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Crystal polymorphism of pharmaceuticals: probing crystal nucleation at the molecular level

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Abstract
Paracetamol, sulfathiazole and L-glutamic acid are presented as examples of pharmaceutical crystal polymorphic systems. The effect of *N*-acylated sulfathiazole derivatives (**3–6**) on sulfathiazole crystallisation is discussed, and possible modes of action presented. Methods for the control of the crystal polymorphism of L-glutamic acid which utilise the principles of conformation mimicry and co-operative binding are presented. The preparation of a series of bis-amides of EDTA derived from sulfathiazole, 5-aminoisophthalic acid and 4-hydroxyaniline (i.e. compounds **9a–c**) is presented, as is data on the effect of these compounds on the crystallisation of, respectively, sulfathiazole, L-glutamic acid and paracetamol.

Keywords: *Crystal polymorphism, paracetamol, sulfathiazole, L-glutamic acid, EDTA*

Introduction

The majority of pharmaceutical substances are crystalline solids, i.e. consist of solid particles characterised by well-defined faces and angles between faces. The internal supramolecular architecture of these particles consists of motifs which repeat with regular periodicity and which are anisotropic. The existence of more than one such supramolecular architecture for any given molecular entity gives rise to crystal polymorphism. A good example of this phenomenon is given by paracetamol (**1**; Figure 1). When crystallized from water or ethanol, paracetamol usually gives crystals with a monoclinic space group. The structure of these crystals consists of regular two-dimensional hydrogen-bonded networks, which are stacked upon each other in a "herringbone" pattern, as illustrated in Figure 2 [1].

Crystals of pharmaceutical paracetamol are of this monoclinic form. The highly-interlocked crystal architecture results in crystals with elasticity, which is disadvantageous for the manufacture of paracetamol tablets [2]. When crystallized from melts, paracetamol crystals can be obtained which possess an orthorhombic space group. The structure of these crystals also consists of layers of regular two-dimensional hydrogen-bonded networks which are stacked upon each other. However in this case, the layers are not interlocked and are separated by "slip planes" [3] Figure 3. Crystals of orthorhombic paracetamol are hence more suitable for formulation as tablets [2] [4]. However, the monoclinic form is the more thermodynamically stable [5]. Issues of stability and bulk crystallization control mitigate against pharmaceutical use of the orthorhombic form.

A number of high-profile cases have generated greater awareness of the issue of crystal polymorphism in the pharmaceutical context. The Glaxo vs. Genpharm legal action in the early 1990s turned on the intellectual property protection of individual crystal polymorphs of ranitidine hydrochloride [6]. Batches of a formulation of ritonavir failed specification tests two years after commercial start-up due to the unexpected appearance of a more stable and less soluble crystal polymorph [7]. These are just some of the better known

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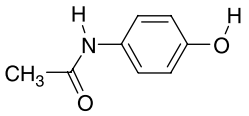

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Figure 1. Paracetamol (**1**).

instances in which crystal polymorphism has affected pharmacokinetics, dosage formulation, process development, scale-up, product compliance or patents. The issue of crystal polymorphism is often marked by unexpected outcomes and lack of general rational control strategies. The work described in this paper concerns two pharmaceutical compounds, sulfathiazole and L-glutamic acid, for which crystal polymorphism has been a significant issue.

Methods

General methods

All materials were purchased from Sigma-Aldrich. Melting points were determined on a Reichert hot-stage microscope and are uncorrected. Infrared spectra (pressed KBr discs) were recorded on a Perkin Elmer Spectrum One FT-IR spectrometer in the range 4000 to 500 cm^{-1}. ^{1}H NMR spectra were recorded at 300 MHz and ^{13}C NMR spectra were recorded at 75 MHz on a Bruker Avance 300 spectrometer. High resolution precise mass spectra (HRMS) were recorded on a Waters LCT Premier LC-MS instrument in electrospray ionisation (ESI) positive mode using 50% acetonitrile-water containing 0.1% formic acid as eluent; samples were made up in acetonitrile.

