Cocrystallisation by Freeze-Drying: Preparation of Novel Multicomponent Crystal Forms

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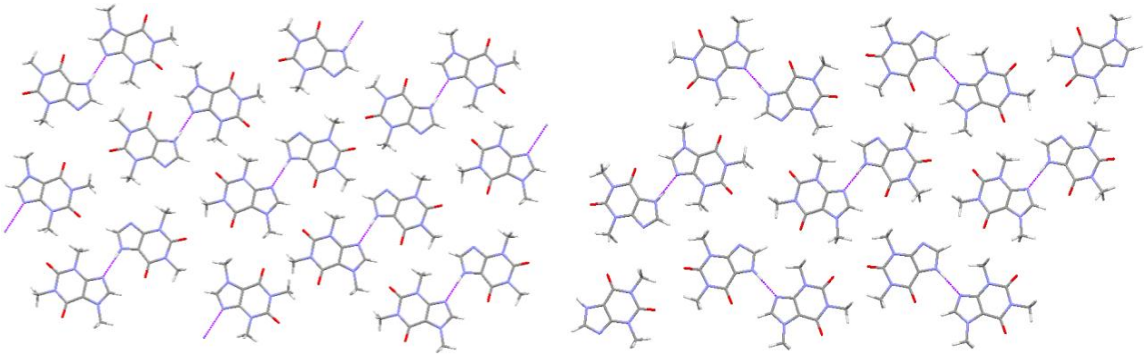

Caffeine:theophylline cocrystal Form I

Caffeine:theophylline cocrystal Form II

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INTRODUCTION

Increasing interest in cocrystals, crystal forms containing two or more neutral molecules in a crystal lattice,[1-5] in several areas of research including the pharmaceutical sector has stemmed from work which demonstrated that cocrystal formation can improve the physical properties of the constituent compounds (coformers). For example, cocrystals of the pharmaceutical compound itraconazole were found to have a dissolution rate similar to that of amorphous itraconazole,[6] and Trask *et al* showed that cocrystals of caffeine and theophylline with dicarboxylic acids showed a greater stability to hydrate formation than the free forms of these compounds.[7, 8] Subsequently, cocrystallisation has been used to modify many other properties such as chemical stability,[9] propensity for polymorphism,[10] tableting behavior,[11] solubility profile[12] and melting point.[5, 13]

Several techniques are widely used for the preparation of cocrystals including solution crystallisation, dry grinding, liquid assisted grinding, slurrying and crystallisation from the melt.[4, 14-23] From an industrial manufacturing perspective, solution crystallisation would be the preferred method of generating cocrystals, but this approach is often undermined by solubility differences between the coformers, which result in their crystallisation as separate phases rather than as a cocrystal.[14, 19, 24, 25] Not only does this make cocrystals potentially difficult to prepare on a large scale from solution, it also means that solution based screens for identifying pairs of coformers that can cocrystallise may be inefficient as a negative result could be due to solubility differences between the coformers rather than an indication that two molecules are unable to form a stable cocrystal.[26]

Grinding and slurrying approaches to cocrystallisation avoid these solubility issues by involving little or no solvent.[19] These processes are, however, likely to be difficult to apply to industrial scale manufacturing,[27, 28] with continuous processes such as twin screw extrusion offering greater potential in this regard.[29] In addition, the input material for grinding and slurrying experiments is usually a mixture of crystalline coformers, and when using these methods to screen for cocrystals there is the possibility that these phases may persist rather than converting to a more stable cocrystal phase (through a kinetic phenomenon similar to seeding).

Freeze-drying is a technique where a solution of a compound is prepared, rapidly frozen and the held under a high vacuum causing the solvent to sublime. The solute remains and forms a low density, often amorphous, powder. Though freeze-drying is a technique primarily used to prepare amorphous forms,[30] if the glass transition temperature of the amorphous material is at or below ambient temperature, it will be liable to spontaneous crystallisation.[30, 31] The rationale for using freeze-drying as a cocrystallisation method is that it enables a solid amorphous mixture of two coformers to be prepared, from which a cocrystal can crystallise without the kinetic barrier of the presence of crystalline seeds of the two cocrystal formers. Samples for freeze-drying are usually prepared by dissolving compound(s) of interest in water or t-butanol (or a water:t-butanol mixture),[32, 33] but several other solvents including acetonitrile, chloroform, dioxane and DMSO can be employed, as long as the instrument is chemically resistant,[34-37] meaning that it should be possible to identify a solvent, or solvent mixture, which is suitable for dissolving both coformers. Freeze-drying is also routinely used to prepare pharmaceutical solid forms and formulations on an industrial scale.[38] An approach to cocrystal formation based on spray-drying, which is likely to involve similar crystallisation processes, has recently been described by Alhalaweh *et al*.[39]

Here we demonstrate the general applicability of freeze-drying for the preparation of cocrystals, using several pharmaceutical compounds as examples, and how it can be used to produce additional solid forms not readily accessible by standard methods. This work lead to an investigation into polymorphism in the caffeine:theophylline cocrystal system.

EXPERIMENTAL SECTION

All chemicals were purchased from Sigma-Aldrich and used as received.

Solutions for freeze-drying were prepared by dissolving compound(s) in water or t-butanol in a round bottom flask. The solutions were rapidly frozen by cooling the flask in liquid nitrogen. A Virtis Advantage 2.0 EL instrument and Leybold vacuum pump were used for freeze-drying, with the round bottom flasks held on nozzles on the outside of the instrument (at ambient temperature).

Ball milling was performed in a Retsch MM200 grinder for 30 minutes at a frequency of 30 Hz. The grinding was done in a steel vial with two 7 mm diameter steel balls. For liquid assisted grinding 20 µl of nitromethane was also added. Typically, experiments were performed on a 300 mg scale. Grinding at -10 °C was performed at Université Lille-1 in a Fritsch planetary mill.

As a part of the polymorphism study of the caffeine:theophylline cocrystal, we applied the global lattice energy minimisation method[40] to predict the possible low energy 1:1 cocrystal structures. Putative crystal structures of the cocrystal were generated with the CrystalPredictor program,[41] using rigid molecular geometries of caffeine and theophylline derived from quantum mechanical geometry optimisations of the isolated molecules. Crystal structure generation involved quasi-random sampling of unit cell dimensions, molecular positions and orientations

within the 15 most commonly observed space groups for molecular organic crystal structures were considered ($P1$, $P\bar{1}$, $P2_1$, $P2_1/c$, $P2_12_12$, $P2_12_12_1$, $Pna2_1$, $Pca2_1$, $Pbca$, $Pbcn$, $C2/c$, Cc, $C2$, Pc, and $P2/c$), all with $Z'=1$ (one of each molecule in the asymmetric unit). Over 10^6 structures were generated and lattice energy minimised using CrystalPredictor, with intermolecular interactions described by an empirically parameterised exp-6 repulsion-dispersion potential (Williams' W99 potential)[42, 43], coupled with atomic partial charges fitted to the calculated molecular electrostatic potentials. After removal of duplicate structures, the 10,000 lowest energy crystal structures were then re-optimised using the program DMACRYS.[44] These final energy minimisations used the same exp-6 repulsion-dispersion parameters, but with a more accurate model of intermolecular electrostatic interactions, involving a multipole series up to hexadecapole on each atomic site, with multipoles derived from a distributed multipole analysis[45] of the calculated molecular charge density. Charge-charge, charge-dipole and dipole-dipole interactions were summed using Ewald summation, while repulsion-dispersion and all higher order electrostatics were summed using a 15Å direct space cutoff. The optimised crystal structures were then clustered to remove duplicates using the COMPACK algorithm,[46] by comparing interatomic contacts within a 25-molecule molecular cluster taken from each crystal structure using a tolerance of 15%. Molecular energies and charge densities throughout the predictions were calculated at the B3LYP/6-311G(d,p) level of theory using the Gaussian03 software.[47]

