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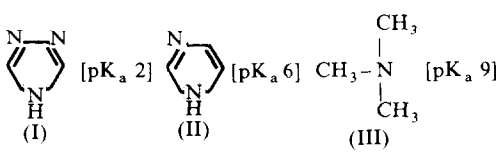
Tregoe, 1976) of decision analysis and potential problem analysis to aid the selection of a salt form. Although their application is more exemplary of the KT method rather than of the specific application, the rational process decision analysis approach which defines essential and desirable attributes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

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

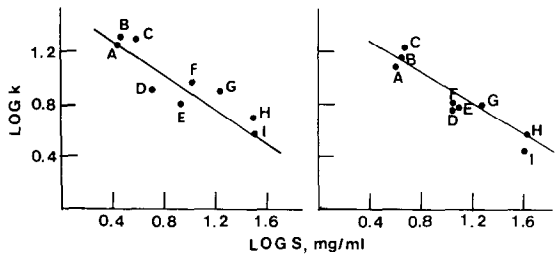
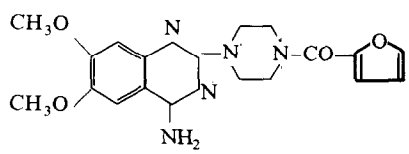


Fig. 1. Relationship between solubility in water and salting-out constant at 25°C (left) and 37°C (right). Key: A = phenazopyridine; B = cyproheptadine; C = bromhexine; D = trihexyphenidyl; E = isoxsuprine; F = chlortetracycline; G = methacycline; H = papaverine; and I = demeclocyline.

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?

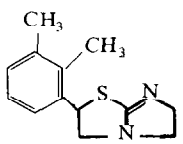
The pivotal issues for salt selection

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	–

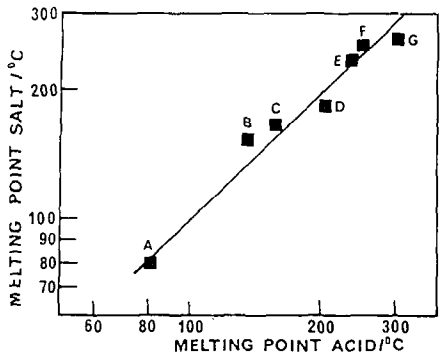
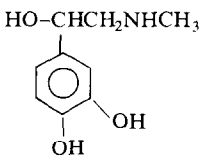
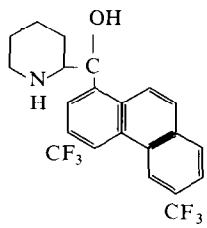


Fig. 2. Plot of melting point of UK47880 salts vs melting point of conjugate acids. Legend given in Table 2.

epinephrine



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



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

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).

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

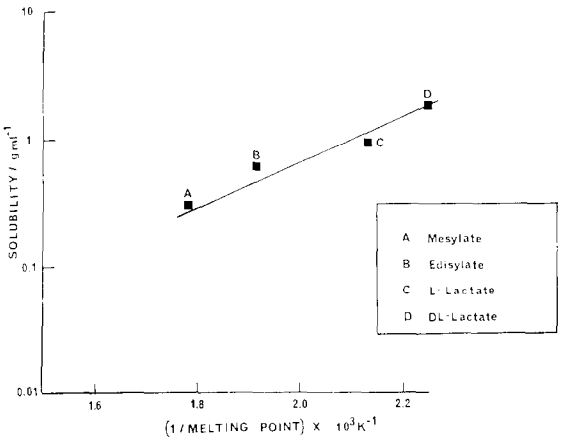


Fig. 3. Plot of aqueous solubility vs inverse of absolute melting point for a series of salts of a hydrophobic antimalarial drug. Data taken from Agharkar et al. (1976).

required to break chemical bonds, liquefaction of the solid (and an increased frequency of molecular collisions) occurs before degradation begins. Thus the melting point of a compound can be an important factor in determining stability.

Degradation of solid drugs, when it is observed, usually occurs in the surface film phase and is accompanied by the formation of a liquid phase at temperatures below the normal melting point of the solid. Using this so-called 'liquid layer' approach, Guillory and Higuchi (1962) investigated the stability of esters of vitamin A employing the following equation to determine the relationship between degradation rate and melting point.

$$\log K = \frac{A\Delta H[1]}{R[T_m]} - \frac{\Delta H}{RT_d}$$

where T_m = normal melting point; T_d = depressed storage temp. = storage temperature; K = degradation rate constant; ΔH = heat of fusion.

