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Salt selection for basic drugs

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Summary

An attempt has been made using a Kepner-Tregoe decision analysis approach to provide rationale to salt selection for basic drugs. The selection objectives are reviewed in terms of the 'essential' (MUSTS) and 'desirable' (WANTS) issues. The desired characteristics of the salt form, given sufficient strength and toxicological suitability of the conjugate acid, are then discussed on the basis of the various pivotal physicochemical properties; melting point, aqueous solubility and dissolution rate, stability and hydrophobicity. Several trends are established which can then assist the decision of which range of salt forms to evaluate to overcome a particular problem with a basic drug. It is concluded that it is important to view the choice of salt form for development as a compromise, with particular focus on the correctly weighted desires to obtain the best balanced choice.

Introduction

Salt formation provides a means of altering the physicochemical and resultant biological characteristics of a drug without modifying its chemical structure. The importance of choosing the 'correct' salt form of a drug is well outlined in a published review (Berge et al., 1977) but, although salt form can have a dramatic influence on the overall properties of a drug, the selection of the salt form that exhibits the desired combination of properties remains a difficult semi-empirical choice.

In making the selection of a range of potential salts, a chemical process group considers issues on the basis of yield, rate and quality of the crystallisation as well as cost and availability of the conjugate acid. The formulation and analytical groups are, on the other hand, concerned with the hygroscopicity, stability, solubility and processability profile of the salt form, while the drug metabolism group is concerned with the pharmacokinetic aspects and the safety evaluation group on the toxicological effects of chronic and acute dosing of the drug *and* its conjugate acid. Thus, a clear compromise of properties for the salt form is required, but the difficulty remains of assessing which salt forms are best to screen for a particular drug candidate.

Little, if any, literature has been devoted to discussing the compromise of properties for salt form selection. This review addresses the problem of salt form selection for basic drugs.

Approach to the salt selection process

Walking and Appino (1973) have used the Kepner-Tregoe (KT) techniques (Kepner and

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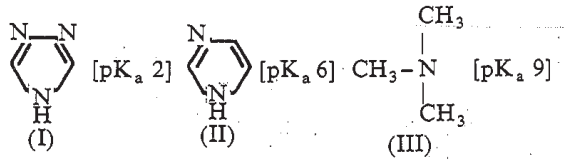
Tregoe, 1976) of decision analysis and potential problem analysis to aid the selection of a salt form. Although their application is more exemplary of the KT method rather than of the specific application, the rational process decision analysis approach which defines essential and desirable attributes as 'MUSTS' and 'WANTS', respectively, provides a route to initially address the problem of salt form selection.

"GO"/"NO-GO" issues

The major "GO"/"NO-GO" (MUSTS) issue for salt selection of an ionizable drug is the consideration of the relative basicity of the drug and the relative strength of the conjugate acid. Clearly to form a salt the pK_a of the conjugate acid has to be less than or equal to the pK_a of the basic centre of the drug.

Thus the potential range of salts of drugs containing for example triazoyl bases (I; $pK_a \sim 2$) is restricted to strong acids (mineral and sulphonic, but excluding the carboxylic), whereas imidazole bases (II; pK_a 6–7) are far less restricted and the greatest scope for salt formation occurs for the aliphatic tertiary amines (III; pK_a 9–10).



(I) (II) (III)

The relative acid/base strength of the resultant salts also dictates their stability to disproportionation, since all salts will be acid and therefore potentially reactive towards basic formulation additives.

The other essential selection issue for a salt form is the relative toxicity of the conjugate anion; some salts clearly fall into a desirable category, some acceptable but less desirable (both "GO") and some undesirable ("NO GO"). A table of salts used in pharmaceutical products marketed in the U.S. up to 1974 is given in Table 1. It would seem sensible that any acid relating to normal metabolism, or present in food and drink can be regarded as a suitable candidate for preparing salts. Clearly anions that cause irritancy to the

TABLE 1

FDA-APPROVED COMMERCIALLY MARKETED SALTS

Anion	Percent [a]	Anion	Percent [a]
Acetate	1.26	Iodide	2.02
Benzenesulfonate	0.25	Isothionate [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
Gluceptate [f]	0.18	Polygalacturonate	0.13
Gluconate	0.51	Salicylate	0.88
Glutamate	0.25	Stearate	0.25
Glycollylarsnilate [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	Aluminium	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] Laurylsulfate. [e] Ethanesulfonate. [f] Glucoheptonate. [g] p-Glycollamidophenylarsonate. [h] N,N′-Di(dehydroabietyl) ethylenediamine. [i] 2-Hydroxyethanesulfonate. [j] 8-Chlorotheophyllinate. [k] N,N′-Dibenzylethylenediamine. [l] N-Methylglucamine.

