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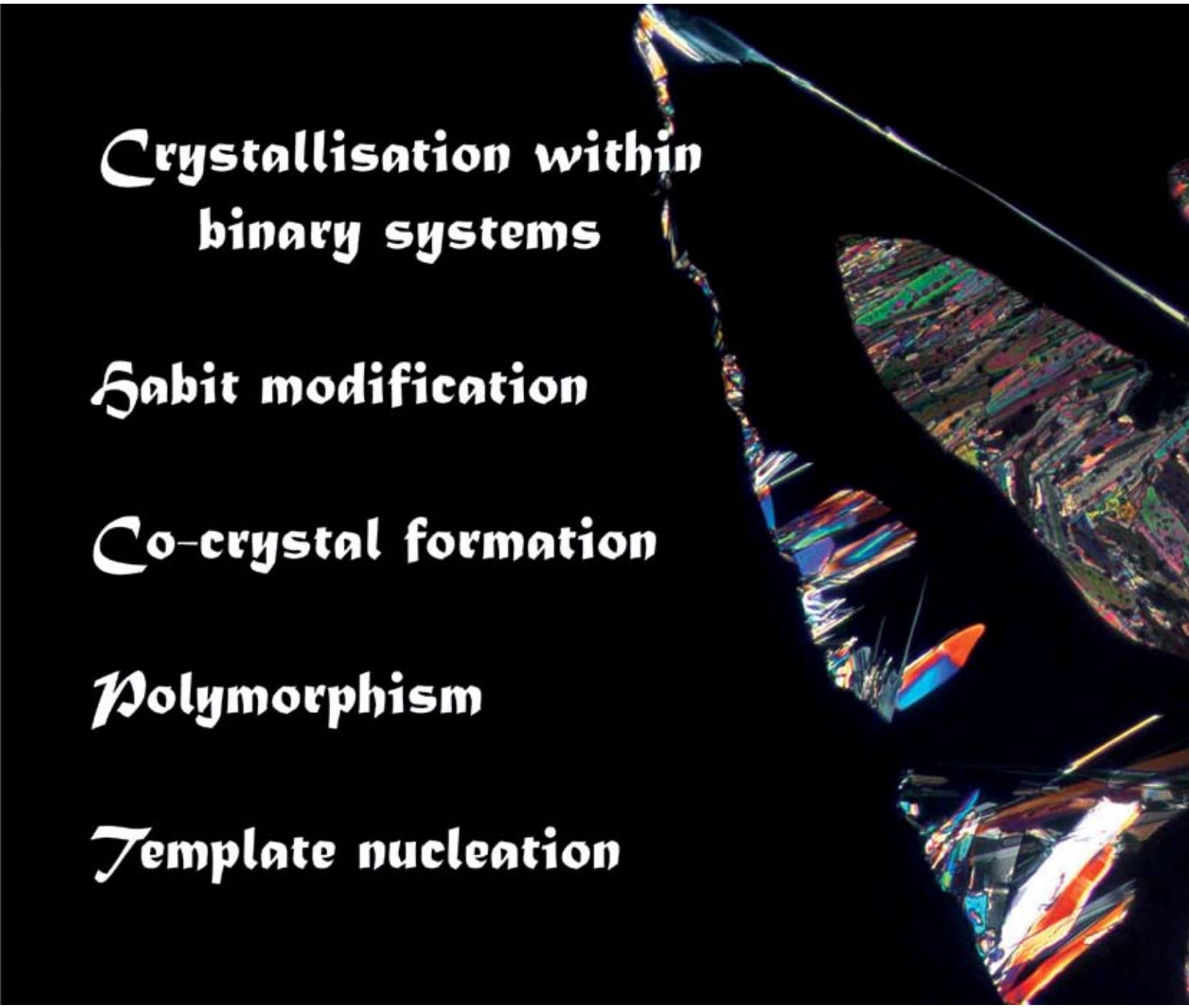

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Current directions in co-crystal growth

Nicholas Blagden,*[a] David J. Berry,[a] Andrew Parkin,[b] Hafsa Javed,[a] Asim Ibrahim,[a] Pauline T. Gavan,[a] Luciana L. De Matos[a] and Colin C. Seaton[a]

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In this feature article we will focus on the issues relating to the crystal growth of co-crystals, with a particular emphasis on drug development. The initial focus of this perspective is on the relevant literature examples that may be able to inform our understanding with regards co-crystal crystallisation and the allied supramolecular concepts. The second part of this perspective contains selected examples from our own work, which add to the literature perspective. Topics include; nucleation templates, *in situ* synchrotron XRD studies, solid-state synthesis through mixing and screening strategies.

1.0. Introduction

The application of molecular complexes and co-crystals in pharmaceutics is driven by the need to improve the physico-chemical properties of an active pharmaceutical ingredient (API) during drug development. Recently the focus has been on the crystal engineering of co-crystals,[1] and this activity has displayed potential to improve drug solubility and dissolution leading to an alteration in bioavailability. Historically co-crystals have been referred to as molecular complexes or, for clarity, multi-component crystals containing charge neutral species, as opposed to salts.† Within the literature a variety of other multi-component assemblies including hydrotropes[2] have also been utilised. In this particular effect a solution state complex is formed to improve the solubility of a drug entity.

Typically, pharmaceuticals are processed as molecular solids and co-crystallisation is emerging as an attractive solid state alternative to the usual salts and solvates. This is especially important during the drug development process where designing the dosage form of an API is critical.[1] The intention of this step is to improve the bulk material and physico-chemical properties of the API whilst preserving the intrinsic activity of the drug molecule. Allied with this intent is an intellectual property issue, by virtue of the desired modifications which may be achieved.

The re-emergence of interest in the synthesis of these binary materials as dosage forms has focused on a design approach[3] that requires developing a supramolecular library of co-crystallising agents.[4] Within the library, a hierarchy of guest functional groups exists, classified according to a specific contribution to a crystal packing arrangement which is dependent on the functionalities contained on the host molecule.[5] These are derived from examining structure–property relationships present in classes of known crystal structures contained in the Cambridge Structural Database (CSD).[6]

2.0. Co-crystal design

The literature is extensive on the strategies for co-crystal design; two complementary approaches have been employed. One is the structural fit between the components, based upon

[a] *Solid State Pharmaceutics Group, The Institute of Pharmaceutical Innovation, and The Bradford School of Pharmacy, University of Bradford, Bradford, West Yorkshire, UK BD7 1DP. E-mail: N.blagden@brad.ac.uk; Tel: +44(0) 1274 23 4765*
[b] *WestCHEM, Department of Chemistry, University of Glasgow, Glasgow, UK G12 8QQ*

† This notion of classification has appeal for our current activities, and has been communicated to N. B. by Prof. Roland Boese.

Dr Nick Blagden is a Reader in Solid State Pharmaceutics at the University of Bradford. His research has focused on the isolation of polymorphs through solvent selection, and designer additives. Dr Blagden's contribution to this area is to place the influence of polymorph transformation by solvents and additives on a molecular recognition basis. This is now being extended to the study of co-crystallisation.

David Berry, after having registered as a pharmacist, spent a year practising clinical pharmacy in Sheffield. In 2005 he returned to Bradford to undertake postgraduate studies within the Blagden group, investigating the application of polymorph selection techniques to the growth of co-crystals.

Miss Hafsa Shamim Javed graduated from Manchester Metropolitan University and completed an MSc in Cheminformatics from UMIST. In 2005 she joined Dr Nicholas Blagden and his Group at the University of Bradford to pursue a PhD in Solid State Pharmaceutics.