Thus, for a series of related compounds subject to a storage temperature T_d, the logarithm of the degradation rate constant is inversely related to the absolute melting point of the compounds. Although this approach may be somewhat simplistic it may have utility as a method of assessing the bulk stability of non-hygroscopic salt forms.

The melting point of a salt form also has some influence on its relative compatibility with drug combinations (Hirsch et al., 1978) or formulation excipients (Li Wan Po and Mroso, 1984) since it essentially controls the formation and extent of eutectic melts.

As an additional aspect to the strength of crystal forces, the balance of the amorphous to crystalline nature in solid salts can dramatically affect their stability. This is exemplified by the sodium salts of ethacrynic acid (Yarwood et al., 1983).

	Sodium ethacrynate	
	Crystalline	Amorphous
m.p. (°C)	200	–
% remaining after 9 days @ 60°C	100	92

These results are consistent with the concept of an amorphous material being a highly viscous concentrated solution and show that the stronger crystalline lattice forces result in superior solid state stability.

Melting point and formulation processing

Salt formation is frequently employed to raise the melting point (and crystallinity) of the drug species being processed. However, published work concerning this type of manipulation is somewhat sparse.

The melting point of drug salts can dramatically affect their physical storage. Drugs (or salts) with low melting points generally exhibit plastic deformation (Jones, 1979) and thus during storage the stress exerted by the bulk mass on the asperity points of interparticulate contact can lead to the formation of localized welds leading to bulk aggregation. Also, if the sublimation temperature is low (e.g. ibuprofen, m.p. 76°C), intraparticulate voids can be bridged by sublimed drug again leading to aggregation. Thus on storage, the bulk drug salt will begin to cake and aggregate, thereby altering significantly its flow, compression and long-term dissolution properties.

Melting point also has a crucial role in drug processing, in particular comminution and tableting. Since low melting compounds tend to be plastic, rather than brittle, they comminute poorly, and frictional heating causes melting and deposition of the drug on the screens and pins of the mill causing it to 'blind'. For production of fine pharmaceutical powders this aspect is crucial to judging the correct level of filler to allow efficient

manufacture using a cost-effective feed rate.

Salt melting point can also have important implications for particle bonding on compression for tableting. Since bonding on compression occurs by point welding at the deformed or fragmented particle surfaces, then at a fixed temperature and pressure, a lower melting species would be expected to improve bonding. However, the pressure on the powder (and the eutectics formed with the other excipients) suppress the melting point further. The Skotnicky equation defines the fall in melting point (T_m) with the pressure on the solid (P_s)

$$\frac{dT_m}{dP_s} = \frac{-V_s T}{\Delta H_f}$$

where ΔHf = heat of fusion; V_s = volume of solid; T = temperature, and therefore as well as those salts which are intrinsically low melting, salts of different values of ΔHf would be expected to have different abilities to cold weld in the compression process. If we compare, for example, the melting points and heats of fusion of the salts of an experimental drug candidate:

Salt	T_m (°C)	ΔH_f (kJ·mol^{-1})
Hydrochloride	280	56.5
Mesylate	135	20.5
Tartrate	213	63.6
Citrate	180	27.2
Phosphate	250	136.5
Acetate	180	167.9

the data suggest that the low melting point and low ΔH_f for the mesylate salt would make it the most suitable candidate, on bonding grounds, for a direct compression tablet. Since the melting points of compounds are reduced under pressure, the solubility of salt forms would be expected to increase with increasing pressure. This can potentially cause the formation of solutions of the salts in the film of absorbed moisture on the surface of the drug (and excipient) particles which then may have an effect on drug bonding (Parrot, 1982) or cause the drug to adhere to the punches on compression (Wells and Davison, 1985).

Conclusion

The consideration of melting point is a key parameter in assessing the 'viability' of certain salt forms. In general, an increase in melting point, usually by maximizing or encouraging crystal symmetry, leads to reduced solubility *in all* solvents, but generally improved stability, particularly if salt formation results in a crystalline solid, and easier formulation processing. For a specific salt form for parenteral use, i.e. where solubility and resultant pH is a major issue, a low melting point salt produced using a soluble fairly weak acid (see next section) probably made in situ is likely to be preferable.

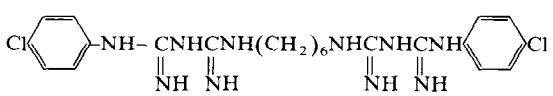
The pivot of drug solubility

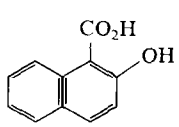
There are various solubility issues that can decide the viability of a particular salt form and it is perhaps worth addressing these separately to identify trends that may aid salt selection.

