# The role of co-crystals in pharmaceutical design

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**Abstract**

Pharmaceutical co-crystal formation represents a straightforward way to dramatically influence the solid state properties of a drug substance, particularly its solubility and hence bioavailability. This short review summarises this highly topical field covering why the topic is of interest in pharmaceutical formulation, the definitions and practical scope of co-crystals, co-crystal preparation, characterisation and implications for regulatory control and intellectual property protection. Concepts are illustrated with highly selected examples of pharmaceutical co-crystal systems within the wider context of crystal engineering and research in molecular solids.

Keywords: solid form, polymorph, solubility, formulation, solvate

**What is a co-crystal?**

There has been a great deal of excitement about the possibilities offered by co-crystals in a wide variety of fields, with recent publications highlighting exciting prospects for co-crystallization in the controlled design and preparation of porous solids for gas storage and separation applications (1), or in the rational production of room temperature ferroelectrics (2), for example. Contemporary interest in small-molecule co-crystals as materials with modified properties was stimulated by attempts to design co-crystalline materials for non-linear optical applications (3) and a series of rules governing the propensity of common compounds to form co-crystals were elucidated in the early 1990's (4,5).The most obvious and perhaps most realistic potential impact of co-crystals, however, is in the rational control of pharmaceutical solid form and dosage properties (6-10) and a comprehensive book has been published on the subject (11). Co-crystals have also generated their fair share of hype and controversy in recent years both in terms of what constitutes a co-crystal and whether they will have real applications in a pharmaceutical solid form dosage context. Much of the debate has concerned nomenclature and definitions. Barbour *et al.* have very recently provided a lucid and concise summary of the issues (12) and for the most part their definitions and suggestions will be adopted here. Very broadly, a co-crystal is a multi-component molecular crystal, *i.e.* a crystalline substance comprising two or more chemically different molecules (13,14). Such a definition includes solvates, hydrates and both stoichiometric and non-stoichiometric lattice inclusion compounds.

There have been efforts in the literature to narrow or at least focus the scope of co-crystal research. For example, a working criterion requiring all of the molecular components to be solids under ambient conditions has been suggested (15,16). As a strict definition, such a limitation would cause the same substance to be defined in different ways in labs of differing temperature. However, there

is a practical and 'inventive' difference between co-crystals that include solid co-formers and those which include molecules that might have been included accidentally because they are a potential solvent for the active pharmaceutical ingredient (API). As a result, some workers feel that multicomponent molecular crystals in which one of the components is a solvent molecule are not "proper" co-crystals and it has been proposed that therefore none of the components of a co-crystal should have played the role of solvent during the crystallization process (12). Although in practical terms the deliberate design of co-crystals rarely focuses on solvates, the distinction is a subjective one and should not form part of a formal definition. It is true that well-established terms such as 'hydrate' (for multicomponent crystals comprising water and another compound) and 'solvate' (for multicomponent crystals comprising a solvent and a compound crystallised from that solvent) already exist and are in common usage, and hence represent subcategories of co-crystal. However, co-crystals of pharmaceutical compounds with solvents, water or solid co-crystal formers are conceptually indistinguishable from one another. In contrast, crystals comprising opposite enantiomers of the same substance are not generally regarded as co-crystals even though such enantiomers can be separated (at least in principle). This is because both enantiomers can be related to one another within the crystal by space group symmetry (inversion, improper rotation or glide operations). It is also generally accepted that salts comprising anion-cation pairs are *not* co-crystals because the ions cannot be separated. However, even this stipulation comes with a "government health warning" because temperature dependent proton transfer can, in effect, change salts into co-crystals at different temperatures.

Aakeröy has pointed out (17) that, in practical terms, co-crystal design is usually targeted at crystalline, structurally homogeneous materials in which the two or more component molecules are present in a well-defined stoichiometric ratio. Thus there is less interest in the contemporary pharmaceutical co-crystal community in non-stoichiometric inclusion compounds such as urea channel clathrates (18) and solid solutions (19). The relationships between these various solid forms is shown in Figure 1 (20). This review will focus predominantly on the relatively recent literature

covering the region of the diagram entitled 'molecular complexes'. For a comprehensive survey of the history and chemistry of co-crystals reported before 2000 the excellent overview provided by Stahly should be consulted (21).