Dr Colin Seaton investigated the development of new methods of structure determination of molecular materials from X-ray powder diffraction data under Dr Maryjane Tremayne. He joined the Blagden group in 2003 as a postdoctoral research assistant and has worked on interfacial crystallisation of co-crystals and solvent effects of co-crystal formation.

similarities in packing between the pure components. The other considers specific pairwise interactions (supramolecular synthons[7]). The energetics of these pairwise interactions is one consideration and from examination of existing structures, empirical rules to predict robust supramolecular synthons may be developed. Etter and co-workers proposed guidelines to promote the deliberate design of hydrogen-bonded solids along with graph set descriptors and classification of packing.[8] The inferred rules of hydrogen bonding are:

1. All good proton donors and acceptors are used in hydrogen bonding.

2. Six-membered ring intramolecular hydrogen bonds form in preference to intermolecular hydrogen bonds.

3. The best proton donor and acceptor remaining after intramolecular hydrogen bond formation will form intermolecular hydrogen bonds to one another (but all acceptors may not necessarily interact with donors).

The CSD may be utilised to identify stable hydrogen bonding motifs[9] with the intention that the most robust motifs will remain intact across a family of related structures. For example, carboxylic acids and amides are self-complementary and capable of forming *heterosynthons*. This motif has been studied for some time in the context of crystal engineering and the interaction of carboxylic acids with heterocyclic bases is perhaps the most widely studied type of synthon.[10]

Supramolecular synthon competition and prediction investigations have been made in an attempt to aid the prediction of co-crystal formation.[3] The results of this study suggested that it is often the most energetically stable hydrogen-bonded synthon which features in the structural packing landscape; these assumptions are verified experimentally through comparisons to single-crystal structures generated. A review of progress in this area has recently been published.[11]

Additionally some studies into co-crystallisation have considered the pK_a of the co-crystal components.[11c,12] Solution chemistry empirically demonstrates that a pK_a difference of at least two units (between an acid and a base moieties) is required to form a salt that is stable in water.[12] This point of view is still undergoing re-evaluation as more co-crystal growth experiments, where pK_a profiles would suggest formation of a complex, lead to salt formation. This breakdown of the pK_a rule combined with evidence obtained from examining proton location within hydrogen bonds has developed into the notion of a continuum between salts and co-crystals.[13]

The use of hydrogen bonding rules, synthons and graph sets may aid in the design and analysis of co-crystal systems. Yet the prediction of whether co-crystallisation will occur is not yet possible and must, at present, be answered empirically. Examples include the co-crystallisation of *cis*-itraconazole with a series of 1,4-dicarboxylic acids capable of extended (anti-) conformations.[11] Interaction between succinic acid and the strongest base position of itraconazole, however, was not present in the co-crystal structure. Co-crystals could not be formed from maleic acid with *Z* regio-chemistry about the C=C bond (with pK_{a1} = 1.9), or from 1,3- or 1,5-dicarboxylic acids. Therefore, in this case interactions based on specific directed intermolecular combinations appear to be far more important than acid–base strength complementarities for successful co-crystallisation.

Early examples of co-crystals of APIs reported in the literature as molecular complexes include many sulfonamides,[14] with a specific example being sulfadiamine.[15] Co-crystals in the more contemporary sense however, as a product of more rational design, have been reported more recently.[16] As with other crystalline systems, polymorphic co-crystals are not uncommon.[17] Observation of such systems should be rationalised in the context of previous work on polymorph selection.[17] In particular, the challenge would be to integrate the demands of co-crystal phase growth with those of polymorph selection. The ideal result would be a component required for co-crystal formation disrupting, on a molecular basis, the nucleation of one polymorphic phase over another; biasing the subsequent crystal growth in addition to any effect from solvent or additives.

Previous studies into co-crystallisation have focused on the interpretation of the final crystal structure and role played by supramolecular synthons in creating this structure. Consideration of the mechanics of crystal growth and how concepts such as supramolecular synthons interact with those concepts such as growth units from crystal growth theory have been studied less. An understanding of such factors is required to develop successful co-crystal screening methodologies and the reproducible production of co-crystals as suitable phases for drug delivery.

3.0. Phase diagrams for co-crystallisation

Within crystal growth the first rational step is to define the equilibria between the solid phases and, where applicable, with the chosen solvent; the phase diagrams deliver this information. The binary phase diagram between the two components exhibits eutectic points between each phase and so indicates the existence and number of co-crystalline phases for a given system. A recent issue for some binary systems is whether or not a submerged eutectic is present. In this situation solid-state contact between one component and another leads to the formation of the co-crystal phase *via* a melt interface.[18] Solvent crystallisation adds a further layer of complexity and when solvent is used phase space can be mapped by use of a ternary phase diagram. Discussion here only relates to isothermal methods, accounts of variable temperature phase space manipulation are available in the literature.

Ternary phase diagrams allow understanding of co-crystal formation from a given solution, since they describe the three-phase behaviour of a system (for the components, the co-crystal and the solvent). A limited number of experimentally derived phase diagrams exist,[14,19] of those reported the trends that emerge are summarised in Fig. 1(a) and (b).

Component solubilities are an important feature in these diagrams, as differences alter the location and size of the phase space regions where a potential co-crystal phase is thermodynamically stable.[20]

From Fig. 1(a) (components with similar solubilities), solution crystallisation with equimolar components will lead to the formation of the 1 : 1 co-crystal from solvent evaporation. For systems with non-equivalent component solubilities a more complicated picture exists, such as that described by Fig. 1(b). As can be seen in this example, solution co-crystallisation from

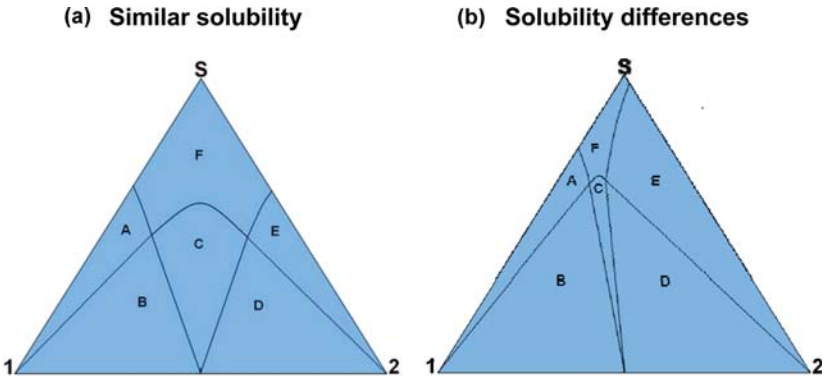


Fig. 1 Schematic representations of isothermal ternary phase diagrams with (a) similar solubilities between components **1** and **2** in solvent **S** and (b) different solubilities of **1** and **2** in **S**. Region **A** = component 1 and solvent, **B** = component **1** + co-crystal, **C** = co-crystal, **D** = component **2** + co-crystal, **E** = component 2 and solvent, and **F** = solution.

slow evaporation of an equimolar solution may result in the growth of purely the starting material, or a mixture of co-crystal and single component phase. This situation develops when the crystallisation route passes either through the mixed phase region **D** or the single phase region **E**. For both Fig. 1(a) and (b), if a kinetic phase were embedded into one of the phase regions it would account for the possible early formation of a metastable phase over a stable phase, as well as the observation of new polymorphs of either of the components[21] or the co-crystal. Application of such phase space observations leads to a starting point with regards to rational design of a crystallisation experiment.

4.0. Accessing the binary phase diagram using *hot-stage polarised optical microscopy*

Early indication of co-crystal phase formation and the phase behavior of the components in the presence of each other and a co-crystal phase is essential. Multi-component DSC screening[22] has recently been used to this end, though historically hot stage microscopy has offered a proven route to access the binary phase diagram. The technique most useful in this arena is the mixed fusion method. The mixed fusion (or contact) method was first described by Lehmann[23] in 1877 and Kofler and Kofler[24] then refined the methodology as instrumentation improved.[25] McCrone has also published extensively on the subject. The technique has also been mentioned in texts by Kitaigorodsky[26] and Bernstein[27] and is recognised as a means to identify phase behaviour between two components; hence its use as a co-crystal screening strategy. In this method one component is melted then allowed to solidify, before another molten component is brought into contact with it, solubilising a proportion of the first component (Fig. 2).

