Solvent-drop grinding: green polymorph control of cocrystallisation†

Andrew V. Trask,[a] **W. D. Samuel Motherwell**[b] **and William Jones*[a]**

[a] *Pfizer Institute for Pharmaceutical Materials Science, Department of Chemistry, University of Cambridge, Lensfield Road, Cambridge, UK CB2 1EW. E-mail: wj10@cam.ac.uk; Fax: 44 1223 336362; Tel: 44 1223 334468*

[b] *Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, UK CB2 1EZ*

By grinding with a minimal addition of a solvent of appropriate polarity, control over the polymorphic outcome of a novel cocrystallisation involving the model pharmaceutical compound caffeine may be achieved.

The technique of cocrystallisation continues to gain significance for its application to the design of new supramolecular structures with desired functional properties.[1–3] Most recently, in the field of pharmaceuticals, cocrystallisation has been shown to be an effective means of altering a drug's physical properties, such as solubility and melting point.[4,5] However, one notable obstacle in the path of rational cocrystal design is the phenomenon of polymorphism. Different crystal forms of a given chemical entity will possess different physical properties;[6] thus, in the field of crystal engineering, polymorph control amounts to the control of physical properties. Polymorphic cocrystals are not uncommon, and at least 20 systems have been reported to date.[7] Herein we demonstrate a novel, eco-friendly means of controlling the outcome of a previously unreported polymorphic cocrystallisation of the model pharmaceutical compound **caffeine**.

The system under study specifically consists of two polymorphs of an unionised molecular cocrystal containing **caffeine** and glutaric acid (**GA**). Slow evaporation at ambient temperature of a chloroform solution containing both **caffeine** and **GA** produced crystals of two morphologies: rods and blocks.[8] Single crystal X-ray diffraction analysis identified the rods as monoclinic (form I) and the blocks as triclinic (form II).‡ Both polymorphs possess 1 : 1 **caffeine** : **GA** stoichiometry and exhibit identical secondary architecture, such that a two-dimensional sheet results from an array of hydrogen bond-containing ribbons. A conformational difference between the two crystal forms exists in the torsion of the methylene carbons of **GA** (Fig. 1).[9]

Caffeine   **GA**
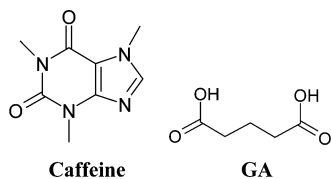
Given the calculated densities of 1.486 and 1.482 Mg m^{-3} for forms I and II, respectively, it may be assumed that the energies of these two polymorphic cocrystals are quite similar based upon the density rule.[10] That they precipitated concomitantly from solution is another indication of their comparable energies. Control of this polymorphic system was desired so that pure samples of each form could be obtained for subsequent study of physical properties.

Precipitation from solution is the most common route to obtaining cocrystals. An alternative approach is that of solid-state grinding, in which two solids are ground together with a mortar and pestle or in a mixer mill to induce cocrystal formation. In addition to its 'green' nature, in that it avoids excessive use of crystallisation solvent, solid-state grinding also offers a means of obtaining nearly quantitative yields with a common particle size. The technique of

cocrystal formation by solid-state grinding has been established for some time.[11,12] A significant enhancement to solid-state grinding was recently illustrated, whereby the cocrystallisation kinetics may be considerably enhanced by the addition of a few drops of solvent.[13] We now observe that this 'solvent-drop grinding' methodology can provide a successful means of controlling the polymorphic outcome of a cocrystallisation.

Equimolar quantities of anhydrous **caffeine** and **GA** were combined in a stainless steel grinding jar with two grinding balls, and the material was ground together either with or without the addition of a few drops of solvent.[14] The resulting material was then characterized by PXRD,[15] having allowed any small amount of solvent present to evaporate. When **caffeine** and **GA** are ground together in the absence of solvent, cocrystal form I predominantly results. Similarly, the addition of four drops from a pipette of a nonpolar solvent, such as n-hexane, cyclohexane, or heptane also produces form I. Conversely, upon addition of four drops of a more polar solvent, including chloroform, dichloromethane, acetonitrile, and water, the grinding experiment results in predominantly form II.[16]

