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RESEARCH ARTICLE

Impact of the counterion on the solubility and physicochemical properties of salts of carboxylic acid drugs

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Abstract

Aim: Salt formation is a widely used approach to improve the physicochemical and solid state properties of an active pharmaceutical ingredient. In order to better understand the relationships between the active drug, the selected counterion and the resultant salt form, crystalline salts were formed using four different carboxylic acid drugs and a closely related series of amine counterions. Thirty-six related crystalline salts were prepared, characterized and the relationship between solubility and dissolution behaviour and other properties of the salt and the counterion studied.

Methods: Salts of four model acid drugs, gemfibrozil, flurbiprofen, ibuprofen and etodolac were prepared using the counterions butylamine, hexylamine, octylamine, benzylamine, cyclohexylamine, tert-butylamine, 2-amino-2-methylpropan-1-ol, 2-amino-2-methylpropan-1,3-diol andtris(hydroxymethyl)aminomethane. Salt formation was confirmed, the salts were characterized and their corresponding solubilities determined and rationalized with respect to the counterions' properties.

Results and conclusion: The properties of the salt highly dependent on the nature of the counterion and, although there is considerable variation, some general conclusion can be drawn. For the alkyl amines series, increasing chain length leads to a reduction in solubility across all the acidic drugs studied and a reduction in melting point, thus contradicting simplistic relationships between solubility and melting point. Small, compact counterions consistently produce crystalline salts with high melting point accompanied with a modest improvement in solubility and the nature of hydrogen bonding between the ions has a major impact on the solubility.

Keywords: Salt selection, counterion, solubility, gemfibrozil, flurbiprofen, ibuprofen, etodolac, tris(hydroxymethyl) aminomethane

Introduction

Solid state modification is offers the opportunity to alter unfavourable properties of active pharmaceutical ingredients (APIs) that may impact on successful development. Salification for ionisable drugs is a commonly employed strategy[1,2] as the formation of a salt from a weakly acidic or basic drug will have a major impact on its properties including solubility, dissolution rate, hygroscopicity, stability, impurity profile and particle characteristics[3]. Modern high throughput automated processes of drug discovery are producing more lipophilic and increasingly insoluble drugs[4] and there are a number of studies focusing on streamlining the process of selection of an appropriate counterion for salt formation, often driven by physicochemical requirements, with non-optimal salt forms being systematically eliminated until the choice is narrowed down to likely candidates[5–7]. Early identification of potential salt forms within the preformulation process can avoid delays and expense later in the development process[8], however, the relationship between different solid crystalline forms and their properties is generally poorly understood, thus their properties are

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difficult to predict[9] and conclusions regarding relationships between physicochemical properties and solubility have been contradictory and variable.

The most desirable properties are usually high solubility and dissolution rate, stability and crystallinity with the absence of polymorphic forms, usually followed by consideration of the ease of manufacture, formulation and processibility. For dosage forms wherein the drug forms a large percentage of the formulation, the latter characteristics become more important with drug-carrying capacity of directly compressible tablets often limited to 25%[10].

Inorganic counterions are most often used to modify a drug's properties: sodium is the most common cationic counterion used (65.3%[3,11]) but the trend toward a broader diversity of counterions might be anticipated as more challenging molecules are selected for development. The solid state properties of crystalline salts depend largely on the nature of the counterion and rational salt selection, to optimize such properties based on predictive relationships between counterion choice and desired properties, has been suggested but only limited work exists in this area[1,12]. Chowan[13], Anderson and Conradi[14] and Forbes et al[15]., investigated the effect of choice of counterions on the solubility of different carboxylic acids while Cheong and Choi[16] sought to improve the physicochemical properties of piroxicam using ethanolamine. Only a small number of studies involve comparative evaluations of salts of weakly acidic drugs, including diclofenac[17–20], flurbiprofen[14] and tris(hydroxymethyl)aminomethane salts of four anti-inflammatory drugs[21].

The aim of this work was to conduct a systematic investigation of the impact of the counterion on salts of acidic drugs with the view to understanding the role of the counterion. Four carboxylic acids were selected due to their limited solubility in the unionized state: flurbiprofen, etodolac, gemfibrozil and ibuprofen (Figure 1). A range of different organic counterions was used to form the salts and the impact of the counterion on physicochemical and technological properties was studied. Rather than selecting only commonly used counterions, this study employs a related series of counterions, thus the impact of small structural changes on the properties can be studied in a systematic manner. The counterions used as the salt formers were butylamine (butyl), hexylamine (hex), octylamine (oct) benzylamine (benz), cyclohexylamine (cyclo), tert-butylamine (tertBA), 2-amino-2-methylpropan-1-ol (AMP1), 2-amino-2-methylpropan-1,3-diol (AMP2) and tris(hydroxymethyl)aminomethane (tris) (Table 1).

Materials and methods

Materials

Gemfibrozil was supplied by DiPharma (Italy) and flurbiprofen was supplied by Erregierre (Italy). Ibuprofen was supplied by Sigma-Aldrich (Poole, UK). Etodolac was supplied by Ulkar Kimya (Istanbul). Tert-butylamine, AMP1, AMP2, tromethamine, benzylamine, cyclohexylamine, octylamine, hexylamine and butylamine were supplied by Sigma-Aldrich. Acetonitrile and methanol were supplied by Fisher (Loughborough, UK). All materials were of pharmaceutical, analytical or HPLC grade as appropriate.