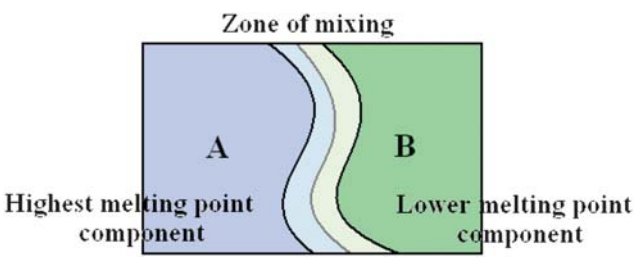


Fig. 2 Higher melting point component, (A), melted and re-crystallised before molten component, (B), is brought into contact with it, creating a zone of mixing.

Once all material is re-crystallised a zone of mixing is created. This zone is then comparable to the composition of the binary phase diagram for two components. One side of the mixing zone represents 100% of one component and the other side 100% of the other component and with a concentration gradient across the zone. It is then possible to identify the number of phases present within a system, when viewed under crossed polar filters on a light microscope, whilst heating. This is achieved by visually tracking the emergence and number of eutectic melting points for the potential co-crystal system being screened. This method offers direct visualisation of the binary phase diagram, yielding information on the number of phases and melt temperatures. It also offers the potential to witness polymorphic transitions both in the single components and any co-crystal phase. In our work we have used material from melt zones to seed solution crystallisations in order to further develop the crystallisation protocol.

5.0. Solubility models

To optimise a crystallisation protocol, an appreciation of the solubility behaviour of co-crystals is needed. Historically, the application of a solubility model to this problem has been reported. In this early study on the molecular compounds of organic medicines, the application of the solubility product principle and consideration of the phase rule to the solubility phenomena of the molecular compound of sulfanilamide and sulfathiazole was undertaken.[14] Significant refinement and improvements to this approach have only recently appeared.[28] The key findings, without a recount of the theory of the model are as follows.

The theoretical and experimental analysis of solubility profiles for carbamazepine (CBZ) co-crystals have been shown to be dependent on the concentration of co-crystal components in solution with nicotinamide, NCT.[28] The profile of this dependency may be explained by the application of a solubility product model to the complexes formed in solution, the relative ratio of components present in solution and the respective binding constants of the complexes formed in

solution. It was noted that the solubility behavior was analogous to that of sparingly soluble salts. The co-crystal solubility dependence on ligand concentration highlighted the interdependence of 1 : 1 and 2 : 1 complexes in solution on the overall 1 : 1 co-crystal and indicates how such analysis can aid tuning the crystallisation of co-crystals. The studies on CBZ–NCT co-crystal solubility, showed a decrease in solubility as the NCT concentration increases in organic solutions. A theoretical minimum was observed at a 2 : 1 loading of components, this was rationalised in terms of the effect of the coupled equilibria of the system and solubility product of the co-crystal. These findings present a route to gaining an appreciation of solution supramolecular complexation as described by the solubility profiles and defines a route to inducing co-crystal formation by virtue of component composition.

6.0. Physicochemical property improvements by co-crystals

The overall motivation of examining API co-crystals as an alternative during the drug development is one of physiochemical property adjustment to improve the overall stability and efficacy of a dosage form.

Supramolecular complexes of carboxylic acid APIs with di-pyridyl co-crystallizing agents have been prepared: $(\text{ibuprofen})_2$(4,4′-bipyridine), **A**, $(\text{flurbiprofen})_2$(4,4′-bipyridine), **B**, $(\text{flurbiprofen})_2$(1,2-bis(4-pyridyl)ethylene), **C**, and $(\text{aspirin})_2$(4,4′-bipyridine), **D**, and their respective melting points determined.[29] The melting points of **A–C** were higher than their pure individual components, whereas the melting point of **D** (which exhibited dramatically different molecular packing compared to the other co-crystals) had a significantly lower melting point than its pure components.

The melting points of thirteen carbamazepine co-crystals have also been cited, with only two having a melting point higher than pure carbamazepine, as part of a study into the crystal engineering of pharmaceutical phases.[30] However, many of the systems formed with materials that are liquids at room temperature *e.g.* acetone and acetic acid. In addition, only three of the co-crystallizing agents are generally regarded as safe (GRAS); saccharin, nicotinamide and acetic acid, limiting the pharmaceutical applications of this work.

Another important intrinsic property of APIs is stability to hydration, as hydrate formation alters the physical behaviour. Again co-crystals have proved useful in this area; as displayed by a number of caffeine systems.[16] In this work the model API (caffeine) was found to be more stable to 98% relative humidity (for up to 7 weeks) when a caffeine–oxalic acid 2 : 1 co-crystal was employed. Recent advances have also tied this effect to crystalline symmetry.[10j]

Remenar *et al.*[12b] compared the dissolution of co-crystals of itraconazole (a triazole drug) with succinic acid, malic acid and tartaric acid, with that of the pure crystalline and amorphous drug. In general, the co-crystals behaved in a similar manner to the amorphous form compared with the crystalline drug in achieving and sustaining from 4- to 20-fold higher concentrations on dissolution testing. The practical implications of this finding are important, as the capacity to form and sustain a supersaturated solution can have a dramatic impact on drug absorption and bioavailability.[31]

It has also been shown that glutaric acid co-crystals of a development candidate API have eighteen times the aqueous dissolution rate compared to the homomeric crystalline form.[32a] Studies in beagle dogs showed the co-crystal form also gave notably increased plasma bioavailability compared with the parent crystal form. Further evidence of such bioavailability improvements have recently appeared in the literature.[32b,c]

Nevertheless, whilst these studies have shown the potential benefits of co-crystal formation on drug dissolution and bioavailability, this embryonic area of pharmaceutical research is still relatively unexplored and requires further study before co-crystals are considered a reliable toolbox technology for enhancing oral drug absorption.

7.0. Practical considerations for co-crystal design

Co-crystal screening is a process similar to salt screening and is suited to high-throughput technologies,[16a] although co-crystal formation as described in the literature indicates difficulty concerning preparation for some systems. For example it has been known to take six months or more to prepare a single co-crystal of suitable quality for single X-ray diffraction analysis.[12a] Combined with this is a high attrition rate in identifying successful co-crystal formers. An example is given from the study into carbamazepine co-crystals; for the 10 new co-crystals of carbamazepine reported, approximately 50 co-crystal agents were used, giving a success rate of 20%.[30] This is partly because such a heteromeric system will only form if the non-covalent forces between two (or more) molecules are stronger than between the molecules in the corresponding homomeric crystals. Design strategies for co-crystal formation are still being researched and the mechanism of formation is far from being understood.[1]

Once an API has been selected for co-crystallisation studies, a pharmaceutically acceptable, non-toxic co-crystallising agent(s) should be chosen. This limits the co-crystallising agent to those that have been approved for consumption by humans. This would include pharmaceutical excipients and compounds classified as GRAS for use as food additives (as classified by the US department of Health and Human Services). For example the maximum additive level of malic acid (which has been co-crystallised with the antifungal drug itraconazole), in hard candy is $<7\%$.[33] A number of co-crystals have been formed with co-crystallising agents classified as GRAS.[33] For a viable application in drug development, the required therapeutic level will have to be balanced with the level of active drug. Therefore, unless the resulting stoichiometric amount of co-crystal agent is less than the allowed additive level, their pharmaceutical applications will not be realised.

Co-crystallisation between two APIs has also been proposed as a basis for both compounds to be pharmaceutically acceptable. This may require the use of sub-therapeutic amounts of drug substances such as aspirin or acetaminophen,[16b] or the APIs would have to exhibit similar levels of therapeutic active concentration.

