JPP Journal of Pharmacy and Pharmacology

Royal Pharmaceutical Society of Great Britain

JPP Journal of Pharmacy and Pharmacology

JPP 2010, 62: 1547–1559

Received January 7, 2010
Accepted April 26, 2010
DOI
10.1111/j.2042-7158.2010.01133.x
ISSN 0022-3573

Review

Benefits of cocrystallisation in pharmaceutical materials science: an update

Tomislav Friščić and William Jones

Abstract

Objectives We provide a brief overview of recent applications of cocrystals for improving the physico-chemical and materials properties of active pharmaceutical ingredients, including solubility, humidity and thermal stability, dissolution rates and compressibility for tablet formation.

Key findings This overview illustrates the pharmaceutical applications of cocrystals, with a selection of recent examples and also attempts to foresee future developments by proposing several directions not yet explored in the area of pharmaceutical cocrystallisation.

Summary Reliable strategies for the synthesis and design of pharmaceutical cocrystals have now been established, and the potential of cocrystallisation for enhancing the solid-state properties of drugs is well recognised; the field is now moving towards the understanding of cocrystal structure–property relationships, for which systematic structural studies and computational approaches will play a key role.

Keywords crystal structure; materials properties; pharmaceutical cocrystals; solid forms; solubility; stability

Preamble

Pharmaceutical cocrystal formation was introduced into the vocabulary of pharmaceutical research by Almarsson and Zaworotko.[1] Despite its relatively recent application, cocrystal formation has rapidly established itself as a general method for modifying, albeit largely by trial and error, the solid-state properties of active pharmaceutical ingredients (APIs). The intention of this brief review is to provide an update of various applications of cocrystals, with a particular focus on advances and new opportunities in understanding the structure–property relationships between cocrystal architecture and associated solid-state properties. Since the general properties of pharmaceutical cocrystals and methods for their preparation and design have been covered in several reviews,[2–6] we highlight for each type of application a small number of suitable examples from the recent literature.

Introduction

In pharmaceutical development the properties of an API are frequently improved by developing an amorphous or salt form of the pure drug molecule. More recently, attention has turned to the advantageous use of cocrystals. Cocrystals, or crystalline molecular complexes, are multicomponent crystalline solids composed of an API along with one or more pharmaceutically acceptable molecules, known as the pharmaceutical cocrystal former (or coformer). While the role of the API in the cocrystal is the origin of pharmacological activity, the purpose of the cocrystal former is to modify or generate a particular physico-chemical property of the API solid form. Consequently, cocrystallisation can be referred to as non-covalent derivatisation. Cocrystals are inextricably related to other pharmaceutically relevant multicomponent solids, especially salts and solvates or hydrates (Figure 1). However, it is useful to distinguish cocrystals from other multicomponent pharmaceutical solids by recognising that cocrystal formation is at least partially based on a design involving directional and robust sets of complementary non-covalent interactions, such as hydrogen or halogen bonds.[2] In addition, different authors prefer somewhat different and more specific definitions of cocrystal, for example ones that are more specific about the nature or state of aggregation of the cocrystal constituents.[3] This ability to partially design the crystal architecture offers cocrystals a significant advantage over salts or solvates as functional solids, as it allows, in principle, the deliberate design and construction of solid-state structures using established crystal engineering principles.

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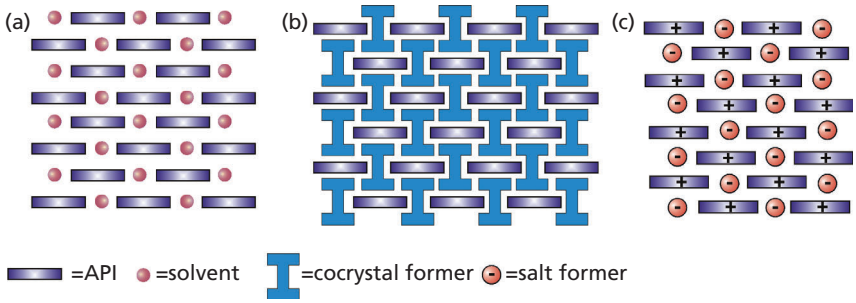

Figure 1 Schematic representation of pharmaceutically relevant multicomponent crystalline solids. (a) Solvate; (b) cocrystal; (c) salt. API, active pharmaceutical ingredient.

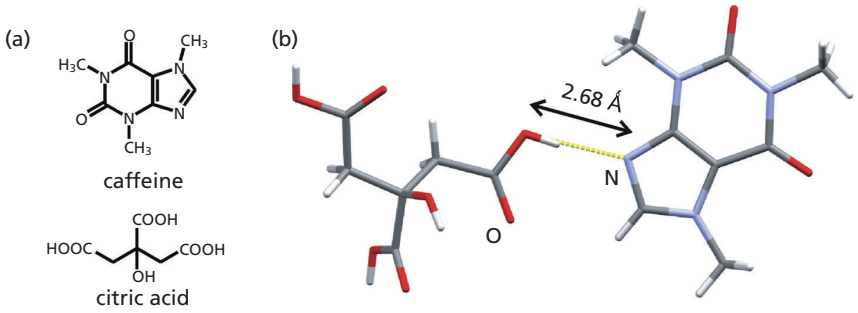

Figure 2 Caffeine, citric acid and their cocrystals. (a) Molecular diagrams of caffeine and citric acid. (b) Fragment of the crystal structure of the cocrystal between caffeine and citric acid.[12]

Although cocrystals have only recently been introduced in pharmaceutical science, the term was first employed in materials science almost two decades ago. Cocrystal synthesis was used by Etter *et al*.[7] to generate new crystalline solid materials following the principles of supramolecular chemistry and molecular recognition, primarily with hydrogen bonding and supramolecular synthons. This early work, which focused on the design of new organic solid-state materials with non-linear optical properties, illustrates well the two properties of cocrystals that are the basis of their rapid success as pharmaceutical materials: (1) synthesis by design[8] and (2) modularity.[9] While the early work largely focused on optical properties, cocrystal formation was soon applied to generate new forms of pharmaceutically active compounds, such as sulfadimidine and salicylic acid.[10]

It is often argued that the use of cocrystals in API formulations has not been demonstrated and that commercial products containing cocrystals had limited impact in the marketplace. This discouraging perspective is misleading as it is very likely that cocrystal products have already been on the market for a considerable period of time.[11] We have recently illustrated this point in the case of caffeine citrate, a well-known apnoea drug.[12] By using room-temperature crystal structure analysis, we revealed that caffeine and citric acid form a cocrystal with an extended, hydrogen-bonded structure composed of neutral molecules. In the cocrystal, the interaction between caffeine and citric acid corresponds to a $R_2^2(7)$ supramolecular ring synthon,[12] well established in the design of pharmaceutical cocrystals between imidazole-like molecules and carboxylic acids (Figure 2). In particular, there is no evidence for proton transfer in the solid.