Methods

Salt preparation

Crystalline salts were prepared by mixing equimolar amounts of drug and counterion dissolved in acetonitrile and the resultant crystals recovered by filtration under vacuum or following cooling to–4°C until crystals

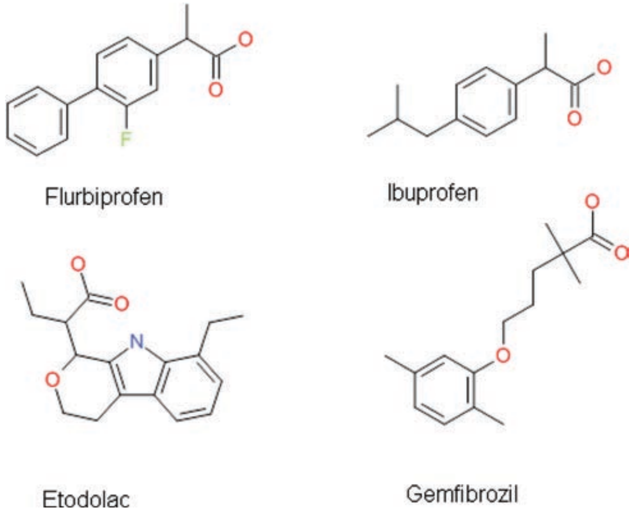

Figure 1. Chemical structures of the four carboxylic acid drugs.

Table 1. General molecular descriptors of amines used as counterions. *pK_a and logP values from the SPARC online calculator and ClogP version 4.0.

Drug	CLogP	pK_a	Counterion	CLogP*	pK_a*	Counterion	CLogP*	pK_a*
Etodolac	3.52	4.33,	Butylamine	0.92	10.33	Tert-butylamine	0.59	10.52
		4.65[a]	Hexylamine	1.98	10.33	AMP1	-0.59	9.20
Flurbiprofen	3.44	4.35	Octylamine	3.04	10.33	AMP2	-0.59	7.94
		4.22[b]	Benzylamine	1.09	9.36	Tris	-0.94	6.44
Gemfibrozil	4.16	4.72				Cyclohexylamine	1.37	10.52
		4.70[c]						
Ibuprofen	3.68	4.55						
		4.31[d]						

[a]Lee et al.[45]; [b]Anderson and Conradi[14]; [c]Gerbino[46]; [d]Slater et al.[47].

appeared. For AMP1 and AMP2-containing salts, the amines were dissolved in a warmed solution of methanol which was added to a solution of the drug in acetonitrile, and the crystals collected by filtration. Products were dried overnight under vacuum and stored in sealed containers at room temperature until used.

Salt characterization

Nuclear magnetic resonance (NMR) and fourier-transform infra red spectroscopy (FTIR). Formation of 1:1 monovalent salts was confirmed using NMR and FTIR. Samples were dissolved in deuterated chloroform and chemical shifts and ^{1}H-NMR spectra were recorded on a Bruker AC 250 NMR (250 MHz) and a MAC Quadra 800 PC using WIN-NMR version 3.0 software was used to interpret the results. FTIR analysis of the drug or salt in KBr was carried out using a Unicam Mattson 3000 over 4000–400 cm^{-1} with Galaxy software.

Thermal analysis. Differential scanning calorimetry (DSC) was performed using a Perkin Elmer PYRIS Diamond DSC. Each sample (3–5 mg) was accurately weighted and heated under nitrogen in vented pans at a scan rate of 10°C/min from 0°C to a temperature exceeding the melt or a maximum of 250°C. Thermogravimetric analysis (TGA) was performed on samples of between 5 and 10 mg using a Perkin Elmer Pyris 1 TGA over the temperature range 25–250°C in a nitrogen atmosphere.

Microscopy and powder X-ray diffraction. Crystal habit was assessed using a Nikon polarized light microsope over a range of magnification. Powder X-ray diffraction patterns of drug and salt samples and compacts were analyzed using a Rigaku Miniflex diffractometer (Rigaku, Sevenoaks, Kent, UK) with Cu Kα radiation at 30 kV/15 mA. All samples were scanned from 2 to 60° 2θ at a rate of 2° min^{-1}. Verification or standardisation tests for the instrument were conducted using mica and alumina reference standards.

True density measurements. The densities of the drug and salt powders were measured in triplicate using a Gemini Helium Pycnometer (Micromeritics, Dunstable, UK) and the pycnometer was calibrated before use.

Dynamic vapour sorption (DVS). Water vapour adsorption and desorption isotherms of the drugs and salts were measured in triplicate using a DVS-1 (Surface Measurement Systems, Alperton, UK). Samples (~10 mg) were dried at 0% RH until a constant mass was obtained. Isotherms were constructed at 20°C over 0–100% humidity increased in increments of 10% after the equilibration of sample mass.

HPLC analytical method

High-performance liquid chromatography (HPLC) was performed using an Agilent 1100 series HPLC system (Agilent Technologies, Wokingham, UK) with a G1312A Binary Pump, G1313A ALS Auto-injector, G1316A COLCOM column section and a G1314A VWD variable wavelength detector. An ODS-2 Hypersil 150 cm × 4.6 mm 5 µm column (ThermoScientific, Hemel Hempstead, UK was used for all samples with a mobile phase of 65:35 acetonitrile:water (phosphoric acid 0.005% v/v), a flow rate of 1 ml/min and injection volume of 1 µl. Gemfibrozil and its salts were analyzed at 276 nm; flurbiprofen and its salts were analyzed at 250 nm; ibuprofen and its salts were analyzed at 225 nm and etodolac and its salts were analyzed at 254 nm.

Determination of saturated solubility and intrinsic dissolution rate

Excess solid was added to double distilled water in triplicate, the vials sealed and stirred for 48 h under ambient conditions. Extracted samples were filtered through a 0.45 µm PTFE syringe filter, the pH measured and samples diluted as appropriate with mobile phase prior to HPLC analysis. The saturated solubilities of model drugs and prepared salts were also measured at pH 6 using phosphate buffer.

Compressed tablets of drug or salt powder were made using a Specac KBr press and 13 mm die using a pressure of seven tonnes on a powder of weight 0.01 moles ± 2 mg with a 5 min dwell time and a 24 h recovery time. This was shown to provide a compact whose X-ray diffraction pattern closely matched that of the raw powder (XRPD not shown). The tablets were attached to PTFE holders[22] which exposed only one face of the compact. USP apparatus 2 (Hanson SR11 6-flask dissolution system) was used at 50 rpm for dissolution studies and phosphate buffers at pH 6.8 and 7.2 were used for flurbiprofen experiments and gemfibrozil experiments respectively in order to achieve the equivalent degree of ionisation in the solutions. According to the SPARC online calculator (Table 1) there is a 0.4 unit difference in pK_a values which is subsequently represented in the choice of pH values that were used to run the experiments.

