed greater activity in every case.

With the successful formation of 8-halothephyllinates of organic bases, Morozowich and Bope (48) proposed that, if the halogen moiety was replaced with a more electro-negative substituent such as a nitro group, a more acidic compound would be formed. Presumably, more stable salts would result and precipitation of the free xanthine derivative in the stomach would be less likely to occur. On this premise, they successfully prepared pharmacologically effective 8-nitrothephyllinates of several pharmaceutically useful bases.

Duesel *et al.* (19), in their study of choline theophyllinate, prepared the 8-chloro-, 8-bromo-, and 8-nitrothephylline salts of choline. Oral toxicity studies in mice showed that the LD₅₀ of the 8-nitrothephyllinate was much greater than that of either 8-halothephylline. In fact, it remained nonlethal at doses as high as 5 g.

Polygalacturonic acid, a derivative of pectin, has been used to prepare quinidine salts exhibiting reduced toxicity (49, 50). The compound possesses special demulcent properties and inhibits mucosal irritation. The rationale for use of this agent is to reduce the ionic shock to the GI mucosa resulting from the flood of irritating ions liberated by rapid dissociation of the conventional inorganic quinidine salts. Studies have shown that it is four times less toxic orally than the sulfate. This difference was attributed to the slower release of quinidine from the polygalacturonate.

Other compounds reported to be potentially useful as pharmaceutical salt forms are listed in Table III.

PHYSICOCHEMICAL STUDIES

Biological activity of a drug molecule is influenced by two factors: its chemical structure and effect at a specific site and its ability to reach—and then be removed from—the site of action. Thus, a knowledge of the physicochemical properties of a compound that influence its absorption, distribution, metabolism, and excretion is essential for a complete understanding of the onset and duration of ac-

Table III—

Salt
Acetylaminoe
<i>N</i> -Acetyl-L-a
<i>N</i> -Acetylcyst
Adamantoic e
Adipic acid
<i>N</i> -Alkylsulfam
Anthraquinol
Arabogalacta
Arginine
Aspartate
Betaine
Bis(2-carboxy
Carnitine
4-Chloro- <i>m</i> -t
Decanoate
Diacetyl sulfa
Dibenzylethyl
Diethylamine
Diguaiacyl ph
Diocetyl sulfos
Embonic (pan
Fructose 1,6-d
Glucose 1-pho
6-phosphori
L-Glutamine
Hydroxynaph
2-(4-Imidazol
Isobutanolam
Lauryl sulfate
Lysine
Methanesulfo
<i>N</i> -Methylgluc
<i>N</i> -Methylpiper
Morpholine
2-Naphthalen
Octanoate
Probenecid
Tannic acid
Theobromine
3,4,5-Trimeth
Tromethamine

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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.

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

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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

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Sync your system to PACER to automate legal marketing.