Supramolecular design

The ability to design cocrystals is largely based on reliable patterns of directional non-covalent interactions, such as hydrogen bonds or halogen bonds, which bring molecules together to form one-, two- or three-dimensional molecular complexes in the crystal. Such patterns are known as supramolecular synthons[13] and can be identified through searches of the Cambridge Structural Database. In the context of pharmaceutical materials, hydrogen-bonded synthons have been principally investigated to date, although a potential role for halogen bonds is suggested by the recent discovery of such interactions in biomolecular recognition.[14] The number of supramolecular synthons that are regularly used in crystal engineering and cocrystallisation is relatively small and is probably less than ten.[15] Cocrystal formation can be recognised as a natural choice to construct new solid forms of APIs when it is realised that the functional groups that are most important in cocrystal design are also frequent in pharmaceutically active molecules. Typical examples of such supramolecular synthons include amide–amide dimers, carboxylic acid–amide dimers and pyridine–carboxylic acid dimers or imidazole–carboxylic acid dimers (Figure 3).[13]

There are three major reasons why pharmaceutical cocrystallisation may be promoted as superior to salt formation. The first, and the most obvious, is the versatility of the approach. While cocrystal formation depends only on mutual recognition of the API and the cocrystal former, salt formation is limited to acid–base pairing determined by a suitable difference of pK_a values between the API and the potential salt former.[16–18] The number of pharmaceutically acceptable compounds that could be used as cocrystal formers is, therefore,

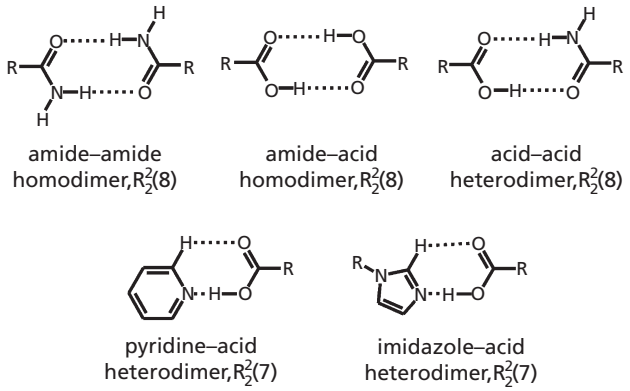

Figure 3 Typical supramolecular hydrogen-bonded synthons used in crystal engineering of pharmaceutical cocrystals. Graph-set notation is indicated.

significantly larger than the number of salt formers, and molecules without any obvious protonation or deprotonation sites can be considered as candidates for pharmaceutical cocrystallisation. Moreover, all FDA-approved salt formers can be considered a subgroup of cocrystal formers. Importantly, when salt formation does not occur, cocrystal formation is a viable method to explore the phase space of molecules that are sensitive to strongly acidic or basic conditions.

Another important benefit of cocrystals is the ability to at least partially control the structure of the new solid. This is a consequence of the directionality of hydrogen bonds and supramolecular synthons, and allows planned construction of discrete molecular complexes[19] or, following the concept of a crystal as a supramolecule,[20] of extended structures such as chains[21] or tapes[22] (Figure 4). As a result, it should be possible to use cocrystals to impart a solid API form with a particular structure and, therefore, with a desired solid-state property. This was recently demonstrated by modification of paracetamol compressibility.[23]

In salts, the directionality of intermolecular interactions is normally overshadowed by the non-directional nature of the Coulombic interactions that dominate the salt structure. However, the success of supramolecular synthons in pharmaceutical cocrystallisation also promoted the investigation of their applicability for the design of pharmaceutical salts. For example, Wenger *et al*. used extensive database searches and screening experiments to propose the $R^2_4(8)$ supramolecular synthon as a design element for the construction of solid forms of γ-aminobutyric acid and gabapentine held together by charge-assisted hydrogen bonds.[24,25] In some cases, supramolecular synthons responsible for cocrystallisation act as pathways for intermolecular proton transfer. The result is an ionic structure where conventional hydrogen bonds have been transformed into charge-assisted hydrogen bonds.[26,27] These examples suggest an opportunity to construct solid forms that would combine the benefits of cocrystals and salts: control of structure through directionality of hydrogen bonding with the stability and aqueous solubility arising from an ionic structure. Such a design would take advantage of the concept of the 'salt–cocrystal continuum',[28] a realisation that cocrystallisation and salt formation are not mutually exclusive

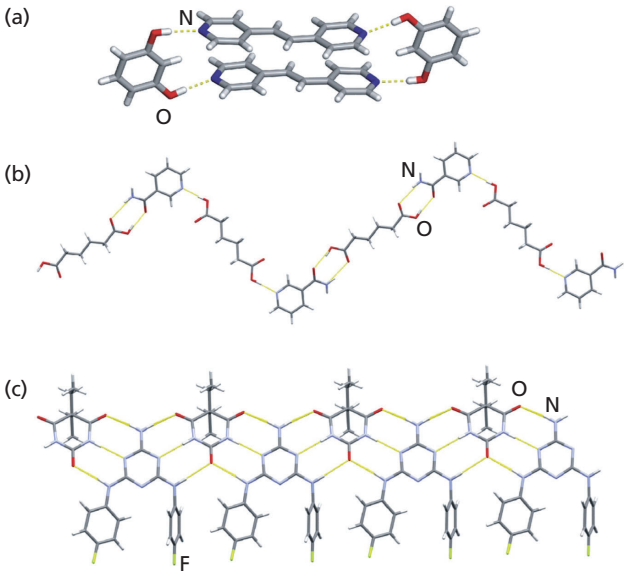

Figure 4 Design of hydrogen-bonded molecular assemblies in cocrystals. (a) Discrete assembly between a bypridine and a resorcinol.[19] (b) Zigzag chains in cocrystals of nicotinamide.[21] (c) Flat hydrogen-bonded tapes in cocrystals of diethylbarbituric acid with a melamine derivative.[22]

approaches to the design of solid forms, but extremes in a wide spectrum of multi-component materials. Indeed, cocrystallisation is readily employed to construct new solid forms of ionic API materials, as demonstrated by Childs *et al*. in the cocrystallisation of fluoxetine hydrochloride.[28,29]

Modularity, structure–property relationships and screening

Cocrystallisation between two molecules is expected to depend only on the choice of complementary molecular functionalities which constitute a supramolecular synthon. Consequently, a synthon-based design for cocrystallisation should be applicable to a wide variety of molecules that contain matching functionalities. As a result, cocrystal components are exchangeable and cocrystallisation represents a modular approach to controlling solid-state properties.[9] In such an approach, the peripheral parts of the cocrystal formers can be decorated with groups that would impart the entire cocrystal with a selected physicochemical property, such as solubility,[29–31] photoactivity,[32] conductivity,[33] colour or chirality.[34,35]

In this way, modular design has been used for the systematic study of the structure–property relationships of pharmaceutical solids, such as the influence of chirality on stability.[35,36] Cocrystallisation of nicotinamide with either *S*- or *RS*-ibuprofen (Figure 5a) is an example. The resulting cocrystals are isostructural, exhibit identical supramolecular architectures based on amide–amide dimers, but differ in symmetry.[35,37] Similarly, cocrystallisation of theophylline with L- or DL forms of tartaric or malic acids (Figure 5a) provides pairs of chiral and centrosymmetric cocrystals with similar (in the case of tartaric acid) or identical (in case of malic acid) architectures (Figure 5b,c).[36,38] In all cases, the chiral cocrystal proved less stable to humidity or temperature than its