*Sulfathiazole EDTA bisamide (**9a**)*

To a solution of EDTA-bisanhydride (**8**) [8] (1.00 g, 3.90 mmol) dissolved in distilled dimethylformamide (10 mL) was added triethylamine (0.79 g, 7.80 mmol) followed by the portion wise addition of sulfathiazole (1.99 g, 7.80 mmol). The resulting solution was stirred for 24 h at room temperature. Concentration under reduced pressure yielded the crude product as a red viscous oil which was then stirred at room temperature in excess isopropyl alcohol for 24 h and collected by vacuum filtration to yield a beige solid 2.90 g (99%); m.p. 126–130°C.; IR υ_{max}/cm^{-1} (NaCl) 2929 (OH), 1664 (NC═O), 1316, 1144 (SO_2). ^{1}H-NMR (d_6-DMSO) δ: 2.82 (4 H, s, N(CH_2)$_2$N), 3.47 (8H, s, NCH_2CO), 6.81 (2H, d, ^{3}J 4.5 Hz, NC*H*═C), 7.25 (2H, d, ^{3}J 4.5 Hz, NC═C*H*), 7.72–7.87 (8H, m, ArC*H*), 7.96 (6H, br s, N*H*), 10.46 (2H, br s, O*H*). ^{13}C-NMR (d_6-DMSO) δ: 52.72 (2 × *C*H$_2$), 56.51 (2 × *C*H$_2$), 58.80 (2 × *C*H$_2$), 108.26 (2 × *C*H), 118.89 (4 × *C*H), 127.13 (4 × *C*H), 127.23 (2 × *C*H), 137.34 (2 × *C*), 142.00 (2 × *C*), 169.17 (2 × *C*), 170.83 (2 × *C*), 173.82 (2 × *C*; HRMS: calcd. for $C_{28}H_{30}N_8O_{10}NaS_4$ $[M + Na]^+$789.0865, found 789.0843.

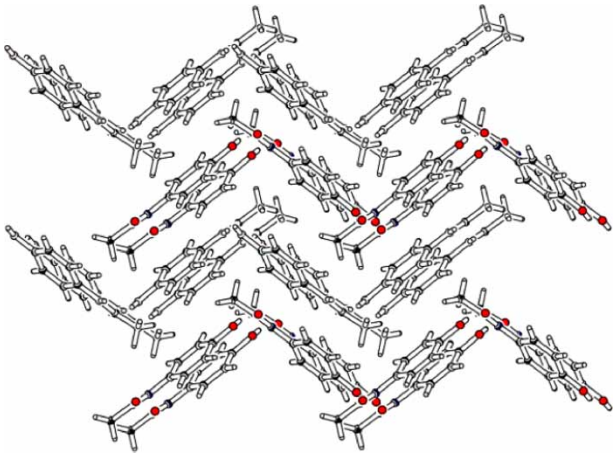

Figure 2. Crystal structure of the monoclinic form of paracetamol viewed down the *c* axis showing the interlocking herringbone pattern.

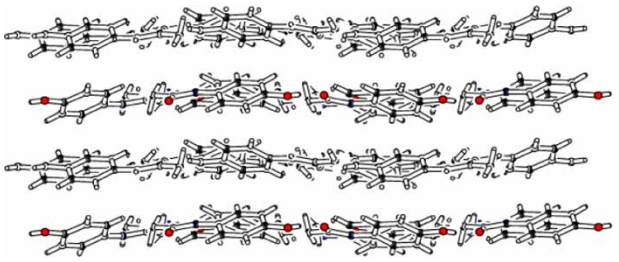

Figure 3. Crystal structure of the orthorhomic form of paracetamol viewed along the *b* axis slowing slip planes.