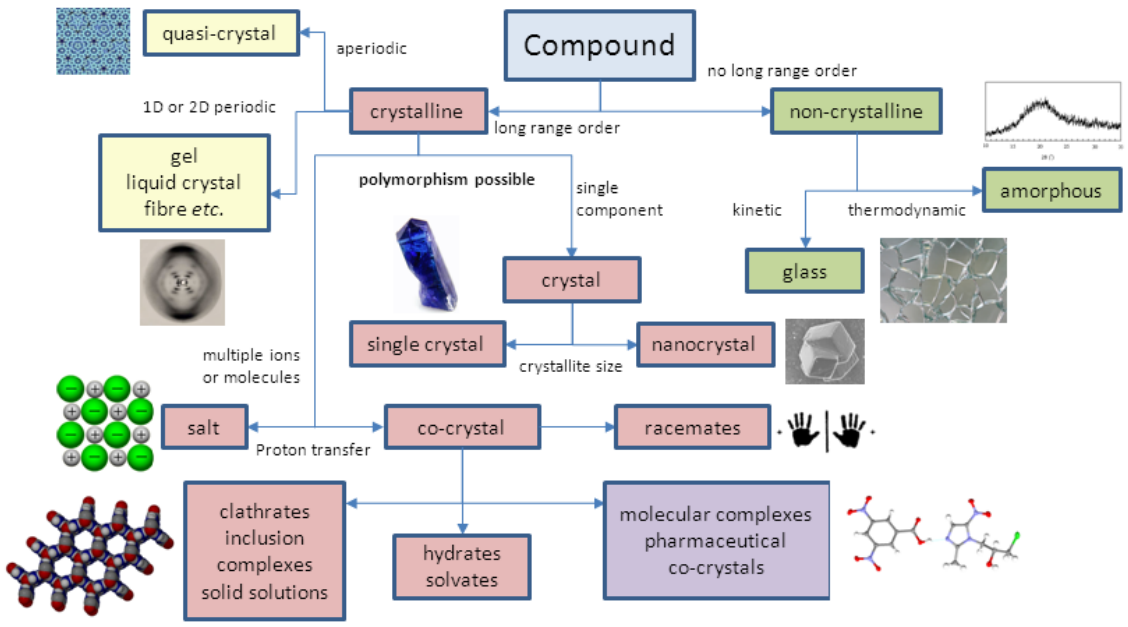


Figure 1 classification of solid forms (adapted from ref. (20)).

So, how prevalent are co-crystals? American Microscopist Walter McCrone once famously said "every compound has different polymorphic forms, and that, in general, the number of forms known for a given compound is proportional to the time and money spent in research on that compound" (22). McCrone's words may yet also prove true for co-crystals! As of January 2012 only 3.1 % of crystals reported in the Cambridge Structural Database (CSD) are known to be polymorphic (23). This figure of course does not take into account unpublished proprietary data on pharmaceuticals, which are often the most studied compounds in terms of their solid state behaviour. In contrast, around 15% contain water either in a co-crystal or as part of a metal aquo complex. A perhaps truer representation (albeit on a much smaller sample size) is given by data from contract solid form screening company SSCI reported in 2007 (20). Of 245 polymorph screens on organic compounds, some 91% existed in more than one crystal form and around half proved to have more than one

pure polymorph. A total of 64 sets of screening experiments designed to reveal co-crystals indicated that around 61% of compounds studied formed co-crystals, whereas around a third of the compounds studied formed hydrated or solvated forms. These numbers are consistent with the proportions in the 1999 European pharmacopeia (24).

The behaviour of salt and non-salt forms proved to be somewhat different. Although both types of compounds existed as multiple solid forms around 91 % of the time, non-salts showed a greater polymorphic tendency (55 % *vs.* 39 %), whereas salts, with their greater propensity to hydrate ionic sites, exhibited a significantly greater tendency to form hydrates (48 % *vs.* 30 %) (Figure 2). A recently launched web resource, Hydrateweb.org, collated published data on pharmaceuticals monographed in *Pharmacopeia Europa* 6.2, 2012 and revealed that of some 955 substances 287 form hydrates (30.1 %) with an overall 415 different hydrated crystal forms. Interestingly there seems to be a statistically significant relationship between co-crystal formation and crystallization with multiple symmetry-independent molecules (a kind of 'self-co-crystallization'). For example, based on the unusual three independent molecule structure of the antibacterial ornidazole, the existence of co-crystals forms was predicted and a co-crystal with dinitrobenzoic acid prepared experimentally shortly after the discovery of a hydrate form (25,26).

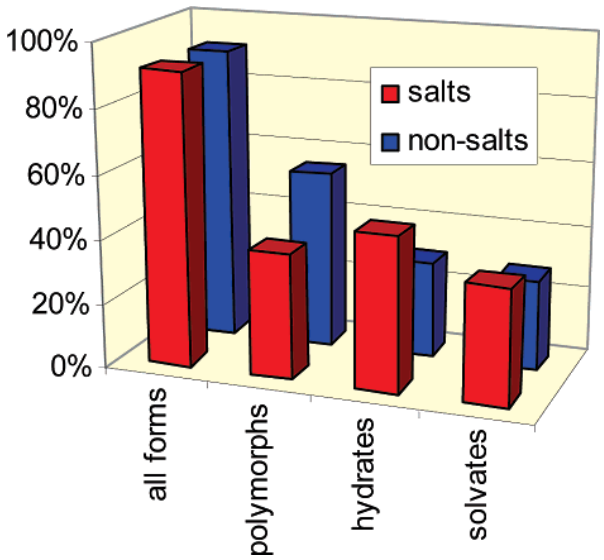

Figure 2. Statistical tendency of the propensity of salts and non-salts to occur in different solid forms based on screening by SSCI (reproduced with permission from ref. (20)).