Fig. 2 shows the powder XRD patterns calculated for both polymorphs[17] in addition to powder XRD results from solvent-drop grinding with cyclohexane and chloroform. It is apparent that the experiment involving cyclohexane produced predominantly form I, while the solvent-drop grinding with chloroform produced form II. A small peak at 11.9° 2θ corresponds to the most intense peak of the anhydrous **caffeine** starting material, indicating that the cocrystallisation with cyclohexane has not proceeded entirely to completion within the 60 min grinding time.
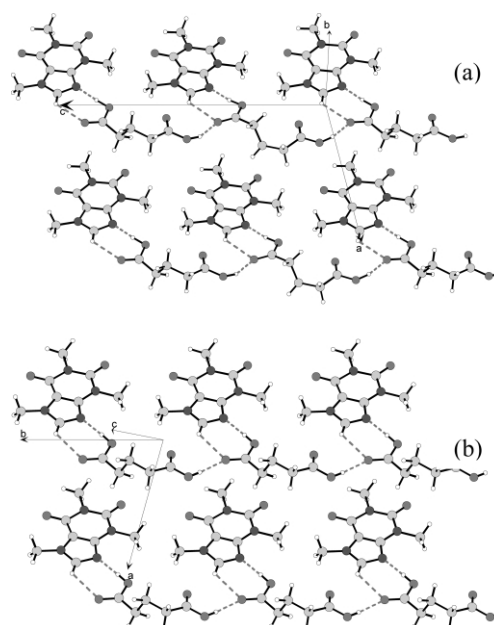

Fig. 1 Crystal packing diagrams of (a) **caffeine–GA** form I and (b) **caffeine–GA** form II, each showing a planar sheet composed of two hydrogen-bonded ribbons.

† Electronic supplementary information (ESI) available: additional powder XRD patterns. See http://www.rsc.org/suppdata/cc/b4/b400978a/

A detailed look at crystal packing reveals a difference which may be important in rationalising the observation that solvent polarity together with solid-state grinding offers a means of controlling polymorphism. While the two cocrystals possess a common secondary level of architecture, their tertiary level of architecture differs (Fig. 3). Orienting form I along the *c* axis provides a perspective down the length of the hydrogen-bonded ribbons. It can be seen that the sheets of form I stack along the *b* axis; one ribbon exactly overlays the next. This leads to what may be interpreted in form I as a non-polar cleavage plane (200) between the stacks of ribbons along the *b* axis. With only methyl and methylene groups exposed, it is possible that non-polar solvents would preferentially stabilise this exposed plane upon grinding-induced cleavage. In contrast, viewing form II from an analogous perspective reveals that sheets stack in a staggered fashion, so that the non-polar cleavage plane is not observed.

We have demonstrated that solvent-drop grinding represents a novel means of obtaining a particular cocrystal polymorph in a green chemistry fashion. Ongoing investigations include further rationalising this observation and exploring the possibility that this technique may have more general applications to other polymorphic systems, including single component systems.
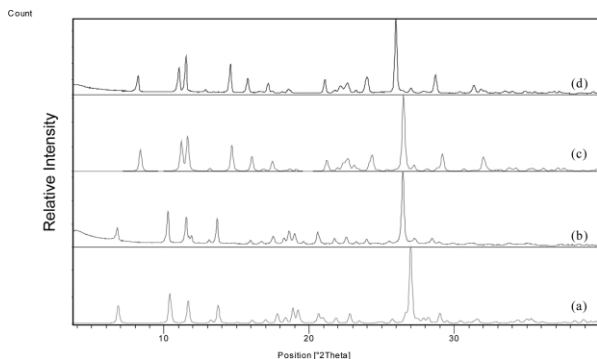
Fig. 2 Powder X-ray diffraction pattern of (a) simulated pattern from single-crystal structure of form I, (b) result of solvent-drop grinding of **caffeine** and **GA** with cyclohexane, (c) simulated pattern from single-crystal structure of form II, (d) result of solvent-drop grinding of **caffeine** and **GA** with chloroform (see ref. 15).
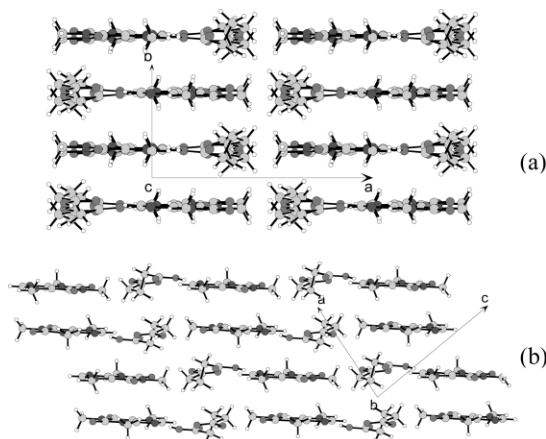