*5-Aminoisophthalic acid EDTA bisamide (**9b**)*

To a solution of EDTA-bisanhydride (**8**) [8] (1.00 g, 3.90 mmol) dissolved in distilled dimethylformamide (8 mL) was added triethylamine (0.79 g, 7.80 mmol) followed by the portion wise addition of 5-aminoisophthalic acid (1.41 g, 7.80 mmol). The resulting solution was stirred at room temperature for 24 h. Concentration under reduced pressure yielded the crude product as a light brown viscous oil. The crude product was stirred overnight in excess isopropyl alcohol. The product was isolated as a beige solid by vacuum filtration. The product was dried under vacuum to leave a cream solid 1.90 g (78%). m.p. 117–122°C. IR υ_{max}/cm^{-1} (KBr) 2998 (aromatic C—H), 1712 (C═O), 1651 (NC═O), 672 (O—C═O). ^{1}H-NMR (d_6-DMSO) δ: 2.09 (4H, s, N(CH_2)$_2$N), 3.47 (8H, s, NCH_2CO), 7.95 (2H, s, ArC*H*), 8.45 (4H, s, N-ArC*H*), 10.58 (2H, s, COO*H*). ^{13}C-NMR (d_6-DMSO) δ: 52.53 (2 × *C*H$_2$), 56.03 (2 × *C*H$_2$), 58.65 (2 × *C*H$_2$), 123.80 (4 × *C*H), 125.01 (2 × *C*H), 132.47 (4 × *C*), 139.55 (2 × *C*), 167.04 (2 × *C*), 170.66 (4 × *C*), 173.73 (2 × *C*). HRMS: calcd. for $C_{26}H_{27}N_4O_{14}$ $[M + H]^+$619.1524; found 619.1533.

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*4-Hydroxyaniline EDTA bisamide (**9c**)*

To a solution of EDTA-bisanhydride (**8**) [8] (1.00 g, 3.90 mmol) dissolved in distilled dimethylformamide (8 mL) was added triethylamine (0.79 g, 7.80 mmol) followed by the portion wise addition of 4-aminophenol (0.85 g, 7.80 mmol). The resulting solution was stirred for 24 h at room temperature. Concentration under reduced pressure yielded the crude product as a brown oil. The crude product was stirred for 24 h in excess isopropyl alcohol at room temperature. The product was isolated as a light brown solid by vacuum filtration 1.30 g (69%). m.p. 116–119°C; IR υ_{max}/cm^{-1} (KBr) 3284 (acid OH), 3050 (aromatic C—H), 1654 (NC=O), 1560 (N—H bend), 696 (Ar-OH). ^{1}H-NMR (d_6-DMSO) δ: 2.73 (4H, s, N(CH_2)$_2$N), 3.33 (8H, s, NCH_2CO), 6.60 (4H, d, ^3J 8.85 Hz, ArC*H*), 7.34 (4H, d, ^3J 8.85 Hz, ArC*H*), 9.89 (2H, br s, O*H*); ^{13}C-NMR (d_6-DMSO) δ: 52.72 (2 × CH_2), 56.35 (2 × CH_2), 58.70 (2 × CH_2), 115.33 (4 × C*H*), 121.21 (4 × C*H*), 130.80 (*C*), 153.64 (*C*), 169.19 (*C*), 173.75 (*C*); HRMS: calcd. for $C_{22}H_{27}N_4O_8$ $[M + H]^+$475.1829; found 475.1818.

Sulfathiazole crystallizations

Boiling acetone (76.9 mL), n-propanol (154.0 mL) or water (91 mL) was added to sulfathiazole (2.0 g, 5.87 mmol) to form solutions of concentrations 26 gL^{-1}, 13 gL^{-1} and 22 gL^{-1} respectively. (**9a**) was added to the solution in the quantities listed in Table I. Hot filtration was employed to remove any remaining insoluble material. The resulting solution was allowed to cool to room temperature in a 250 cm^3 conical flask while remaining uncovered and unstirred. Crystallizations were also carried out in the absence of (**9a**). Crystal form was assigned by optical microscopy and by powder XRD as described previously [9].