**Pharmaceutical Co-Crystals**

A pharmaceutical co-crystal is simply a co-crystal in which at least one of the molecular components is an API in conjunction with another type of molecule termed a co-crystal former. More strictly, in order to be useful, the non-API component should be non-toxic with no adverse side effects. Ideally the co-crystal former should be included on the USA Food and Drug Administration (FDA) "Everything Added to Food in the United States" (EAFUS) list which comprises over 3000 substances that are suitable as food additives, or approved as Generally Regarded as Safe (GRAS) (27,28). Interest in pharmaceutical co-crystals arises from the fact that, as different crystal forms to the pure API, they dramatically expand the range of solid forms available for formulation. Co-crystals have different physical properties such as habit, bulk density, solubility, compressability, friability, melting point, hygroscopy and dissolution rate. Formation of a co-crystal often offers scope to transform an amorphous or hard-to-crystallise API into a readily handled, stable crystalline solid. Indeed, it is far more likely to be poor biopharmaceutical characteristics rather than toxicity or lack of efficacy that prevent a candidate active compound progressing in clinical trials; estimates suggest that fewer than 1 % of candidate drugs eventually reach the market (29). Although amorphous APIs are used and form the basis of an increasing number of dosage forms (examples include rosuvastatin calcium, quinapril hydrochloride, and cefuroxime), crystalline products are generally preferred because of their easier and more reproducible characterisation, lower hygroscopicity and greater chemical stability. Co-crystal formation also offers considerable scope to solubilise a poorly soluble API (10), although solubility measurements on highly soluble co-crystals must be treated with caution because the substance can undergo a recrystallization to the most stable pure API form on contact with solvent . In one example, the 1:1 co-crystal of a candidate sodium channel blocker and glutaric acid proved to

dissolve some 18 times faster than the pure drug crystal and the co-crystal has three times the bioavailability as measured by the plasma Area Under Curve (AUC) value (30). Work by Aakeröy *et al.* showed that the solubility and melting point of the anti-cancer drug hexamethylenebisacetamide can be systematically increased by changing the chain length of the dicarboxylic acid, with improvements of up to a factor of 2.5 in aqueous solubility (29). Co-crystal formation does not by any means necessarily enhance API solubility, however. For example, solvate forms are the least soluble forms in the solvent they contain (31). This decreased solubility can also be a useful property; lowering the solubility of a highly soluble active ingredient is of interest in the agrichemicals industry, where low solubility is desirable to avoid rapid leaching of the applied substance in run-off (29).

Discovery or design of a new, useful co-crystal solid form also offers new opportunities for the exploitation of intellectual property, and there are now a number of patents covering co-crystals One example is the nucleoside analogue reverse transcriptase inhibitor stavudine which forms patented co-crystals with melamine, 2-aminopyridine (32), or *N*-methyl-2-pyrrolidinone (33) (Figure 3). In legal terms, patent protection for co-crystals is thought to be significantly easier to enforce that other solid form intellectual property because of allegations of obviousness are more difficult to establish (27).

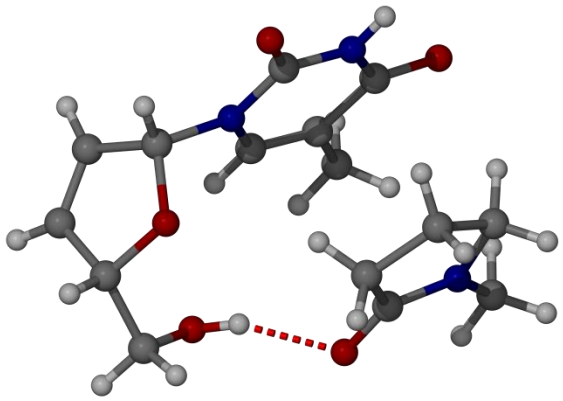

Figure 3. X-ray structure of the 1:1 stavudine *N*-methyl-2-pyrrolidinone co-crystal (33). The structure exhibits hydrogen bonding from the best donor, the OH group to the best acceptor, the highly polar pyrrolidinone amide carbonyl oxygen atom.

**Pharmaceutical co-crystal synthesis**

The most obvious way to produce a pharmaceutical co-crystal is to simply crystallise the API from a supersaturated solution in the presence of (varying amounts of) the co-crystal former. Most commonly (in *ca.* 40 % of cases) supersaturation is achieved by slowly cooling an undersaturated mixture until the solubility limit is reached. Alternative procedures may involve the slow diffusion of the two components together across a liquid concentration gradient at constant temperature, although co-crystals with a higher solubility than the pure solid forms often do not result from this approach. Key to the rational synthesis of co-crystals is an understanding of the binary or ternary phase diagrams for the equilibria involving the solvent (if present) and two solute mixture. The binary phase diagram for the two co-crystal components exhibits eutectic points in between each phase and hence implies the existence and number of co-crystal phases. The ternary phase diagram is highly influenced by the relative solubilities of the two components. Figure 4a shows a schematic ternary phase diagram for two components of similar solubility in the given solvent. The diagram shown in Figure 4b is more complicated and represents the case in which the components have very different solubilities. From these diagrams it can be seen that slow evaporation of a 1:1 solution of two components **1** and **2** can result in either a mixture of co-crystal and single component phases or solely starting material depending on whether the crystallization pathway passes through the mixed phase region D or the single phase region E (9).