PXRD analysis was performed on a Philips X'Pert Diffractometer equipped with an X'celerator RTMS detector using CuKα radiation at a wavelength of 1.5406 Å. Data were collected between 3 and 50 °2θ at ambient temperature. A step size of 0.0167 °2θ was used and a collection time of 5 minutes. Typically, 20 mg of solid was used for analysis and pressed gently

on a glass slide to give a level surface. PXRD overlays are plotted with an arbitrary intensity scale and were generated using X'Pert Highscore software.

Optical microscopy was performed on a Leica DM1000 instrument with a polarising filter.

Transmission electron microscopy characterisation was performed at room temperature on a Philips CM30 instrument operating at 300 kV, and data were collected on photographic films which were scanned in order to generate digital images. A double tilt sample holder was used and the samples supported on holey-carbon films on 400 mesh copper grids.

RESULTS AND DISCUSSION

The cocrystal systems listed in Table 1[3, 4, 7, 8, 21, 48-50] were selected for freeze-drying investigation work. For each system, a solution containing equimolar amounts of the two cocrystal formers was prepared and then rapidly frozen by cooling in liquid nitrogen before being freeze-dried. The resulting solids were analysed by PXRD and observations are shown in Table 1.

Table 1. A table listing attempted freeze-drying cocrystal formation experiments and outcomes as determined by PXRD analysis.

Cocrystal System	Ratio of coformers	Solvent	Outcome of experiment
Caffeine:theophylline	1:1	Water	New crystal form
Caffeine:oxalic acid	2:1	Water	Known cocrystal form

Caffeine:glutaric acid	1:1	Water	Known cocrystal form
Caffeine:adipic acid	1:1	Water	No cocrystal formation
Theophylline:oxalic acid	2:1	Water	New crystal form
Aspirin:carbamazepine	1:1	Water/t-butanol	Known cocrystal form
Phenazine:mesaconic acid	1:1	t-Butanol	Known cocrystal form
RS-Ibuprofen:nicotinamide	1:1	t-Butanol	Known cocrystal form
RS-Ibuprofen:4,4-Bipy	1:1	t-Butanol	Known cocrystal form

Cocrystal formation was achieved in all but one of the freeze-drying experiments, that with caffeine and adipic acid, suggesting that freeze-drying is a reliable method for preparing cocrystals. This would indicate that the rate of crystallisation of the cocrystal from the amorphous mixture resulting from freeze-drying was greater than that of either of the individual coformers, and can perhaps be rationalised by considering that before individual coformers could crystallise a certain amount of diffusion would be required to form domains of pure coformer sufficiently large for nucleation to occur. With caffeine and adipic acid, however, the rate of nucleation of one or both of the coformers from the amorphous mixture was greater than that of the cocrystal, resulting in formation of a sample containing the cocrystal formers as separate crystalline phases. It is worth noting that early attempts to cocrystallise caffeine and adipic acid by grinding were also unsuccessful.[7] As grinding is another cocrystallisation method where conversion is believed to proceed via an amorphous intermediate,[19, 51] this observation can again be explained by a slower rate of crystallisation of the cocrystal in comparison to the individual

coformers from the amorphous phase. The caffeine:adipic acid cocrystal was later isolated by liquid assisted grinding,[52] and also by slurrying caffeine with adipic acid, an approach which tends to drive a system to the thermodynamic product.[21]

It is also worth noting that the aspirin:carbamazepine cocrystal, which is readily obtained by freeze-drying, was not obtained during liquid assisted grinding experiments with aspirin and carbamazepine (ball mill grinding experiments were performed in the presence of the solvents nitromethane, methanol and water using a 30 minute grinding duration at a frequency of 30 Hz with 20 μl of liquid). This may be because the grinding experiments used coformers in crystalline form as input material, and there is the potential for any amorphous intermediate phase which is generated during the grinding to crystallise on the surface of these existing crystals rather than to nucleate as a cocrystal form (self-seeding).

Two new crystal forms were obtained from the freeze-drying experiments, one with theophylline and oxalic acid and one with caffeine and theophylline. Further work was conducted to determine the nature of these forms. To date, it has not been possible to determine the crystal structure of the theophylline:oxalic acid form, but PXRD and thermal analysis indicate that this phase is a pentahydrate of the 2:1 theophylline:oxalic acid cocrystal (see Figure 1 and Supplementary Information). Interestingly, the cocrystal hydrate is only obtained on grinding with water when seeds of the hydrate are also added. In the absence of seeds the anhydrous 2:1 cocrystal is generated (grinding both with and without seeding was performed using 200 mg of theophylline, 69.98 mg of oxalic acid dihydrate and 50 μl of water (5.0 mole equivalents with respect to oxalic acid) in a ball mill for 30 minutes at a frequency of 30 Hz).