L-Glutamic acid crystallizations

Crystallizations were carried out in 100 mL round bottom flasks. Three aqueous solutions of L-glutamic acid were prepared at 35 g/L. (**9b**) was added in the quantities listed in Table II and the solutions were boiled gently to dissolve the acid and additive. Hot filtration was used to remove any remaining insoluble material. The solutions were maintained at 38°C during crystallisation. Crystal form was assigned by optical microscopy and by powder XRD as described previously [10].

Table I. Crystallizations of sulfathiazole in the absence or presence of compound (**9a**).

Solvent	Without additive	w/w additive	Crystal form
Acetone	Form III	5%	No crystals
Acetone	Form III	1%	Forms I/III
n-Propanol	Form I	5%	Form I
n-Propanol	Form I	1%	Form I
Water	Form III	5%	Form I
Water	Form III	1%	Form III

Table II. Crystallization of L-glutamic acid from water at 35 gL^{-1} and 38°C in the absence or presence of compound (**9b**).

Without additive	w/w additive	Crystal form
β	10%	α
β	5%	α
β	1%	α + β

Paracetamol crystallizations

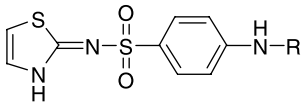
Crystallizations were carried out in 250 cm^3 conical flasks which were kept uncovered and unstirred at room temperature. Boiling water (50 mL) was added to paracetamol (2.00 g) containing 5% w/w or 1% w/w of EDTA bis(amide) (**9c**). Any insoluble material was removed by hot filtration and the solution was allowed to stand at room temperature. This process was repeated using 20 mL boiling ethanol. Crystal form was assigned by infra-red spectroscopy and powder XRD as described previously [11].

Results and discussion

Sulfathiazole

To date, five crystal polymorphs have been reported of the anti-microbial sulfathiazole (**2**; Figure 4) [9]. Work by Blagden et al has shown the actual form obtained is influenced by the presence of the *N*-acetyl synthetic precursor (**3**). When present as a process impurity, compound (**3**) tends to promote the appearance of the least stable sulfathiazole polymorph, form I [13].

Detailed analysis by Blagden et al. of the hydrogen-bonding patterns of the crystal polymorphs of sulfathiazole identified a feature unique to form I. In form I, only one of the two arylamino N—H groups is hydrogen-bond donating, whereas in all the other forms, both N—H groups are hydrogen-bond donating [14]. On this basis, Blagden et al. proposed that compound (**3**) can enter the surface of form I unnoticed, as the *N*-acetyl group replaces an 'un-used' N—H group. But once in the



(**2**) R = H
(**3**) R = $COCH_3$
(**4**) R= CHO
(**5**) R = $COC(CH_3)_3$
(**6**) R = $CO(CH_2)_{14}CH_3$

Figure 4. Sulfathiazole (**2**) and *N*-acylsulfathiazole derivatives **3–6**.

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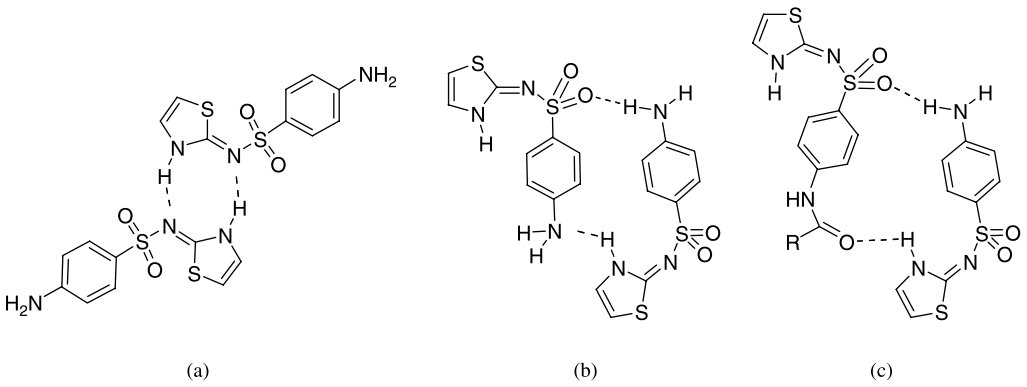