Aqueous solubility per se

As indicated earlier, the solubility of a drug can be enhanced dramatically by salt formation (Agharkar et al., 1976). This enhancement may arise from a reduction in melting point, or from improved water-drug interactions. A good example of this is with the salts of chlorhexidine (Senior, 1973), where increased water solubility was not only produced by a lowering of melting point, but by increasing the hydroxylation of the conjugate acid.

Chlorhexidine



Salt	Structure	Melting point (°C)	Solubility % w/v @ 20°C
base	above	134	0.008
dihydrochloride	HCl	261	0.06
di-2hydroxy-naphthoate		–	0.014
diacetate	CH_3CO_2H	154	1.8
dilactate	$CH_3CHOHCO_2H$	–	1.0
digluconate	$HO_2C(CHOH)_4CO_2H$	low	70

The above data exemplify the importance of considering the hydrophilic nature of the conjugate anion, as well as its role in controlling crystallinity, when considering the potential solubility of salts.

Reduced aqueous solubility may occasionally be a crucial development factor for a drug, e.g. for an organoleptically acceptable or chemically stable suspension. Such systems demand salts of low solubility, but recent experience with a series of purposely designed insoluble salts of an experimental drug candidate also highlighted the need to consider the solubility and pK_a of the conjugate anion.

$$\underset{\text{salt}}{BH^+X^-_{(S)}} \rightleftharpoons BH^+_{(aq)} + X^-_{aq} \qquad B = \text{free base of experimental drug}$$

$$\Downarrow K_b \quad K_a \Downarrow + H^+$$

$$B_{(S)} \rightleftharpoons B_{(aq)} \qquad HX_{(aq)} \rightleftharpoons HX_{(S)}$$

$$H^+$$

The above ionic equilibria show that even sparing solubility of the salt means that the level of the conjugate anion in solution will depend markedly on the pH of the fluid. Consideration of the above for a pamoate salt, which has pK_a's of the parent acid of 2.5 and 3.1 and virtually insoluble unionized form, indicates that solutions of pH 5–6 will drive the equilibria to the right, with full precipitation of the free acid $HX_{(S)}$ and liberation of a full component in solution of the ionized base (BH^+). However, if we consider the hydroxynaphthalene sulphonic acid ($pK_a = 0.11$) then this system provides 'insolubility' over a much wider pH range and is therefore far more tolerant to fluctuations in the fluid pH.

The above aspect is important when considering the potential use of 'insoluble' salts (e.g. pamoate) to control the absorption of a drug candidate. For example, the in vitro dissolution rates of the dimaleate and pamoate salts of a drug candidate were compared in simulated gastric and intestinal fluid. The dissolution rates were essentially identical in the former fluid, with rapid deposition of the pamoic acid and liberation of the free base, whereas in the latter the pamoate salt exhibited a much slower dissolution rate than the maleate. Therefore 'control' on the drug absorption (and toxicity) may then depend on the duration of gastric residence and the pH of the gastric contents. Thus aspects such as food vs the fasted state are also important. In fact in this case, the bioavailability in the dog of the two salt forms when dosed orally from a standard capsule formulation were of the same order; 24% for the pamoate and 39% for the maleate.

Usually it is the dissolution rate of a drug which is of major importance to the formulation and as a rule a salt exhibits a higher dissolution rate than the base at an equal pH, even though they have the same equilibrium solubility. This latter effect, which is exemplified by theophylline salts (Nelson, 1957), is due to the salt effectively acting as its own buffer to alter the pH of the diffusion boundary layer, thereby increasing the apparent solubility of the parent drug in that layer. Thus, administration of basic drugs as their salt forms (e.g. tetracycline hydrochloride) ensures that stomach emptying rather than in vivo dissolution will be the rate-limiting factor in their absorption. It is also possible that increased drug absorption may occur with salts due to their effect on the surface tension of the gastrointestinal fluids (Berge et al., 1977).