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GI tract should be avoided for some types of drug, e.g. anti-inflammatories, laxative surfactant anions for anti-secretory drugs and conjugate anions with intrinsic toxicity, e.g. oxalate.

Properties desired of the salt form (WANTS)

The desires or 'WANTS' of a salt form are dictated by the nature of the required dosage forms, their process and desired biological performance. Thus, it is somewhat difficult to provide a complete overall specification of 'WANTS' for a series of salt forms, but ideally the bulk salt should be completely chemically stable, non-hygroscopic, not cause processing problems, and dissolve quickly from solid dosage forms.

Because of simple availability and physiological reasons, the monoprotic hydrochlorides have been by far the most frequent (~ 40%) choice of the available anionic salt-forming species. Thus, there is clear precedent, and an overwhelming argument on many grounds to immediately progress to the hydrochloride salt and evaluate other forms only if problems with the hydrochloride emerge.

Prepare the hydrochloride; pros and cons

Kramer and Flynn (1972) suggest that the solubility of an amine hydrochloride generally sets the maximum obtainable concentration for a given amine.

Many reports (Miyazaki et al., 1980, 1981) have shown that hydrochloride salt formation does not necessarily enhance the solubility of poorly soluble basic drugs and result in improved bioavailability. This finding is based on the common ion effect of chloride on the solubility product equilibrium:

$$BH^+Cl^-_{(s)} \overset{K_{sp}}{\rightleftharpoons} BH^+_{aq} + Cl^-_{aq}$$

Hydrochloride salts therefore, have the potential to exhibit a *reduced* dissolution rate in gastric fluid because of the abundance of chloride ion (0.1–0.15 M). Indeed, the Setschenow salting-out constants (k) for chloride are greatest for drugs of very low solubility (Fig. 1), and can decrease the dissolution rate of the salt to below that of the free base form (Migazaki et al., 1980), which shows

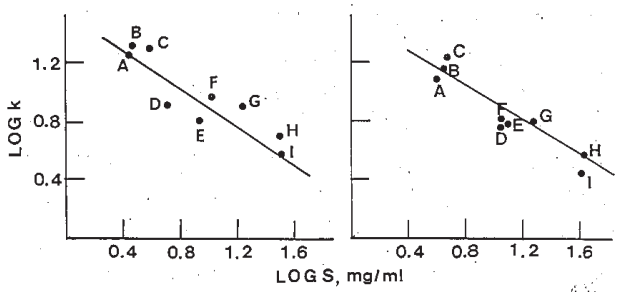
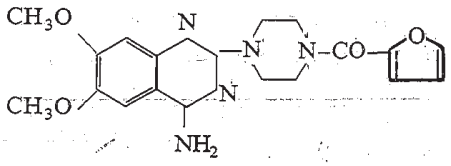


Fig. 1. Relationship between solubility in water and salting-out constant at 25°C (left) and 37°C (right). Key: A = phenazopyridine; B = cyproheptadine; C = bromhexine; D = trihexyphenidyl; E = isoxsuprine; F = chlortetracycline; G = methacycline; H = papaverine; and I = demeclocyline.

Adapted from Miyazaki et al. (1981). Reproduced with permission of the copyright owner (*J. Pharm. Sci.*).

that a precipitous drop in drug solubility occurs as the free Cl^- level is increased.

An example of a basic drug showing a strong chloride-ion dependence is prazosin.



$K_{sp} = 2.2 \times 10^{-6}$ M @ 30°C

Solubility/mg.ml^{-1} @ 30°C

Hydrochloride		Base
0.1 M HCl	water	water
0.037	1.40	0.0083

Chloride, as well as other inorganic anions have the potential to form insoluble complex salts with weak bases (Dittert at al., 1964), which are then potentially less bioavailable than the free base form. The formation of these complex salts is controlled by their stability constant K_c.

$$Drug_{(s)} \rightleftharpoons Drug_{(aq)} + xH^+ \overset{K_c}{\rightleftharpoons} Drug \cdot H^+_x(aq)$$

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