The majority of co-crystallisation research has rarely involved using pharmaceutically acceptable co-crystallising agents and

conditions. Forming paracetamol adducts with hydrogen-bond acceptors has been reported.[16c] However, the co-crystallisation agents used were not GRAS substances, and piperazine, dihydrochloride and morpholine as the salt(s) of one or more fatty acids, are only permitted as food additives at the relevant level.[34]

It has been suggested that it may be useful to consider polymorphic compounds as co-crystallising components.[35] If a molecular compound exists in several polymorphic forms it has demonstrated a structural flexibility and is not locked into a single type of crystalline lattice or packing mode. Thus, the chance of bringing such a molecule into a different packing arrangement in coexistence with another molecule is increased.[4b] Again, polymorphism of a component alone does not guarantee the functionality of a compound to act as a co-crystallising agent, but the ability of a molecule to participate in intermolecular interactions obviously plays a critical role.[1]

8.0. Methods of preparation of co-crystals

A range of methodologies for the synthesis of co-crystals has been reported in the literature. These include evaporation of a heteromeric solution, solid state grinding, kneading, sublimation, growth from the melt, reaction crystallisation, and slurry preparation.[10,16,17]

When preparing co-crystals, the product obtained from grinding is generally consistent with that obtained from solution.[10j] This may indicate that hydrogen-bond connectivity patterns are not idiosyncratic or determined by non-specific and unmanageable solvent effects or crystallisation conditions. Nevertheless, there are exceptions where a given co-crystal phase can only be obtained through grinding.[36] An example is given by the co-crystallisation of 1,3,5-trinitrobenzoic acid and indole-3-acetic acid, where different crystal forms are obtained from solution compared with grinding.[37]

Co-crystal formation by solid-state grinding has been established since the mid-nineteenth century.[38] The recent technique of adding small amounts of solvent during the grinding was shown to enhance the kinetics and promote co-crystal formation and this has lead to increased interest of solid-state grinding as a method of co-crystal preparation.[39] Cyclohexane-1,3-*cis*,5-*cis*-tricarboxylic acid with bipyridine,[3,9] was previously found to co-crystallise from methanol solutions, while grinding an equimolar mixture for 60 min results in partial conversion. The addition of $\sim$0.05 ml of methanol to the milling accelerated co-crystallisation and complete conversion was achieved in 20 min. When a solvent in which neither starting component was soluble was added to the milling process (cyclohexane), kinetic enhancement was not observed and reaction did not occur even after 90 min grinding. This kinetic enhancement was rationalised by the additional degrees of orientational and conformational freedom open to the molecules at the various interfaces with increased opportunities for molecular collisions. The details of a possible mechanism are starting to emerge.[40]

A mixture of two components is capable of spontaneous co-crystal formation,[18] if the eutectic points between the components form a metastable 'submerged' point. The effect of this is that on placing the two components together, a melt is formed; this solution is then seeded by remaining solid material and the co-crystal forms. In addition, a diffusion step of one component into the other is reported to occur for solid-state co-crystal formation.[40a] The diffusion process relates to an increase in particle size, and this aspect of particle mixing, defines the propagation of the components.

The role of solvents at low percentage compositions where a slurry or capillary state is present (leading to a localised surface dissolution process) have also been discussed in the literature.[40b] In this mechanism quantities of component dissolve in adsorbed atmospheric water (*via* deliquescence) and due to the supersaturation generated, allow co-crystal formation. Another reported route relies on the application of amorphous phases of the components being metastable to the co-crystal phase, and on grinding or melting an intermediate amorphous phase is generated.[40c] Once in this plastic state, consequent transformation to the stable crystalline co-crystal phase occurs.

It has also been noted previously that for systems with no submerged eutectic, and with pre-milled components, a significant shearing force above a threshold needs to be applied in order for transformation to occur.[40d]

8.1 Summary of co-crystal crystallisation strategies

Considering the literature to date the strategies for co-crystal crystallisation include:

- Conducting the crystallisation with a molar excess of one of the components, and taking advantage of the dip in solubility of the co-crystal in the presence of one of the components.
- Conducting the crystallisation in a slurry situation as defined by the low percentage solvent region of the phase diagram.
- Manipulation of solvent choice in order to utilise phase space considerations, thus maximising the pure co-crystal regions available or broadening the region, where strategies using an excess of one component to drive complex formation would be an option.
- Seeding solutions, using samples generated from hostage-melt.
- Wet milling, with prudent choice of solvent which leads to saturation of the co-crystal phase.
- Use of an amorphous or hydrate as an intermediate phase during synthesis using a solid-state route.
- Use of a metastable polymorphic form of one of the components to provide an energetically unstable intermediate phase from which the co-crystal may form. Or to build in a wider flexibility into the pairwise association between the components by virtue of the diversity a polymorphic system exhibits with regards hydrogen bonding; as identified by examining the packing landscape of polymorphs.

In addition to thermodynamic requirements, a clear synergy needs to exist between the pairwise associations of the co-crystal in the envisaged co-crystal as previously discussed.

9.0. Examples with regards co-crystal synthesis and design

The outcomes of crystallisation studies on the benzoic acid–isonicotinamide co-crystal system will be given, highlighting a route which exploits solubility differences across two solvents

therefore targeting the desired regions of ternary phase space, as a means of directed crystallisation design. This experience yields a number of crystal growth observations that may be transferable to other systems. These include nucleation template behaviour and *in situ* monitoring of co-crystallisation using a previously developed energy-dispersive X-ray diffraction (ED-XRD) protocol. The impact of particle size on the formation of caffeine–malonic acid co-crystals by a solvent-free synthesis is presented. Allied to this activity the authors have also continued to explore the challenges of non-ideal former pairing (with benzamide and nicotinamide), an issue which may arise when preparing API co-crystals. Along with this a low-throughput screening approach to co-crystal formation will be presented.

9.1 The 2 : 1 benzoic acid–isonicotinamide co-crystal

The crystal structure of the 2 : 1 benzoic acid–isonicotinamide molecular complex has been determined by single-crystal X-ray diffraction.[41] The structure displays the same supramolecular synthons as other complexes of carboxylic acid with isonicotinamide. Computational studies of the molecular pairs indicate that these bindings are the lowest energy pairs for the individual molecules, yet the relative ordering of energies is dependant upon the choice of solvent. This is supported by the experimental studies where co-crystallisation from ethanol results in only the 1 : 1 complex independent of the initial composition. However, the final product from aqueous and methanolic solutions is dependant on the initial concentrations. Methanol predominately forms the 1 : 1 complex with trace amounts of the 2 : 1 complex with increasing amounts of benzoic acid. Aqueous solutions result in the 2 : 1 complex for systems with excess benzoic acid or for dilute equimolar solutions. Increasing the concentrations of both components, results in an increased formation of the 1 : 1 complex.

Therefore, selection of the desired form of the complex is achieved through tuning of the experimental conditions. These outcomes in general agree with the trends identified by the studies into co-crystal phase diagrams.[14,18] The large difference in solubility of isonicotinamide and benzoic acid in water would be expected to result in a skewed phase diagram and so equimolar solutions would be unlikely to form a 1 : 1 co-crystal. By contrast, the solubilities in ethanol and methanol are similar, and so the 1 : 1 co-crystal would grow from an equimolar solution. The crystal growth of this system has been further studied in relation to nucleation templates and *in situ* monitoring. While this work has focused on solution growth, it has been reported that variation of the solvent used to form the $Fe(\eta^5\text{-}C_5H_4C_5H_4N)_2$–pimelic acid co-crystal by vapor digestion can be used to control the final composition between 1 : 1 and 1 : 2.[42] Solubility differences again play a role in the selection of the product. While the organometallic compound has a similar solubility in all solvents except water, protic solvents, where pimelic acid is highly soluble, form 1 : 1 complexes, while aprotic solvents, where pimelic acid is almost insoluble, form the 1 : 2 complex.

