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Research Paper

Comparative physical, mechanical and crystallographic properties of a series of gemfibrozil salts

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Abstract

Objectives Understanding the impact of the counterion on the properties of an acidic or basic drug may influence the choice of salt form, especially for less potent drugs with a high drug load per unit dose. The aim of this work was to determine the influence of the hydrogen bonding potential of the counterion on the crystal structure of salts of the poorly soluble, poorly compressible, acidic drug gemfibrozil and to correlate these with mechanical properties.

Methods Compacts of the parent drug and the salts were used to determine Young's modulus of elasticity using beam bending tests. Crystal structures were determined previously from X-ray powder diffraction data.

Key findings The free acid, tert-butylamine, 2-amino-2-methylpropan-1-ol and 2-amino-2-methylpropan-1,3-diol salts had a common crystal packing motif of infinite hydrogen-bonded chains with cross-linking between pairs of adjacent chains. The tromethamine (trsi) salt, with different mechanical properties, had a two-dimensional sheet-like network of hydrogen bonds, with slip planes, forming a stiffer compact.

Conclusions The type of counter ion is important in determining mechanical properties and could be selected to afford slip and plastic deformation.

Keywords crystal; gemfibrozil; salts; slip plane; Young's modulus

Introduction

The physicochemical, pharmaceutical and hence clinical properties of drugs can be modified using different salt forms. There has been an increase in interest in the adaptation and selection of optimal salt forms for formulation development in recent years. The high-throughput processes used in current drug discovery programmes result in a tendency towards early-stage drug candidates with higher molecular weights, higher lipophilicities and hence poorer aqueous solubilities.[1] The majority of drug candidates in early drug development studies are either weak acids or bases and salt formation is a simple way to modify the solubility of any candidate containing ionisable moieties in order to attempt to overcome its adverse properties. Over 50% of approved drugs are in salt form.[2] In order to be absorbed systemically following oral delivery, a drug must have adequate solubility within the pH range of the gastrointestinal tract, and an adequate dissolution rate and permeability. Therefore there is an increased need for salt formation and there has been some attempt to rationalise the physicochemical characteristics of the resultant products.[3–5]

Due to the less favourable properties being presented by new chemical entities (NCEs) and a requirement to improve physical and chemical properties, a greater diversity of counterions is being used for salt formation,[2] and the selection process is thus becoming more complex.[3] Amine salts such as tromethamine, diethylamine, diethanolamine and megulmine exist, with different salt forms of the same drug used for different applications (e.g. diclofenac).[6]

A rational method for salt selection should involve a tiered approach, such as that proposed by Morris *et al*., which allows elimination of potential salt forms on the basis of the simplest tests first.[7] This should be combined with a goal-orientated approach, where the major issue with the parent compound is considered first (usually solubility), followed by any secondary issues. As solid-state properties will be affected by the counterion, the

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properties of the ion used will impact on the bioavailability, stability and manufacture of the salt form and it may be possible to select a salt form with advantages over the parent, such as favourable compression properties. Thus, screening strategies should consider maximising solubility and bioavailability but processibility, formulation and scale-up may also be considered. The mechanical properties of the drug will determine whether it is feasible to form a robust tablet using direct compression and will influence the type and amount of excipient required to be added to facilitate this, if at all possible. This becomes even more important when the parent compound is not potent and the counterion is of a relatively high molecular weight, thus restricting the quantities and range of excipients that can be added to an oral tablet formulation. The comparative mechanical properties of alternative salts of drugs have not been extensively studied to date and so there is little guidance in the literature as to selection of counterion in respect of improving salt mechanical properties.

A number of different techniques have been used to investigate the mechanical properties of materials, usually requiring relatively large amounts of material, which are not normally available in a screening process.[8,9] When limited amounts of material are available, it is more useful to study mechanical properties such as Young's modulus and the yield stresses that are known to influence the compaction behaviour of powders. Young's modulus has been measured using three- and four-point beam-bending methods on rectangular compacts of different properties,[10] and has been shown to be useful for comparative purposes.[11] The analysis of Young's modulus at zero porosity thus provides a means of quantifying elastic behaviour. This technique has been used to relate the influence of crystal structure of different polymorphic forms to mechanical properties.[12]

It is known that the physical and physicochemical properties of a substance such as the mechanical properties and solubility are related to the crystalline structure of the material. It would be useful to understand any relationship existing between the counterion used, the crystal structure and the mechanical properties of the salt. Factors affecting the mechanical properties of salt forms have not been reported to any large extent but it is recognised that the counterion will have an influence on the tableting properties.[13]