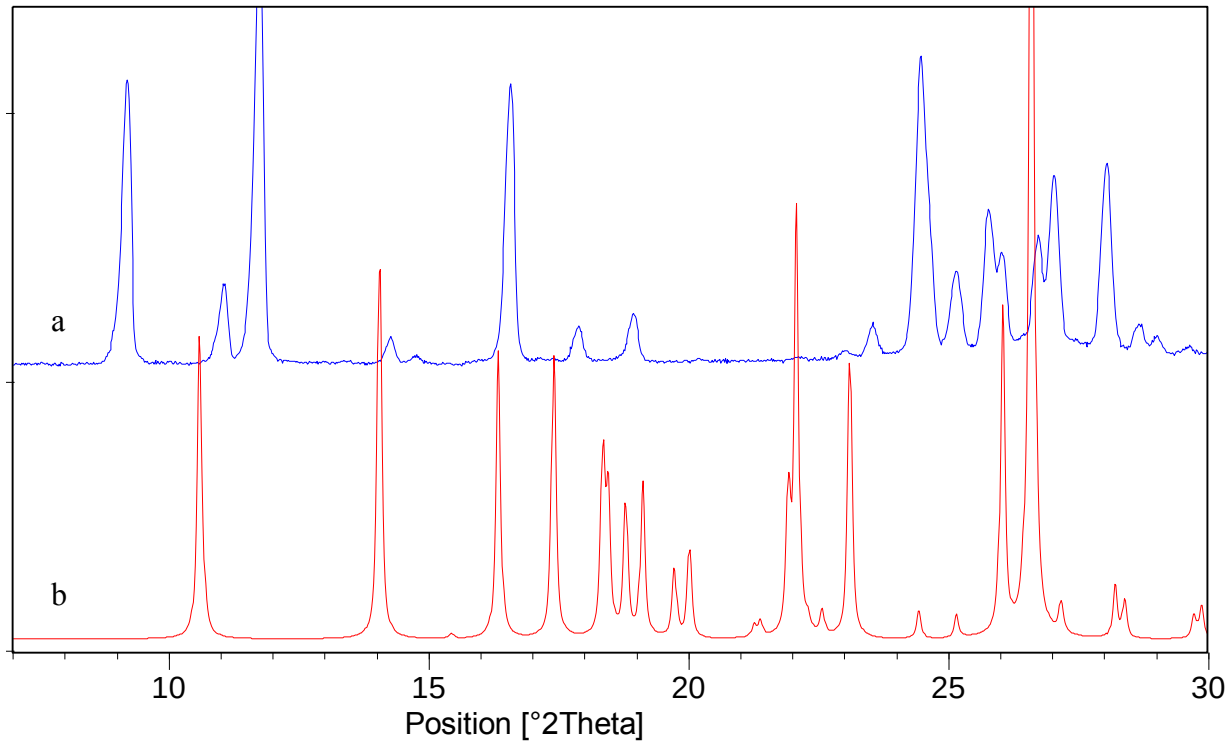

Figure 1. (a) PXRD trace of the hydrated crystal form of the 2:1 theophylline:oxalic acid cocrystal. (b) Reference trace of the previously reported anhydrous 2:1 theophylline: oxalic acid cocrystal (calculated from Cambridge Structural Database (CSD) structure XEJWUF)[8].

Characterisation of the product of freeze-drying caffeine and theophylline

The PXRD trace of the sample obtained on freeze-drying a 1:1 solution of caffeine with theophylline is shown in Figure 2, along with a reference trace of the only previously reported form of the 1:1 caffeine:theophylline cocrystal[49] (which will be referred to here as Form I), showing clear differences between the two traces. The trace of the freeze-dried sample is, however, similar to that of Form I of caffeine, the metastable hexagonal polymorph (Figure 2c).[53, 54] On close inspection, the PXRD reflections of the freeze-dried sample are shifted slightly

to higher or lower 2θ positions with respect to the caffeine reflections, indicating that it is a different, but related crystal form. Additionally, there are no reflections that can be attributed to a single component phase of theophylline in the trace of the freeze-dried sample, and the lack of an amorphous halo in the PXRD trace indicates that theophylline is not present as an amorphous phase. These observations indicate that the product of freeze-drying caffeine and theophylline is a solid solution of these two compounds. This was confirmed through an additional set of freeze-drying experiments where the ratios of caffeine and theophylline were varied. As the ratio of theophylline to caffeine in the freeze-dried material was increased, the positions of PXRD reflections deviated progressively further from those of Form I of caffeine (as shown for the peak corresponding to the {110} reflections in Figure 3). It should be noted that the new crystal phase was not obtained when samples containing theophylline only were freeze-dried.

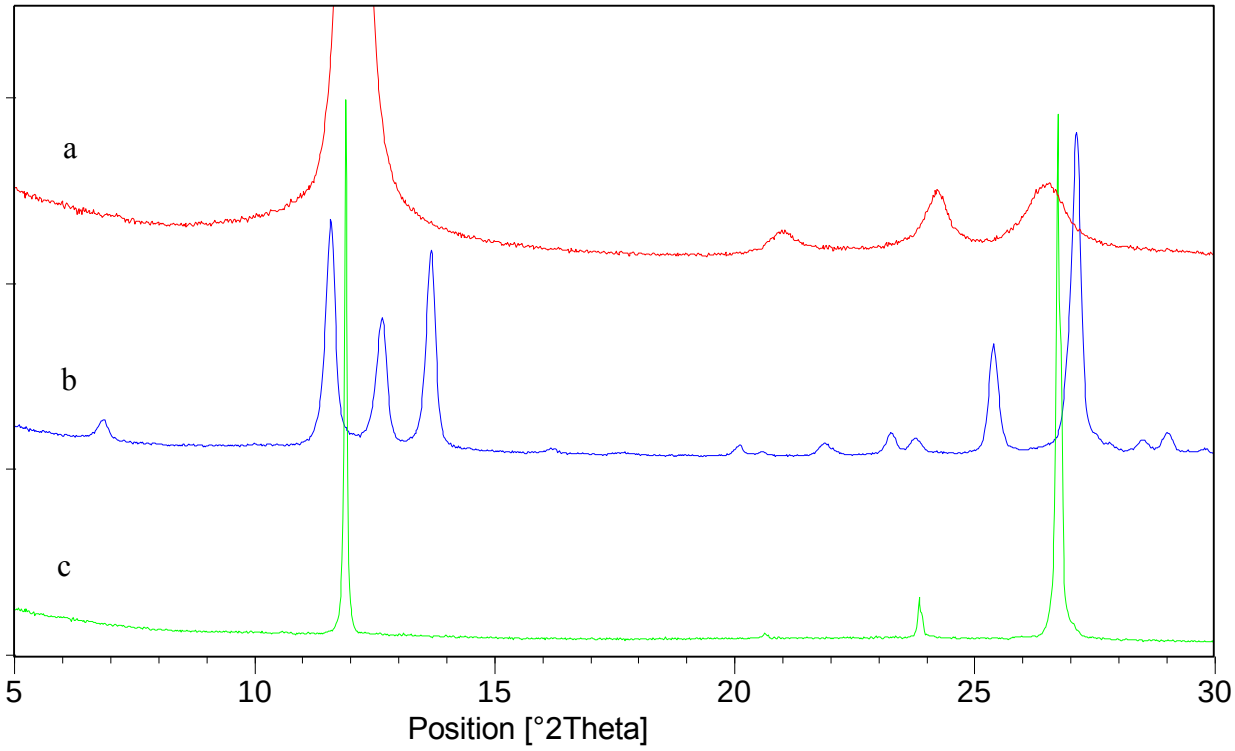

Figure 2. PXRD analysis of a sample prepared by freeze-drying caffeine and theophylline in a 1:1 molar ratio. (a) PXRD trace of a sample prepared by freeze-drying caffeine and theophylline in a 1:1 molar ratio. (b) Reference trace of the previously reported form of the 1:1 caffeine:theophylline cocrystal, Form I. (c) Reference trace of Form I of caffeine.