9.2 Nucleation templating studies[43]

The potential of nucleated growth of co-crystals by a suitable sub-phase was investigated for the benzoic acid–isonicotinamide system. This system is suited to these studies due to the significant differences in solubility between single components and so saturated solutions for benzoic acid may be easily prepared. Template crystals of benzoic acid (BZ-template) were grown by slow evaporation of an aqueous solution; these were then used as the sub-phase. The overall composition of the growth solution for the epitaxy studies was based on the solubility of benzoic acid in water to ensure a saturated solution at 40 °C.

For the template studies, an equimolar solution of benzoic acid (0.355 g, 0.003 mol) and isonicotinamide (0.334 g, 0.003 mol) in water (50 ml) was heated to 70 °C to ensure complete dissolution of the components. This solution was then cooled to 45 °C over 3 h and the BZ-template was suspended in the solution. During the growth cycle, the solution was further cooled to 30 °C over a 15-h period. After this time the BZ-template crystal was removed, washed and examined using optical micrographs and previously reported characterization profiles of the 2BZ : INA and BZ : INA co-crystals.

Through molecular modelling, epitaxy registry calculations and an examination of the habit of crystals in relation to the crystallography, the following molecular registry is proposed. A successful template at the molecular level requires creating an interaction between an INA molecule and the BZ-template, since the alternative would just increase the benzoic acid surface. From consideration of the existing co-crystal structures this would occur through either $CO_2H\cdots N_{ring}$ or $CO_2H\cdots C(O)NH_2$ interactions. Subsequent addition of benzoic acid would then form the packing motifs of 2BZ : INA (Fig. 3). Epitaxial calculations indicate that both the {100} and {001} faces of 2BZ : INA would have lattice agreement with the {010} of benzoic acid that the crystals were observed to grow upon. They also offer the required functionality to bind through such motifs and so are the faces are the most likely binding sites to support a nucleation template process. Critical to this interpretation of the interface, was a single-crystal study of 2BZ : INA habit which identifies the {001} face as potential binding face, and the 2BZ : INA interface with BZ was subsequently identified using this indexing; this is also labelled in Fig. 3.

The ability of achieving a nucleation templates process adds to the number of underlying crystal growth process, which may occur whilst examining multi-component crystallisation. These

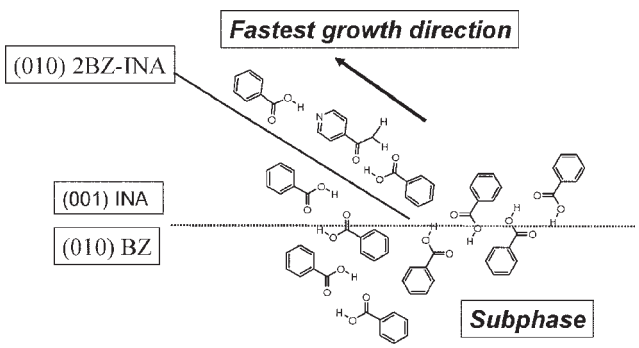


Fig. 3 Schematic projection of the crystallographic relationship between the component and co-crystal.

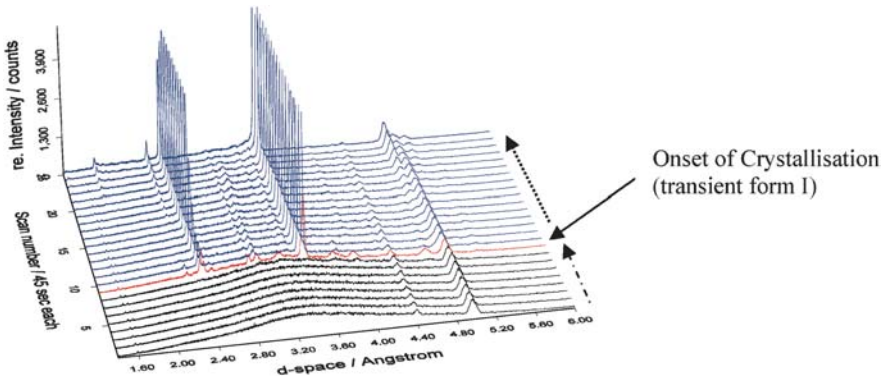


Fig. 4 Time-resolved diffractogram using ED-XRD. Regions relating to the dashed arrow show the solution prior to nucleation, transient form I (full arrow), and evolution of form III (dotted arrow). Peaks due to Teflon occur at 4.4 and 4.9 Å.

may include habit modification, polymorph selection, reactive crystallisation and polymorphic or solvated co-crystal phases.

9.3 Synchrotron studies

Previously, a purpose-built clarifying crystalliser cell with a cooling over the range 10–80 °C, has been utilised to examine the polymorph inter-conversions of piracetam during crystallisation.[44] For this reported study the nootropic drug piracetam was crystallised from different solvents using a multistep quench-cooling method and three polymorphs were isolated (forms I, II and III). The respective solution crystallisations were monitored *in situ* by energy dispersive X-ray diffraction (ED-XRD) performed with synchrotron radiation at station 16.4 of Daresbury Laboratory CCLRC, UK. The modifications implemented to the previously used ED-XRD protocol[45] at Station 16.4 enabled good temperature and stirring control throughout and generated consistent results.

A typical example observed for piracetam when cooling from methanol (Fig. 4), showed piracetam form I appearing at around 33 °C (identified by characteristic diffraction lines at 3.09, 4.00 and 4.73 Å). Form I competes with form III which dominates within 1 min after cooling to 31 °C with strong peaks at 2.41 and 3.47 Å.

This solid-state transition explains the appearance of only polymorph III in all previously performed crystallisations from methanol. Piracetam forms I, II and III and phase inter-conversions in water and propanol were evident from the diffraction data, although the effect of agitation on phase conversion needs to be examined.

The step heating–cooling system enabled good control over experimental conditions and generated consistent results from which polymorph inter-relationships were examined. Complementary observations from the diffraction monitoring indicated the link with Raman data that provides key insights into the molecular organisation of the studied environments and how this initial molecular recognition process translates to polymorph crystallisation in solution.

Building from the success in studying polymorphism, the initial work on the application of this approach to studying co-crystal crystallisation was undertaken. This has focused on the BZ–INA systems as a result of the solvent dependent behaviour of the appearance of the 1 : 1 and 2 : 1 phase, described earlier. The experimental approach was the same as that described for the polymorphic system. A 2 : 1 composition ratio of benzoic acid (0.825 g, 0.007 mol) and isonicotinamide (0.440 g, 0.0036 mol) was dissolved in 50 ml of water. This composition was investigated since the phase diagram indicated the potential for both the 1 : 1 and 2 : 1 co-crystal to crystallise.

Upon cooling from 60 °C, the onset of crystallisation occurs at 23 °C (Fig. 5). The first phase to appear is BZ-INA, identified by the peaks at 11.2 Å. This 1 : 1 phase rapidly converts to 2BZ–INA at 14 °C, with the diffractograms showing peaks of the 2 : 1 phase at ~14.4 Å. Heating of the crystallised solution to 60 °C reveals the dissolution of the 2 : 1 phase and no transformation back into the 1 : 1 co-crystal. This may be indicative of a monotropic phase stability between the two phases. This type of study is still ongoing and the intention is to examine the crystallisation from other solvents in order to identify any solvent mediated processes.