Statistical analysis

SPSS (version 12.0.1) statistical package was used to perform an analysis of variance (ANOVA) on the solubility and intrinsic dissolution data. A one-way ANOVA test was performed using a Tukey *post hoc* at a significance level of 0.001 ($P = 0.05$).

Results and discussion

Salt characterization

In order to develop an understanding of how the counterion impacts the salt properties, we have used a number of structurally related series of amine counterions which will impact on the physicochemical properties of the resultant salts formed. The estimated pK_a and logP values from the SPARC online calculator and ClogP version 4.0 were calculated for all materials and are summarized together with literature values in Table 1.

The salts were formed by combining an amine ($R\text{-}NH_3^+$) ion with the anion of an organic carboxylic acid (COO^-). As the bases had sufficiently high pK_a values, the salts were generally easily formed and precipitated from organic solvents. NMR and FTIR were used to verify salt formation with the total proton count in ^{1}H-NMR studies confirmed that all the salts had the expected number of hydrogen atoms present, had formed in a 1:1 ratio (as expected from the valencies) and the ^{1}H-NMR traces had an acceptable signal to noise ratio. A signal at 1684 cm^{-1} in the FTIR spectra for the parent drugs, attributed to a C=O stretching of the carboxylic acid group[17,18,23,24], was absent in the salts and was replaced by bands characteristic of carboxylic acid salts, at 1650–1550 cm^{-1} and 1440–1335 cm^{-1}(ref. 25). An additional band was present between 3350–3150 cm^{-1}, and is attributable to NH_3^+ stretching of solid amine salts[25].

Salt forms of an API may be useful for reasons of purity, thermal stability, manufacturability, and ease of production and the goal is a solid, crystalline, stable material with improved physicochemical and mechanical properties. Melting point relationships are complex when considering salts, which are a combination of covalent bonds, ionic bonds and intermolecular forces. Whereas the melting points of covalently bonded molecules can be related to aqueous solubility[26], once another molecule is added by ionic bonds, this alters the physicochemical characteristics in an unpredictable way. Generally on addition of the amine counterion to the carboxylic acid drug, a crystalline product was formed with a sharp melting point(s), confirmed by DSC and each salt had a characteristic and unique XRPD pattern indicative of the crystalline nature of the particular salt form. There was a reduction in melting point and enthalpy of fusion as chain length increased for the alkylamine homologous series of salts of all drugs (gemfibrozil, etodolac, flurbiprofen and ibuprofen; Tables 2–5). Some of the salts with longer alkyl chain lengths, often associated with increasing mobility, have lower melting points than the parent probably due to an increased chain length creating disorder in the crystal lattice[27–29].

The melting points of all tertBA, AMP1, AMP2 and tris salts are higher than the parent drug (Tables 2–5) with the exception of Etodolac AMP2. A desolvation/melt peak was seen using DSC with a concomitant weight loss at 100°C upon TGA suggesting the salt may be a solvate. DVS of this salt resulted in a mass change of 0.05% w/w when the humidity was reduced to zero which corresponds to the monohydrate form of the salt (Figure 2). The extent of hydrogen bonding in crystal lattices of tertBA, AMP1, AMP2 and tris salts will vary with the number of hydroxyl groups in the counterions impacting their melting point. The AMP2 salts have lower melting points than the other salts in the series

Table 2. Measured physicochemical properties and solubilities of etodolac salts.

Etodolac	Mean density (g/cm^3) ±SD	Mp (°C)	Enthalpy of fusion (kJ/mole)	Aqueous Solubility (mol/L)	pH of saturated aqueous solution
Drug	1.24 ± 0.001	151–153	29.4	7.72×10^{-4}	4.42
Butylamine	1.15 ± 0.001	148–155	25.2	0.0489	6.78
Hexylamine	1.10 ± 0.004	140–143	28.8	0.0151	6.79
Octylamine	1.08 ± 0.013	111–113	27.6	3.69×10^{-3}	6.42
Benzylamine	1.20 ± 0.001	164–165	48.2	8.01×10^{-3}	6.97
Cyclohexylamine	1.60 ± 0.001	199–203	28.8	0.0126	7.30
Tert-butylamine	1.15 ± 0.001	177–185	23.7	0.0435	7.34
AMP1	1.24 ± 0.002	165–167	33.2	0.199	8.68
AMP2	1.25 ± 0.001	116–122*	32.1	>0.510	n/a
Tris	1.24 ± 0.001	159–161	58.2	0.248	7.26

*based on combined desolvation/melt peak.

Table 3. Measured physicochemical properties and solubilities of flurbiprofen salts.

Flurbiprofen	Mean. density (g/cm^3)	Mp (°C)	Enthalpy of fusion (kJ/mole)	Aqueous Solubility (mol/L)	pH of saturated aqueous solution
Drug	1.29 ± 0.001	115–117	24.7	1.35×10^{-4}	4.20
Butylamine	1.16 ± 0.002	139–141	23.6	0.0169	7.43
Hexylamine	1.12 ± 0.001	87–91	27.5	0.021	7.20
Octylamine	1.10 ± 0.002	103–104	33.8	6.93×10^{-3}	7.30
Benzylamine	1.21 ± 0.001	136–138	38.9	8.12×10^{-3}	6.44
Cyclohexylamine	1.20 ± 0.002	197–201	47.8	1.08×10^{-3}	6.50
Tert-butylamine	1.17 ± 0.002	193–198	46.7	8.74×10^{-3}	7.00
AMP1	1.24 ± 0.001	154–157	33.6	0.0268	7.56
AMP2	1.32 ± 0.033	123–126	36.4	0.0311	6.00
Tris	1.32 ± 0.002	150–152	39.4	0.0304	6.70

Table 4. Measured physicochemical properties and solubilities of gemfibrozil salts.