In this work, we used an organic amine series as the counterion, with increasing capacity for hydrogen bond formation. We thus had a range of structurally related chemistries available, so the impact on mechanical properties and the crystal structure could be studied in a systematic manner. Gemfibrozil is a high-dose, poorly compressible drug; it is employed as the free acid in 300 and 600 mg tablets or capsules to allow a daily divided dose of up to 1.2 g to be administered to treat hyperlipidaemias. The counterions used as the salt formers in this work were tert-butylamine (tert-BA), 2-amino-2-methylpropan-1-ol (AMP1), 2-amino-2-methylpropan-1,3-diol (AMP2) and tromethamine (tris) (Figure 1), enabling us to study the influence of hydrogen bonding on the crystal structures and mechanical properties. The aim was to understand the influence of hydrogen bonding potential in the counterion on the crystal structure and the mechanical properties of salts.

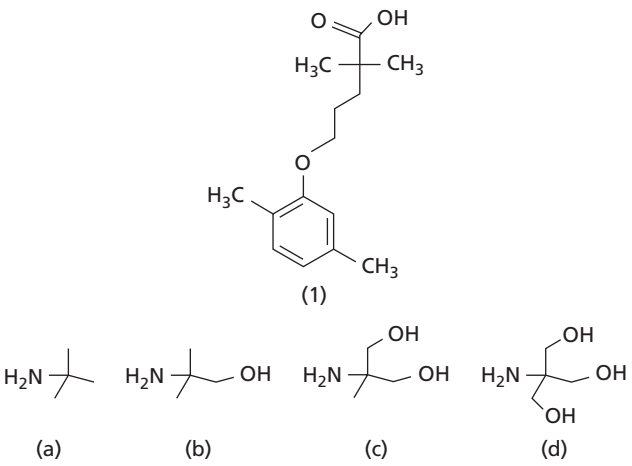

Figure 1 Molecular structure of gemfibrozil (1) and related molecules. Gemfibrozil (1) is shown alongside molecules of the type $H_3NC(CH_3)_{3-n}(CH_2OH)_n$ where $n = 0, 1, 2, 3$ (a–d respectively).

Materials and Methods

Gemfibrozil was supplied by DiPharma (Italy). Tert-butylamine, AMP1, AMP2, and tromethamine were supplied by Sigma-Aldrich (Poole, UK). Acetonitrile and methanol were supplied by Fisher (Loughborough, UK). All materials were of pharmaceutical, analytical or HPLC grade as appropriate.

Salt formation and characterisation

Salts were prepared by mixing equimolar amounts of drug and counterion dissolved in acetonitrile and allowing them to crystallise. The salt crystals were recovered immediately by filtration under vacuum. For salts containing AMP1 and tris, the counterions were dissolved in a warmed solution of methanol, which was added to a solution of the drug in acetonitrile. The crystals were then collected by filtration. Products were dried overnight under vacuum and the melting point was determined using differential scanning calorimetry. Samples were stored in sealed containers at room temperature until used.

Saturated aqueous solubility ($n = 3$) was determined under ambient conditions and statistical analysis on the differences in solubility was carried out using one-way ANOVA and Tukey post-hoc analysis.

Preparation of compacts

Following sieving through a 750 μm aperture sieve, compacts were obtained ($n \geq 6$) by uniaxial compression in a hardened steel die (G & F Press Tools Ltd, Birmingham, UK), similar to that of Roberts.[14] The punch faces and walls were coated with a suspension of 1% (w/v) magnesium stearate in ethanol to provide lubrication before use. Powder of a suitable weight was poured into the die cavity of fixed dimensions ($20 \times 7 \times 1$ mm), allowing for preparation of compacts of varying porosity by controlling the weight of

powder added. The compacts were all formed using the same load (4 tonnes) and dwell time (1 min).

Determination of Young's modulus

The dimensions of the wafers were measured after 24 h (Linear Tools electronic digital calliper, Middlesex, UK). A Hounsfield Universal Tester S Series (Tineus Olsen, Surrey) was used to study the mechanical properties with a 5 N load cell, operating with an accuracy of ±0.5%. A bespoke miniature three-point bend jig that housed the dimensions of a typical compact was constructed to use with the S Series and deformation was measured with a linear displacement unit capable of measuring deformation of up to 1 ± 0.001 mm.