These results clearly indicate a co-crystal crystallisation for a specific ratio may go *via* an intermediate composition for the crystallisation route encountered. Any end point crystal screening studies indicates that a 2 : 1 composition from water yields the 2 : 1 complex as a solid or a trace of the 1 : 1 composition. The route to any phase diagram is obtained in a

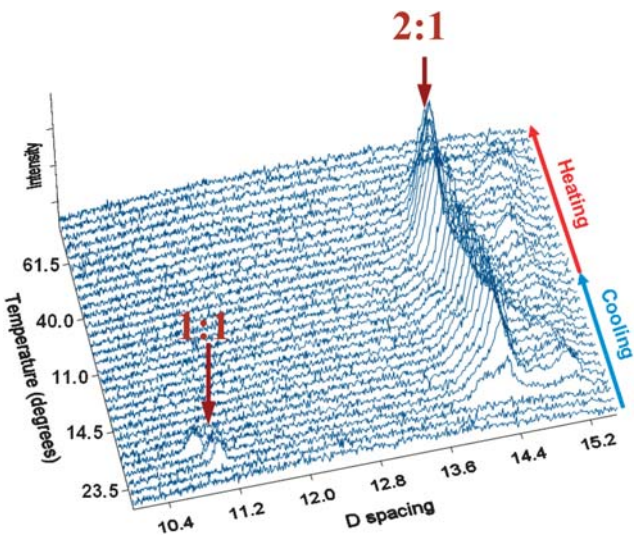


Fig. 5 Time-resolved diffractogram measured by ED-XRD for BZ–INA system.

similar manner, and would leave an unclear picture of inter-conversions, as only mixtures may be observed for this system and the level of mixture seen would be dependant only on the weight fraction of all components. In contrast, the *in situ* results reveal that transformations between the potential phases may occur. The observation of a transformation renders one of the available compositions as a metastable phase to the other solid-state composition.

9.4 Influence of particle size and co-crystal formation through mixing only[46]

Determining the processes that control the creation of co-crystals during solid-state grinding or milling are important for the further development of such methods. One largely unstudied aspect is the affect of particle size on the rate of conversion although work in this field does exist.[40a] In this work the caffeine–malonic acid 1 : 1 co-crystal system was investigated. This system has been well documented in the literature.[47] To ensure that only the particle size contributed to rate changes, the components were pre-ground and sieved to specific particle size and then low-energy convection mixing was used to introduce the components together.

The progression of the co-crystal formation, from the sieved starting components, was monitored using X-ray powder diffraction for particle size fractions of 45, 125 and 250 μm (Fig. 6). The 45 μm particles converted within 2 days, the 125 μm particles within 4 days and 250 μm particles after 14 days. Overall transformation can be seen in the diffractograms as the physical mixture possesses a pair of peaks with a 2θ value of 27° whereas the co-crystal posses a single peak at 28°. The transformation is further characterized by the evolution of peaks at 15 and 25°.

In our work decreasing the initial particle size accelerates the formation of the co-crystal upon convection mixing. Historically systems with a submerged eutectic are reported to have an accelerated formation as the particle size increases.[40a] This suggests that in our system the surface energetics of the particles are increased as particle size is reduced. Thus favouring any surface aided processes. The possibilities with regards a mechanism driving the co-crystal formation may include submerged eutectic, role of an amorphous state or uptake of water from the atmosphere (deliquescence).[40] From observations of single-crystal contact (components held together for 48 h at 25 °C on a hot-stage microscope) no conversion to the co-crystal phase was seen. DSC and TGA have been undertaken on mixed un-sieved powder fractions pre and post 2 days and no change indicative of water uptake or new phase formation was observed.

With regards to the role of an amorphous phase, the PXRD and DSC do not show the presence of such a phase, although further study is required to rule out the presence of sub-micron surface domains of amorphous material due to milling. At this stage we can state that no eutectic route appears available and no *significant* bulk levels of water or amorphous material are present, at the thresholds previously seen for these factors to contribute.[40]

The current findings suggest that on mixing it is the resulting particle contact of the pre-milled crystals that contributes to co-crystal formation; with the observation that the rate of the process increases as the particle size decreases. This also suggests that the sub-micron detail of the surface would yield insight into the driver of solid-state co-crystal formation.

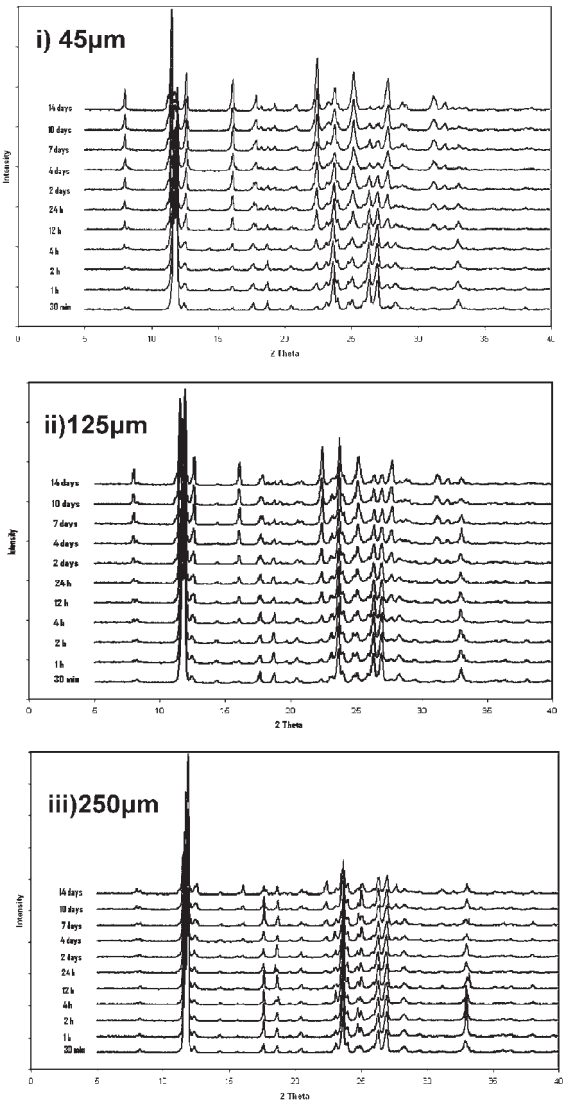


Fig. 6 XRPD of the phase transformation from components to co-crystal in gently mixed powders of caffeine–malonic acid. The process was monitored within the differing size fraction: (i) 45 μm, (ii) 125 μm, (iii) 250 μm.

This approach does not rule out contributions from surface defects, arising from milling which generate amorphous or polymorphic surface zones, or water droplets on the surface of a drug particle which can then contribute to conversion. The issue of localised surface phases have been previously reported with regards physical transformation of pharmaceutical ingredients through drug surface conversion, from amorphous, hydrate and polymorph sites generated by milling.[48] The challenge would be to characterize such surface zones, through AFM analysis, IGC, and sorption in order to determine the rate enhancement associated with these classes of site.

Overall, the mechanisms of co-crystal growth *via* grinding and solid-state interaction have been rationalised by the

additional degrees of orientation and conformational freedom open to the molecules, at the various interfaces; allowing increased opportunities for molecular collision. The additional caveat must be in defining the process by which the interfaces involved are energetically activated to support the transformation. This would require further understanding of how particle size reduction adds to these processes; in order to better grasp the underlying detail of surface catalysis. An ongoing effort is therefore required to define the role of sub-micron environments on the solid-state conversions of the macro environment.

9.5 Low-throughput screening for benzamide co-crystals

Determining efficient approaches to co-crystal screening presents a challenge; one route is through an extensive automated search. This can be defined as the combinatorial approach to identification of new phases. From a crystal growth perspective, this would potentially give rise to a snapshot of the crystallisation behaviour and would include combinations which are thermodynamically unfavourable with respect to co-crystal growth. Another approach, used in this work, is to combine thermal and solution screening, performing multi-solvent solution growth experiments on the thermally favourable combinations. Within our work the solvents include water, methanol, ethanol, ethyl acetate, tetrahydrofuran and nitromethane for instance.