Gemfibrozil	Mean. density (g/cm^3)	Mp (°C)	Enthalpy of fusion (kJ/mole)	Aqueous Solubility (mol/L)	pH of saturated aqueous solution
Drug	1.09 ± 0.001	62–64	22.3	8.79×10^{-5}	5.40
Butylamine	1.07 ± 0.002	75–77	25.5	0.111	8.70
Hexylamine	1.05 ± 0.002	70–72	22.7	0.0106	7.80
Octylamine	1.04 ± 0.001	37–40	28.7	2.32×10^{-3}	7.50
Benzylamine	1.10 ± 0.001	91–93	20.9	7.45×10^{-3}	8.60
Cyclohexylamine	1.09 ± 0.001	135–137	41.2	9.94×10^{-3}	7.10
Tert-butylamine	1.04 ± 0.002	141–146	24.7	0.0243	7.60
AMP1	1.12 ± 0.003	119–122	52.0	0.0353	7.70
AMP2	1.18 ± 0.001	104–106	28.7	0.085	7.70
Tris	1.20 ± 0.001	119–121	68.0	0.0228	7.50

Table 5. Measured physicochemical properties and solubilities of ibuprofen salts.

Ibuprofen	Mean. Density (g/cm^3)	Mp (°C)	Enthalpy of fusion (kJ/mole)	Aqueous Solubility (mol/L)	pH of saturated aqueous solution
Drug	1.11 ± 0.001	76–79	24.2	3.45×10^{-4}	3.67
Butylamine	1.07 ± 0.001	104–106	19.3	0.583	8.37
Hexylamine	0.98 ± 0.004	91–94	20.3	0.0200	7.73
Octylamine	0.75 ± 0.001	80–82	21.4	4.93×10^{-3}	7.19
Benzylamine	1.08 ± 0.001	107–109	25.9	7.99×10^{-4}	7.35
Cyclohexylamine	1.12 ± 0.001	197–201	49.0	3.37×10^{-3}	6.43
Tert-butylamine	1.02 ± 0.001	185–190	35.9	0.018	6.53
AMP1	1.11 ± 0.001	130–134	51.1	0.458	8.21
AMP2	1.15 ± 0.001	112–116	23.3	>0.643	n/a
Tris	1.20 ± 0.001	160–164	60.8	0.0274	6.67

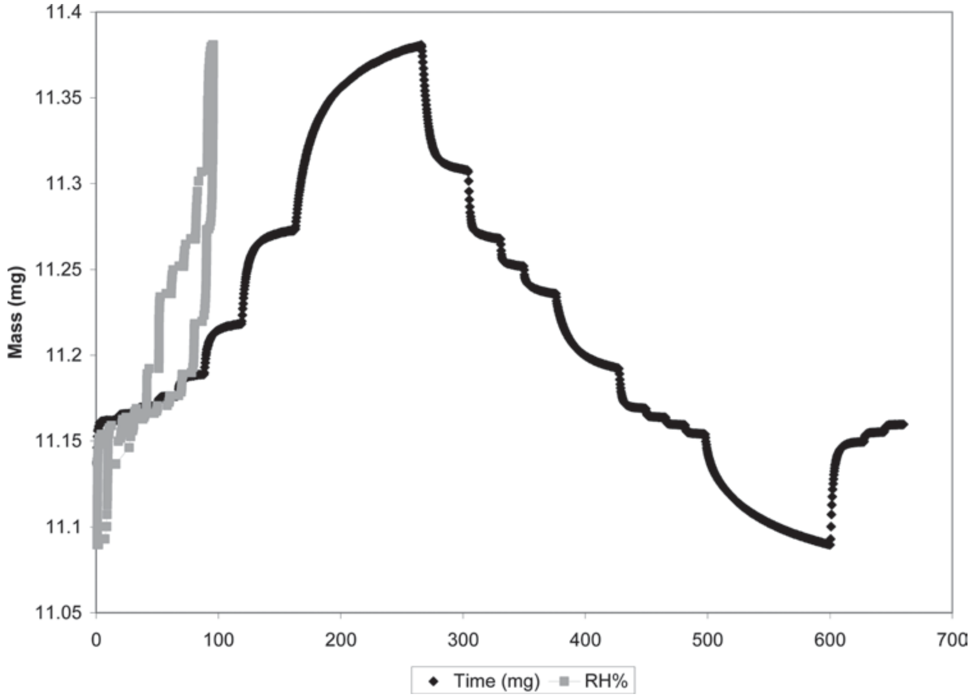

Figure 2. DVS data for etodolac AMP2 representing weight change over time and RH%.

(Tables 2–5) and generally have lower enthalpy values (ΔHkJ/moles) which, if a simple model were followed, would imply these would have the highest solubility within the groups[30].

The cyclohexylamine salts of all the drugs have high melting points, relative to the other salts, and have high enthalpies of fusion but the introduction of a benzylamine group may increase the risk of polymorph formation, with both gemfibrozil benzylamine and ibuprofen benzylamine showing evidence of polymorphism. The ibuprofen benzylamine salt DSC analysis showed two peaks between 100°C and 120°C, (Figure 3). On reheating the sample under the same conditions a single peak was produced at 109°C, Figure 2. DVS results for ibuprofen benzylamine indicated that water was not present in the molecule but TGA revealed a decrease in mass (–1.5%) at a temperature exceeding the endothermic event on the DSC scan. No weight was lost at the temperature corresponding to the onset of the first endothermic event, therefore, two polymorphic forms of this salt may exist, one of which converts to the other on heating.

Upon heating, the TGA of gemfibrozil benzylamine reveals a loss of ~1% at a temperature exceeding the endothermic events on the DSC scan, indicating possible polymorph formation. The two forms of gemfibrozil benzylamine that are shown in Figure 4 resulted from the same preparation conditions and production of polymorphs is common when crystallising salt forms and has previously been described by O'Connor and Corrigan[18] for benzylamine and AMP1 salts of diclofenac.

