Expert Opinion

Pharmaceutical co-crystals–an opportunity for drug product enhancement

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By maximizing our understanding of materials and the relative importance of interactions on all levels (i.e., molecular, particle, powder, product), we can improve the manufacture of drug dosage forms and thus meet target specifications for mechanical durability, stability and biopharmaceutical performance. Pharmaceutical co-crystals are the latest material being explored in order to enhance drug properties using this bottom-up approach. In this review we provide a general introduction to pharmaceutical co-crystals. We also address common aspects of co-crystal formation, discuss screening strategies and outline methodologies for co-crystal functionality. Pharmaceutical co-crystals that have a distinct solid phase possess a unique set of properties, thus co-crystal formation can act as an advantageous alternative to other solid-state modification techniques. More research is needed in order to scale up co-crystal systems and implement manufacturing of final dosage forms on large scale.

Keywords: co-crystal formers, co-crystals, crystal engineering, solid-state characterization, supramolecular chemistry

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1. Introduction

Using complementary molecules to design binary compounds is one of the many applications of crystal engineering. Pharmaceutical molecules inherently contain molecular recognition sites that bind selectively to biomolecules. These sites can be used to form supramolecular self-assembling complexes with desired physicochemical properties [1]. Pharmaceutical co-crystals–crystalline molecular complexes of two or more neutral molecules–are the latest example of how supramolecular chemistry can be used to enhance the properties of active pharmaceutical ingredients (APIs), including dissolution rate, mechanical properties and stability [2]. Co-crystal formation has several potential advantages over traditional solid-state modification techniques (e.g., salt formation). For example, all types of drug molecules in theory have the capability to form co-crystals; therefore, covalent modification of APIs is unnecessary when using co-crystals. There has recently been increased activity in the area of pharmaceutical co-crystal research and a wide range of insightful studies has been published [3-21].

There is growing interest in pharmaceutical co-crystals and they are emerging as an attractive option to polymorphs, salts, solvates and crystal habit manipulation in dosage form design. When using co-crystals, the bulk material and the physicochemical properties of the API can be modified while still maintaining the intrinsic activity of the drug molecule [2]. From a physical properties perspective, a key advantage of using co-crystals to transform an API into a solid form is the possibility of achieving a high dissolution rate comparable to that of the amorphous form while maintaining the long-term chemical and physical stability that

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crystalline forms provide [22]. Also, the enhancement of downstream processability and functionality can be achived. The co-crystal approach can offer valuable advantages for pharmaceutical companies in terms of opportunities for intellectual property protection and the possibility of extending the life cycles of established APIs [1]. Many ways of producing co-crystal systems have been reported. Co-crystallization experiments are usually involve selected co-crystal formers and various specialized techniques, such as solution-based crystallization, crystallization from the melt and neat solid-state grinding [23].

In the context of crystal engineering, the main criterion for co-crystal selection is chemical complementarity between the molecular counterparts. Within such a highly regulated industrial sector as the pharmaceutical industry, however, the spectrum of potential formats is limited as co-crystals have to have no toxic effects and be pharmaceutically acceptable (i.e., preferably already in use in commercial drug products). Generally recognized as safe (GRAS) status is awarded to compounds that are safe under the conditions of their intended use. It is recognized that GRAS compounds are a good non-toxic co-former compounds, but GRAS status does not mean that a compound is suitable for use in pharmaceutical dosage forms. For example, various GRAS compounds are approved for use only as flavorings at parts per million levels and cannot be used as co-crystal formers in dosage forms [10]. Pharmaceutical co-crystals can be defined as co-crystal forms composed of a stoichiometric ration of an API and a pharmaceutically acceptable co-crystal former.

2. General aspects of co-crystal formation

A distinguishing feature of co-crystals, as compared to other crystalline forms of APIs, is that these multicomponent systems can be manipulated using crystal engineering [2,24]. By definition, crystal engineering involves modification of the crystal packing of a solid material by changing the internal arrangement of the molecules that regulate the breaking and forming of noncovalent bonds (e.g., hydrogen bonding, van der Waals forces, π-stacking, electrostatic interactions). In the case of multicomponent systems, the co-crystallizing agent brings additional multiplicity into a crystallizing system, thus increasing its diversity in terms of resulting solid-state forms of APIs. To illustrate this concept, **Figure 1** shows how the crystal packing of caffeine has been modified via co-crystallization with two different excipients, nicotinamide and saccharine. Given that the properties of materials are dependent on their solid-state structure, it is clear that specific characteristics of the APIs can be tailored systematically by varying the co-crystal former. An important initial step in co-crystal design is, therefore, the selection of an appropriate co-crystallizing agent.