Salt solubility and pH of salt solutions

Enhancement of the aqueous solubility of a drug by salt formation can occur due to differences in the pH of the saturated salt solutions. A soluble acid salt of a weakly basic drug will cause the pH to drop as the salt is added to the solution. This pH drop will, in turn cause more drug to dissolve, and this process will continue until the pH of maximum solubility is reached (see Fig. 4). The equilibrium solubility(ies) are then given by:

$$S = S^+(1 + 10^{pH - pK_a})$$

for $pH = pH_{max}$, i.e. when the ionized form is solubility limiting and

$$S = S_i(1 + 10^{pK_a - pH})$$

for $pH = pH_{max}$, where the unionized form is solubility limiting and pH_{max} is given by the solution of the equality of pH for the above two

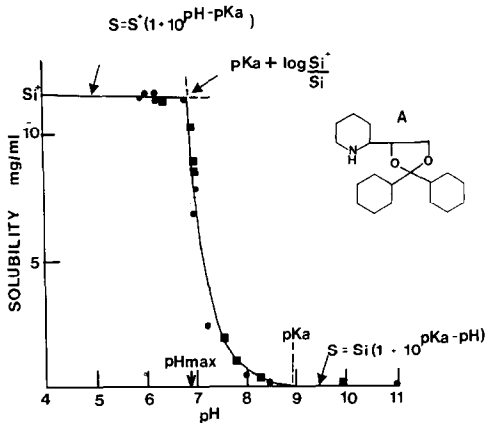


Fig. 4. Solubility of A in water at ambient temperature (~ 23°C) as a function of pH. All data are in mg/ml calculated in terms of free base equivalent. The lines drawn through the data are theoretical and were calculated using 0.067 mg/ml as the free base solubility, 11.5 mg/ml as the hydrochloride solubility and 8.85 as the pK_a. Data by both gravimetric (■) and GLC (●) procedures were in good agreement.

Adapted from Kramer and Flynn (1972), with permission of the copyright owner (*J. Pharm. Sci.*).

equations where

$$pH_{max} = pK_a + \log \frac{S_i^+}{S_i}$$

and implies that both free base and salt form can exist simultaneously in equilibrium with the saturated solution.

Thus, large pH shifts on dissolution of salts suggests that a large amount of conjugate acid is dissociating and therefore, a relatively high solubility is then obtained. If we consider physiological pH, a low pK_a for a conjugate acid of high aqueous solubility, would appear to give the best change of obtaining the lowest pH_{max} and the highest aqueous salt solubility. For example, the solubilities of a series of salts of a drug candidate and the pH of the saturated solutions were as follows:

Type	Salt		Conjugate acid	
	pH_{max}	Solubility (mg/ml)	pK_a	Solubility (mg/ml)
Hydrochloride	2.71	35.9	−6.1	
Mesylate	2.57	51.2	−1.2	
Tartrate	4.21	0.49	3.03	1470
Citrate	3.30	2.16	3.13	2400
Phosphate	5.31	10.31	2.15	
Acetate	5.29	8.04	4.76	

indicating that the salts of stronger acids (HCl, methane sulphonic) produce the lowest slurry pH and the highest salt solubility. In this case the solubility and resultant low pH of the hydrochloride is suppressed by the common ion effect. The solubility of salts such as the lactate (pK_a of conjugate acid is 3.85, with infinite solubility) may offer significant advantage over for example the acetate, tartrate and citrate.

The pH of a salt solution can be a deciding factor in the selection of a salt for a parenteral dosage form. Ideally to avoid pain on injection the pH of i.v. parenterals should be between pH 3 and 9, and so highly acidic salts such as the hydrochloride and mesylate are probably best replaced by an acetate salt.

Kramer and Flynn (1972) have shown that for a series of hydrochloride salts, by making analysis of the differential heat of solutions of the ionized and unionized species, that the temperature dependencies of the solubilities of the hydrochloride salts were considerably lower than those of the corresponding free base form. This may have important implications for solution dosage form design and storage conditions.

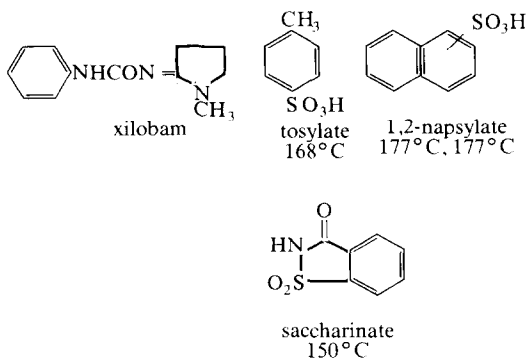
Salt solubility and salt stability

As well as the relationships between salt melting point and stability raised earlier, it is also clear that low solubility and low hygroscopicity can contribute significantly to the stability of a salt form. The former aspect is obviously important in developing a stable aqueous suspension formulation of a hydrolytically unstable water soluble

drug; e.g. penicillin-benzithine.