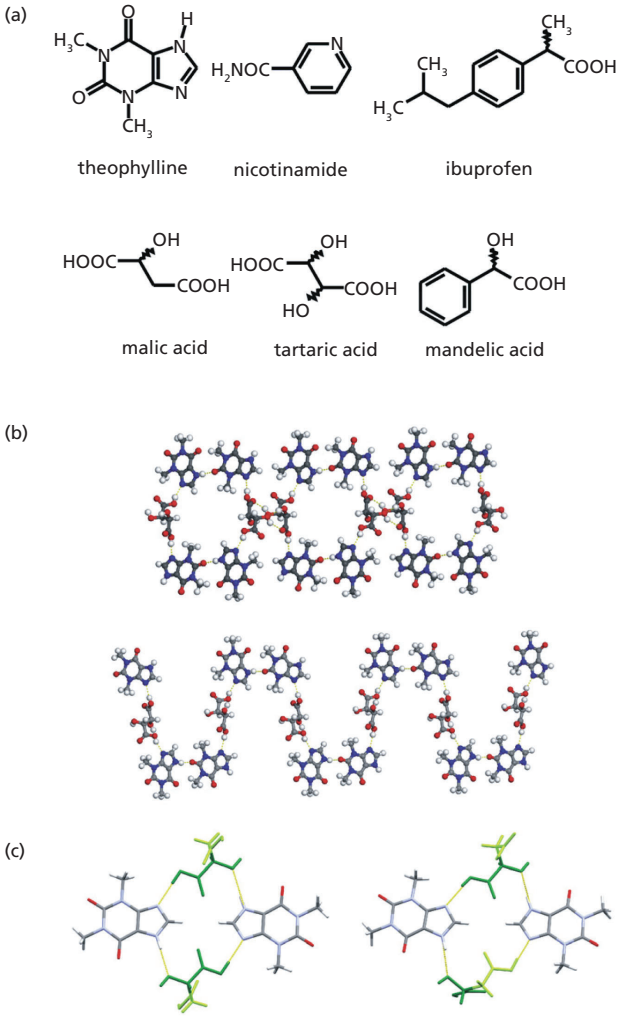

Figure 5 Modular design. (a) Molecular diagrams of relevant APIs and pharmaceutical cocrystal formers. (b) Comparison of crystal structures of racemic (top) and chiral (bottom) theophylline cocrystals with tartaric acid.[38] (c) Comparison of crystal structure fragments in isostructural racemic (left) and chiral (right) cocrystals of theophylline with malic acid.[36] For clarity, the two different halves of malic acid molecule have been coloured dark (containing the alcohol functionality) and bright green (lacking the alcohol functionality).

centrosymmetric counterpart. Consequently, the modularity of cocrystals allows the direct observation of the effects of symmetry on thermal or hydration stability of the crystalline solid, without the need to consider the complicated differences in crystal packing that typically arise in the case of single-component solids.

Exploring a range of potential cocrystal forms requires an efficient, rapid and simple procedure to screen for successful cocrystal formation: our ability to learn about the structure–property relationships in cocrystals will be greatly assisted by the development of rapid methods for cocrystal screening and synthesis. Whereas solution cocrystallisation and cocrystallisation from the melt have been used in the past as methods of cocrystal screening, several comparative reports indicate that the highest screening efficiencies are achieved using mechanochemical methods.[20,39,40] A particularly successful method

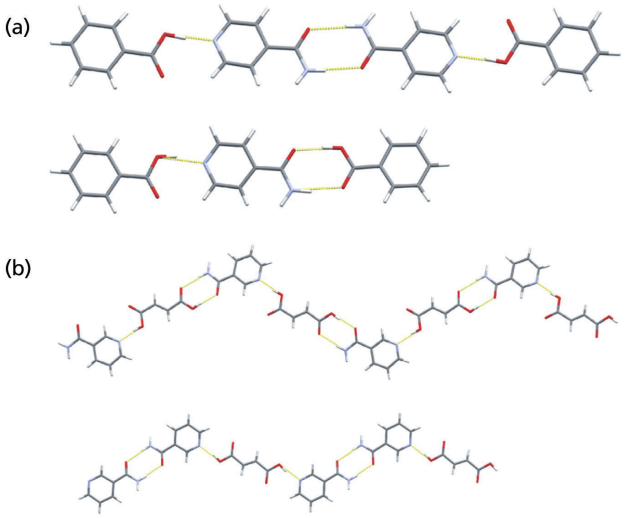

Figure 6 Stoichiometric variations. (a) Discrete hydrogen-bonded assemblies in the 1 : 1 (top) and 1 : 2 (bottom) stoichiometric variations of the isonicotinamide cocrystal with benzoic acid as reported by Aakeröy[49] and by Seaton *et al*.[48] (b) Fragments of zigzag hydrogen-bonded chains in 1 : 1 and 2 : 1 stoichiometric variations of the nicotinamide cocrystal with fumaric acid reported by Orola and Veidis.[50]

of screening is liquid-assisted grinding (LAG, also known as solvent-drop grinding or kneading),[41–43] in which a mixture of potential cocrystal components is mechanochemically treated in the presence of a catalytic quantity of a liquid.[41] Karki *et al*. tested screening methodologies against 20 possible cocrystals of the model API nicotinamide with 10 aliphatic dicarboxylic acids.[21] They found that solution crystallisation revealed the formation of only 10 of the cocrystals and cocrystallisation from the melt, only eight. In contrast, mechanochemical screening (neat grinding or LAG) identified 15 different cocrystals. In addition, a solution-mediated phase transformation (SMPT) approach,[44] based on slurrying of cocrystal components, was recently reported as being a highly efficient method to construct and screen for pharmaceutical cocrystals.[45]

Polymorphism, stoichiometric variations and solid-state characterisation

Like single-component materials, cocrystals exhibit polymorphism. Among the best-studied examples are cocrystals of carbamazepine with either nicotinamide or saccharin.[46] However, in addition to polymorphism, cocrystals also provide one more type of structural flexibility that is not possible for single-component solids. This is the formation of two or more distinct cocrystals involving different stoichiometric ratios of the API and the cocrystal former.[47] Such stoichiometric variations are readily obtained with cocrystal constituents that exhibit two or more significantly different hydrogen-bonding sites, such as nicotinamide or its *para*-isomer, isonicotinamide (Figure 6). The two molecules readily form stoichiometric variations on cocrystallisation with carboxylic acids, either by engaging only the pyridine group in bonding to the coformer or by simultaneously employing both the amide and the pyridine functionalities.[21,48–50]

Unlike polymorphs, which exhibit a tendency to convert to the thermodynamically stable form, different stoichiometric compositions do not represent metastable phases. Cocrystals of different stoichiometric compositions are not expected to spontaneously interconvert, although interconversion can be achieved deliberately by grinding selected cocrystals with excess API or coformer.[21] Thus, the formation of stoichiometric variations is a convenient way of increasing the number of available API solid forms without the need for new counter-molecules. Although the formation of stoichiometric variations can usually be suspected from the molecular structures of cocrystal components, they are still largely discovered through trial and error. A recent report by Cruz-Cabeza *et al*.[51] has described a computational methodology to predict the formation and composition of stoichiometric variations and solvates.[52]