2.1 Co-former selection strategies

The design of pharmaceutical co-crystals is a multi-stage process, as schematically illustrated in **Figure 2**. The key step in this process is the formation of supramolecular synthons [25]–non-covalent bonds between self-complementary functional groups. This concept dictates a need for a detailed understanding of the supramolecular chemistry of the functional groups present in a given API as the very first step for designing a co-crystal. Once the functionality of the API has been examined, a survey of the Cambridge Structural Database is typically performed to identify common (i.e., stable) supramolecular synthons within a family of related structures. Thereafter, potential co-crystal formers that satisfy the complementarity rules for the functional groups present in the co-crystallizing system are selected. As a general guideline, the hierarchy of the supramolecular synthons within a range of common functional groups, as recently revealed by several crystal engineering research groups [26-29], can be utilized. According to these studies, certain functional groups–such as carboxylic acids, amides, and alcohols–are particularly amenable to formation of supramolecular heterosynthons (i.e., intermolecular bonds involving different functional groups). Several reports in the literature, however, underline the need to explore beyond the supramolecular synthons that lead to expected interactions [24,30-32]. High-throughput crystallization represents a more comprehensive approach to the discovery of expected and unexpected co-crystal formation events [33].

Representative examples of pharmaceutically acceptable compounds that are able to form co-crystal systems with APIs are summarized in **Table 1**. As can be seen from this table, carboxylic acids have been investigated as co-crystal formers most extensively, which is attributable to both the fact that carboxylic acid moieties are one of the most commonly studied functional groups in crystal engineering [34] and the fact that they exist in 30 of 100 top-selling prescription drugs in the USA [35]. On the other hand, the data presented in **Table 1** demonstrate that the investigation of excipients as co-crystallizing agents represents an avenue of unexplored possibilities.

2.2 Co-crystal screening methodologies

The major experimental techniques that have been employed for co-crystal screening fall into two categories: solution-based crystallization methods (e.g., solvent evaporation, slurry conversion, cooling crystallization, precipitation) and solid-based techniques (e.g., crystallization from the melt, dry co-grinding, wet co-grinding). Typically, solution-based crystallization is the technique most commonly applied in co-crystal screens [18,36]. The foremost drawback associated with solution-based crystallization methods is the need to know the solubilities of the starting components, as a suitable solvent for all ingoing materials must be identified before the screening experiment [37]. One rational approach