The modulus for each sample was calculated using equation 1:

$$E = \frac{Fl^3}{4st^3w} \quad (1)$$

where l is the length of the beam, s is the deflection from the mid-point, t is the thickness and w is the width.

Young's modulus was calculated for compacts of zero porosity using the Spriggs equation (equation 2), which is applicable over the narrow, typically low porosity range encountered in these samples.[15]

$$E = E_0 \exp^{-bP} \quad (2)$$

where E is the measured modulus at porosity P and b is a constant. E_0 is the modulus at zero porosity. Calculation at zero porosity minimizes particle size effects during compaction, influencing derived mechanical properties.

Calculation of compact porosity

The true densities, ρ_t, of the drug and salt powders were measured in triplicate using a Micromeritics Gemini Helium Pycnometer (Micromeritics, UK). The pycnometer was calibrated before use and each sample was maintained at 40°C for 12 h prior to analysis. The porosity of the compact, ε, was calculated using equation 3.

$$\varepsilon = 1 - \frac{\rho_c}{\rho_t} \quad (3)$$

where ρ_c is the density calculated from the dimensions of the compact.

Results

Salt formation was confirmed using nuclear magnetic resonance and Fourier transform infrared spectroscopy and the crystalline nature was confirmed using X-ray powder diffraction.[16] There was no evidence of polymorph or hydrate formation. All the salts were polycrystalline materials and did not contain crystals suitable for single crystal X-ray diffraction studies. Therefore the crystal structures were solved directly from the powder X-ray diffraction data by employing direct-space strategy as reported previously.[17] The crystal structure of gemfibrozil has also been reported previously.[18]

The physicochemical properties of the parent drug and salt forms were determined as reported previously[16] and are summarised in Table 1. Salt formation increased aqueous solubility in all cases and solubility increased with the number of hydroxyl groups up to the inclusion of two groups. There was no further increase in solubility with additional hydroxyl groups (tris salts) ($P > 0.05$). A similar result was found when the same counterion series was used with the acidic drugs ibuprofen, flurbiprofen, etodolac[16] and diclo-fenac with solubility peaking with the AMP1 salt.[19] Increasing hydrophilicity of the counterion is beneficial in solubility enhancement, up to two hydroxyl groups, beyond which there is no further improvement. As the number of hydroxyl groups increases, the potential for hydrogen bonding increases. We have previously reported that the solubility for a similar series of flurbiprofen salts is directly dependent on pH,[20] but this is clearly not the case for gemfibrozil salts.

There was an increase in Young's modulus with decreasing porosity and the extrapolated values at zero porosity are listed in Table 2. Gemfibrozil itself was brittle and prone to lamination on decompression, and compression of gemfibrozil was only possible over a small porosity range. It was therefore not possible to determine Young's modulus for the parent drug using this technique. The salts formed following addition of the tert-BA and AMP1 counterion were tacky, causing the compacts to stick to the walls of the die and, despite lubrication with magnesium stearate, it was not possible to

Table 1 Melting point and solubility of gemfibrozil and salt forms

	Mean density (g/cm_3)	Mp (°C)	Aqueous solubility (mM)	pH of saturated aqueous solution
Gemfibrozil	1.09 ± 0.001	62–64	0.0879 ± 0.032	5.4 ± 0.1
Gtert-BA	1.04 ± 0.002	141–146	24.3 ± 0.1*	7.6 ± 0.1
G AMP1	1.12 ± 0.003	119–122	34.7 ± 4.5*	7.7 ± 0.2
G AMP2	1.18 ± 0.001	104–106	85.2 ± 2.7*	7.7 ± 0.2
Gtris	1.20 ± 0.001	119–121	22.8 ± 1.3*	7.5 ± 0.2

$n = 3$. Mp indicates melting point measured using differential scanning calorimetry. *Indicates a significantly different solubility compared to the parent drug, $P < 0.05$ G, gemfibrozil.

Table 2 Young's modulus and compaction behaviour of gemfibrozil and salt forms

	E_0 (GPa)	r^2	Properties
Gemfibrozil	Not measurable		Brittle compacts, lamination
G tert-BA	2.5	0.508	Easily compressible, soft
G AMP1	Not measurable		Sticking to die faces
G AMP2	7.95	0.928	Fairly compressible
G tris	18.8	0.993	Strong compacts

G, gemfibrozil.

make compacts in all cases. Gemfibrozil tert-BA (Figure 1a) had a relatively low modulus of 2.5 GPa, representing low inherent strength. It was not possible to form gemfibrozil AMP1 compacts (Table 2). As the hydroxyl group number and thus hydrogen bonding potential of the counterion was further increased, the modulus increased, reaching 7.95 GPa for two hydroxyl groups. As all the moduli are below 10 GPa, these are classified as soft elastic materials.[21] When the hydroxyl group number was increased to three, the Young's modulus was higher (18.81 GPa) and the Tris salt formed a stiffer compact, which was non-tacky and could be ejected easily from the die.