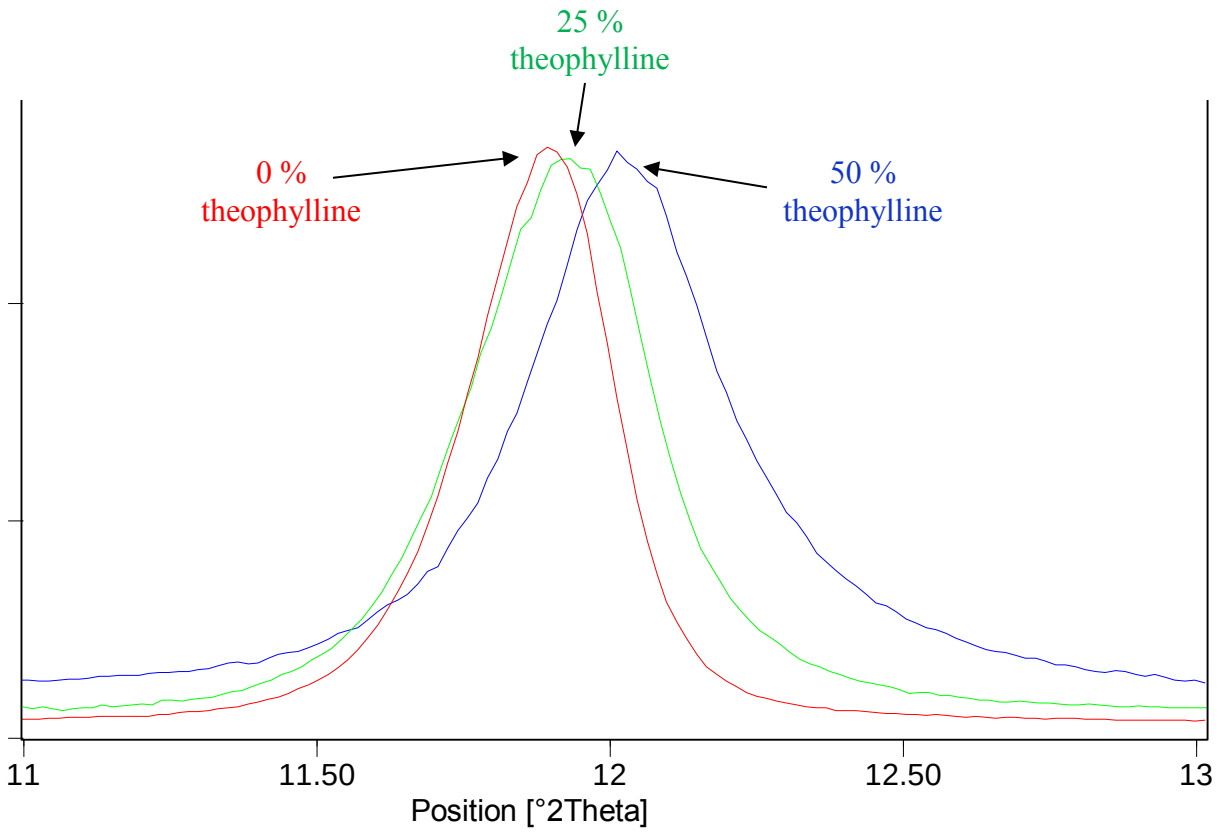

Figure 3. PXRD analysis of freeze-dried samples of caffeine and theophylline showing variation in the position of the {110} reflection as the theophylline content is varied from 0 to 50 %.

It can be concluded that the new crystal phase is a solid solution of caffeine and theophylline which is isostructural with Form I of caffeine and where the unit cell dimensions vary with theophylline content. Theophylline molecules have a similar size shape and polarity to caffeine molecules (Figure 4), and can replace caffeine in this phase without disrupting the crystal packing. As the solid solution is isostructural with Form I of caffeine it must have the same trigonal *R-3c* space group,[54] and hexagonal symmetry, meaning that the molecules of caffeine and theophylline must be orientationally disordered.[55]

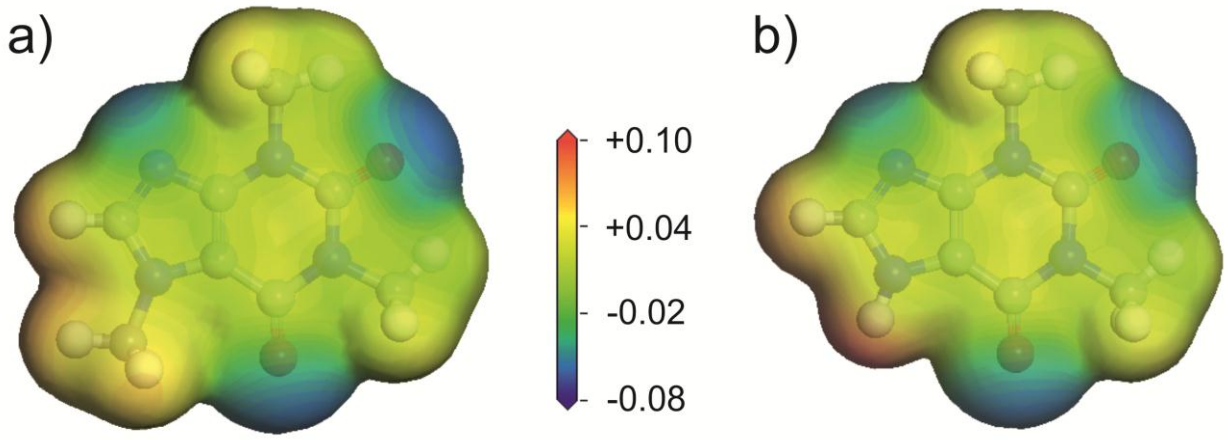

Figure 4. Molecular electrostatic potentials for (a) caffeine and (b) theophylline. The electrostatic potentials are given in atomic units and plotted on the 0.015 au electron density surface, as calculated with B3LYP/DNP using DMol3[56, 57] at the optimised molecular geometry.

In order to determine whether the solid solution of caffeine and theophylline could be obtained by other cocrystallisation methods a series of solution crystallisation, slurrying and liquid assisted grinding experiments were performed. Form I of the cocrystal was obtained by each method (from a 3:2 mixture of DMF and dioxane during solution crystallisation and slurrying, and various different solvents for liquid assisted grinding), whereas the solid solution was not obtained from any of these experiments.

Solution crystallisation screens are widely used as a method of investigating polymorphism of individual compounds, making use of solvents with a wide diversity of properties to generate different crystal forms.[58] During this study, however, solution crystallisation from a majority of solvents resulted in crystallisation of theophylline and caffeine as separate phases, rather than a multicomponent crystal form, due to differences in the solubility of these compounds. This

severely limited the range of solvent conditions that could be used for screening for different forms of the cocrystal, and may explain why the solid solution was not isolated. This observation highlights the limitations of solution crystallisation as a screening tool for investigating cocrystal polymorphism.[26]

As described above, cocrystallisation by both grinding and freeze-drying is expected to involve an intermediate amorphous phase.[19] With caffeine and theophylline, however, two different crystal forms were obtained using these methods (freeze-drying gave the solid solution, whereas grinding gave the cocrystal). This may be an indication that cocrystal formation during liquid assisted grinding proceeded by a different mechanism in this instance, possibly nucleation from a solution phase. Although grinding is usually thought to be a solid state process as the amount of solvent added during liquid assisted grinding is small (20 μl), this amount is enough to cover all of the particles that are present in the grinding vial with many (10 to 30) layers of solvent molecules, and so a solution mediated cocrystallisation mechanism is not unlikely. Furthermore, when grinding conditions were changed to dry grinding at -10 °C, a temperature close to, or below, the glass transition temperature of the amorphous mixture of caffeine and theophylline, where grinding would be expected to promote formation of an amorphous phase,[59, 60] the solid solution was in fact obtained (Figure 5).