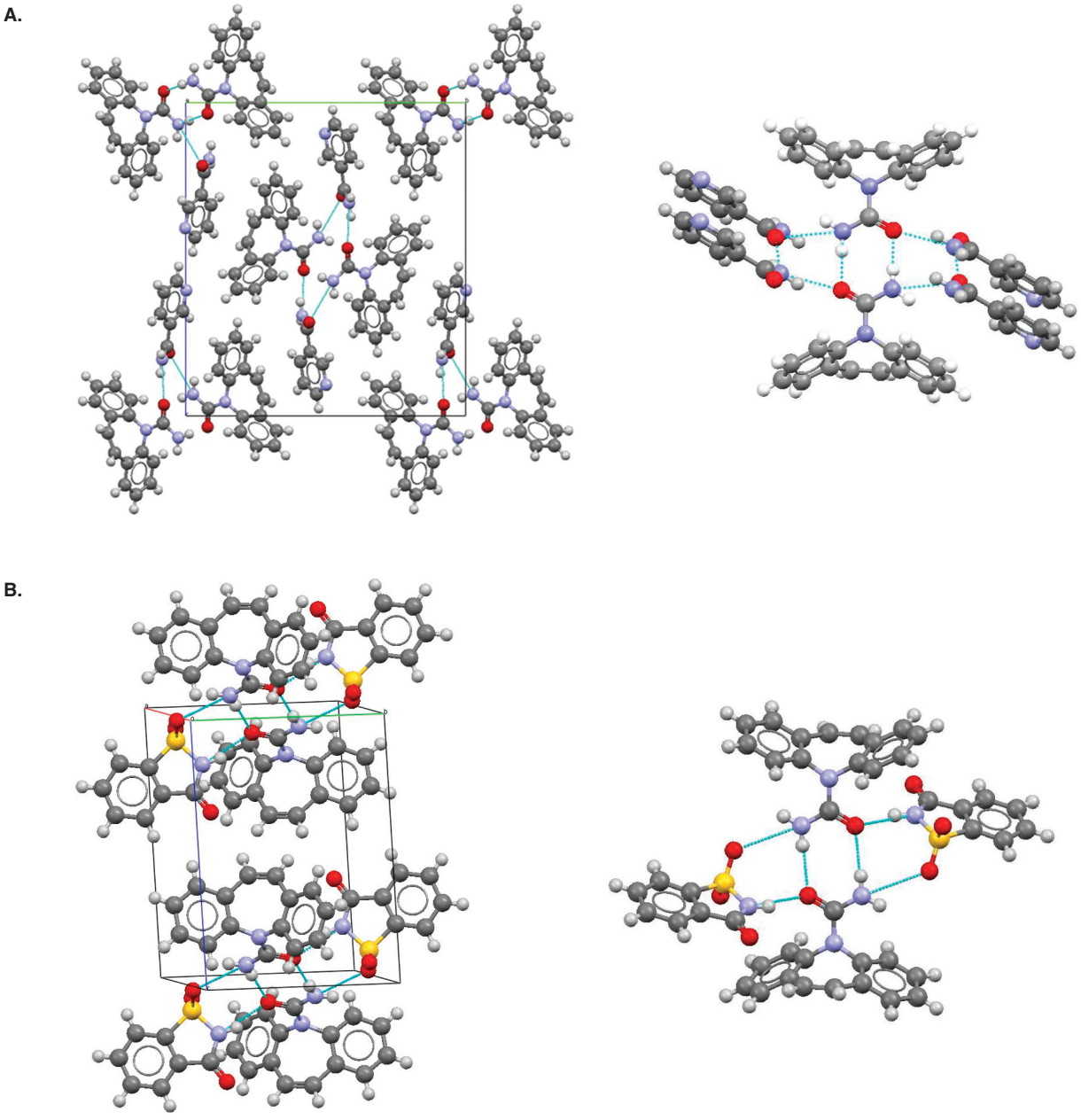


Figure 1. Co-crystal structures of carabamazepine with nicotinamide and with saccharine. A. Co-crystallization of carabamazepine with nicotinamide. **B.** Co-crystallization of carabamazepine with saccharine. These structures illustrating how incorporation of the second molecular component changes the internal arrangement of molecules (left panels) and the environment around carbamazepine dimers (right panels).
Colour legend: Grey: Carbon (C); Purple/blue: Nitrogen (N); Red: Oxygen (O); Yellow: Sulphur (S).

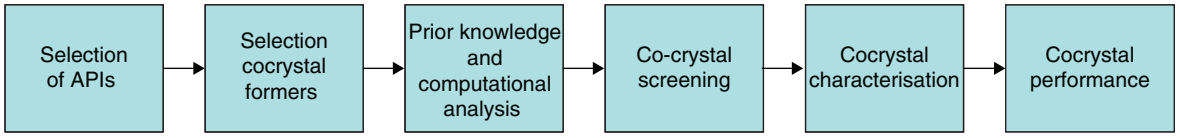
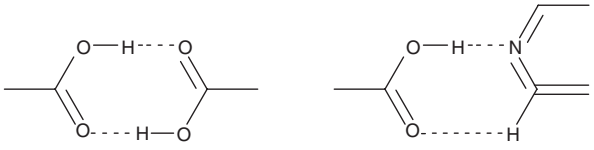
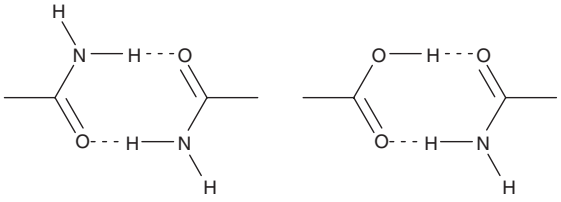
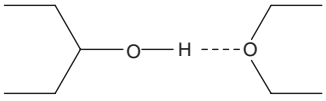


Figure 2. Schematic of steps for co-crystal design.
Abbreviation: API: Active pharmaceutical ingredient.
(Courtesy of Sitaram Velaga)

Table 1. The most common pharmaceutically acceptable co-crystal formers used in pharmaceutical co-crystals.