The discovery and characterisation of cocrystals, their polymorphs and stoichiometric variations is achieved by powder X-ray diffraction (PXRD). Moreover, Karki *et al*.[53] have recently demonstrated the use of PXRD, not only for the identification of cocrystal phases, but also for rapid full structural determination of new cocrystals prepared by grinding. A variety of solid-state spectroscopic techniques are commonly used to support the results of PXRD analyses. While the potential of solid-state ^{13}C, ^{15}N and ^{1}H NMR in pharmaceutical cocrystallisation has only begun to be explored,[36,54] the most common techniques to study cocrystals are FTIR-ATR spectroscopy and solid-state Raman spectroscopy.[55] It was recently demonstrated by Parrott *et al*. that identification of structurally similar cocrystals can be difficult using either PXRD or Raman spectroscopy. Low-temperature terahertz time-domain spectroscopy (THz-TDS)[56] was shown in this case to be an effective probe for structural variability.[57]

Modification of materials properties by cocrystallisation

Solubility of cocrystals

An important factor in API form development is the optimisation of the solubility of the API and/or its dissolution rate.[58] Although the ability to increase (or reduce) the solubility of an API was demonstrated almost simultaneously with the introduction of cocrystals as pharmaceutical materials,[29–31] quantification of the resulting advantage to thermodynamic solubility was not readily accessible. The principal reason behind this difficulty was the precipitation of the API soon after cocrystal dissolution, driven by the API thermodynamic solubility limit. Nevertheless, the improvement in kinetic solubility by cocrystal formation could be readily demonstrated.[59] A method to quantitatively assess the thermodynamic solubility advantage of cocrystallisation was recently described by Good and Rodríguez-Hornedo,[60] who considered solution concentrations of the API (A) and the cocrystal former (B) in equilibrium with the solid cocrystal $A_\alpha B_\beta$ (equation 1).[61]

$$A_\alpha B_{\beta(s)} \overset{K_{sp}}{\rightleftharpoons} \alpha A_{(aq)} + \beta B_{(aq)} \quad (1)$$

So long as an excess of the solid API is also present, the resulting mixture corresponds to an invariant point of the system at which, provided the temperature is kept constant, the equilibrium (transition) concentrations of the cocrystal former and the API are constant and can be precisely measured. The measurement of these transition concentrations ($c_{A,tr}$ and $c_{B,tr}$) allows calculation of the solubility product (K_{sp}) and hence the thermodynamic solubility (S) of the cocrystal using equation 2.

$$S_{A_\alpha B_\beta} = \sqrt[\alpha+\beta]{\frac{K_{sp}}{\alpha^\alpha \beta^\beta}} = \sqrt[\alpha+\beta]{\frac{c_{A,tr}^\alpha c_{B,tr}^\beta}{\alpha^\alpha \beta^\beta}} \quad (2)$$

For cases where the pharmaceutical cocrystal is AB, composed of the API and the cocrystal former in a 1 : 1 stoichiometric ratio, equation 2 simplifies to equation 3.

$$S_{AB} = \sqrt{K_{sp}} = \sqrt{c_{A,tr} c_{B,tr}} \quad (3)$$

Since equations 2 and 3 do not consider solution complexation between the API and the coformer, the calculated cocrystal solubilities are only approximate. However, they provide an important quantitative foundation for the study of relationships between cocrystal structure and solubility. By calculating the cocrystal solubilities in this manner, Good and Rodríguez-Hornedo demonstrated that the increase in solubility of the API on cocrystallisation can adopt a wide range of values relative to its thermodynamic solubility.[60] The values ranged from 0.1 (indicating that the API solubility has been reduced 10-fold by cocrystal formation) to 152 (corresponding to a 152-fold increase in the API solubility).

In addition to enabling the calculation of cocrystal solubility, consideration of the solution equilibrium at the transition point also suggests a rationalisation of the obtained values. At the transition point equilibrium (equation 1) the chemical potentials (μ) of the cocrystal and its components are approximately described by equation 4.[60]

$$\mu_{A_\alpha B_\beta}^{solid} = \alpha(\mu_{A,aq}) + \beta(\mu_{B,aq}) \quad (4)$$

At the transition point the dissolved API (A) is in equilibrium with its pure solid form. Consequently, its chemical potential is constant (C), leading to equation 5.

$$\mu_{A_\alpha B_\beta}^{solid} = \beta(\mu_{B,aq}) + C \quad (5)$$

Equation 5 implies that the cocrystal solubility is proportional to the chemical potential of the dissolved cocrystal former. In other words, the cocrystal solubility is expected to be approximately proportional to the solubility of the coformer. The validity of this approximation was confirmed for a sample of 25 pharmaceutical cocrystals of theophylline and carbamazepine with a variety of coformers.[60] Analysis of acid–base equilibria between the API and the cocrystal former at the transition point was recently reported, and could be

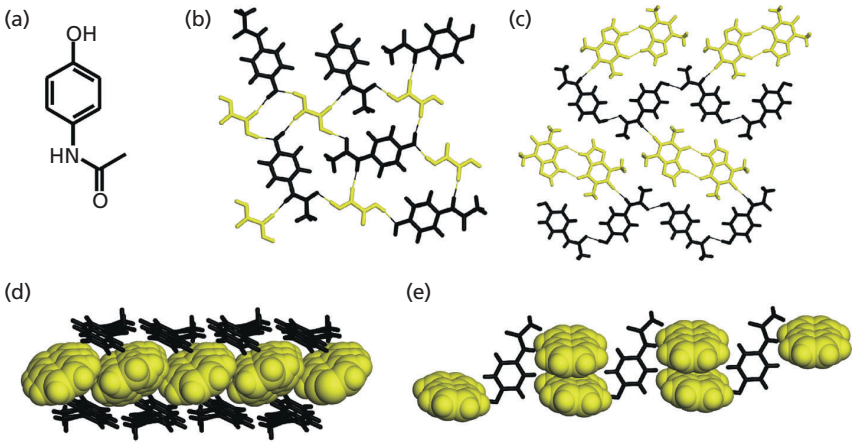

Figure 7 Paracetamol and its cocrystals. (a) Molecular diagram of paracetamol; single hydrogen-bonded sheet in the cocrystal of paracetamol (yellow) with (b) oxalic acid, (c) theophylline, (d) naphthalene and (e) a single hydrogen-bonded and π-stacked chain in the cocrystal of paracetamol and acridine.[23] Cocrystal formers are shown in black.

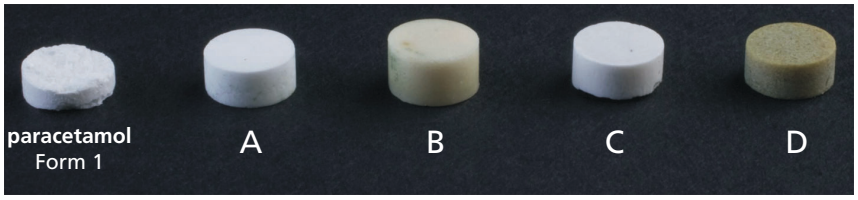

Figure 8 Results of tabletting experiments involving paracetamol form I. (a) Cocrystal with theophylline; (b) cocrystal with naphthalene; (c) cocrystal with oxalic acid; (d) cocrystal with acridine.[23]

considered as a first step towards taking into account other complexation equilibria in solutions of cocrystals.[62]

Mechanical properties: cocrystallisation of caffeine and of paracetamol

The ability to modify the solid-state arrangement of molecules provides a way to control the intrinsic mechanical properties of solids. Such control is paramount in pharmaceutical materials science where it is used to adjust the compression of compounds into tablets. This control was first demonstrated by Sun *et al*. for cocrystals of caffeine and methyl gallate.[63] The cocrystal was demonstrated to have much higher tensile strength and improved tabletting properties compared to either of its constituents in pure form. The improvement in mechanical properties was rationalised by reference to the layered structure of the cocrystal.