Blagden *et al.* have elegantly summarised the various common co-crystallization strategies which include (9):

- use of an excess of one of the co-crystal components with consequent reduction in the solubility of the co-crystal in the presence of the excess component;
- slurry crystallization to access the low percentage solvent region of the phase diagram;
- careful tuning of solvent identity or composition to maximise the pure co-crystal regions in the phase diagram;
- wet milling of the solid components in the presence of a just a few drops of solvent;
- involving an intermediate phase such as a hydrate or amorphous form as part of a solid state synthesis;
- use of a metastable polymorph to give an unstable intermediate that can trigger co-crystal growth;
- and seeding solutions using co-crystal seeds derived from melt crystallization using hot stage microscopy.

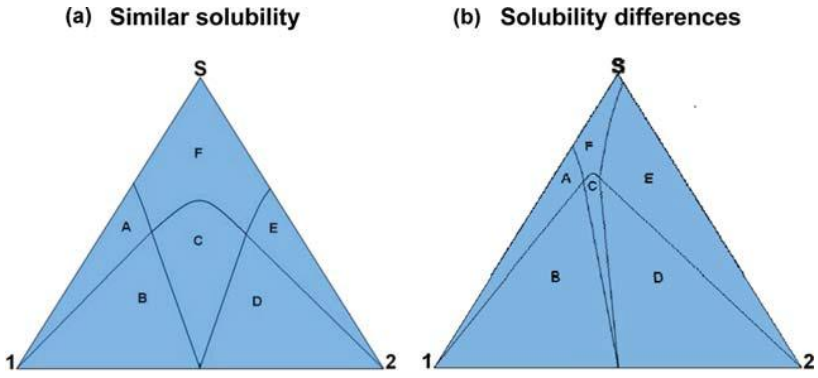


Figure 4. Schematic representations of isothermal ternary phase diagrams with (a) similar solubilities between two co-crystal forming components (**1** and **2**) in solvent **S** and (b) different solubilities of **1** and **2** in **S**. Region A=component **1** and solvent, B=component **1**+co-crystal, C=co-crystal, D=component **2** + co-crystal, E = component **2** and solvent, and F = solution. (reproduced with permission from ref. (9))

Of key importance in all solid-form research is hot stage thermomicroscopy. Thermomicroscopy involves simple visual observation of the sample as a function of temperature using a polarising optical microscope, a technique that can be a very sensitive to phase transformations, and melt/recrystallization events (30,34,35). In one recently reported example, a 1:1 co-crystal of the barbiturates nembutal and phenobarbital was discovered (36) forming in the contact region between the two components (Figure 5). Melt co-crystallization in this way is termed contact preparation (37) or sometimes 'mixed fusion' and is a typical procedure with repeated melting and cooling cycles resulting in co-crystal growth at the interface of the pure materials. The presence of the different forms is generally distinguished by the melting point and by visualisation of the interface region using polarised light. Contact preparation has also been used as a low- to medium-throughput co-crystal screening strategy. The pharmaceutically acceptable co-crystal former nicotinamide has been screened in this way for co-crystal formation with racemic and S-ibuprofen, fenbufen, racemic flurbiprofen, racemic ketoprofen, paracetamol, piracetam and salicylic acid. The screen resulted in the isolation and characterisation of three new co-crystals of nicotinamide with racemic and S-ibuprofen and with salicylic acid (38).

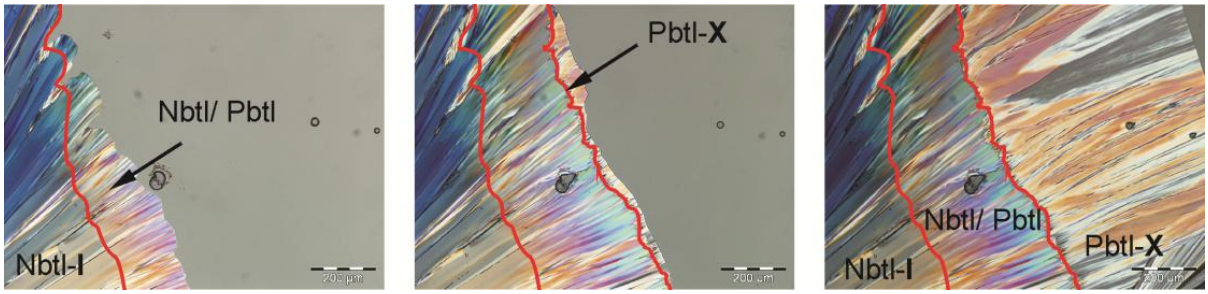


Figure 5. Thermomicroscopic image of a contact preparation of nembutal (Nbtl; left part of each image) with phenobarbital (Pbtl; right part of each image). Left: sample at 90 °C showing the growth of nembutal form-I into the contact zone, resulting in the co-crystal nembutal · phenobarbital with similar morphological features. Centre and right: the co-crystal grows within the contact zone (between the red lines) and induces the formation of phenobarbital form-X which is isomorphic to the co-crystal (reproduced with permission from ref. (36)).