Chemical classification	Typical supramolecularsynthons utilized in crystal engineering
I. Carboxylic acids (e.g., acetic acid, adipic acid, benzoic acid, capric acid, caprylic acid, citric acid, formic acid, fumaric acid, glutari acid, glycolic acid, maleic acid,malonic acid, oxalic acid, salicylic acid, succinic acid, tartaric acid)	
II. Amides (e.g., nicotinamide, saccharin, urea)	
III. Alcohols (e.g., mannitol, sorbitol)	

to overcome this issue is constructing ternary phase diagrams [38,39]. These diagrams describe the three-phase behavior of a multicomponent system (i.e., API, co-former, co-crystal and solvent) and thus enable the prediction of the pathways that lead to co-crystal formation. In particular, it has been suggested that the path of co-crystallization largely depends on the difference in solubility in a given solution between the API and co-crystal former. Two possible scenarios of co-crystallization are illustrated in **Figure 3**.

Solid-based approaches, which can be used when the relative solubility of co-crystallizing components in a given solvent is not a concern, have emerged as a viable alternative to solution-based methods for pharmaceutical co-crystal screening [40-43]. Crystallization from the melt using hot-stage microscopy is an example of a successful solvent-free co-crystal screening strategy applied in our laboratory (**Figure 4**) and by other research groups [12,44]. It should be also underlined, however, that in a number of instances co-crystal screening using solid-based techniques offers better selectivity than does solution crystallization. For example, in a model system of co-crystals formed from caffeine and several monocarboxylic acids, dry co-grinding generated polymorphs, which were initially inaccessible from solution [45]. In the case of wet co-grinding [20], when two or more materials are co-ground and a minor quantity of solvent is added, the catalytic capacity of the solvent further enhances the selectivity of the solid-state synthesis.

2.3 Solid-state characterization of co-crystals

Single-crystal X-ray diffractometry (XRD) can be used for unambitious determination of the solid-state structure of co-crystals at atomic level. Measuring single crystal growth of many APIs can be a very time consuming or even impossible task. For this reason, the formation of co-crystals is primarily verified by X-ray powder diffractometry (XRPD). The major limitation of PXRD is that it cannot distinguish solvates, hydrates or polymorphs from co-crystals. Meanwhile, it should be noted that pharmaceutical co-crystals are especially liable to form isostructural phases; XRPD cannot be used to provide information on solid-state structure of a material. For instance, as many as six isostructural co-crystals of piroxicam have been reported by Childs and Hardcastle [46]. These findings emphasize the need for a multi-technique approach to co-crystal characterization. In particular, Raman spectroscopy has been demonstrated to be a powerful tool for distinguishing isostructural phases [46,47]. In addition, spectroscopic techniques as Infrared (IR), Raman and Near-infrared (NIR) spectroscopy are commonly applied during co-crystal screens [46,48,49], whereas solid-state nuclear magnetic resonance spectroscopy is often used to characterize