The ability to modify the tabletting properties of an API by cocrystallisation has also been demonstrated by Karki *et al*. using the example of paracetamol (Figure 7a).[23] Previous computational work[64] has demonstrated that the improved compressibility of the metastable paracetamol polymorph, form 2, in comparison to the thermodynamically stable form 1, is related to differences in crystal packing. The readily compressible form 2 consists of parallel layers of hydrogen-bonded molecules, while the layers in form 1 are corrugated. The difference in layer topology results in a lower Young's modulus and, hence, better compressibility of form 2. Although the design of layered structures for any given molecule is still beyond the capability of current crystal engineering, Karki and co-workers have successfully constructed three-layered structures of paracetamol as a result of extensive screening for cocrystals using LAG methodology.[23] Only planar molecules were utilised as potential cocrystal formers, in that way increasing the likelihood of forming a layered material. Each of the three cocrystals exhibited a different tiling pattern of paracetamol and coformer molecules (Figure 7b–d). One more cocrystal, of paracetamol with the non-pharmaceutical compound phenazine, was also constructed and demonstrated excellent tabletting properties. Crystal structure analysis demonstrated that $(\text{phenazine})_2\cdot(\text{paracetamol})$ consists of molecular assemblies that interact through π-stacking and weaker van der Waals interactions, suggesting an alternative approach for constructing compressible solids (Figure 7e).

As verified by measurements and calculations, all three cocrystals based on a layered structure exhibited compression properties superior to those of form 1 of paracetamol, evidenced by direct compression to form tablets (Figure 8).

Thermal stability of cocrystals

The non-covalent forces between molecules in a crystal play a key role in controlling lattice energy and, consequently, thermal stability. Thus, melting point is the property of the solid material that is most readily modified by cocrystallisation, and, indeed, is most readily monitored using standard thermal analysis equipment. The control over the melting

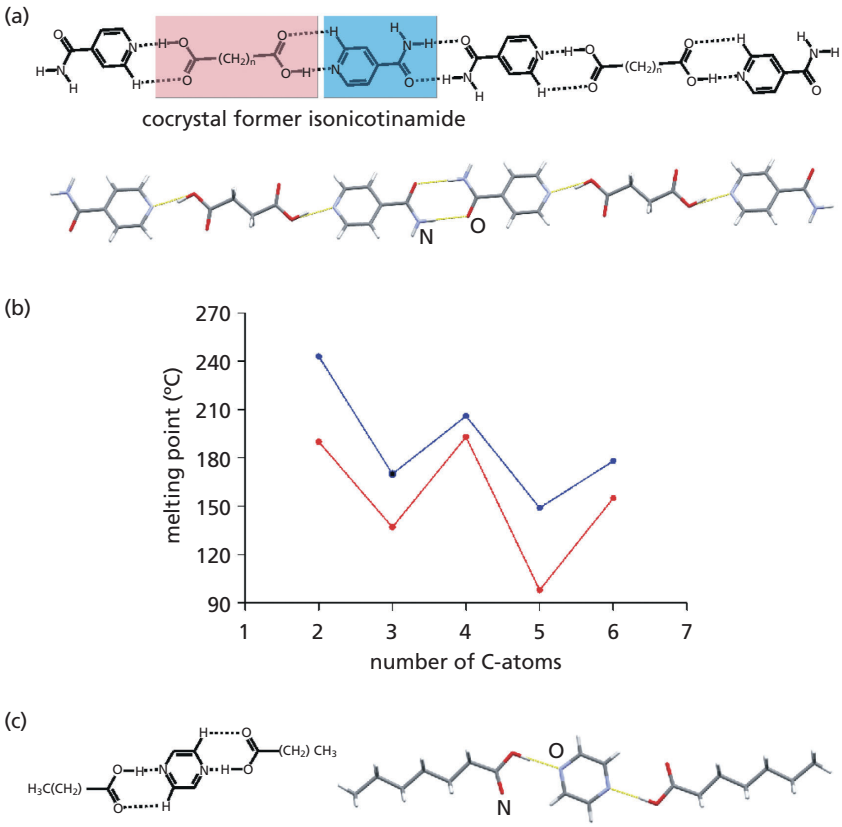

Figure 9 Cocrystals of isonicotinamide. (a) Hydrogen-bonded chain in cocrystals of isonicotinamide with a dicarboxylic acid: molecular diagram (top) and fragment of the chain observed in the cocrystal with succinic acid (bottom). (b) Alternation of melting points for isonicotinamide cocrystals (blue) and for related dicarboxylic acid cocrystal formers (red).[65] (c) Molecular assemblies in cocrystals of pyrazine with aliphatic acids: molecular diagram (left) and the assembly observed in the cocrystal with heptanoic acid (right).[66]

point of the solid API form is of considerable technological importance, as undesired melting can affect many stages in API processing, including granulation, tabletting and preparation of inhalation formulations.

Vishweshwar *et al*. have observed that the melting points of isonicotinamide cocrystals with terminal aliphatic dicarboxylic acids follow the same trend as those of the pure cocrystal formers.[65] Specifically, the melting points of cocrystals were found to alternate with the number of carbon atoms in the cocrystal former, with those involving even-membered diacids being higher than those involving odd-membered diacids (Figure 9a,b). This observation was also extended to densities and crystal packing efficencies. Alternation of cocrystal melting points was also observed by Bond in cocrystals of pyrazine with a series of non-branched aliphatic acids (Figure 9c).[66]

A similar relationship between melting points of cocrystals and cocrystal formers was also observed in pairs of chiral and racemic cocrystals of the model API, nicotinamide.[35] Cocrystallisation of nicotinamide with *S*- or *RS*-ibuprofen provides isostructural cocrystals, based on the same local environment, composed of a homomolecular nicotinamide dimer involving an $R_2^2(8)$ hydrogen-bonded ring synthon.[35,37] In the cocrystal, each dimer is laterally decorated with two ibuprofen molecules through a heteromolecular $R_2^2(7)$ pyridine–carboxylic acid synthon (Figure 10a). For both cocrystals, melting occurs at a temperature between the melting points of the model API and the cocrystal former. However, like the pure ibuprofen forms, the melting point of the *S*-cocrystal was lower than for the racemic analogue.

A similar local architecture predictably resulted from cocrystallisation of nicotinamide with chiral and racemic forms of mandelic acid (Figure 10b). Again, the melting points of both chiral and racemic cocrystals occurred at a temperature between the melting points of nicotinamide and the acid cocrystal former. In this case, however, the melting point of the racemic cocrystal was found to be lower than the melting point of the chiral form.[35] Such behaviour again reflects the behaviour of the cocrystal former in that mandelic acid anomalously opposes Wallach's rule by having a chiral form with greater thermal stability than the racemate.[67]

Although these observations were made on a limited set of samples, a wider analysis given in the comprehensive review of properties of pharmaceutical cocrystals by Schultheiss and Newman[68] suggests they are representative of a general rule. Specifically, for a given API, the melting points of different cocrystals are found to follow the same trend as the melting points of the respective coformers. This observation is empirical and not yet fully understood, but it nevertheless provides a useful and general rule for the control of thermal stability of solid API forms.

