International Journal of Pharmaceutics, 33 (1986) 201–217
Elsevier

IJP 01121

Salt selection for basic drugs

Philip L. Gould

Pharmaceutical Research and Development Department, Pfizer Central Research, Sandwich, Kent (U.K.)

(Received 24 March 1986)
(Accepted 30 May 1986)

Key words: Salt form selection – Pharmaceutical salts

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

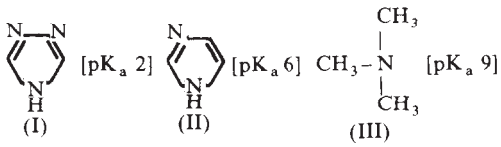
Correspondence: P.L. Gould, Pharmaceutical Group, Product Research and Development Laboratories, Cyanamid of Great Britain Limited, Gosport, Hants, U.K.

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).



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.

Reproduced from Berge et al. (1977) with permission of the copyright owner (*J. Pharm. Sci.*).

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

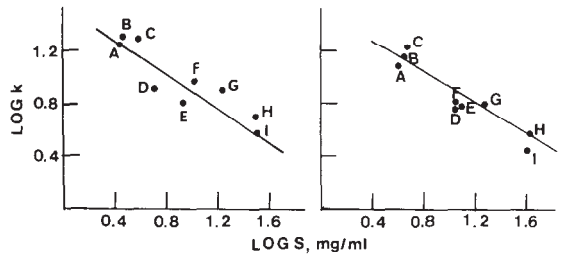
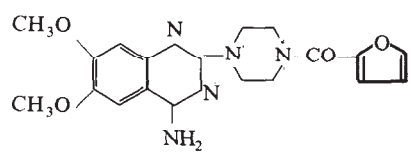


Fig. 1. Relationship between solubility in water and salting-out constant at 25°C (left) and 37°C (right). Key: A = phenazopyridine; B = cyproheptadine; C = bromhexine; D = trihexyphenidyl; E = isoxsuprine; F = chlortetracycline; G = methacycline; H = papaverine; and I = demeclocyline.

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.

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

Evaluation of K_c for triamterene (Tr) yields values of $x = 0.5$ for chloride, suggesting that one proton solubilizes two molecules of the drug, i.e. the complex is Tr_2H^+Cl.

With hydrochloride salts there is frequently an 'overkill' on acid strength, which leads to a very low pH for an aqueous solution (Nudelman et al., 1974) of the salt. This can then limit the utility of hydrochloride salts in certain parenteral dosage forms, or lead to packaging incompatibilities with pharmaceutical metal containers (aerosols).

Other problems frequently arise as the result of the polar nature of hydrochloride salts. Their high hydrophilic nature, favouring wettability probably as a result of the polar ionized groups being exposed on the crystal surfaces, leads to water vapour sorption (hygroscopicity) which on occasions, may be excessive. This can result in processing difficulties (e.g. powder flow) and reduce the stability of a hydrolytically unstable drug. This latter effect is exacerbated by the resulting very low pH of the loosely bound moisture.

These problems can be particularly acute with dihydrochlorides (or disulphates). Also, the difference in the strength of the basic centres in dihydrochloride salts can lead to a gradual loss of one of the hydrochloride moieties by release of hydrogen chloride gas (Lin et al., 1972) at elevated temperatures or under reduced pressure (i.e. freeze-drying). Also, their extreme polar nature results in excessive hydroscopicity (Boatman and Johnson, 1981) eventually leading to deliquescence.

Thus, progression of a hydrochloride salt should be a first move, but if the problems with that salt form arises due to some of the reasons outlined, then the real selection issue for a salt form emerges—what trends are available for guidance?

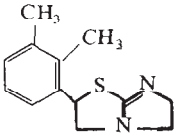
The pivotal issues for salt selection

Each drug and its associated range of dosage forms will present different salt form requirements, and it is perhaps best to discuss salt selection further by outlining some of the trends in salt properties that may facilitate selection.

The pivot of melting point

A change in the development of a compound from the free base to a salt may be promoted by a need to moderate the kinetics and extent of drug absorption, or to modify drug processing. Unfortunately these desires may be mutually exclusive, as the balance between these properties is frequently pivoted around the melting point of the salt form. For example, an increase in melting point is usually accompanied by a reduction in salt solubility (the ideal solubility of a drug in all solvents decreases by an order of magnitude on an increase of 100°C in its melting point), whereas high melting crystalline salts are potentially easier to process.