Particularly important and topical work over the past five years has shown that mechanical grinding of two solids together can often produce pharmaceutical co-crystals (13,39). For example, co-grinding carbamazepine and saccharin readily gives a co-crystal as a solid-solid transition (40). The rate of the reaction is increased at higher relative humidity, and indeed, many grinding reactions proceed more smoothly in the presence of a drop of solvent ('solvent drop grinding' (41)). Solvent drop grinding has been used in the preparation of co-crystals of the non-steroidal anti-inflammatory drug meloxicam with succinic and maleic acids (42). Meloxicam is poorly soluble in water and organic solvents, and hence, co-crystal formation offers a route to its solubilisation. The formation of the co-crystals is accompanied by a colour change from yellow to white. Partial dissolution and recrystallization is generally thought to be partially responsible for the success of solvent drop grinding techniques (43), which is consistent with the formation of meloxicam co-crystals with drops of solvents such as isopropano,l in which the components have a relatively low solubility. A survey of the various methods (grinding, solution and melt co-crystallization) for obtaining co-crystals was undertaken recently by Fucke *et al.* in the context of developing pharmaceutical co-crystal screening methods. Using the example of piroxicam, these researchers found that solvent-drop grinding gave the most 'hits' in terms of co-crystal formation and proved the preferred screening method. Melt crystallisation was also highly successful in obtaining crystalline co-crystals while solution evaporation often gave binary and ternary mixtures of crystal forms. The fact that different co-crystal forms can be obtained from solution and milling crystallisation methods means that a balanced approach across all of the possible techniques is required (44).

There have been reports of other novel means of co-crystal preparation. In particular supercritical fluids such as $scCO_2$ have been used as part of a novel screening technique to give the known indomethacin-saccharin co-crystal form, with some control over particle size in the nanometre to micron range. The novel properties of supercritical fluids such as good solvation power, miscibility with organic solvents as antisolvents, and atomization enhancement make them highly promising in this role (45).

A ‘neat trick’ is to form a host guest inclusion complex in solution with macrocycles such as cyclodextrins. The resulting crystalline product contains the intact API but it is almost fully shielded by the surrounding cyclodextrin macrocyclic host. As a result, the properties of the crystal much more resemble the properties of a cyclodextrin than the API. Moreover, cyclodextrins are safe materials since they are simply glucose oligomers derived from enzymatic degradation of starch (46). Related molecular containers such as the ‘pumpkin-shaped’ cucurbiturils can fulfil a similar role. The striking X-ray crystal structure of the anti-depressant paroxetine included within two β-cyclodextrin units is shown in Figure 6a (47), while Figure 6b shows the anti-cancer drug oxaliplatin included within a cucurbit[7]uril (48).

(a) (b)

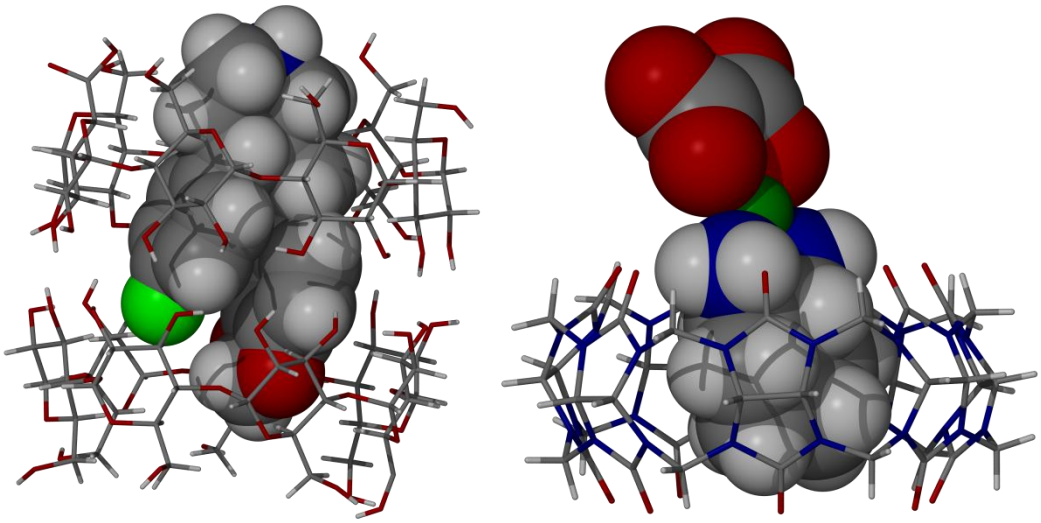

Figure 6 (a) X-ray structure of Paroxetine included within two β-cyclodextrin units (47). The Paroxetine adopts an unusual ‘hairpin’ conformation to fit the available space. (b) The oxaliplatin complex of cucurbit[7]uril (48) in which the hydrophilic portion of the API protrudes beyond the macrocycle. Drug substances shown in “space filling” representation.