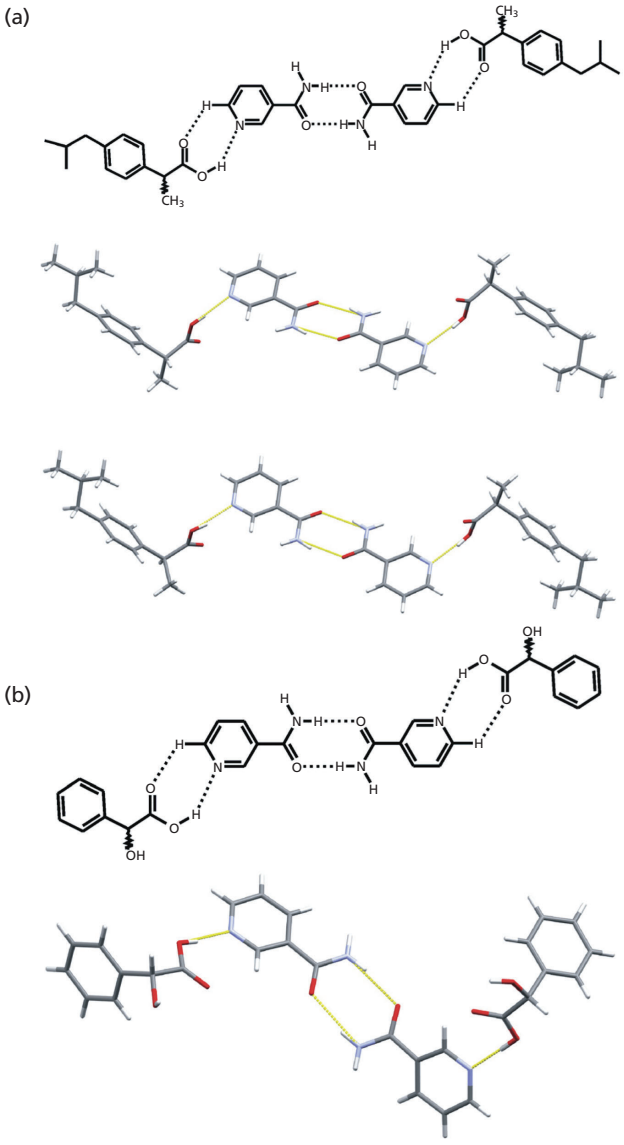

Figure 10 Cocrystals of nicotinamide with ibuprofen and mandelic acid. (a) A single hydrogen-bonded assembly of nicotinamide and ibuprofen: molecular diagram (top), crystal structure based on *RS*-ibuprofen (middle) and crystal structure based on *S*-ibuprofen (bottom).[37] (b) A single hydrogen-bonded assembly of nicotinamide and mandelic acid: molecular diagram (top) and crystal structure based on L-mandelic acid (bottom).[35]

These studies of the thermal stability of isostructural nicotinamide cocrystals illustrate how the modular design of cocrystals can be used to systematically investigate structure–property relationships. The similarity of local API environments in pairs of cocrystals with a chiral or a racemic coformer suggests that the differences in melting points are related to crystal-packing efficiencies inherent to the cocrystal formers. Such a conclusion is often impossible to make for single-component solids, as the crystal structures of racemic and chiral solids are often very different, preventing their systematic comparison.

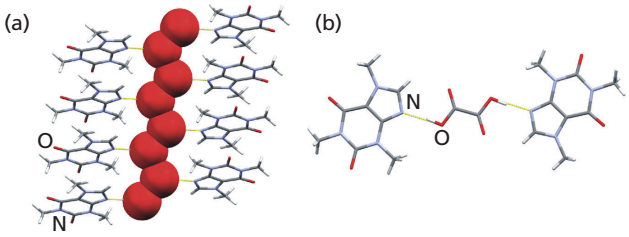

Figure 11 Fragments of crystals of caffeine and its oxalic acid cocrystal. (a) Caffeine hydrate, with oxygen atoms of disordered water molecules shown in the space-filling representation.[70] (b) Cocrystal of caffeine and oxalic acid, displaying a single hydrogen-bonded assembly.[69]

Hydration stability

Controlling the solid-state stability of an API towards atmospheric moisture is ubiquitous in the design of pharmaceutical materials that undergo extended periods of storage or are intended for use in locations with highly variable climates. The ability to use cocrystal formation for this purpose was first demonstrated for the model API caffeine.[69] On exposure to relative humidities above 60%, solid caffeine undergoes a solid–gas transformation to provide a non-stoichiometric channel hydrate with a composition of caffeine·nH$_2$O (where $n \approx 0.1$ to 0.8) (Figure 11a).[70]

Cocrystallisation of caffeine with a homologous series of dicarboxylic acids (oxalic, malonic and glutaric acid) resulted in a series of cocrystals that exhibited significantly different sensitivity to ambient moisture than the pure caffeine solid. In particular, the cocrystal with oxalic acid, of composition (caffeine)$_2$·(oxalic acid), demonstrated a hydration stability that was significantly superior to pure caffeine and to the other prepared cocrystals (Figure 11b).[69] No bulk chemical decomposition of (caffeine)$_2$·(oxalic acid) occurred, even after 7 weeks of exposure to 98% relative humidity. The general applicability of the use of cocrystallisation to improve hydration stability was subsequently confirmed by using the apnoea drug theophylline as the model API.[71] Like caffeine, theophylline exhibits sensitivity to moisture, forming a stoichiometric monohydrate.[72] In this case also, cocrystallisation of the model API with oxalic acid provided a material that was superior in hydration stability to either pure theophylline or to its cocrystals with higher dicarboxylic acids. It is noteworthy that solid oxalic acid also forms a dihydrate form on exposure to moist air. Consequently, cocrystal formation enhanced the hydration stability of both API and the coformer.