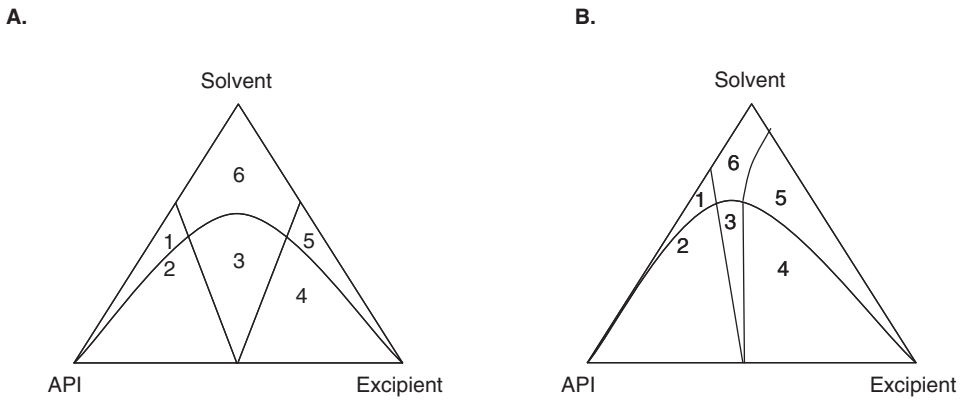


Figure 3. Schematic ternary phase diagrams showing the regions of thermodynamic stability in a multicomponent system with either similar or dissimilar solubility co-crystallizing agents. A. Schematic ternary phase diagrams showing the regions of thermodynamic stability in a multicomponent system with either similar solubility co-crystallizing agent. **B.** Schematic ternary phase diagrams showing the regions of thermodynamic stability in a multicomponent system with a co-crystallizing agent of dissimilar solubility. Region key: 1, API and solvent; 2, API and co-crystal; 3, co-crystal; 4, excipient and co-crystals; 5, excipient and solvent; 6, solution.
Abbreviation: API: Active pharmaceutical ingredient. Modified from reference 38.

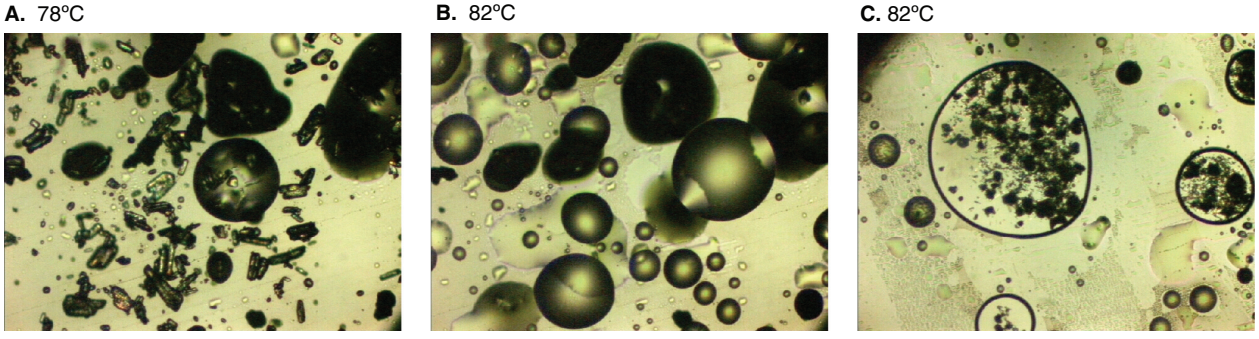


Figure 4. An example of co-crystal screening using hot-stage microscopy. A. The mixture of the active pharmaceutical ingredient (ibuprofen) and the excipient (nicotinamide) upon heating. **B.** At about 82°C the ibuprofen begins to melt. **C.** Subsequently, nicotinamide–ibuprofen co-crystals form at about 85°C.

solid phases that can not be studied by single-crystal XRD [33]. Finally, thermal techniques–including differential scanning calorimetry and termogravi-metric analysis–are routinely used for physical characterization of co-crystals.

3. Expert opinion

The recent progress in pharmaceutical materials science has advanced our understanding of the relationships between the molecular and crystal structure and of the functional properties of APIs. This improved knowledge has brought about the possibility of producing pharmaceutical materials by design. There is a growing understanding of the importance of solid-state and physicochemical material properties of APIs in influencing their acceptability as functional medicines [50]. Co-crystal systems have emerged as an interesting material to exploit in order to design drugs with enhanced functionality.

The main motivation for exploring co-crystals of pharmaceuticals is to potentially modify their physical properties, primarily dissolution rate (and hence bioavailability) and hygroscopicity/physical stability. Hence, this section highlights how co-crystals comprising APIs and various co-crystal formers can be used to enhance these specific properties of solid dosage forms.

With the advent of combinatorial chemistry, APIs possessing limited aqueous solubility (i.e., biopharmaceutics classification system class II drugs) are becoming increasingly prevalent in the research and developments portfolios of pharmaceutical companies. The challenging aspects in the development such drug molecules are associated with their slow dissolution in biological fluids; thus, such APIs receive insufficient and inconsistent systemic exposure and consequently have sub-optimal clinical efficacy. The traditional approaches to addressing the issue of poor aqueous solubility (e.g., salt formation, micronization, solid