(a) (b) (c)

Figure 5. (a) Dimers found in sulfathiazole form I; (b) dimers found in sulfathiazole forms II, III and IV; (c) putative pseudo-dimers.

growing surfaces of other forms, compound (**3**) offers a barrier to further growth [13]. We wished to determine whether this effect was specific to the *N*-acetyl derivative (**3**), or whether other *N*-acyl sulfathiazole derivatives with greater or lesser steric demand than acetyl groups were similarly active. We found that *N*-formylsulfathiazole (**4**) and *N*-pivaloylsulfathiazole (**5**) were similarly active to compound (**3**), i.e. when added in at least 10% w/w quantity to crystallizations of sulfathiazole from water resulted in crystallization exclusively of form I sulfathiazole, rather than one of the more stable forms [9]. We found that the *N*-palmitoyl derivative (**6**) was not active in this manner. This may be due to the amphipathic nature of compound (**6**) which may impede its ability to act on crystal nuclei in bulk solution.

Our findings suggest that compatibility with hydrogen-bonding networks may not be the only factor allowing *N*-acylsulfathiazole derivatives to affect sulfathiazole crystallizations. Another feature unique to form I sulfathazole is the occurrence of hydrogen-bonded dimerisation *via* the 2-aminothiazole groups, as shown in Figure 5(a). The hydrogen-bonded dimers shown in Figure 5(b) occur in forms II, III and IV. *N*-acylsulfathiazoles could be promoting formation of the dimers shown in Figure 5(a), inhibiting formation of the dimers shown in Figure 5(b), or could be promoting formation of modified versions of the dimers shown in Figure 5(b) which then selectively add to nuclei of forms II, III or IV and act as growth inhibitors. For example, a pseudo-dimer, such as that shown in Figure 5(c), could form between a sulfathiazole molecule and an *N*-acylsulfathiazole additive molecule. Such a dimer would have little or no affinity for nuclei of form I, but could be incorporated into nuclei of form II, III or IV sufficiently to inhibit further growth.

L-Glutamic acid

L-Glutamic acid presents a case of conformational polymorphism [15] in that the two known crystal polymorphs are associated with two different molecular conformations. Two polymorphs of this compound have been reported, the less stable α-form [16] and the more stable β-form [17]. A significant difference between the two forms lies in the conformations of the constituent molecules, the β-form molecules having a straight-chain-like conformation and the α-form molecules having a more folded conformation (Figure 6).

This feature was exploited by Davey et al. to identify compounds which could mimic the extended conformation of the β-form, and hence could selectively inhibit the appearance of that form [18]. Trimesic acid (benzene-1,3,5-tricarboxylic acid) was found to closely mimic the disposition of the carboxyl groups of the β-form of L-glutamic acid, while the conformational rigidity of trimesic acid precluded it from adopting the conformation of the α-form. Addition of trimesic acid to crystallizations of L-glutamic acid from water was subsequently found to result in appearance of the metastable α-form [18].

We were interested in combining polymorph-selective conformation mimicry with another approach to additive design: co-operative binding [19]. The inhibition of the β-form of L-glutamic acid by trimesic acid involves trimesic acid molecules adding in place of L-glutamic acid molecules to pre-critical nuclei, or fast-growing faces, of the β-form. It would seem likely that polymeric additives which are capable of cooperatively binding to many L-glutamic acid sites, rather than just one, are likely to be more efficient, i.e. effective in lesser quantity. Polymer-bound 5-amidoisophthalic acid derivatives

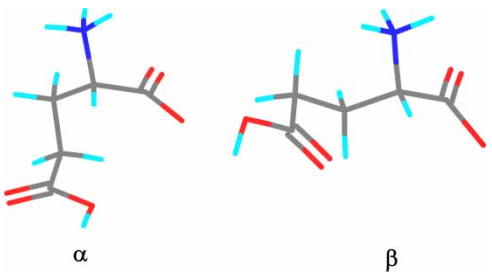

Figure 6. Conformations of L-glutamic acid molecules in the α and β crystal polymorphs.