**Co-crystal characterization**

In some cases co-crystal formation is readily apparent from the resulting physical properties of the new material. Formation of a co-crystal from acetaminophen and 2,4-pyridine dicarboxylic acid is immediately apparent from the red colour of the co-crystal, despite the fact that both components are white solids (Figure 7). The red colour arises from the fact that the pyridine dicarboxylic acid converts to the zwitterionic form in the co-crystal as part of the overall hydrogen bonded crystal packing arrangement, with concomitant reduction of the $\pi$-$\pi^*$ energy gap (49).


Figure 7 A coloured co-crystal formed from white component solids: (a) single crystals of the 1:1 acetaminophen and 2,4-pyridine dicarboxylic acid co-crystal, (b) powdered acetaminophen, (c) powdered 2,4-pyridine dicarboxylic acid, and (d) powdered co-crystal (reproduced with permission from ref. (49).

In other cases co-crystal formation can be deduced from the full battery of techniques conventionally used to characterise crystalline molecular solids. These have been detailed in a number of excellent monographs (50,51) and include primarily single crystal and powder X-ray diffraction (SC-XRD and PXRD), thermal methods such as differential scanning calorimetry (DSC) and thermogravimetric analysis (TGA), polarised optical hot-stage microscopy (particularly for distinguishing precise melting point), vibrational spectroscopy (IR and Raman) and solid state magic angle spinning nuclear magnetic resonance spectroscopy (MAS-NMR). The ‘gold standard’ in terms

of structural characterisation of a co-crystal is single crystal X-ray structure determination. Not only does this method uniquely determine the crystal form (*e.g.* as defined by unit cell dimensions and crystallographic space group), it also gives a full three dimensional representation of the structure allowing elucidation of supramolecular synthons (52) and full details of the crystal packing. SC-XRD is based on the diffraction of X-rays by the electron density in the crystal and hence is relatively insensitive to hydrogen atom positions because of the low electron density of the hydrogen atom. Under these circumstances the much more expensive option of single crystal neutron diffraction is a viable alternative. Neutron work gives very precise hydrogen atom nuclear positions (especially if hydrogen is replaced by deuterium), however it requires relative large and hence difficult to grow single crystals (*ca.* $1mm^3$) and a reactor or spallation neutron source (53). Of particular relevance to co-crystal research is the issue of proton transfer; a stoichiometric crystal containing a neutral acid such as a carboxylic acid, along with a free base drug substance is a co-crystal. However, proton transfer from acid to base would give a carboxylate salt, which is not a co-crystal. As a result, IP or regulatory requirements might make the location of the proton and hence accurate hydrogen atom positions highly important. This nuanced issue has been discussed in depth in several reviews (54-56).

By definition, single crystal X-ray and neutron studies are carried out on one single crystal and hence it represents good practice to confirm the solid form of the bulk material using PXRD. PXRD gives a unique 'fingerprint' diffraction pattern characteristic of a particular solid form and of course does not require the growth of high quality single crystals to obtain the data. For this reason PXRD (also termed XRPD) is ubiquitous in the pharmaceutical industry. In favourable circumstances, structure solution followed by Rietveldt refinement methods can give the full three dimensional crystal structure from powder data with a precision sometimes not a great deal worse than single crystal methods (57). Although excellent data can be obtained on a conventional laboratory copper-K$\alpha$ X-ray source, the higher intensity and narrower line widths offered by synchrotron radiation can enable easier structure solution and more precise structure determination. Synchrotron radiation

also facilitates detailed studies of the evolution of a crystallizing system over time and has been used in energy dispersive X-ray diffraction experiments, for example, to study the *in situ* crystallization of both 1:1 and 2:1 benzoic acid – isonicotinamide co-crystals (9). The data showed the initial appearance of the 1:1 phase on cooling from 60 $^{o}$C to 23 $^{o}$C followed by the rapid and irreversible transformation to the 2:1 form at 16$^{o}$C.

In addition to X-ray methods, IR and Raman spectroscopy of solid samples (measured for example using an attenuated total internal reflectance apparatus or as a KBr pellet) can also give a characteristic fingerprint of a particular solid form. Because vibrational spectroscopy depends on bond vibrational modes which are only moderately perturbed by the molecule's solid state environment, the differences in IR and Raman spectra between different solid forms, or between co-crystal and pure forms, can be relatively minor. However, if particular bands are sensitive to solid form (*e.g.* when there is a significant change in hydrogen bonding mode in different forms) then vibrational spectra represent a useful and facile method of distinguishing different polymorphs and co-crystals.