dispersion formulations) often fail to produce a viable solid form, as the increase in dissolution rate achieved is frequently insufficient to provide adequate enhancement of bioavailability [2]. In this context, pharmaceutical co-crystals that have a distinct solid phase possess a unique set of properties, thus co-crystal formation can act as an advantageous alternative to other solid-state modification techniques. A vivid example that demonstrates the success of the co-crystal approach in enhancing the dissolution rate of APIs is the extremely water-insoluble antifungal agent itraconazole. Remenar and collaborators [33] have shown that the co-crystals of itraconazole and various carboxylic acids exhibit a higher solubility and a faster dissolution rate than free base co-crystals. Moreover, the dissolution profile of such co-crystals in L-malic acid matches that of the commercial product Sporanox™ (Johnson & Johnson, New Brunswick, NJ), which contains amorphous itraconazole. This example demonstrates that dissolution rate of co-crystals is likely to be a function of the solubility of the co-crystal former. This implies that the dissolution profile of pharmaceutical co-crystals can be tailored for a specific drug delivery system by selecting the co-crystal former with the desired range of solubility. Ongoing studies in our laboratory support this concept. More specifically, it has been observed that the dissolution rate of indomethacin that is co-crystallized with nicotinamide increases by a factor of four, whereas in the case of co-crystallization with saccharine the magnitude of the dissolution rate increase was only about 1.5. Nevertheless, there is not yet nearly enough published data to suggest that the dissolution rate of co-crystals is indeed a function of co-crystal former solubility.

It is important to note that in the context of solubility, dissolution rate is directly related to thermodynamic solubility. There is a situation that makes co-crystals different from polymorphs or salts, however–the co-crystal complex may be breaking up as the co-crystal dissolves. This possibility could lead to dissolution profiles that would otherwise not be obtained and, in all probability, will afford pharmacokinetic profiles that are otherwise unobtainable.

The stability of a solid API when exposed a wide range of relative humidities is another essential property, as it has practical implications for pharmaceutical processing, formulation, packaging and storage [51,52]. It is often the case that moisture promotes unwanted solid-phase transformation of an API (e.g., polymorphic transformations, hydrate formation, crystallization of amorphous phase) [53-55], which may compromise drug product safety and bioavailability [52,56]. One approach proposed to inhibit such moisture-induced phase transformations is rational co-former selection for a specific formulation [53]. In this context, co-crystallization of an API with a co-former can be thought as a more-radical strategy to address the poor physical stability of moisture-sensitive pharmaceutical materials. For instance, caffeine/oxalic acid co-crystals have been demonstrated to be superior to caffeine anhydrate in terms of physical stability to humidity [45]. In this setting, the hydrogen-bonding sites that participate in the formation of caffeine monohydrate are used to connect the co-former (oxalic acid) with the API molecule (see **Figure 5**), thus blocking the possibility of caffeine hydrate formation during processing and storage. Interestingly, when the co-former methylgallate was used for co-crystallization of caffeine, a crystalline material with improved mechanical properties was produced as a result of modification of overall crystal packing [57].

Also, an ongoing study in our laboratory has demonstrated that formation of co-crystals of theophylline and capric or stearic acid can be a promising approach to enhancing physical stability of this moisture-labile API (unpublished observation, 2008). Another interesting finding within this research project is that co-crystallization of a low-melting-point drug with a high-melting-point excipient can be used to manipulate the melting point of thermally labile APIs. Some other examples of pharmaceutical co-crystals reported in the literature are presented in **Table 2**.

There are only a few reports of manufactured end products–for example, tablets made up of pharmaceutical co-crystals [22]. The available published data only covers formed co-crystals and does not detail on the formulation of the actual end product (i.e., through granulation and tablet compression), in which the favorable co-crystal properties should remain. It would, therefore, be desirable to see studies that follow the development cycle all the way to the end product. In addition, there is a need for studies that systematically investigate the applicability of agglomeration techniques–such as high-shear and fluidized-bed granulation techniques–for the formation of co-crystal agglomerates with enhanced physical properties that remain in the final product. Such research could provide valuable information for commercial-scale manufacture of co-crystal systems.

Regulatory issues are also of great interest. Trask [60] has discussed this subject thoroughly in terms of the relation of co-crystals to salts and hydrates when it comes to abbreviated new drug approval eligibility. He states that whether a new co-crystal of a marketed API is eligible for regulatory approval via the abbreviated new drug approval mechanism will affect the overall utility of co-crystal technology to the generic pharmaceutical industry and influence future potential co-crystal markets.