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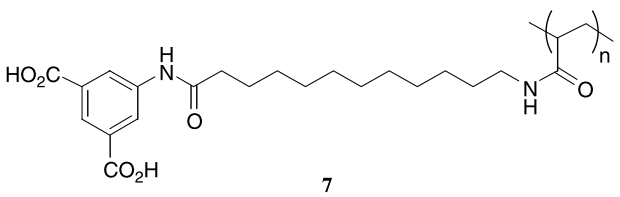

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Figure 7. 5-Amidoisophthalic acid functionalized polymer 7.

would be such additives. Hence, we prepared the 5-amidoisophthalic acid functionalised polyacrylamide (**7;** Figure 7). Polymer (**7**) resulted in exclusive crystallization of the α–form when added in 10%, 5%, 2% or 1% w/w quantities to crystallization of L-glutamic acid from water, i.e polymer (**7**) displays a co-operative binding effect [10]. Polymer (**7**) is one order of magnitude more effective than monomeric analogues such as trimesic acid.

EDTA Derivatives

The principle of co-operative binding offers an attractive strategy for improving the efficiency of crystallization-controlling additives. Crystal nuclei are supramolecular assemblies. Matching the size and shape of the additive to the dimension of pre-critical crystal nuclei might offer further improvements. Experimental determinations of the dimensions of pre-critical crystal nuclei give varying results, however not all reports suggest that such assemblies are always extremely large. For example, studies on paracetamol have suggested that under certain conditions, critical nuclei may consist of between five and fifteen paracetamol molecules [20]. In such cases, additives based on smaller molecular scaffolds may be effective. We were interested in using EDTA as such a molecular scaffold. To this end, bis-amido EDTA derivatives of sulfathiazole, 5-aminoisophthalic acid, and 4-hydroxyaniline were prepared (Figure 8) as putative polymorph-selective crystal nucleation inhibitors of sulfathiazole, L-glutamic acid and paracetamol respectively.

Table I shows the results of using compound (**9a**) [Ar = sulfathiazole] as an additive in crystallizations of sulfathiazole. These experiments show that compound (**9a**) has no effect on crystallizations from n-propanol, form I being obtained irrespective of the presence of additive. In crystallizations from water, a complete inhibitory effect is observed with 5% w/w of (**9a**) added, but the effect is lost when the quantity added is reduced to 1% w/w. In crystallizations from acetone, (**9a**) behaves as a non-selective crystallization inhibitor when added in 5% w/w quantity. Addition of 1% w/w gave partial inhibition of the more stable Form III.

Table II shows the effect on L-glutamic acid crystallizations from water of the addition of quantities of compound (**9b**) [Ar = 5-aminoisophthalic acid].

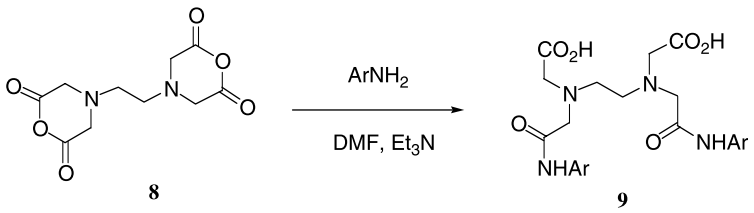

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Figure 8. Preparation of bis-amido EDTA derivatives (**9a–c**).

Crystallizations were carried out at 35 g L^{-1} and 38°C, these being the optimal conditions for crystallization of the more stable β-form [18]. Quantities of 5% w/w or greater of compound (**9b**) were sufficient to fully inhibit crystallization of the β-form. Quantities of 1% w/w resulted in partial inhibition.

Addition of compound (**9c**) [Ar = 4-hydroxyaniline] to crystallizations of paracetamol from water or ethanol in quantities of 5% or 1% w/w had no effect on polymorphic outcome, the more stable monoclinic form being obtained in all experiments.

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