By using theophylline and caffeine as model APIs, the modular architecture of cocrystals was utilised to systematically investigate the possible relationship between cocrystal symmetry and hydration stability.[36] Pairs of chiral and racemic cocrystals were obtained by combining theophylline or caffeine with either chiral or racemic forms of tartaric and malic acid. In every case (except for the cocrystal between caffeine and L-tartaric acid, which was not obtained), the racemic cocrystal exhibited significantly higher hydration stability compared to the chiral analogue (Figure 12a). The lower stability of the chiral cocrystal of theophylline and tartaric acid was rationalised by reference to intermolecular factors, i.e. fine differences in the hydrogen-bonded structure of the

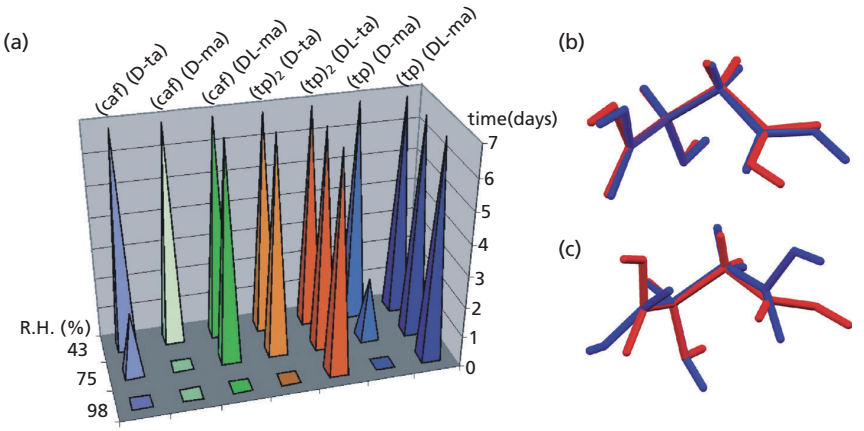

Figure 12 Relationship between cocrystal symmetry and hydration stability. (a) Hydration stabilities of chiral and racemic cocrystals of caffeine and theophylline with tartaric and malic acids. (b) Overlay of the low-energy conformation of malic acid in the chiral cocrystal with theophylline (blue) with the conformation adopted by malic acid in the racemic cocrystal (red). (c) Overlay of the high-energy conformation of malic acid in the chiral cocrystal with theophylline (blue) with the conformation adopted by malic acid in the racemic cocrystal (red).[36]

cocrystals. Such an explanation could not be devised for isostructural theophylline cocrystals with L- and DL-malic acids. Instead, the different stabilities of these two solids were explained as one half of the L-malic acid molecules in the chiral cocrystal adopting a strained conformation, around 15 kJ mol^{-1} higher than the lowest-energy conformer (Figure 12b,c).[36] The strained conformation is key to the isostructurality of the two cocrystals, as it allows an L-malic acid molecule to mimic the structural role of the D enantiomer. Consequently, both intermolecular and intramolecular factors were found to contribute to the higher stability of centrosymmetric cocrystals.

Solid-state isolation of complex or unstable molecules for elucidation of their structure

Solid-state complexation provides an opportunity to screen for crystalline forms of molecules that could be more amenable to crystal structure analysis than the pure constituents. This is an invaluable tool for fundamental studies of molecular recognition and the conformation of large and flexible molecules. In the context of pharmaceutically relevant targets, the cocrystallisation approach was first utilised by Eger and Norton, who used coformers containing an electron-rich heavy atom such as bromine to elucidate the structures of steroids.[73] This approach was recently revived by Bhatt and Desiraju, who used *p*-iodophenol as a heavy atom cocrystal former to help determine the absolute configurations of organic molecules such as pregnenolone and cholesterol.[74] More recently, complexation in the solid state was utilised by Dupont *et al*. to obtain the first structural information on the possible conformations that the important antiseptic chlorhexidine can adopt in the crystal (Figure 13).[75]

Cocrystallisation was also utilised by Liu *et al*.[76] to isolate the highly unstable molecule perbromocumulene in the solid state and to characterise its structure. Although perbromocumulene is not an API, this example nevertheless illustrates a potentially pharmaceutically useful application of cocrystallisation for isolating otherwise unstable molecules as stable solids.

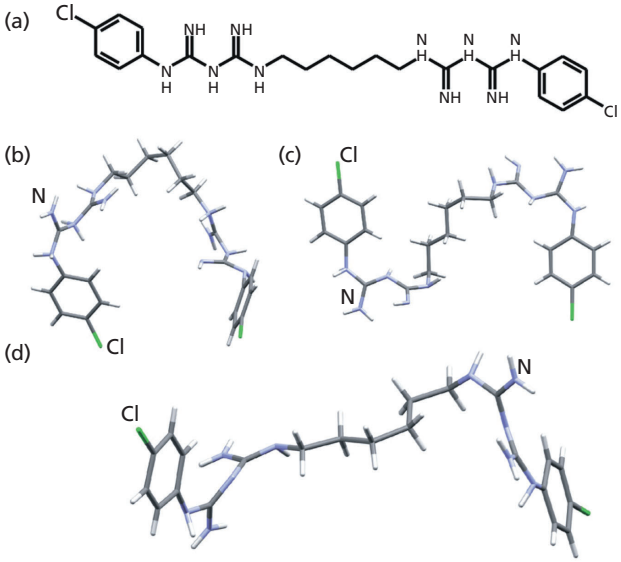

Figure 13 Chlorhexidine and its solid-state conformations. (a) Molecular diagram of chlorhexidine. (b–d) Three different solid-state conformations of chlorhexidine observed by Dupont *et al*.[75]

Future applications

The previous sections have provided a condensed overview of the most recent applications of cocrystals for rational modification of API solid forms. Nevertheless, it is obvious that the potential of cocrystallisation to control materials properties extends far beyond the pharmaceutically relevant cases described here. This section will delineate several non-pharmaceutical examples of such control, which could, in the future, be exploited in the context of pharmaceutical materials science.

Photochemistry control

Cocrystallisation control over the solid-state photochemical properties of molecules has been addressed by

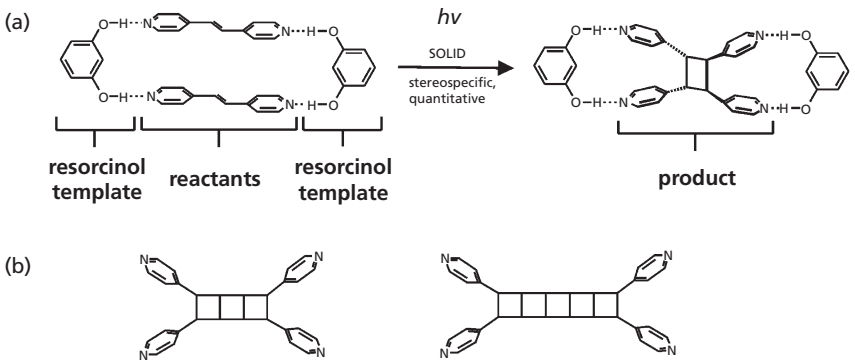

Figure 14 Photochemistry control. Schematic representation of (a) the use of resorcinol as a linear template to control photoreactivity in cocrystals with olefins and (b) 3-ladderane (left) and 5-ladderane (right) targets constructed using photochemical reactions in cocrystals.[77,79]

MacGillivray,[77] who utilised molecules hydrogen-bonding functional groups, such as resorcinol, as templates to align olefins for a [2+2] photodimerisation. Cocrystallisation of resorcinol with reactant olefins equipped with suitable complementary hydrogen-bonding functionalities results in the formation of discrete solid-state assemblies. In the assemblies, the rigid structure of the resorcinol template enforced parallel stacking of the olefins, facilitating intermolecular photocyclisation. In this way a cyclobutane ring was obtained on exposure of the cocrystals to UV light (Figure 14a). The degree of topochemical control accomplished by such template-directed cocrystallisation enabled the quantitative and solvent-free synthesis of complex and biologically significant molecular fragments,[78] such as ladderanes (Figure 14b).[79] Photoreactions in cocrystals have an obvious application in medicinal chemistry for generating molecular structures with potential biological activity. For example, using conventional solution-based chemistry the 5-ladderane structure, crucial for the construction of the natural product pentacycloanammoxic acid, is constructed in approximately 6% yield.[80] Using a photochemical reaction in the cocrystal,[79] the 5-ladderane is accessible quantitatively and in a single step.