The DSC technique comprises a comparison of the power required to maintain a sample and reference at the same temperature as one another, usually while temperature is scanned up or down by a few degrees per minute (variable pressure and isothermal DSC are also used) (58). The technique is particularly useful in detecting phase changes that do not result in a change in mass such as polymorphic transitions and melting, although events such as loss of a volatile co-crystal component are also readily evident. DSC also gives an accurate value for melting onset temperature. DSC data is particularly valuable in constructing semi-quantitative energy-temperature relationships (59,60). The related technique, thermal gravimetric analysis (TGA) records sample mass loss during heating, usually at a constant rate (although oscillatory and isothermal methods are also used). In the context of co-crystals, TGA is an excellent method for determining the onset temperature of co-

crystal decomposition and loss of a volatile component. The quantitation of the mass loss in the case of volatile co-crystal formers provides a confirmation of stoichiometry.

Solid-state NMR spectroscopy represents an interesting complementary technique to diffraction methods in the study of pharmaceutical solid forms. Although diffraction methods can give more detailed structural information, the diffraction pattern represents the average over many unit cells, whereas MAS-NMR is sensitive to the local molecular environment (61). MAS-NMR can also reveal information about the number of symmetry-independent molecules in the unit cell and give characteristic chemical shift values for particular solid forms.

**Ternary and salt co-crystals**

Co-crystals are not necessarily limited to just two components. Obvious examples of ternary multi-component solids are 'co-crystal hydrates' in which water is one of three types of molecule present in the material. For example, mechanochemically grinding theophylline results in the formation of a co-crystal hydrate with citric acid. The closely related caffeine, however, gives only an anhydrous co-crystal even when hydrated starting forms are used (13). An interesting related example is the formation of a 1:1:2 'co-gel' of melamine (M), uric acid (U) and water. Sonication of an aqueous suspension of melamine and uric acid gives a solid gel that was shown by crystal structure calculation and X-ray powder diffraction to comprise co-crystal fibres of composition $M{\cdot}U{\cdot}2H_2O$. The water forms an integral part of the co-gel structure because of the mismatch in hydrogen bond donors between melamine and uric acid (62).

The deliberate synthesis of ternary multi-component co-crystals has been undertaken by Aakeröy and coworkers (17) who carried out a detailed study of supramolecular synthons (i.e. non-covalently bonded interaction motifs (52)), proposing that the probability that a certain motif will appear in a crystal structure can be regarded as a measure of the "yield of a

supramolecular reaction". By carefully balancing the mutual interactions between the "supramolecular reagents" such that the strongest hydrogen bond donors were paired with the strongest hydrogen bond acceptors and so on, these researchers were able to design and realise a series of ternary co-crystals incorporating a "ditopic supramolecular reagent" containing pyridyl and imidazole groups pairing with mono- and dinitrobenzoic acids (Figure 8).

An interesting case is that of salt co-crystals which may be regarded as a binary co-crystal of a salt (conceptually inseparable anion-cation pair) and another neutral molecule. An example is the formation of co-crystals of Prozac™ (fluoxetine hydrochloride) with a range of carboxylic acids. The formation of co-crystals modulates the solubility of the API (34). Although fluoxetine hydrochloride is clearly a salt, a simple proton shift from base to chloride would transform this material into a ternary co-crystal of fluoxetine, hydrogen chloride and a dicarboxylic acid. In more ambiguous cases it may become vital to firmly establish proton location, particular if IP protection is contemplated. Since hydrogen atoms are difficult to locate by X-rays, the expensive and challenging alternative of single crystal neutron diffraction may be required (53). An extensive range of inorganic and coordination complex salt co-crystals (or ionic co-crystals (63)) have been prepared by Braga and co-workers, who discovered that grinding an organometallic carboxylic acid with KBr resulted in the formation of a crystalline molecular KBr adduct (64).

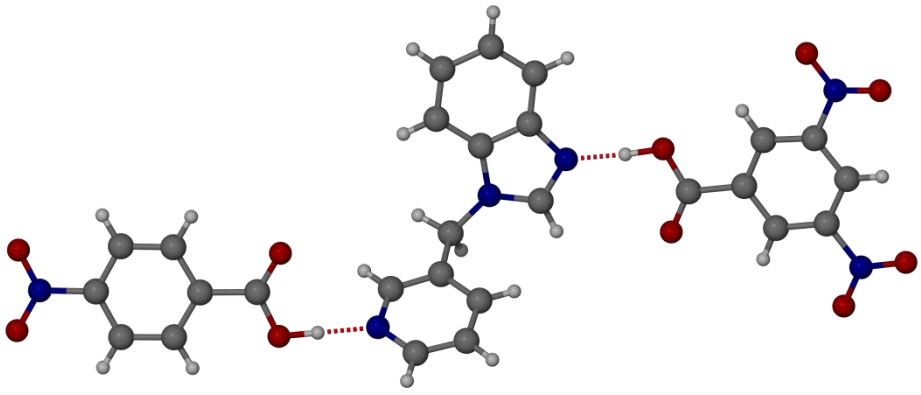

Figure 8. A designed ternary co-crystal – the stronger acid binds to the stronger base (right-hand side), and the second-best acid binds to the second-best base (left-hand side) (17).