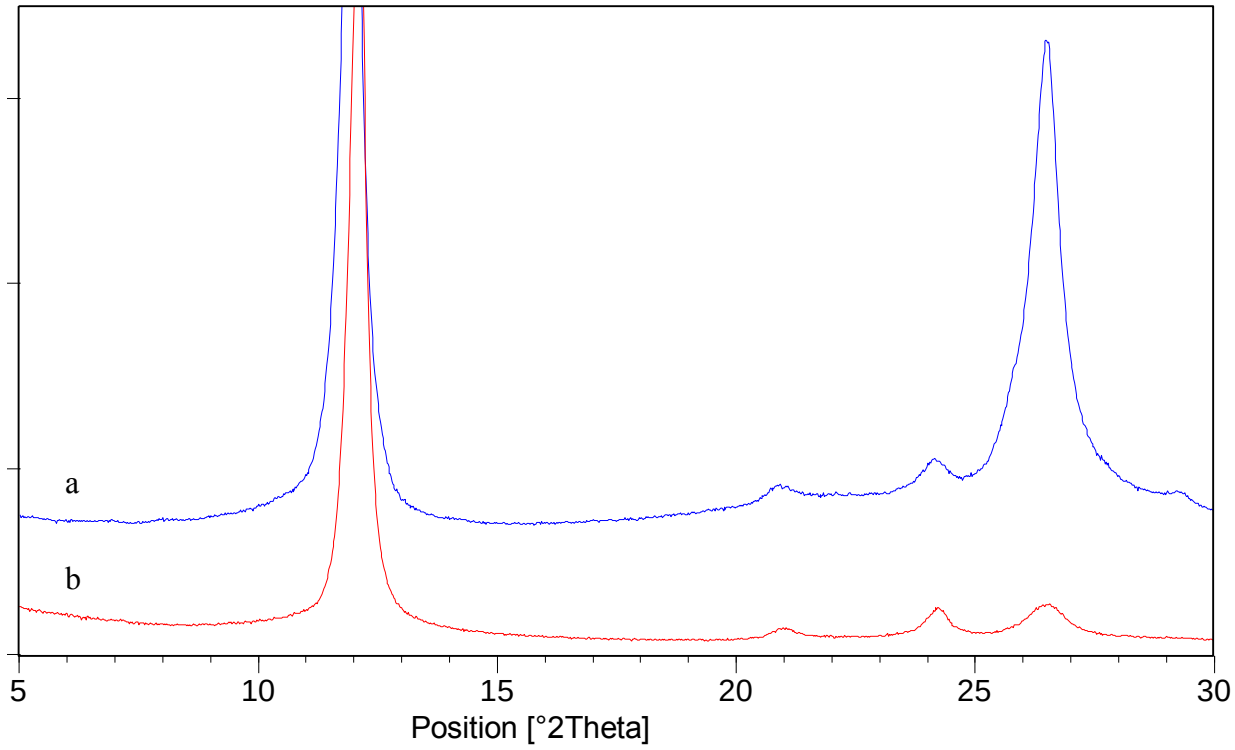

Figure 5. PXRD analysis of a sample prepared by grinding caffeine and theophylline in a 1:1 molar ratio at -10 °C. (a) PXRD trace of a sample prepared by grinding caffeine and theophylline in a 1:1 molar ratio at -10 °C. (b) Reference trace of the solid solution of caffeine and theophylline.

Polymorphism of the caffeine:theophylline cocrystal.

On storing the solid solution of caffeine and theophylline under ambient conditions changes in particle size and morphology were observed indicating a change in crystal form. Polarised light microscopy (PLM) and transmission electron microscopy (TEM) images of crystals of the solid solution of caffeine and theophylline are shown in Figure 6. The crystals have lath or needle-like habits and lengths of up to 20 μm. It is evident from the TEM image that what appear to be lath shaped particles in the optical image are agglomerations of aligned needle-shaped crystals. On

re-analysing the sample after 6 days of storage under ambient conditions, a decrease in crystal size was observed (Figures 6c-d). PXRD analysis confirmed that the change in crystal morphology occurs as a result of a change in crystal form (Figure 7).