The increase or decrease in melting point of a series of salts is usually dependent on the controlling effect of crystallinity from the conjugate anion. This is exemplified by considering an experimental drug candidate (UK47880) which has a basic pK_a of 8, and therefore gives access to a wide variety of salt forms:



UK-47880
melting point, 74°C

Salts prepared from planar, high melting aromatic sulphonic or hydroxycarboxylic acids yielded crystalline salts of correspondingly high melting point (see Table 2), whereas flexible aliphatic strong acids such as citric and dodecyl benzene sulphonic yielded oils. Thus, the comparative planar symmetry of the conjugate acid appears important for the maintenance of high crystal lattice forces. This is shown by the melting point of the conjugate acid being highly correlated with the melting point of the resultant salt form (Fig. 2). Therefore the highly crystalline salts are in this case best suited to reducing drug solubility.

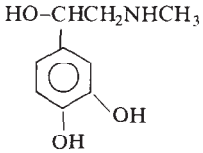
Alternatively it should also be feasible to build up crystal lattice forces of drugs with good hydrogen bonding potential, by considering symmetry and hydrogen bonding potential of the conjugate acid. One salt series of interest is that for

TABLE 2

MELTING POINT OF SALTS OF EXPERIMENTAL COMPOUND (UK47880) AND THE CORRESPONDING CONJUGATE ACID

	Melting point (°C)		Legend Fig. 2
	Salt	Conjugate acid	
UK 47880; free base	74		A
pamoate (embonate)	235	280	G
4-hydroxynaphthalene-1-sulphonate	170	190	D
Salicylate	156	158	C
3-hydroxynaphthalene-2-carboxylate	223	220	E
2-hydroxynaphthalene-1-carboxylate	145	120	B
anthraquinone-3-sulphonate	234	225	F
dodecylbenzene sulphonate	20	–	–
mesylate	113	20	–
citrate	20	153	–

epinephrine



Salt form	Melting point (°C)
epinephrine	157
tartrate	149
maleate	182
malate	170
fumarate	103

where small highly hydrogen bonding acids such as malonic and maleic gave higher melting salts, whereas the larger bitartrate and presumably symmetrically unfavoured fumarate gave salts of lower melting point.

Melting point and aqueous solubility

The trends in melting point (m.p.) and aqueous solubility alluded to above are exemplified in the salts of a high melting antimalarial drug (Agharkar et al., 1976).

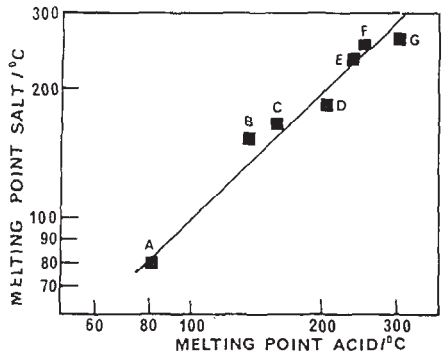
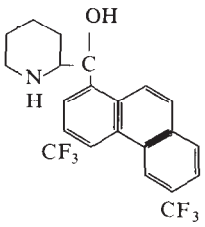


Fig. 2. Plot of melting point of UK47880 salts vs melting point of conjugate acids. Legend given in Table 2.



Salt form	m.p. salt (°C)	m.p. acid (°C)	solubility (mg/ml)
Free base	215		7.5
HCl	331		13
DL-lactate	172	17	1850
L-lactate	192	53	925
2-hydroxyethane sulphonate	251		620
Mesylate	290		300
Sulphate	270		20

The relationship between aqueous solubility (S_w) and melting point is shown diagrammatically in Fig. 3, where log S_w is correlated over a range of salts with the inverse of the melting point. Interestingly with this compound, the solubility of the hydrochloride salt in water is only approximately twice that of the free base, whereas the low melting DL-lactate provides a 200-fold advantage over the free base in terms of solubility, which is a result in part of the reduced lattice energy.

Melting point and chemical stability

The stability of organic compounds in the solid state is intimately related to the strength of the crystal lattice. Since the forces between molecules in a crystal are small compared with the energy

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.