**Pharmaceutical co-crystals approaching the market**

A key question concerning the practical application of a co-crystal of a commercial API is whether the co-crystal is in some sense a physical mixture and hence might fall within current compendial guidelines, or whether the co-crystal should be regarded as a new chemical entity with all the concomitant safety and toxicological testing such substances require (6). The (FDA has recently (December 2011) released draft guidance on the regulatory classification of pharmaceutical co-crystals for applicants for New Drug Applications (NDAs) and Abbreviated New Drug Applications (ANDAs) (65). The FDA defines co-crystals as "solids that are crystalline materials composed of two or more molecules in the same crystal lattice" – the implication is that it is two or more *types of* molecules that are referred to here. The FDA also regards co-crystals as dissociable "API-excipient" complexes, blurring the boundary between co-crystals and physical mixtures. This guidance has generated a strong response from some researchers in the co-crystal field who propose alternative, yet also potentially controversial definitions that distinguish multicomponent APIs and their co-crystals from solvates and hydrates (66). As of the time of writing, no commercial pharmaceutical co-crystal has yet been approved for sale as a drug substance, and it will perhaps be a brave drug company with deep pockets that undertakes the first 'test case'. However, regulatory classification is driven by the increasing numbers of reports and patents covering applications of pharmaceutical co-crystals. Given current levels of interest, coupled with the trend towards increasing molecular weight, hydrophobicity and

hence poor dissolution characteristics of recently developed drug substances it seems only a matter of time before a successful co-crystal NDA comes about.

Among many recent patents relating to potential commercial co-crystal products, the possibility of combining two active ingredients in a single co-crystal is an interesting one and has been claimed in the co-crystallization of quercetin (a plant-derived flavonoid, used as a nutritional supplement and reputed to offer some anti-cancer properties) with antidiabetic agents such as metformin or tolazamide. The combination drug has been suggested to have physical properties and biological activity that are distinct from the individual properties of the two components (67).

Interesting research pointing the way to applications of co-crystals in the modification of drug pharmacological action has been reported for insulin, a peptide hormone used for the treatment of diabetic patients. Insulin has poor oral bioavailability and is commonly injected. Human insulin has been co-crystallised with a lipophilically modified, closely related insulin analogue octanoyl-$N^{\varepsilon}$-LysB29-human insulin (68). The lipophilic formulation was designed to provide a slow release profile compatible with an improved physiological insulin profile. After optimisation of the side chain length to a $C_8$ substituent the co-crystals were found to give comparable activity to the parent insulin and a more uniform and prolonged absorption rate compared to crystals of the commonly used ‘‘Neutral protamine Hagedorn” intermediate-acting insulin.

Finally, a note of caution regarding unexpected co-crystal toxicity effects was sounded by the unexpected toxicity of co-crystals of melamine and cyanuric acid. In 2004 and 2007 there were separate reports of kidney failure in domestic pets in Asia and North America, respectively. The deaths were traced to contaminated pet food containing both

melamine and cyanuric acid which together form a highly stable hydrogen bonded co-crystal. Both Melamine and cyanuric acid are relatively non-toxic by themselves, and the toxicity effects arise from insoluble co-crystal formation catalysed by the animals' acidic urine. It was suspected that the melamine was artificially added to increase the nitrogen content, making the products appear protein rich. The cyanuric acid appeared to be a by-product of the melamine manufacture (69).

**Concluding remarks**

It is clear that co-crystals are highly likely to be far more abundant than the currently known proportion of total solid forms indicates. Co-crystal formation offers tremendous scope for controlled modification of key pharmaceutical properties such as habit, bulk density, solubility, compressability, friability, melting point, hygroscopy and dissolution rate. Progress in the application of co-crystals in commercial dosage forms is currently limited by an uncertain regulatory framework and, to some extent, by relatively minor differences of opinion concerning nomenclature. Deliberate co-crystal formation offers some new opportunities in intellectual property protection and exploitation. It can be hoped that co-crystal IP may be a little more clear-cut than IP issues surrounding accidentally discovered solvates (classically called '*pseudo*polymorphs'). A significant concern is the design of effective pharmaceutical co-crystal screening methodologies. Although the basic principles of co-crystal screening are very similar to the well-established (albeit wide ranging) principles of polymorph screening (70), the number of possible combinations and methods even using GRAS co-crystal formers in staggeringly large and represents a considerable practical limitation. Intelligent choice of co-crystal former (perhaps based on a library of co-

crystallising agents (9,71)), assisted by computational crystal structure calculation (72,73), is likely to become the approach of choice.

Acknowledgements

I would like to thank EPSRC for funding our work on molecular solids (grant numbers EP/F063229/1 and EP/E031153/1).

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