Drug salts should normally be selected to be non-hygroscopic, i.e. normally an upper limit of 0.5% at 90% RH[31] although this figure has been reported to be as high as 2% at 25°C/60% RH[32,33]. Without formation of a stable hydrate, water uptake of more than 5% at this condition will probably require major efforts in formulation development and compound handling. Despite the hygroscopic nature of some of the amine counterions used (e.g. tris) salt forms were generally stable to humidity as indicated by limited hysteresis in the change in mass versus humidity graphs (data not shown). The largest change in mass was observed with gemfibrozil AMP1 and flurbiprofen AMP2 which showed a slight hysteresis on desorption and over 1% change in mass over the humidity range studied (2.00% and 1.30%, respectively).

True density

The true density plays a critical role in determination of powder porosity[34] and particle mechanical properties[35,36], indicating on a macro scale how the crystal lattice is arranged. Differences in the true density between polymorphic forms can be attributed to different packaging of molecules in the crystalline structure. For the straight-chain alkylamine series, the highest densities corresponded with the shortest chain length (Tables 2–5).

A variety of crystal habits resulted from the specified crystallisation conditions which will influence their pharmaceutical handling properties. Over 60% of the 40 crystalline materials studied were either needle-like crystals or agglomerated needle crystals, such as Gemfibrozil AMP1 crystals (Figure 5A) and would be predicted to have poor flow and poor compressional properties. Flurbiprofen hexylamine and octylamine salts formed plate-like crystals (Figure 5B) and gemfibrozil butylamine and tris salts formed prisms and tabular crystals (Figure 5C), which could improve compression and flow properties. Etodolac salts had different crystal morphologies, e.g, the benzylamine salt formed prisms while the tert-butylamine salt existed in plates. The ibuprofen tris and hexylamine salts formed lath-like crystals, whereas ibuprofen AMP1 salt existed as small tabular crystals.

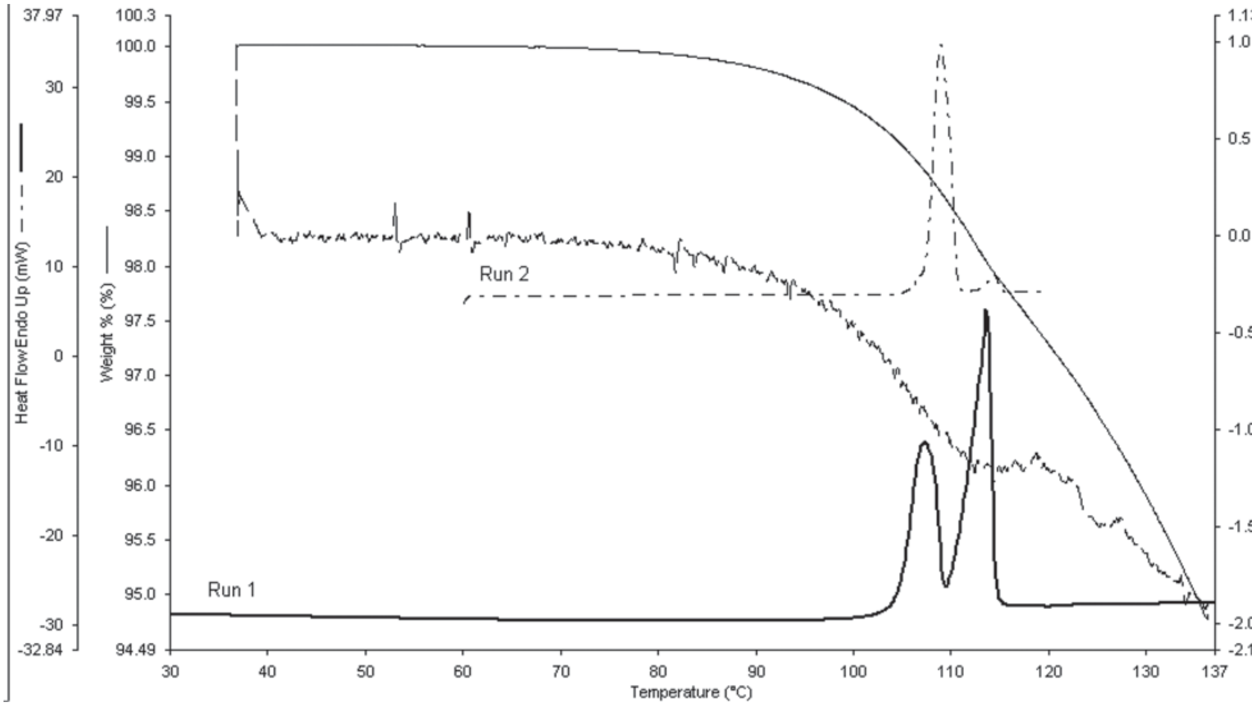

Figure 3. DSC and TGA profiles for ibuprofen benzylamine. Ibuprofen benzylamine upper scan is the second repeat of the run.