Discussion

For pharmaceutical compacts, Young's modulus at zero porosity provided a means of categorising the mechanical characteristics of salts in terms of elasticity, rigidity (stiffness) and brittleness on a quantitative scale.[10] Moduli determined using this method have been shown to be consistent with values in the literature determined using other techniques[22] and are useful for comparing the properties of a series of related compounds.

The ease of plastic deformation is influenced by crystal structure and occurs preferentially along slip planes, facilitating a sliding motion and providing greater plasticity. Slip planes, or cleavage planes, correspond to crystallographic planes within the crystal structure with relatively strong intra-planar interactions compared to inter-planar interactions.[23] They usually exhibit the highest molecular density and largest d-spacing when compared to other planes within the crystal.[24] For example, the presence of water between layers of dimers in crystals of *p*-hydroxybenzoic acid monohydrate maintains a three-dimensional hydrogen bonding network between the planes and facilitates slip during compression, enhancing bonding strength compared to the anhydrous form.[25] The presence of water in crystals of hydrated forms of sodium naproxen has also been proposed to weaken intermolecular forces, thus facilitating slip.[26] The arrangement of the crystal lattice into slip planes in the polymorhpic form I of sulfamerzaine has been reported as being responsible for facilitating the improved compression properties compared to form II.[9]

The main summary characteristics of the crystals of gemfibrozil and its salts are detailed in Table 3. Gemfibrozil has a long thin unit cell and is therefore likely to form needle-like crystals.[18] The crystal lattice is connected in the *y*-axis (*b* plane) by hydrogen bonds. All the oxygens of the carboxylic function are involved in hydrogen bonding, forming a channel of hydrogen bonds. The benzene rings and the alkyl chains form sheets parallel to the *a–c* plane and the sheets are linked by hydrogen bonds, so that slipping of planes is mechanically inhibited by rigid benzene rings in the *b* direction, which may result in the observed lamination on compaction.

Gemfibrozil tert-BA comprises chains of alternating molecules of gemfibrozil and the counterion along the *a*-axis (Figure 2). Each pair of adjacent molecules within the chain is linked by an N–H···O hydrogen bond. Each carboxylate oxygen atom of gemfibrozil is the acceptor in an N–H···O hydrogen bond within such a chain, and each $–NH_3^+$ group of tert-BA contributes two N–H bonds to the chain. The remaining N–H bond of the $–NH_3^+$ group forms an N–H···O hydrogen bond to a carboxylate oxygen atom of the acid in an adjacent chain, thus effectively providing a cross-link between adjacent chains. Each molecule of gemfibrozil receives one cross-linking N–H···O hydrogen bond from an adjacent chain in this manner. Pairs of adjacent chains are exclusively cross-linked to each other, do not form cross-links to any other chain and there are no additional sites

Table 3 Summary of unit cell dimensions for gemfibrozil and salts

	Cell dimensions (Å)					
	a	b	c	Volume (Å^3)	ß	R factor
Gemfibrozil[a]	14.84	7.32	30.68	3053	93.4	0.0209
G tert-BA[b]	6.44	9.68	33.10	2064	91.7	0.0177
G AMP1[b]	26.88	6.37	23.92	4090	91.7	0.0194
G AMP2[b]	27.08	6.32	22.89	3918	92.3	0.0358
G tris[b]	18.50	10.04	11.00	2024	97.4	0.0299

Sources: [a]Bruni *et al*.[18], [b]Cheung *et al*.[17].