For salts of weak bases, the moisture associated with the bulk can be very acidic (the salt will buffer the available moisture), and can potentially cause severe hydrolytic degradation of the parent drug. Classic examples of this phenomenon are thiamine salts (Yamamoto et al., 1956, 1957) where the stability is related to their hygroscopicity, aqueous solubility and the resulting pH.

Thus, to improve drug stability by salt formation, it is clearly not only important to control hygroscopicity, but also to consider carefully the strength of the conjugate acid used to form the salt. This is particularly important for compacted dosage forms where salt and excipient *share* the available moisture, particularly when the majority of the available moisture comes from the excipient rather than the drug. Thus, assessment of salt stability in compressed and non-compressed systems is an important activity in preformulation studies. However, in selection terms salts of mineral acids will produce a lower pH, and higher solubility in the available moisture and therefore produce a more hostile stability environment than that from a sulphonate or carboxylate type salt. It is also apparent that another consideration in the relationship of salt stability is the hydrophobic portion of the conjugate acid. This is exemplified with xilobam (Walking et al., 1983), where aryl sulphonic acids salts were prepared to protect this easily hydrolyzed base.



The rationale behind the choice of these salt forms was that they comprise fully ionized acids and therefore present pH-independent aqueous solubility in biological fluids. However, as opposed to the poorly stable hydrochloride and sulphate salts, the aryl groups present a hydrophobic barrier to minimize hygroscopicity and dissolution in the surface moisture. The highest melting (least soluble?) salt, 1-napsylate, proved to be the most stable, with full retention of potency following 7 days storage at 70°C/74% RH, whereas only 18% of the base remained after this challenge. The 1-napsylate salt also provided full and rapid dissolution in vitro ($t_{90\%}$, 15 min).

The pivot of salt hydrophobicity

Although the xilobam example above serves to demonstrate that one has to consider the hydrophobicity of the conjugate anion to control salt stability, it is clear that this property is pivotal on two others; salt hygroscopicity and wettability. Thus, once again, a balance of salt properties is required so that hygroscopicity is not reduced at the gross expense of salt wettability leading ultimately to dissolution rate and bioavailability problems.

Hydrophobicity and hygroscopicity

Soluble 'polar' salts have a propensity to be hygroscopic, presumably through favourable hydrogen bonding interactions with the available atmospheric moisture; i.e. by a similar mecha' ism that contributes to their high aqueous solu..lity. Thus, the more polar or less hydrophobic the conjugate acid and salt form, the greater will be the propensity to adsorb moisture at a set humidity and this accounts for the frequent acute hygroscopicity of dihydrochloride over monohydrochloride salts (Boatman and Johnson, 1981).

The high solubility and associated hygroscopicity of hydrophilic salts can preclude their isolation and exploitation in certain dosage forms. For parenterals or topical solutions they are usually made in situ. A good example is that provided with the gluconate salt of chlorhexidine (Senior, 1973).

It is also apparent that the hygroscopic character of polar salt forms will also depend on the nature of the solid. For crystalline materials hy-

groscopicity will depend on the nature of the exposed surfaces which will vary with crystal habit (i.e. the balance of hydrophobic to hydrophilic faces) as well as the more obvious physical properties like particle size distribution. Furthermore, the degree of crystallinity in the solid may be important, as an increase in amorphous nature may prevent the dominant exposure of hydrophobic faces, and lead to a consequent increase in hygroscopicity. It should also perhaps be noted that different polymorphs have the potential for yielding salts of varying hygroscopicity due to different arrangements of the hydrophobic and hydrophilic crystal faces.

Hydrophobicity and wettability

The ability of a dissolution fluid to wet a solid is intimately related to the polarity of that solid. Usually the wettability of a solid, as indicated by the magnitude of the contact angle, θ, is linearly related to the surface tension of the fluid, and interpolation of surface tension for $\cos \theta = 1$ ($\theta = 0$) yields values for the critical surface tension for wetting γc. Polar solid surfaces (e.g. polydroxy acids) would have high γc values (i.e. near water) and are consequently wetted more easily than hydrophobic surfaces with low γc values. Thus salt stability exerted using hydrophobic conjugate strong acids may be difficult to wet and therefore ultimately lead to prolonged dissolution.

Selection of the most suitable salt forms to evaluate

The 'pivots' on the properties of salt forms outlined above need to be considered before deciding on the most suitable range of salt forms to prepare. Clearly one can use the broad generalizations already outlined, but there remains a need to consider 'balance'. With a specific problem (e.g.