Using the above (thermal then solution based) screening methodology an investigation into related molecules which theoretically favour the formation of isostructural supramolecular entities/synthons was undertaken. The first example was led by the differing application of isonicotinamide compared to benzamide as a co-crystal former. Consideration of potential supramolecular synthons suggests that both would be successful co-crystal formers. However, examination of the literature and the CSD reports six co-crystals of benzamide (2 : 1 succinic acid, 1 : 1 and 2 : 1 pentafluorobenzamide, 1 : 1 pentafluorobenzoic acid, 1 : 1 (*E*)-benzaldehyde oxime and 1 : 1 *N*-pentafluorophenylurea).[49] In contrast over thirty co-crystals of isonicotinamide are reported. Therefore, a co-crystal screen was undertaken between benzamide and arboxylic acids that have been shown to successfully form co-crystals with isonicotinamide. Benzamide was found to co-crystallise with 5 of the 13 acids investigated but displayed a lower quality of crystal growth. These factors may contribute the differences in number of reported structures.

The observation was that isonicotinamide out-performed benzamide in these respects. The supramolecular synthons obtained in the benzamide co-crystals were the expected acid···amide ring motif, as shown by the 2 : 1 co-crystal with fumaric acid and the 1 : 1 co-crystal with 4-nitrobenzoic acid (see Table 1 for the relevant crystallographic data).

The pairs of molecules in the benzamide–fumaric acid co-crystal bind together about a pair of two $R_2^2(8)$ acid···amide interactions (Fig. 7). These molecular clusters are then stack along the *b*-axis by π···π interactions. The stacks pack in a herringbone fashion to form the final 3-D structure (Fig. 8).

The hydrogen bonding distances and angles for the acid–amide dimer in benzamide : fumaric acid are listed in Table 2.

The two components in the benzamide–4-nitrobenzoic acid co-crystal are bound together through a $R_2^2(8)$ acid···amide motif. These pairs of molecules assemble through a discrete amide···acid interaction to form a 2-D sheet in the *a*–*c* plane (Fig. 9). However, the poor quality of the crystal (indicated by the relatively high *R* factor of 12%) prevents location of the hydrogen atoms attached to acid and amide groups. Growth of crystals of a greater quality is currently underway. The sheets stack along the *b*-axis through π···π interactions to generate the final 3-D structure.

Table 1 Crystallographic data for benzamide co-crystals

Compound	Benzamide–fumaric acid	Benzamide–4-nitrobenzoic acid
Formula	$C_9H_9NO_3$	$C_{14}H_{12}N_2O_4$
M_r	179.18	272.26
T/K	150(2)	296(2)
Crystal system	Monoclinic	Triclinic
Space group	$P2_1/n$	$P\bar{1}$
Z	4	4
a/Å	5.318(6)	6.3184(4)
b/Å	5.351(6)	6.8802(5)
c/Å	29.64(4)	15.6401(11)
α/°	90	95.749(5)
β/°	96.03(5)	98.806(4)
γ/°	90	106.239(4)
V/Å^3	838.8(18)	637.72(8)
R-Factor (%)	5.69	12.03

The creation of co-crystals also allows for the exploration of structural effects on crystal packing as the thermal environment is varied.[50] This approach reveals the effect of packing and complexation on the proton equilibrium behaviour, and also contributes to the body of evidence around the co-crystal salt continuum, as previously discussed.

From a crystal growth point of view the critical issue is the variation in the weak interaction between viable growth sheets. In effect switching from benzamide to isonicotinamide introduces this by virtue of *ortho* atom on the phenyl ring being activated for hydrogen bonding in isonicotinamide and deactivated in benzamide. This leads to an important concept in multi-component crystal design, where consideration of the possible packing landscapes and the interactions that arise can outweigh the structural contribution from the typical pairwise descriptors.

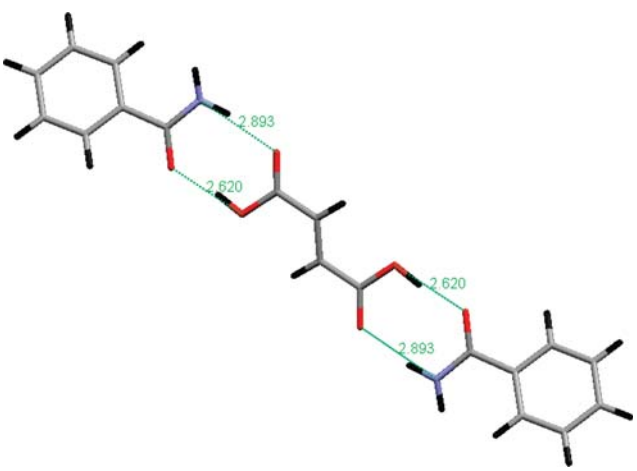


Fig. 7 Formation of molecular cluster in the benzamide–fumaric acid co-crystal.

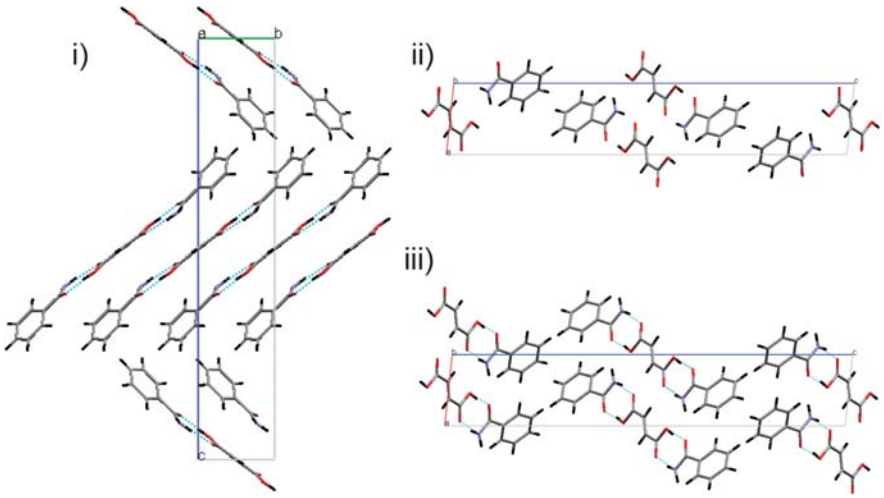


Fig. 8 Herringbone stacking packing (i) down the *a*-axis, highlighting the stacking in the zig-zag stack, (ii) packing in a single unit cell, (iii) shows the packing down the *b*-axis.

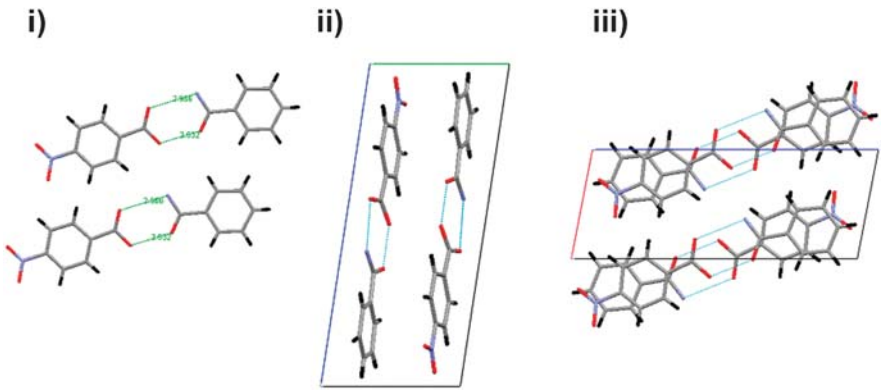


Fig. 9 (i) Dimer hydrogen bonding, (ii) view of the packing down *a*-axis, (iii) packing down *b*-axis, which shows the offset stacking over the nitro group.