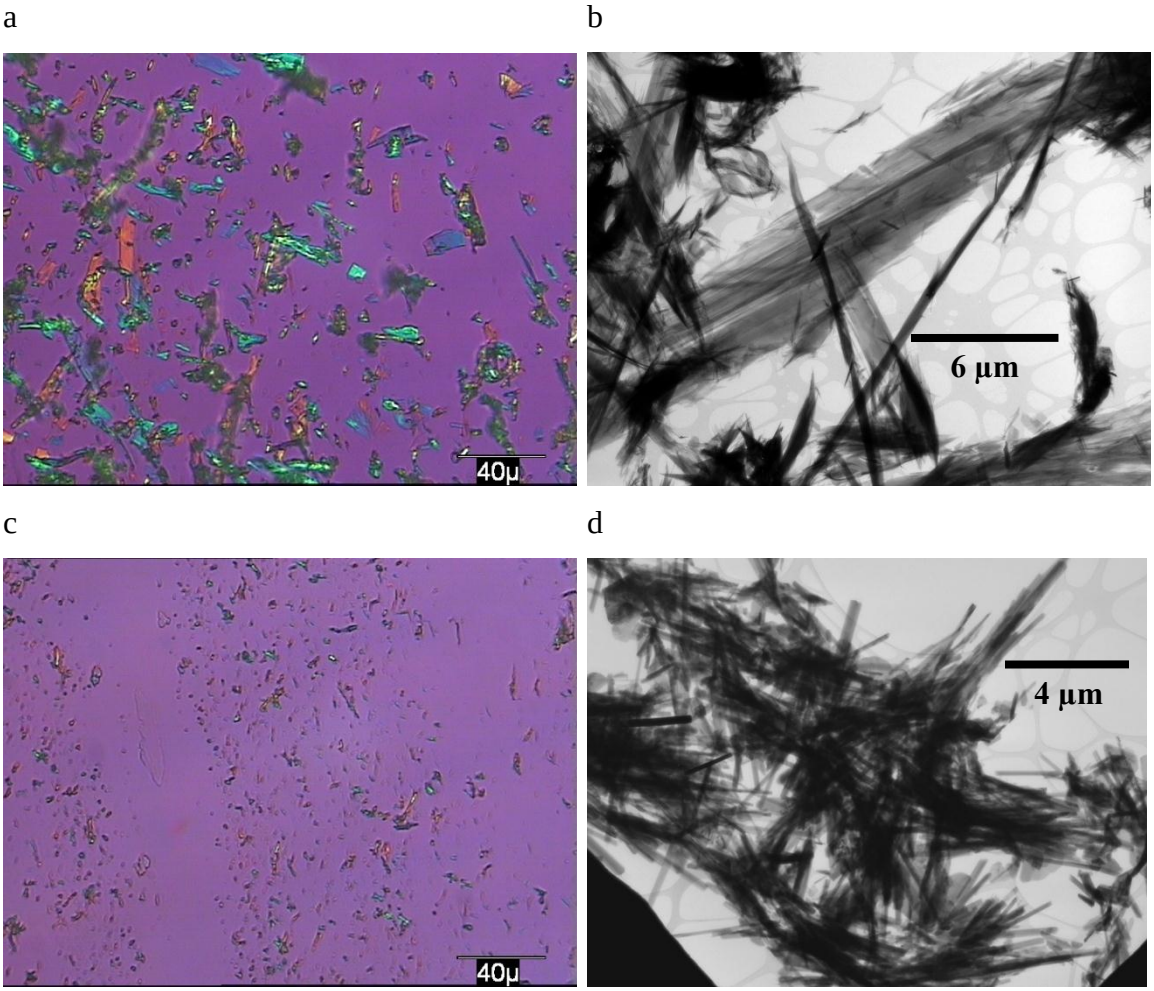

Figure 6. Microscopic analysis of the solid solution of caffeine and theophylline before and after storage under ambient conditions. (a) PLM image and (b) TEM image of the solid solution after preparation by freeze-drying. (c) PLM image and (d) TEM image of the same sample after storage under ambient conditions for 6 days (Form II of the caffeine:theophylline cocrystal).

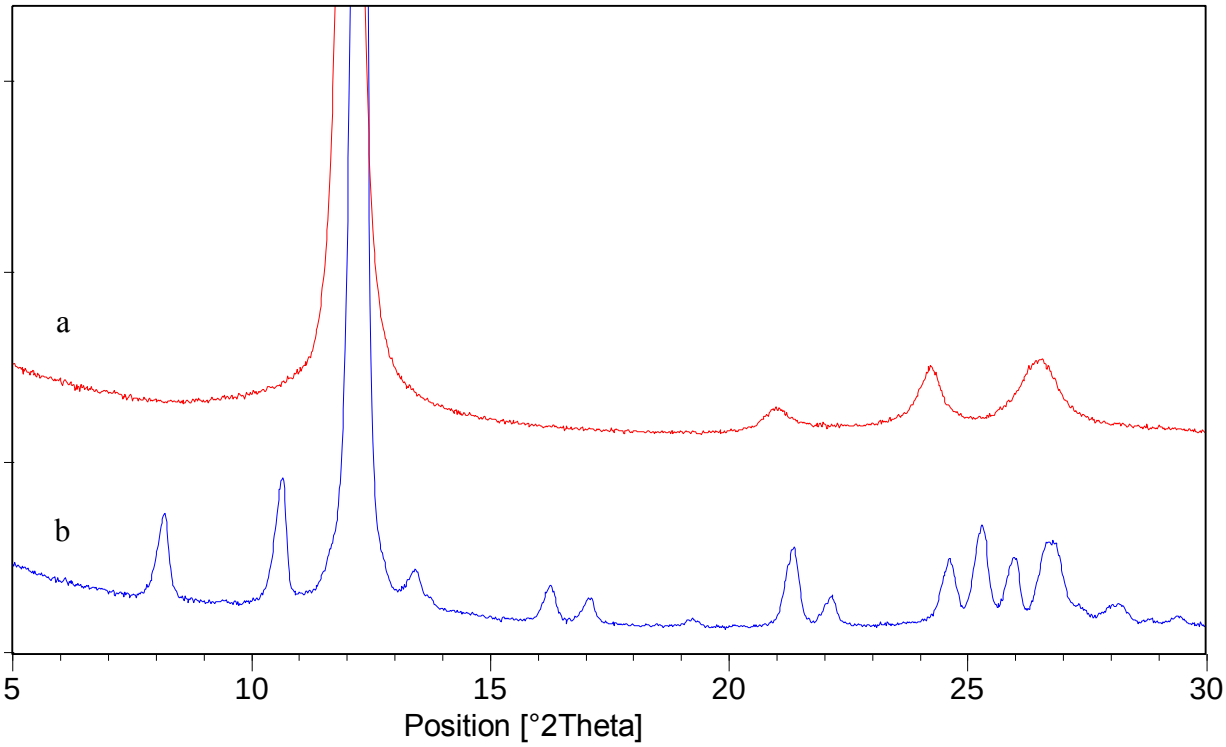

Figure 7. PXRD analysis of the solid solution of caffeine and theophylline before and after storage under ambient conditions. (a) PXRD trace of the solid solution of caffeine and theophylline immediately after preparation by freeze-drying. (b) PXRD trace of the same sample after storage under ambient conditions (Form II of the caffeine:theophylline cocrystal).

This new crystal form is a second polymorph of the 1:1 caffeine:theophylline cocrystal (Form II) as determined by comparing the PXRD trace to the simulated traces of low energy putative 1:1 cocrystal structures generated by crystal structure prediction. A match to the observed PXRD trace was found to the predicted structure with the 9th lowest calculated lattice energy (Figure 8), which was calculated to lie 2.6 kJ mol^{-1} above the lowest energy predicted structure. Form II crystallises in the monoclinic *P21/c* space group and the unit cell parameters of the predicted structure are: a = 7.009 Å, b = 14.563 Å, c = 16.587 Å, β = 90.33 °, V = 1693.0 $Å^3$. The excellent

agreement in peak positions between the observed PXRD and the simulated pattern from the predicted structure demonstrate that the predicted unit cell parameters are an accurate representation of the structure. The slight differences in peak positions at high 2θ are due to small differences in the unit cell lengths and angles between the predicted and experimental structures. These small errors result from approximations in the intermolecular potential, neglect of thermal effects in the simulations, and the assumption that molecular geometries are unaffected by the crystal packing environment. Caffeine and theophylline molecules form pairwise interactions through a single N-H···N hydrogen bond. The 3 dimensional structure results from close packing of the dimers (Figure 9).