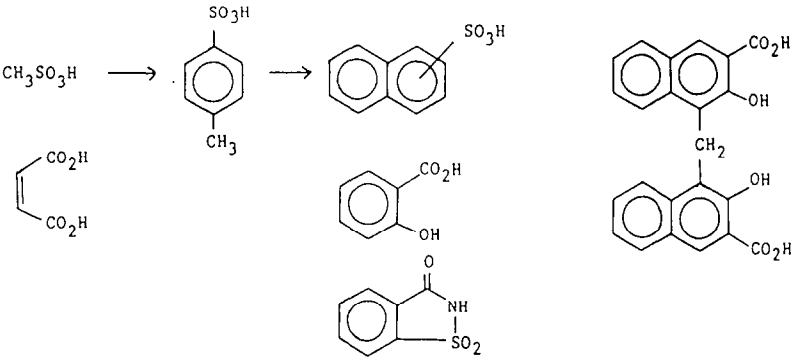
ACTION	DECREASE CHANGE AND REASON	PROPERTY	INCREASE CHANGE AND REASON	ACTION
. use more flexible aliphatic acids with aromatic bases . move to more highly substituted acids that destroy crystal symmetry	DECREASE . increase solubility . form oil	MELTING POINT	INCREASE . process problems . reduce solubility	. use small counter ions e.g. Cl , Br . use aromatic conjugate annions if aromatic base . use small hydroxy acids if drug has good hydrogen bonding potential
. increase melting point . increase hydrophobicity of conjugate annion	DECREASE . suspensions . controlled release	SOLUBILITY (DISSOLUTION) RATE	INCREASE . bioavailability . liquid formulation	. decrease pKa and increase solubility of conjugate acid . decrease melting point . increase hydroxylation of conjugate acid . if common ion dependence move to small organic acid
	DECREASE	STABILITY	INCREASE	. reduce hygroscopicity by increasing hydrophobicity of acid. Also move to carboxylic rather than sulphonic or mineral acid . use acid of higher pKa to raise pH of sorted water . decrease solubility and increase crystallinity by increase of melting point
. increase hydrophobicity of conjugate annion	DECREASE . to control to some degree hygroscopicity	WETTABILITY	INCREASE . dissolution/ bioavailability	. increase polarity of conjugate annion . lower pKa of conjugate acid . attempt recrystallisation from different solvents to alter crystal habit . move to acid with high degree of hydroxylation

Fig. 5. Flow chart for manipulation of drug characteristics by change of salt form.

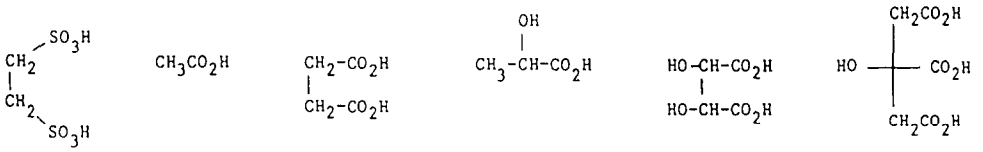
TABLE 3

SERIES OF SALTS WHICH MAY PROVIDE SET PROPERTIES AS REFERRED TO IN "SELECTION OF THE MOST SUITABLE SALT FORMS TO EVALUATE".

SERIES 1 HCl CH_3SO_3H



SERIES 2



SERIES 3 $CH_3(CH_2)_4CO_2H$ $CH_3(CH_2)_5CO_2H$ $C_{12}H_{25}SO_3H$

$CH_2{=}CH{-}(CH_2)_8\ CO_2H$

$CH_3(CH_2)_7CH{=}CH{-}(CH_2)_7CO_2H$

stability) there is probably a need to consider a specific range of salts, whereas at other times, e.g. to control in vivo absorption it may be more fitting to consider a wider spectrum of salts in order to assess the most suitable salt forms for progression.

Conjugate acids can be 'clustered' into groups for addressing specific issues. The following, which is summarized in Fig. 5, may provide some first line generalization.

(i) Manipulation of melting point

For aromatic type bases, melting point could conceivably be increased by considering the range of acids given in series (1) of Table 3. For more flexible low melting basic drugs of a hydrophilic nature, acids with good hydrogen bonding potential may provide a route to increasing melting point, e.g. by exploiting hydroxy acids within series (2).

Alternatively, series (2) can be used on occasions to reduce melting point (probably with a desire to increase aqueous solubility) in planar symmetrical aromatic drugs.

Alternatively to reduce melting point, e.g. to give hydrophobic oils (ion pairs?), e.g. for intramuscular injection or vaginal ovules, it may be more feasible to use long chain, flexible saturated or unsaturated acids such as decanoic (e.g. heptaminol), octanoate (e.g. heptaminol), or undecylenic.