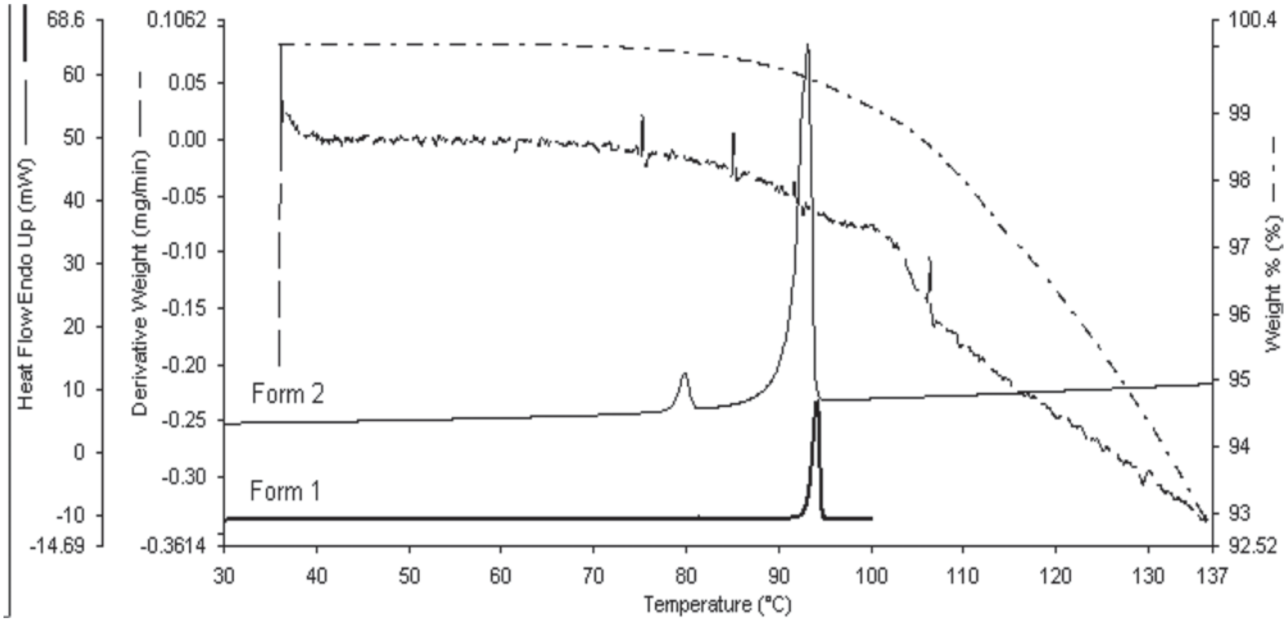

Figure 4. DSC and TGA profiles for the benzylamine salt of gemfibrozil showing the presence of proposed polymorphic form 2.

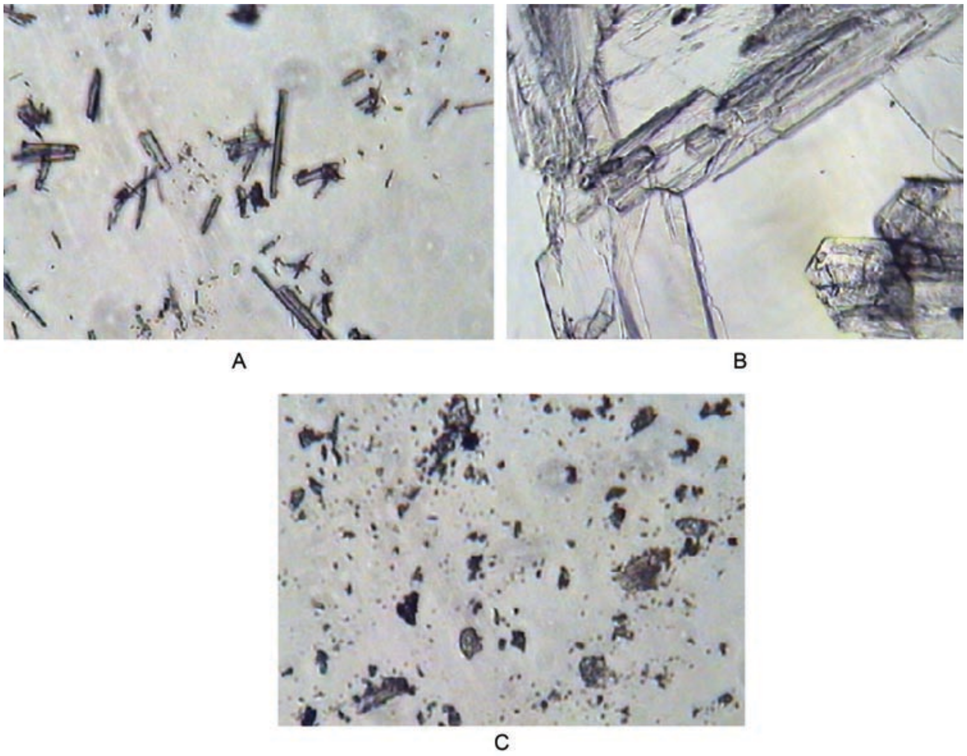

Figure 5. (A) Gemfibrozil AMP1 crystals x20. (B) Flurbiprofen octylamine crystals x10. (C) Gemfibrozil tris crystals x20.

Effect of the counterion on solubility and intrinsic dissolution rate

The molar solubilities of the salt forms vary over several orders of magnitude, over four orders of magnitude for ibuprofen salts. Solubility increases with chain length for salts of all drugs of the homologous alkylamine series, from highest to lowest (i.e. butylamine> hexylamine> octylamine). As the chain length increases the lipophilicity of the counterion increases and aqueous solubility reduces. Combining these data with the melting point information from the DSC identifies a trend such that as melting point reduces, solubility is also reduced. This contradicts the attractive notion that as melting point reduces, solubility increases due to the reduced energy required to break the crystal lattice[1].

Over the range of amine salts studied here (etodolac ($n=10$), flurbiprofen ($n=11$), gemfibrozil ($n=10$) and ibuprofen ($n=10$)), no relationship was found between salt melting point and solubility. This implies that melting point relationships are complex when considering salts, due to the complex nature of association with the counterion. Studies correlating solubility and melting point for salts of acidic drugs have produced mixed results including an inverse linear relationship between the logarithm of salt solubility and melting point[30,37], a direct relationship between the inverse of the melting point and the logarithm of the solubility[38] while Anderson and Conradi[14] reported a non-linear relationship between the salt melting point and log K_{sp} (stoichiometric solubility) for a series of flurbiprofen salts. O'Connor and Corrigan[18] observed a trend between salt melting point and the logarithm of the solubility and between the inverse of the melting point and the logarithm of the solubility for a selection of amine salts of diclofenac. Conversely, Gu and Strickley[21] concluded that no simple solubility-melting point relationship could be established for tris(hydroxymethyl)aminomethane salts of four anti-inflammatory drugs.