Fig. 3 Crystal packing diagrams of (a) **caffeine–GA** form I and (b) **caffeine–GA** form II, oriented perpendicular to the ribbon long axis, so as to reveal potential vertical cleavage planes.

Notes and references

‡   *Crystal data* for **caffeine–GA** form I: $C_{13}H_{18}N_4O_6$, $M = 326.31$, monoclinic, space group $P2_1/c$; $a = 13.1029(5)$, $b = 6.6017(2)$, $c = 17.1427(8)$ Å, $\beta = 97.8360(10)°$, $U = 1458.93(10)$ Å^3, $T = 180(2)$ K, $Z = 4$, μ(Mo-Kα) = 0.119 mm^{-1}, $D_c = 1.486$ Mg m^{-3}, $\lambda = 0.71073$ Å, $F(000) = 688$, $2\theta_{max} = 27.52°$. 8983 reflections measured, 3343 unique ($R_{int} = 0.0418$). Final residuals for 217 parameters were $R_1 = 0.0645$, $wR_2 = 0.1870$ for $I > 2\sigma(I)$, and $R_1 = 0.1061$, $wR_2 = 0.2271$ for all 3343 data. *Crystal data* for **caffeine–GA** form II: $C_{13}H_{18}N_4O_6$, $M = 326.31$, triclinic, space group $P\bar{1}$; $a = 8.3212(8)$, $b = 8.6667(8)$, $c = 11.3636(12)$ Å, $\alpha = 68.955(4)$, $\beta = 78.559(4)$, $\gamma = 74.236(4)°$, $U = 731.43(12)$ Å^3, $T = 180(2)$ K, $Z = 2$, μ(Mo-Kα) = 0.119 mm^{-1}, $D_c = 1.482$ Mg m^{-3}, $\lambda = 0.71073$ Å, $F(000) = 344$, $2\theta_{max} = 27.47°$. 5689 reflections measured, 3094 unique ($R_{int} = 0.0442$). Final residuals for 217 parameters were $R_1 = 0.0572$, $wR_2 = 0.1569$ for $I > 2\sigma(I)$, and $R_1 = 0.0815$, $wR_2 = 0.1771$ for all 3094 data. In both crystal structures the carboxylic acid protons were located crystallographically and their positions were refined, confirming that proton transfer had not occurred. CCDC 229592 and 229593. See http://www.rsc.org/suppdata/cc/b4/b400978a/ for crystallographic files in CIF or other electronic format.

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14 Experiments consisted of *ca.* 750 mg total material, ground for one hour at 30 revolutions per second with a Retsch Mixer Mill. Ratio of moles of added organic solvent per mole of total cocrystal material varied between 0.2 and 0.6, so that the solvent only slightly moistened the crystalline powder. This contrasts with conventional solution cocrystallisations, where the mole ratio of solvent to solid is commonly in the hundreds.
15 Powder XRD data were collected with a Philips X'Pert diffractometer with Cu Kα radiation and an X'Celerator detector.
16 In preliminary solution cocrystallisation work, equimolar solutions of the two components in chloroform and in dichloromethane produced crystalline powder of mixed polymorph content. Conversely, a solution cocrystallisation from acetonitrile provided predominantly form II, while cocrystallisation from water produced crystalline caffeine hydrate. Solution cocrystallisation from non-polar solvents was not possible due to poor solubility.
17 Calculated powder XRD patterns were generated from single crystal XRD data using X'Pert Plus, Philips Analytical B.V. The calculated PXRD patterns exhibit a peak shift which is particularly noticeable toward high 2θ values. A form II crystal was recollected near ambient temperature to confirm that this shift results only from crystal lattice contraction at the low temperature used for the single crystal data collection.