(ii) Solubility

The above rationale for the latter portion of series (1) would also serve for movement to potentially more insoluble salt forms; for example, for

suspension formulation, to control taste, or control of drug absorption.

An often overlooked series of conjugate acids is the ion-exchange resins. These have virtues that the systems are essentially insoluble in water, but release drug rapidly by proton exchange in the gut. They also have potential for taste masking organoleptically unpleasant drugs, since the pH of saliva is considerably higher than the gut and so minimal exchange occurs in the mouth. In this latter respect there seems some rationale also to consider the preparation of a saccharinate or aspartamate salt to mask the taste of a bitter drug.

To increase aqueous solubility for basic drugs it would seem appropriate to proceed half way up series (1) (i.e. before crystal forces dominate the solubility) or to extend into the hydroxy acids series (2). For pH-independent solubility it would seem sensible to progress with fully ionized acids, e.g. sulphonic, using a moderately hydrophobic organic portion to control hygroscopicity. If stability is a problem, and the salt is hygroscopic it would seem more sensible to select a less polar acid, e.g. carboxylic.

(iii) Stability

If a salt form proves unstable, then a salt form with an increase in melting point should help to increase crystallinity, decrease the effects of any surface liquid amorphous film and also decrease solubility in the available moisture. A balance of these effects, together with considerations of overall salt hydrophobicity, and the strength of the acid moiety are also required. Investigating around the lower to middle of series (1) would seem a sensible place to start for attempting to identify a stable salt form.

Other salt opportunities

Amino acids such as choline, and acid vitamins such as ascorbic and pantothenic, together with the ion-exchange resin systems already mentioned, give a wider possibility for alternative salt forms. Other possibilities include carbohydrate type acids such as alginic to exert some oral controlled release, e.g. streptomycin, pilocarpine, or polygulacturonic (a derivative of pectin) to reduce mucosal irritation (Berge et al., 1977).

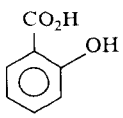
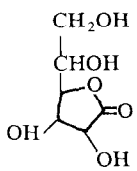
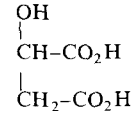
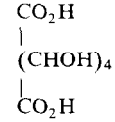
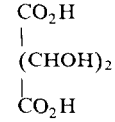
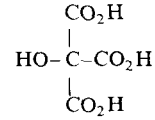
Conclusion

The balance required in assessing the correct salt form to progress into drug development makes it a difficult semi-empirical exercise. Clearly, issues exist for rejecting certain salt forms, but generally a plethora of conjugate acids may still be available for exploitation. The pivots on salt properties discussed above, and the broad generalizations in trends outlined, enables the most suitable group of salt to be assessed. To assist this selection details of a wide series of conjugate acids including details on structure, melting point, pK_a, LD_{50} and examples of use are provided in the appendix. On occasions, there appears some rationale for investigating non-standard salt forms, as opportunities for correcting or addressing a specific problem of the drug substance in its target dosage form.

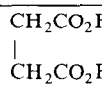
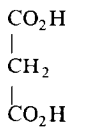
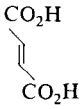
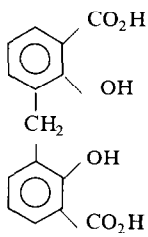
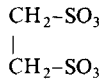
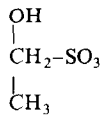
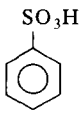
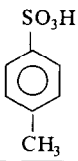
APPENDIX

COMPILATION OF CHARACTERISTICS OF VARIOUS SALT FORMING ACIDS

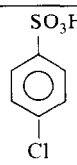
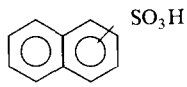
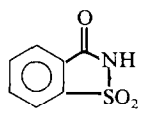
Toxicity data from 1980 registry of toxic effects of chemical substances. If acid polybasic, more acidic pK_a given.