Within the extended range of amine salts studied here for four different carboxylic acid drugs (etodolac ($n=9$), flurbiprofen ($n=9$), gemfibrozil ($n=9$) and ibuprofen ($n=9$)), no relationship was found between salt melting point and solubility, and simplistic relationships based on lipophilicity of the counterion have limited predictive reliability and a deeper understanding of the role of the counterion is required. Neither the cyclohexylamine nor benzylamine is as effective at improving solubility as the butylamine or the hydrophilic counterions (AMP1, AMP2 and tris). Benzylamine and cyclohexylamine are closely related structurally counterions and all their salt forms studied are more soluble than the acid (Tables 2–5), and cyclohexylamine as a counterion results in a greater enhancement of molar solubility (8–118-fold) in all cases. Thus, cyclohexylamine salts have higher melting points, are slightly more lipophilic and are yet more soluble than corresponding benzylamine salts similar to the results of Parshad et al[39]. who found that salt solubility increased as lipophilicity increased for salts of benzylamine derivatives with *p*-substituted benzoic acids.

The tert-butylamine counterion results in a over 50- to over 225-fold increase in solubility across the range of drugs (Tables 2–5). The presence of a single hydroxyl group (AMP1 salts) in the four carbon amine series increases the solubility compared to the parent drug from 200-fold to more than 1300-fold; a substantial enhancement compared to the tert-butylamine salts. For AMP2 salts, there is a large increase in solubility, over 1800-fold for ibuprofen AMP2, compared to the acidic drug, an increase factor similar to that of the butylamine counterion. For two salts within this study, etodolac AMP2 and ibuprofen AMP2, it was not possible to obtain a saturated aqueous solution. As the concentration was increased above 200 mg/ml, "foaming" was observed, and these materials were shown to demonstrate surfactant-like properties and CMC values were determined (7.65×10^{-2} M for etodolac AMP2 and 6.43×10^{-2} M for ibuprofen AMP2) (data not shown). For these samples a maximum measurable solubility was used to demonstrate the effect of the AMP2 counterion on solubility.

There is no further increase in solubility with additional hydroxyl groups (i.e. tris salts). Thus increasing hydrophilicity of the counterion is beneficial in solubility enhancement up to two hydroxyl groups. A similar result has been reported for diclofenac but solubility was maximal with the AMP1 salt[18] and the diclofenac tris salt had the lowest solubility in the series[40]. As the number of hydroxyl groups increases, the potential for hydrogen bonding increases. We have previously shown that the

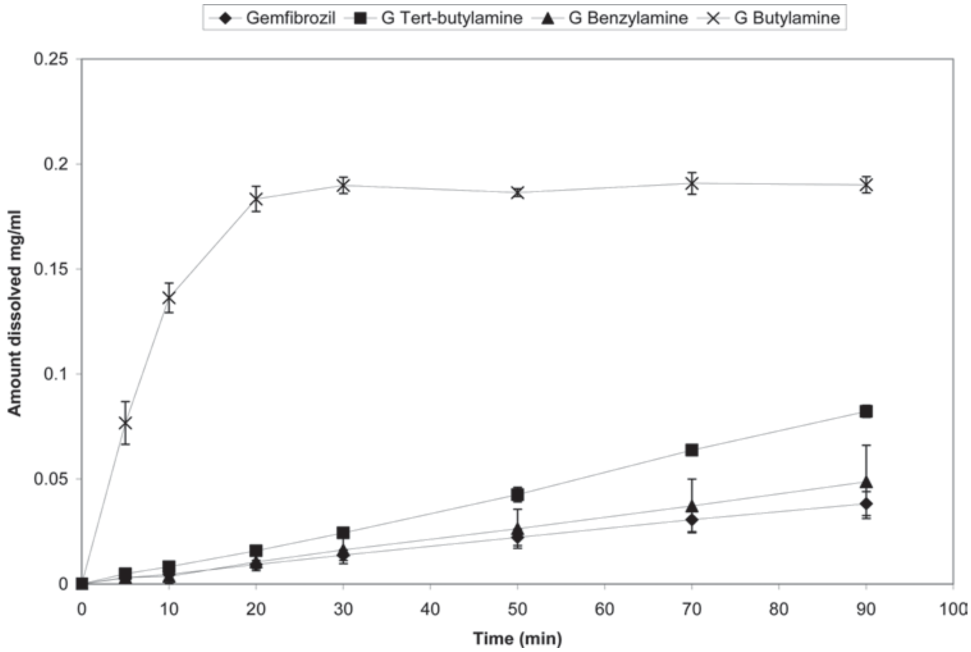

Figure 6. Intrinsic dissolution profiles for gemfibrozil and its salts in phosphate buffer pH 7.2.

Table 6. Solubility of selected salts in pH 6 buffer ($n = 3$; mean ± SD).

Material	Solubility (mg/ml)	pH	Material	Solubility (mg/ml)	pH
Etodolac	2.11 ± 0.399	5.97	Flurbiprofen	0.480 ± 0.038	5.80
E butylamine	2.52 ± 0.357	6.15	F butylamine	0.735 ± 0.102	5.93
E hexylamine	1.32 ± 0.223	5.75	F hexylamine	0.955 ± 0.086	6.40
E AMP1	2.19 ± 0.156	6.12	F AMP1	0.569 ± 0.159	5.88
E AMP2	2.51 ± 0.346	6.22			
Gemfibrozil	0.038 ± 0.058	6.50	Ibuprofen	1.62 ± 0.284	6.10
G butylamine	0.263 ± 0.020	6.48	I butylamine	1.33 ± 0.130	5.89
G hexylamine	0.475 ± 0.020	6.62	I hexylamine	1.93 ± 0.041	6.35
G AMP1	0.232 ± 0.056	6.28	I AMP1	1.58 ± 0.110	6.05
			I AMP2	4.71 ± 0.034	6.55

F indicates salts of flurbiprofen and E, etodolac; G indicates salts of G, gemfibrozil and I, ibuprofen ($n = 3$; G butylamine data represents first three data points only).

free acid and t-butylamine, AMP1, AMP2 salts of gemfibrozil have a common crystal packing motif comprising infinite H-bonded chains with cross-linking between pairs of adjacent chains. The sets of chains interact via van der Waals forces. The tris salt, with its increased capacity for hydrogen bonding, forms a different crystal structure comprising a two dimensional sheet-like network of H-bonds with complex intermolecular forces which are more difficult to break[41]. This accounts for the relatively lower solubility of the tris salt[42].