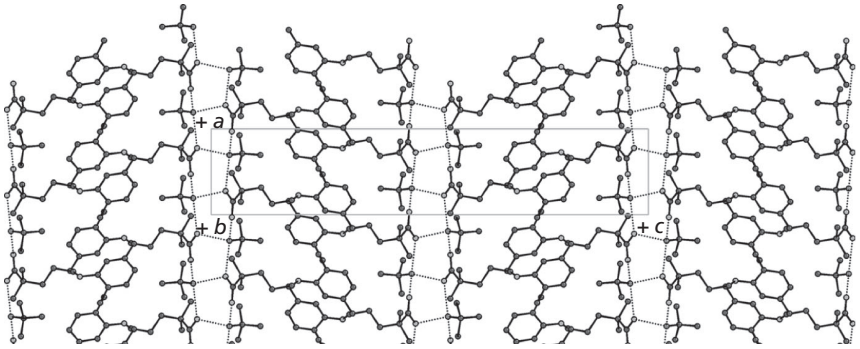

Figure 2 Crystal structure of gemfibrozil tert-BA viewed along the *b*-axis

for hydrogen bonding. This may afford some small degree of slip as the distance between the nearest contact points in the chains is 1.9 Å (Table 3).

Gemfibrozil AMP1 has an additional site for hydrogen bonding provided by the OH group of the cation. It has a similar motif to the previous salt, with crosslinked chains of alternating molecules of parent and counterion linked by an N–H···O bond and a ladder type structure (Figure 3). The hydrogen bonds crosslinking the chain are different, however, and are of the N–H···O–H···O type with the OH originating from the counterion. It has a low elastic modulus. The addition of a second hydroxyl group in the AMP2 counterion creates further opportunities for hydrogen bond formation and each of the potential bond forming units are involved (Figure 4). As in the previous salt forms, there are crosslinked chains of alternating molecules with a similar N–H···O hydrogen bonded ladder structure. The crosslinks are of the type N–H···O–H···O–H···O and form a twisted pathway for the ladder rungs. Three-dimensional hydrogen bonds form a strong crystal lattice and both the AMP1 and AMP2 salts have visible slip planes in the crystal lattice, with distances of 0.41 and 0.495 Å, respectively. Although it was not possible to determine Young's modulus by this method for the AMP1 salt, the AMP2 salt had improved mechanical properties compared to the parent drug.

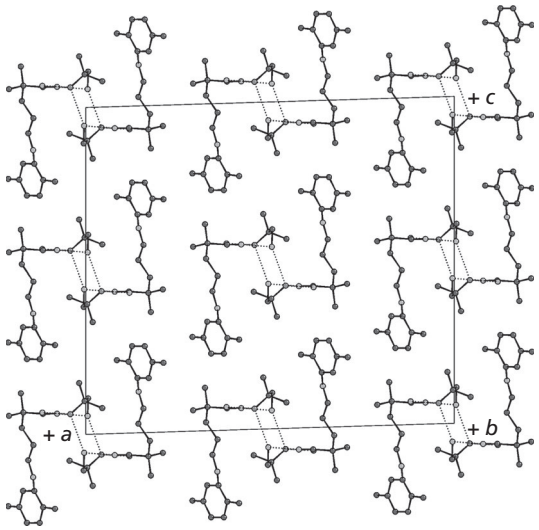

Figure 3 Crystal structure and unit cell of gemfibrozil AMP1

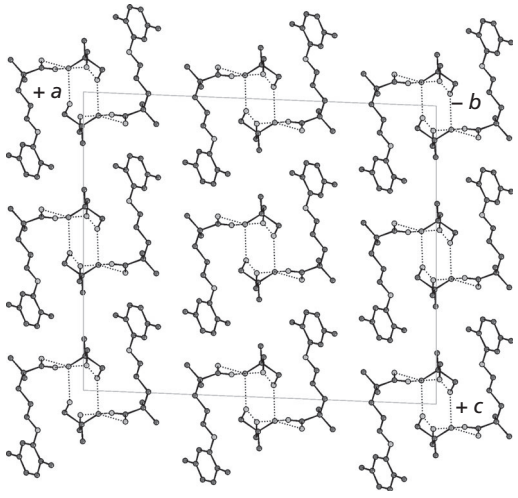

Figure 4 Crystal structure and unit cell of gemfibrozil AMP2

In the gemfibrozil tris salt there are six potential hydrogen bond donors (three OH groups and three N–H groups) but the crystal structure only has one N–H···O bond, the other carboxylate oxygen of gemfibrozil accepting a hydrogen bond from one hydroxyl group on the counterion (Figure 5a). In total, there are six independent types of hydrogen bond in the structure and instead of the ladder structure, the tris salt forms a two-dimensional sheet-like network (Figure 5b), creating a strong but complicated network comprising layers with relatively high molecular density, with no hydrogen bonding between them and the drug extending outwards from the layers. This structural arrangement may afford a greater opportunity for slip along the plane of the rigid, hydrogen-bonded sheets, resulting in improved plastic deformation and mechanical properties that are very different to the other salt forms.