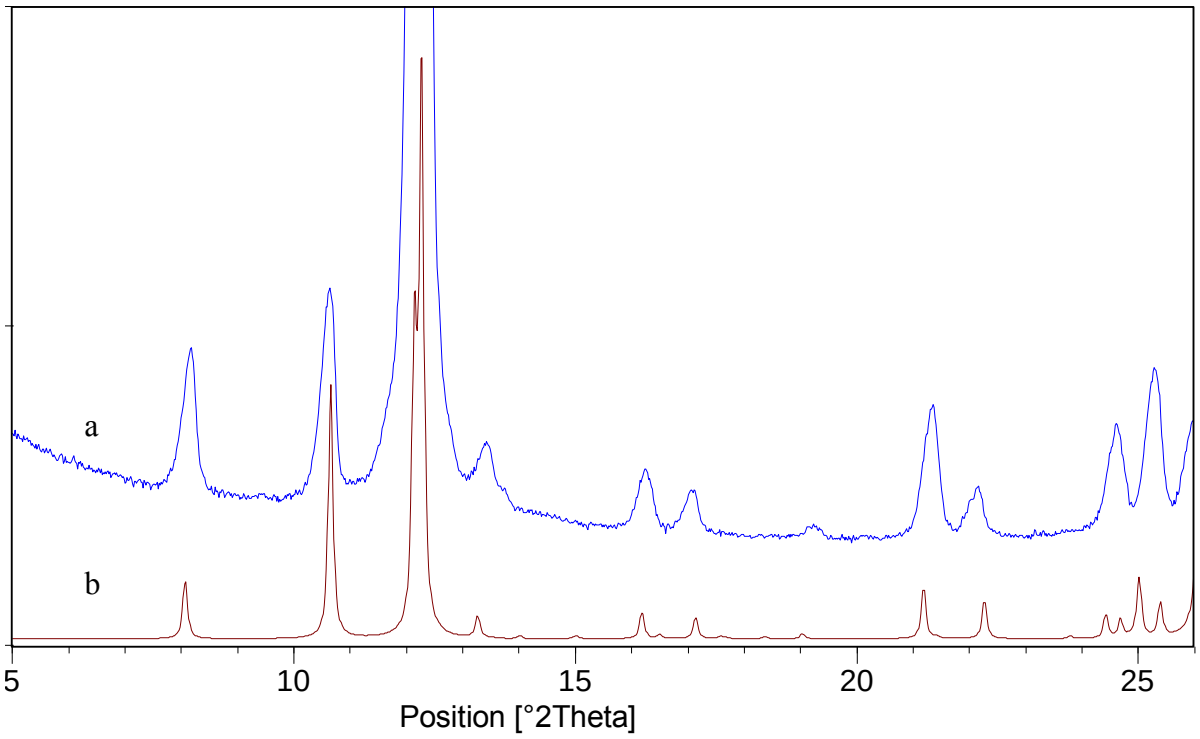

Figure 8. Overlay of experimental and simulated PXRD traces of Form II of the caffeine:theophylline cocrystal. (a) PXRD trace of Form II of the caffeine:theophylline cocrystal. (b) PXRD trace simulated from the 9th lowest energy predicted cocrystal structure of 1:1 caffeine:theophylline.

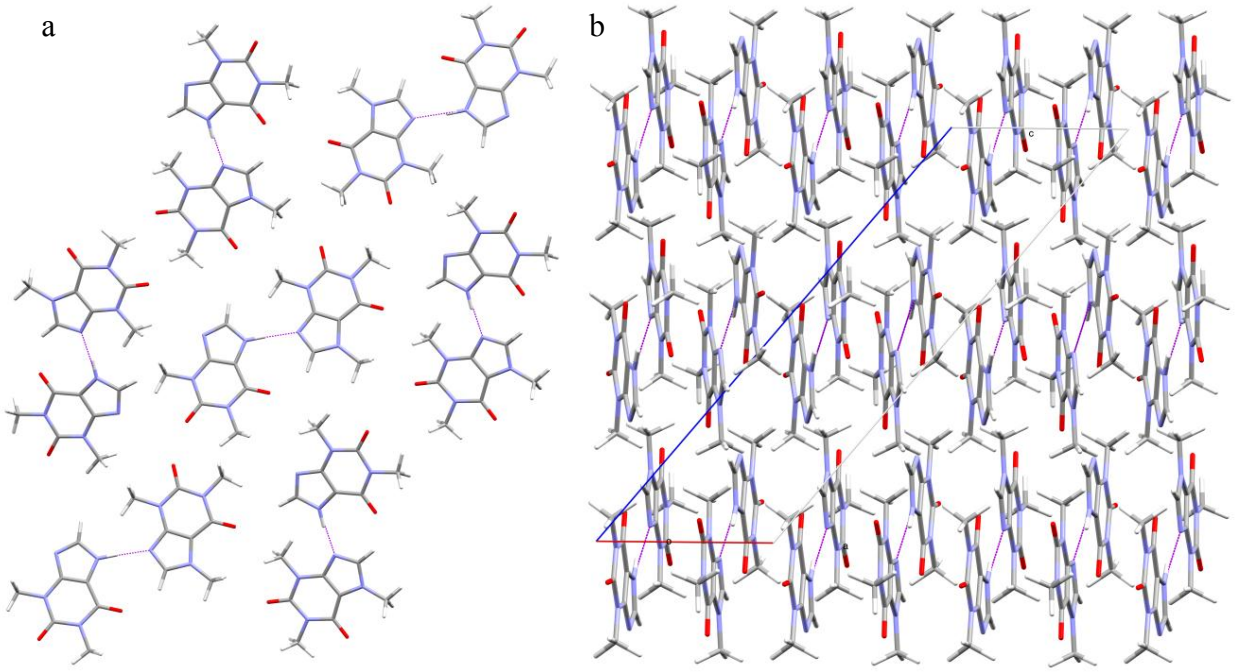

Figure 9. The crystal structure of Form II of the 1:1 caffeine:theophylline cocrystal. (a) A single layer showing pairwise hydrogen bonding interactions between caffeine and theophylline molecules. (b) View down the b-axis showing the layered arrangement of the pairs.

The relative thermodynamic stability of the three different crystal forms of caffeine and theophylline was determined to be Form I > Form II > solid solution. As shown above, the solid solution readily converts to Form II of the cocrystal under ambient conditions, a process which takes between 24 and 48 hours. A much slower conversion of Form II to Form I was observed in a sample of Form II which was stored under ambient conditions for a period of three years (Figure 10). The slow rate of this conversion may result from an inability of molecules to re-organise from the arrangement found in Form II to that in Form I. For the transformation to occur without crystal collapse, and without breakage of hydrogen bonds between dimers of caffeine and theophylline molecules, the dimers would have to both move apart and rotate, and

this is likely to result in a large energy barrier (Figure 11). It is also highly unlikely that the two forms could interconvert through a concerted layer-by-layer mechanism, such as has been recently reported for other organic systems,[61, 62] as adjacent rows of dimers interdigitate slightly.