Name	Trivial salt name	Structure	pK_a @ 25°C	Melting point (°C)	LD_{50} (mg/kg)	Examples of use
Acetic	acetate	CH_3CO_2H	4.76	16.6	3310, oral rat 4960, oral mouse 525, i.v. mouse	Chlorhexidine, guanabenz, saralasin, leurolium, mafenide
Benzoic	benzoate	$C_6H_5CO_2H$	4.20	122	2530, oral rat 2370, oral mouse 2000, oral dog 2000, oral rabbit	Denatonium, Sphaerophysine
Oleic	oleate	*cis*-9-octadecinoic	~ 4	~ 4	230, i.v. mouse 74,000, oral rat	morphine
Undecylenic	undecylenate	dec-9-ene-1-carboxylic acid	~ 4	24	25,000, oral rat	Clemizole
Salicylic	salicylate		2.97	158	500, i.v. mouse 891, oral rat 480, oral mouse 400, oral cat 1300, oral rabbit	Quinidine, carbazochrome, choline, phenazone, aceclidine
Ascorbic acid	ascorbate		4.21	191	643 i.p. mouse LDL_0 = 2300 man	Dihydrostreptomycin
Glycolic	glycolate	$OH \cdot CH_2CO_2H$	3.82	80	1950, oral rat 1920, oral g.pig	
(+)-Lactic (±)-Lactic	lactate	$CH_3CHOH \cdot CO_2H$	3.85	53 17	3730, oral rat 4875, oral mouse 1810, oral g.pig	Prenylamine
(−) Malic	malate			100	LDL_0 1600, oral rabbit	Pizotifen, triethylperazine
Gluconic	gluconate		3.60	131		Chlorhexidine, quinidine
(+)-tartaric (−)- (±)-	tartrate		2.93	170 170 205	485, i.v. mouse	Metoprolol, metarminol
Citric	citrate		3.13	153	111,700, oral rat 5040, oral mouse 42, i.v. mouse 330, i.v. rabbit	Various, e.g. tamoxifen, lithium

APPENDIX (continued)

Name	Trivial salt name	Structure	pK_a @ 25°C	Melting/ point °C	LD_{50} (mg/kg)	Examples of use
Succinic	succinate		4.19, 5.64	185	LDL_0 2000 s.c. frogs	Doxylamine
Malonic	malonate		2.85, 5.70	136	1310, oral rat 4000, oral mouse	Pyridoxine
Fumaric	fumarate		3.03 4.38	302	10,700, oral rat 5000, oral rabbit	Various: propiram, recefemine, clemastine, methapyrilene, ketotoifen
Maleic	maleate		1.96 6.28	131	708, oral rat 2400, oral mouse	Prochlorperazine, timolol, perhexiline, thiethylperazine
Pamoic (embonic)	pamoate (embonate)		2.51 3.1	280	390 i.p. mouse	Viprynium, cycloguanil, amitriptyline, imipramine, chlorpromazine, promazine, hydroxyzine
Methane sulphonic	mesylate	CH_3SO_3H	−1.2	20		Various, poldine, phentolamine, benztropine
Ethane sulphonic	esylate	$CH_3CH_2SO_3H$				Ergotoxine, piminodine
2-Ethane sulphonic	edisylate			173		Chlormethiazole, prochlorperazine
2-hydroxy-ethane sulphonic	isethionate					Dibromopropamidine, phenamidine
Benzene sulphonic	besylate		1.58	43	890, oral rat	Atracurium, cobaltous
p-Toluene sulphonic	tosylate		−1.34	70	2480, oral rat 400, oral mouse	Improsulfan, bretylium, pempidine, intramin

APPENDIX (continued)

Name	Trivial salt name	Structure	pK_a @ 25°C	Melting/ point °C	LD_{50} (mg/kg)	Examples of use
p-chloro-benzene sulphonic acid	closylate			67		Thenium (veterinary)
1,2-naphthalene sulphonic	napsylate		(1) (2)	90 + 124 + + both hydrates		(2) dextropropoxyphene, talampicillin, levopropoxyphene
Saccharin	sacharrinate		1.60	229	1700, oral mouse	
Lauryl sulphonic	estolate	$C_{12}H_{25}SO_3H$				Erythromycin (as ^{i}Pr ester)
Sulphonic acid resin	resinate	polystyrene-divinylbenzene sulphonic acid				Isoxsuprine, phenteramine
Hydrochloric	hydrochloride	HCl	−6.1		900, oral rabbit 40 i.p. mouse $LDL_0 = 81$	Various, e.g. oxytetracycline
Hydrobromic	hydrobromide	HBr	−8			Various, e.g. homatropine, hyoscine, tigloidine, hydroxy-amphetamine, dextromethorpan
Sulphuric	sulphate	H_2SO_4	−3		2140, oral rat	Various, e.g. Videsine, Vincristine, neomycin, morphine
Phosphoric	phosphate	H_3PO_4	2.15 [7.20] [12.38]		1530, oral rat	Varios, e.g. codeine, clindamycin, tetracycline

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