Table 2 Hydrogen-bond geometry (Å, °) in benzamide : fumaric acid co-crystal

D–H···*A*	*D*–H	H···*A*	*D*···*A*	*D*–H···*A*
N8–H81···O4	0.95	1.95	2.893 (2)	169
O3–H31···O7	0.96	1.67	2.620 (2)	171

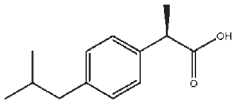
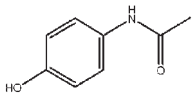
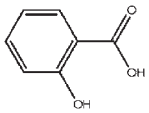
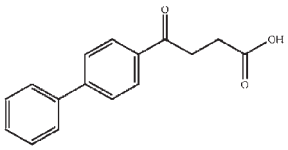
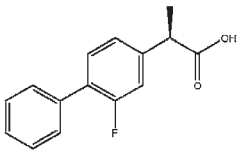
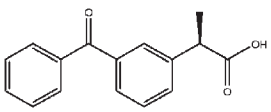
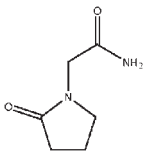
9.6 Low-throughput screening for API with nicotinamide co-crystal[51]

To further explore the application of a thermal, then solution screen approach co-crystal growth experiments with an API and nicotinamide have also been undertaken. The outcomes from this are as follows. Five out of eight potential API co-crystal systems were identified using the Kofler hot-stage method (Table 3) with nicotinamide. These were ibuprofen (*R*/*S* and *S*), salicylic acid, flurbiprofen and fenbufen, each of which displayed three eutectic points over the course of the hot-stage profile. A composition was verified for the ibuprofen systems, with the previously reported melting points (82 °C for *S*, 91 °C for *R*/*S*)[52] agreeing well with those seen in the melt material here, confirming (in combination with X-ray data) growth of the identified co-crystal phase. There is no indication that the co-crystal phases are polymorphic as no morphological changes within the binary (co-crystal) phase were observed during the heating process.

Significantly, neither of the nitrogenous APIs led to the production of a new phase, with both systems displaying simple (single) eutectic profiles. From the acid drugs only ketoprofen fails to form a new phase. Systems in which a new phase was formed were taken forward to a solution screen to obtain single-crystal structures.

The combination of ibuprofen–nicotinamide as forming a co-crystal has been reported in the literature[52] however due to the difficulties in growing crystal suitable for single crystals the crystal chemistry has only recently been discussed, and a summery is as follows. Both the co-crystal formed by the racemic and *S*-phase ibuprofen bind to nicotinamide through acid···pyridine motif. Pairs of dimers are then bound through a $R_2^2(8)$ amide···amide motif between the nicotinamide molecules. This is reinforced by an amide···acid interaction between the nicotinamide and the ibuprofen, the combination of which forms a supramolecular macrocycle structure (Fig. 10). The remaining packing features of these structures have been reported.[51]

Table 3 New phases found in the hot-stage screen

API	Structure	New phase formed	Mp of new phase/°C	Polymorphic API
Ibuprofen (*R*/*S* and *S*)		Yes Yes	89.5 80.3	No
Paracetamol		No	N/A	Yes
Salicylic acid		Yes	138	No
Fenbufen		Yes	150.8	Reported polymorphism
Flurbiprofen		Yes	73.4	Yes
Ketoprofen		No	N/A	No
Piracetam		No	N/A	Yes

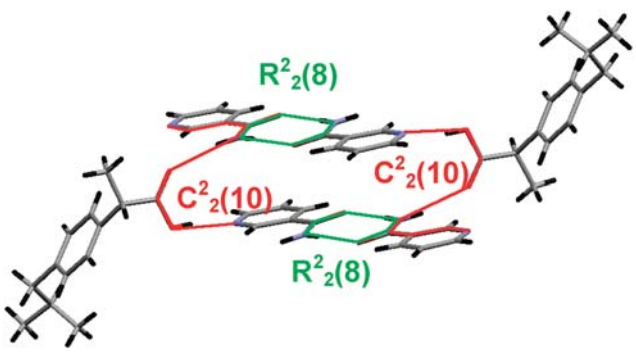


Fig. 10 Hydrogen bonding patterns in the *R*/*S* and *S* co-crystals of ibuprofen–nicotinamide.

It is worthwhile to note that this ternary mode of packing in the *R*/*S* and *S* co-crystals of ibuprofen–nicotinamide are also found in the salt of squaric acid and nicotinamide (EMINUJ). This situation adds to the debate that salts and co-crystals are essentially the two extremes of interaction possible.[13] Ongoing effort into rationalising the impact of crystal packing contribution focused on whether or not protonation occurs from system to system, utilising the same localised packing, is essential for refining this debate.

10.0. Conclusions

Successful growth of co-crystals requires an understanding of not only the intermolecular pairwise interactions from the crystal engineering design strategy, but also an appreciation of the crystal growth process for multi-component materials. The work reported in the literature and the authors' findings to date point to an awareness of the crystallographic concepts underlying co-crystal formation, and the increasing selectivity achievable by applying classical phase diagram approaches. In this respect the phase diagram, be it binary or ternary, maps

the conditions needed to optimise the growth of a desired co-crystal.

Through this appreciation of the phase space and crystal engineering strategies, a small-scale low-throughput approach was developed and this has resulted in a successful approach to API co-crystal identification and potential co-crystal former utilisation (benzamide, and nicotinamide in this instance). In the authors' experience the contrast of well documented co-formers to those less well documented tends to be due to crystal quality, with those well documented formers producing 'good' crystals, and those less well documented found to have issues. This is highlighted by the benzamide and nicotinamide studies presented herein. One issue allied to this is that for many of the API co-crystal systems studied there is a tendency towards atypical complementarity between the target components; such an issue is intensified by the constraints induced by pharmaceutical regularity issues. Alongside this debate the propensity towards large unit cells with systems containing $z' > 1$, requires analysis and correlation between solution chemistry and nucleation for such systems.[53]

Phase diagrams may also be used to identify experimental conditions that allow for the creation new materials, such as nucleation templated composites or alternative phases of co-crystals. Within this activity, the authors own findings develop concepts in co-crystal growth by component sub-phase support. Such ideas are rooted in a lock-and-key concepts of crystal growth. These have been applied to crystal habit modification, where an impurity disrupts the growth of a set of faces over another, expressed by the morphology of the crystal. These nucleation templates are part of a set of crystal growth processes which include twinning, epitaxy and polymorph selection or intergrowth crystal through capping additives. This area lays the foundation of truly composite crystals across two length scales; utilising molecular (co-crystals) and multilayer crystals (co-crystal on component). Looking ahead for polymorphic systems, be it of a component or co-crystal, the recognition that stabilisation may occur within phase domains of excess component would need to be developed with an appreciation of co-crystal growth linked to criteria defined by the underlying principled of Ostwald's rule of stages.

Expansion of these associated ideas will allow better understanding of co-crystal phase domains and their relationship to the components, the polymorphic behaviour of these components and that of the co-crystal.

Within this thermodynamic picture of the co-crystallisation process and optimisation, the issue of kinetic effects is never far away; in this respect the application of *in situ* dispersive X-ray diffraction is being pursued. Kinetic factors also play a role in co-crystal formation by solid-state grinding. Investigations have shown that acceleration of co-crystal formation accompanies a reduction in particle size, if pre-milling and low-energy mixing of the components is undertaken.

The suggestion we wish to leave with is that alongside the molecular focused debate; a parallel debate should be engaged in, around habit modification, polymorph selection, and composite crystal within co-crystallisations. With a focus on determining the impact these processes may have on co-crystal isolation. This will be a particular challenge when scaling up the co-crystallisation of active pharmaceutical ingredients (within the context of the pharmaceutical sector) as solution crystallisation routes are typically adopted on the large scale and variability has led to consequences on API processing and formulation.

All of which challenge what is meant by intent and control and the underlying debate on solution chemistry, nucleation[54] and the impact these issues have on crystal engineering.[55] This is an important next step, and will need to continued to further any understanding of co-crystallisation beyond a structural perspective.

To conclude, the future direction of the area requires the continuing collaboration of the crystallography and crystal growth disciplines; with the product of this interaction fuelling progress.

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