O'Connor and Corrigan[18] reported that there was a linear log-log relationship between $[H^+]$ and salt solubility for a range of diclofenac salts including benzylamine, tert-butylamine, AMP1, AMP2 and tris. In this study, there was a linear relationship between the logarithm of the concentration and the pH of the saturated solution, ($R^2 = 0.71$ $n = 9$), flurbiprofen ($R^2 = 0.45$ $n = 9$), gemfibrozil ($R^2 = 0.69$ $n = 9$) and ibuprofen ($R^2 = 0.71$ $n = 9$) was determined. When the pH of the vehicle is not controlled, the diffusion layer model proposes that the pH of the saturated solution represents the pH of the theoretical diffusion layer surrounding the salt as it dissolves.

When using a buffer at a controlled pH, the diffusion layer is maintained at that fixed pH, thus inhibiting the dissolution of the drug-salt within the diffusion layer. The saturated solubility of selected salts was therefore also determined at pH6 and only a small increase in solubility was observed and in some cases, there was a reduction in solubility compared to the parent compound (Table 6). DSC studies showed that incubation with aqueous buffer did not lead to any phase changes in the material. The solubility of gemfibrozil at pH 6.5 was lower than that of the other acids, according to its very low intrinsic solubility (calculated here as 0.0038 mg/ml) and solubility has been found to remain below 0.03 mg/ml until pH 5.5[43]. The etodolac salt series showed no increase in solubility for each salt and the hexylamine counterion reduced the solubility. Only the ibuprofen AMP2 salt showed a 2.9-fold increase in solubility, but this result could be due to the elevated buffer pH compared to parent (Table 6). From these data, it can be concluded that the increased solubilities observed when the pH of the saturated solution was not controlled are due to the counterion affecting the pH of the solution. This explains why the solubility is not elevated for all of the salts formed.

Table 7. IDR results for flurbiprofen, gemfibrozil and its cyclohexylamine, tert-butylamine and benzylamine salts.

Material	IDR (mg/min/cm^2)	Correlation coefficient r^2
Flurbiprofen	0.00062	0.9886
F cyclohexylamine	0.00013	0.9945
F tert-butylamine	0.00046	0.9998
F benzylamine	0.00057	0.9998
Gemfibrozil	0.00032	0.9991
G butylamine	0.00890	0.9200
G tert-butylamine	0.00089	0.9976
G benzylamine	0.00041	0.9985

It was not possible to produce a full set of IDR results due to the poorly compressible nature of the parent drugs and some of the salt forms[44]. The IDR profiles for both flurbiprofen and gemfibrozil and their salts are linear (Table 7) with the exception of gemfibrozil butylamine which dissolved too rapidly to accurately determine IDR (Figure 5). IDR rank order for the salts mirrors the order of solubility i.e. flurbiprofen benzylamine>tert-butylamine>cyclohexylamine. The salts of gemfibrozil show the largest enhancement in dissolution, significantly higher for gemfibrozil butylamine ($p = 0.05$), compared to the other salts and gemfibrozil. Flurbiprofen has the highest IDR at pH 6.8 but it is only significantly different to the flurbiprofen cyclohexylamine salt ($p = 0.05$), and is similar to the other salts tested. For the flurbiprofen series, the cyclohexylamine salt has a significantly different IDR than benzylamine ($p = 0.05$), and the tert-butylamine salt has a similar IDR to the other salts ($p = 0.05$). From the IDR experiments it can be concluded that dissolution characteristics can be related to saturated aqueous solubility data and that a rank dissolution order can be elucidated from solubility data.

Conclusion

Modification of the molecular properties of a drug to overcome a limiting factor, most often solubility, is common but the salt form will influence a range of other properties including dissolution rate, melting point, stability, hygroscopicity, crystal form and mechanical properties. Rational salt selection could therefore improve dissolution rates, solubility, bioavailability and may influence the mechanical properties of poorly soluble compounds. This paper employs a series of amine counterions with a selection of carboxylic acid drugs with the view to understanding the role of the counterion in salt formation.

Using a homologous series of amines, the significance of the counterion in controlling salt properties was investigated and increasing chain length leads to a reduction in melting point and a reduction in solubility across all the acidic drugs studied.

Addition of hydrophilic groups within the amine counterion increases solubility, reduces melting point and increases the likelihood of surface activity, up to a threshold of value of two OH groups in the counterion series studied. Despite the additional hydroxyl group in tris salts, solubility is not enhanced further as complex intermolecular hydrogen bonding can contribute to a strong crystal lattice.

Rational salt selection should begin with selecting small, compact counterions to improve solubility. Addition of a hydrophilic group improves the solubility characteristics however, the presence of additional H-bonding capacity can result in additional, possibly undesirable properties; for example polymorphism and hydrate formation. Benzylamine (unsaturated species) salts are prone to polymorphs so should not be used for salt formation. Cyclohexylamine and tert-butylamine counterions (small, rigid and compact) consistently produce a crystalline product with a high melting point and a modest improvement in solubility, which can improve the characteristics of an unstable drug. These counterions do not have a tendency for polymorphism or hydroscopicity so may be a useful salt formers. The nature of the hydrogen bonding between the anion and cation will change for each counterion and this will have an impact on the crystal structure and properties.

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Declaration of interest

The authors report no declarations of interest.

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