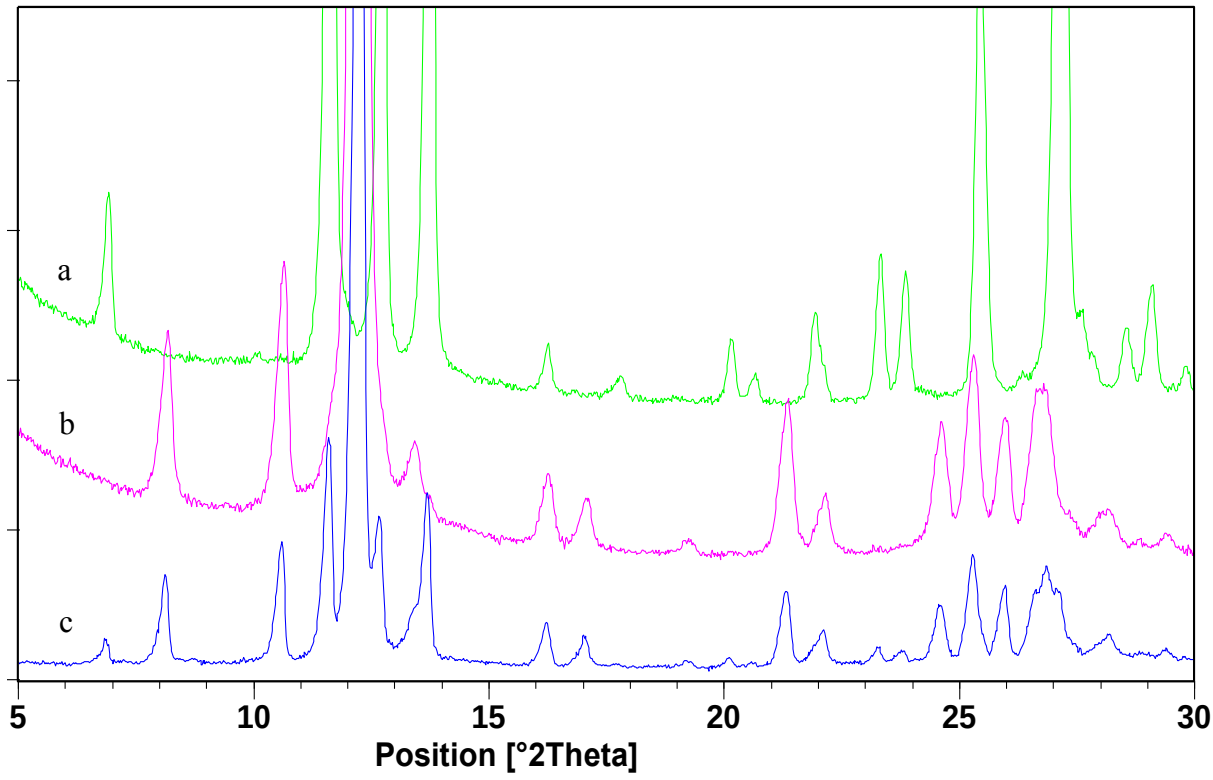

Figure 10. PXRD analysis of Form II of the caffeine:theophylline cocrystal after storage under ambient conditions for 3 years. (a) Reference trace of Form I of the caffeine:theophylline cocrystal. (b) Reference trace of Form II of the caffeine: theophylline cocrystal. (c) PXRD trace of Form II of the caffeine:theophylline cocrystal after storage under ambient conditions for 3 years showing partial conversion to Form I.

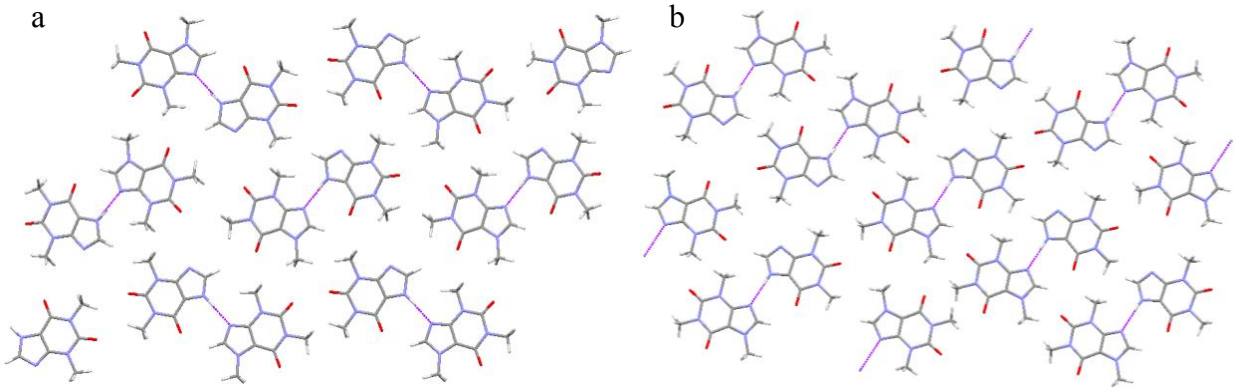

Figure 11. The local arrangements of hydrogen bonded dimers of caffeine and theophylline in (a) Form II and (b) Form I of the caffeine:theophylline cocrystal.

CONCLUSION

Freeze-drying has been shown to be a facile and robust method for preparing cocrystals, and has advantages over other cocrystallisation methods. Freeze-drying can be used on a large scale, avoids issues with incongruent solubility of coformers, and the possibility of coformers persisting as separate crystal phases due to self-seeding.

A new solid solution of caffeine and theophylline identified during this study is a rare example of a solid solution which contains two pharmaceutically active compounds. Solid solutions offer a key advantage over cocrystals for use in combination therapy pharmaceutical products as the relative ratio of the two APIs can be varied allowing the therapeutic dose of both to be delivered to the patient. This crystal form was obtained by freeze-drying, but not by conventional cocrystallisation techniques, suggesting that freeze-drying could be an important way of screening for new multi-component crystal forms.

Early work with cocrystals led to suggestions that they may be inherently less polymorphic than single component forms.[10, 63, 64] More recently, Porter *et al* have suggested that low numbers of reported polymorphic cocrystal systems may be more due to difficulties with methods of screening for polymorphs.[65] The findings of this study support the Porter hypothesis. Freeze-drying provides an alternative approach to cocrystallisation which can yield new polymorphs of cocrystals that are not obtained using more traditional methods, indicating that it is an approach that should be routinely investigated during polymorph screening with cocrystals.

In summary, freeze-drying could be useful at several stages of the cocrystal development process, from initial cocrystal screening and investigation of cocrystal polymorphism, through to preparation of cocrystals on an industrial scale.

Supporting Information. Characterisation data for the 2:1 theophylline:oxalic acid cocrystal hydrate. Crystal structure file (.res) for Form II of the caffeine:theophylline cocrystal. This material is available free of charge via the Internet at http://pubs.acs.org.

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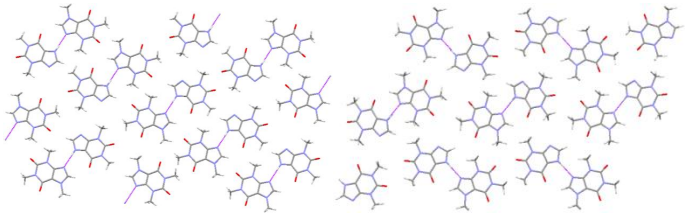
Freeze-drying is demonstrated to be a general method for cocrystal synthesis and the generation of new solid forms of cocrystal systems. Cocrystal formation proceeds via an amorphous phase which is generated as solvent sublimes during the freeze-drying process. Using this approach, a novel solid solution of caffeine and theophylline and a new form of the theophylline:oxalic acid cocrystal were prepared.



Caffeine:theophylline cocrystal Form I

Caffeine:theophylline cocrystal Form II