The ability to manipulate the photochemical behaviour of molecules by cocrystallisation also suggests that the stability of light-sensitive APIs[81] in the solid state could be improved by using cocrystal formers that discourage the topochemical alignment of reactive centres.

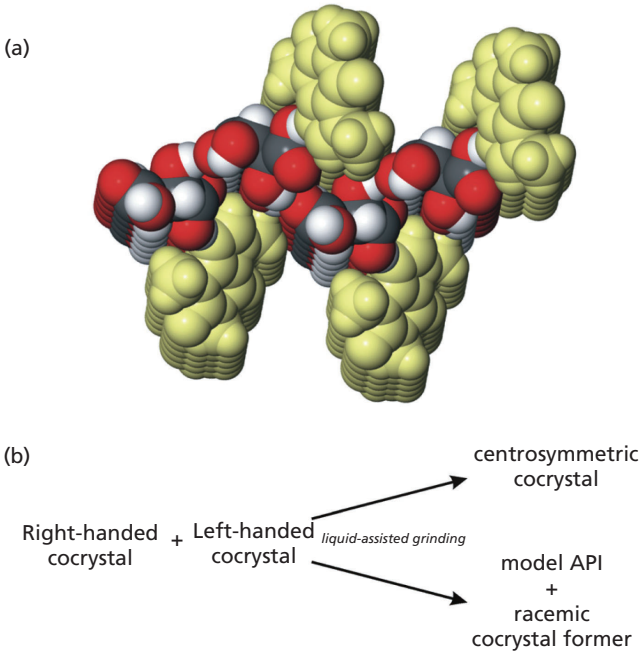

Figure 15 Recognition of chirality. (a) Fragment of the crystal structure of the (caffeine)·(L-tartaric acid) cocrystal. (b) Two possible outcomes of a solid-state reaction between enantiomerically related cocrystals.[38]

Recognition of chirality

Solid-state cocrystallisation reactions are strongly affected by differences in the lattice energies of reactant and product crystals. As a result, the formation of cocrystals can distinguish between enantiomerically pure and racemic coformers. This was demonstrated in the mechanochemical (i.e. solid-state) cocrystallisation of caffeine with tartaric acid.[38] Whereas the cocrystal of caffeine with either L- or D-tartaric acid forms readily on liquid-assisted grinding (Figure 15a), the cocrystal with DL-tartaric acid could not be obtained at all. Indeed, grinding together the (caffeine)·(L-tartaric acid) cocrystal with the enantiomeric (caffeine)·(D-tartaric acid) cocrystal resulted in a disproportionation reaction that yielded pure caffeine and DL-tartaric acid (Figure 15b).

Solid-state cocrystallisation reactions that distinguish between chiral and racemic forms have also been extensively studied by Kuroda and coworkers, who employed ternary cocrystal systems based on a general combination of *p*-benzoquinone, bis-β-naphthol and an aromatic guest molecule, such as naphthalene (Figure 16a).[82,83] These cocrystals are held together by strong O-H···O hydrogen bonds, as well as charge-transfer interactions. The latter provide the cocrystals with intensive colours that permit simple differentiation of chiral and racemic forms using a simple colour test.

Grinding of *p*-benzoquinone with racemic bis-β-naphthol and naphthalene provides a blue three-component (or ternary) cocrystal (*rac*-bis-β-naphthol)$_2$·(*p*-benzoquinone)·(naphthalene)$_2$. The cocrystal consists of a three-component π-stacked motif involving a single benzoquinone molecule sandwiched between the aromatic groups of two *rac*-bis-β-naphthol molecules (Figure 16b).[84] In contrast, grinding of the

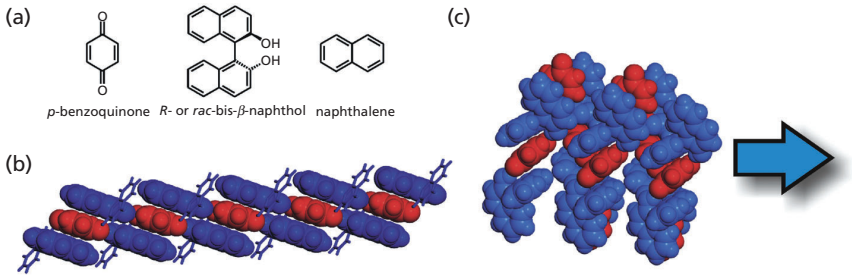

Figure 16 Distinguishing racemic and chiral forms. (a) Molecular diagrams of *p*-benzoquinone, bis-β-naphthol and naphthalene. (b) A hydrogen-bonded chain of three-component stacks (shown using a space-filling model) of quinone (red) and naphthol (blue) groups. (c) Space-filling view of a helical hydrogen-bonded chain of quinone and naphthol in the (*R*-bis-β-naphthol)$_2$·(*p*-benzoquinone)$_2$·(naphthalene)$_3$ cocrystal. The direction of propagation of the helical chain is indicated by the arrow.[85,86]

optically pure *R*-bis-β-naphthol with *p*-benzoquinone and naphthalene results in the formation of a red ternary solid (*R*-bis-β-naphthol)$_2$·(*p*-benzoquinone)$_2$·(naphthalene)$_3$.[85,86] The different colours of the cocrystals with racemic and chiral bis-β-naphthol were explained by the distortion of the chromophoric three-membered stack in the chiral cocrystal (Figure 16c).

Summary

In summary, we have attempted to evaluate the progress that has been made towards rational construction of pharmaceutical solids using cocrystallisation. We consider the development of cocrystals as vehicles for rational construction of pharmaceutical solids as divided into three phases. The first phase encompasses the discovery of new cocrystals, evaluation of their properties and the development of efficient methodologies for cocrystal synthesis and characterisation. The intermediate second phase involves the partial rationalisation of observations made in the first phase and the generation of empirical rules to predict properties of cocrystals. The final phase involves the complete understanding of processes that control cocrystal formation and determine their properties. In this phase, the complete design of cocrystals, including synthesis, choice of components and physicochemical properties, will be possible from first principles. The developments presented in this review indicate that the first phase, of understanding the structure–property relationships of pharmaceutical cocrystals, is largely finished and that the field is now entering the second phase. This is illustrated by the first empirical structure–property rules for cocrystals, which reveal that the solubility and thermal stability of cocrystals are predictable from the corresponding properties of their constituents, and that the thermal and hydration stabilities for centrosymmetric cocrystals tend to be higher than for their chiral counterparts. Also, the design of functional cocrystals is now moving beyond individual intermolecular synthons towards the crystal structure as a whole. Experimentally, this is demonstrated by the construction of supramolecular sheets for improving the tabletting properties of paracetamol. Theoretically, this is supported by impressive developments in crystal structure prediction,[87,88] an area that will undoubtedly play a crucial role in the further development of pharmaceutical cocrystallisation.

Declarations

Conflict of interest

The Author(s) declare(s) that they have no conflicts of interest to disclose.

Funding

The Pfizer Institute for Pharmaceutical Materials Science is acknowledged for support. The Herchel Smith Fund is acknowledged for a research fellowship in pharmaceutical materials (TF).

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