Conclusions

The increased capacity for hydrogen bond formation with the changing counterion had an influence on the crystal structure of the salt. The presence of six potential hydrogen bonding sites resulted in a different packing of the crystal, changing from ladders to a sheet-like structure. A sequence of strong hydrogen bonds extending throughout the sheet-like layers facilitated slip and resulted in higher mechanical strength. The identification of slip planes within the salt form is important in understanding the influence of the crystal structure on important pharmaceutical processes such as compaction. The nature of the hydrogen bonding between the anion and cation has an impact on the crystal structure and mechanical properties, and an understanding of the relationship can be used to inform counterion selection.

Declarations

Conflict of interest

The Author(s) declare(s) that they have no conflicts of interest to disclose.

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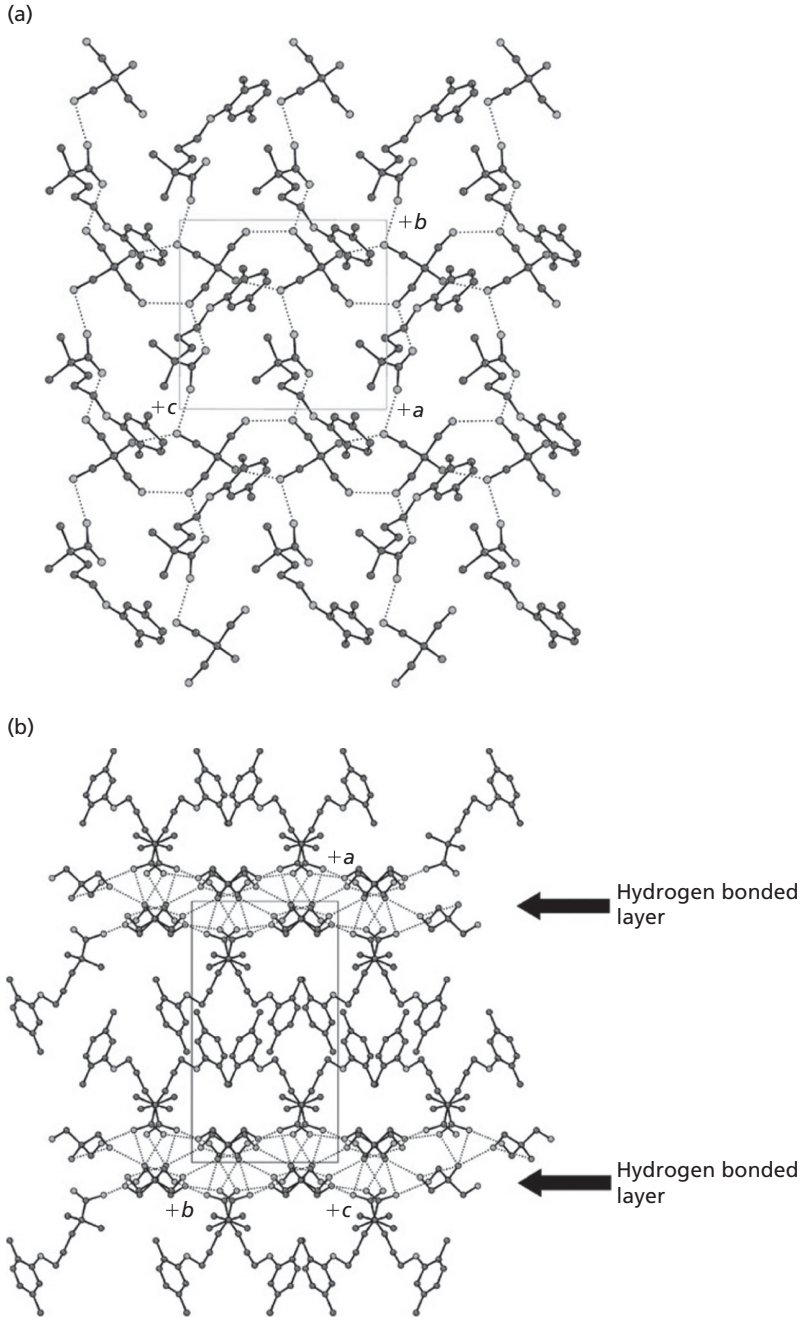

Figure 5 Gemfibrozil tromethamine salt

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