4. Conclusions

The ability to deliver a drug to the patient in a safe, efficacious and cost-effective manner depends largely on the physicochemical properties of the solid state. Manipulation of the material properties of drugs has clear therapeutic, manufacturing and commercial implications. It is of indisputable importance to focus on fundamental material properties in the development of drug products in order to be able to produce medicines with optimum and desired properties. There are

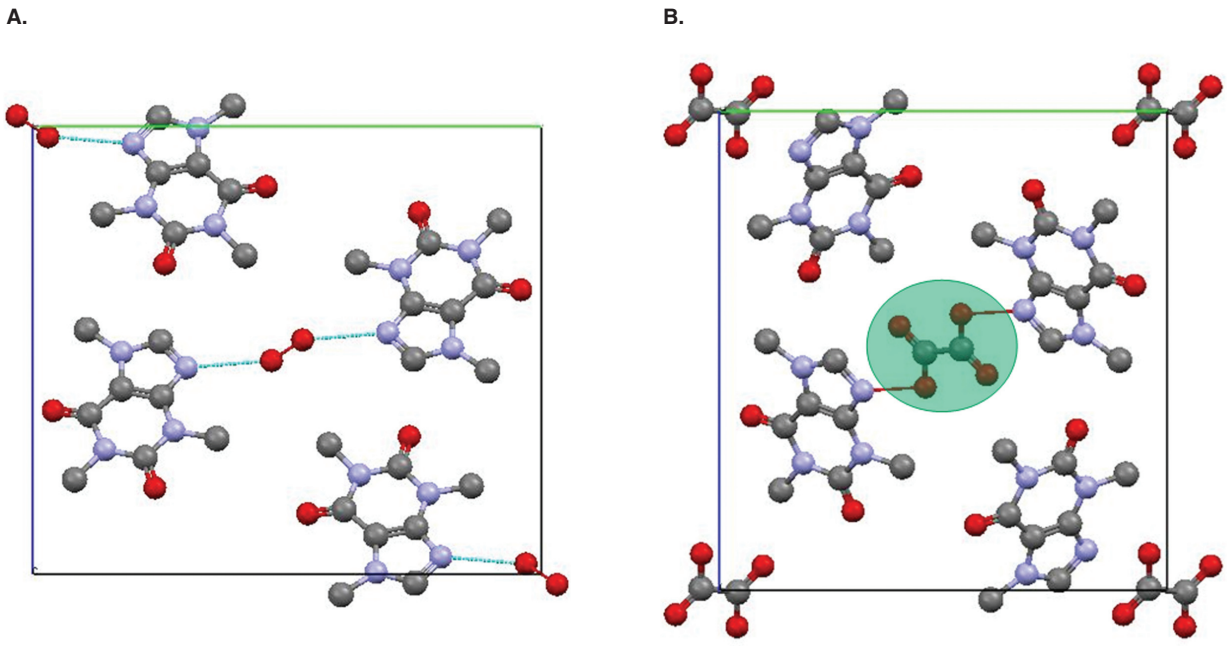


Figure 5. Crystal structures of caffeine monohydrate and the caffeine/oxalic acid co-crystal. A. Caffeine monohydrate. **B.** The caffeine/oxalic acid co-crystal. Note that the same hydrogen bonds are used to connect the host and guest molecules in both crystal structures.

Table 2. Selected examples of pharmaceutical co-crystal systems reported in the literature.

Active pharmaceutical ingredient	Co-crystal former	Preparation method	Enhanced property	Ref.
Caffeine	Oxalic acid Glutaric acid	Solvent-assisted grinding	Physical stability	[45]
Carbamazepine	Nicotinamide Saccharin	Cooling crystallization	Physical stability Dissolution rate Oral bioavailability	[22]
Fluoxetine hydrochloride	Benzoic acid Succinic acid Fumaric acid	Solvent evaporation	Intrinsic dissolution rate	[58]
Ibuprofen	4,4-Dipyridyl Nicotinamide	Solvent evaporation	Solubility	[44,59]
Indomethacin	Saccharin	Solvent evaporation or solvent-assisted grinding	Physical stability Dissolution rate	[14]
Itraconazole	Malic acid Tartaric acid Succinic acid	Solvent evaporation	Dissolution rate	[33]
Norfloxacin	Isonicotinamide Succinic acid Malonic acid Maleic acid	Solvent evaporation	Solubility	[48]

many potential enhancements that can be made by solid-state modification through co-crystals, such as improvements in dissolution and the generation of new pharmacokinetic profiles and physical characteristics such as compressibility and hygroscopicity. Many challenges exist, however, for example in the area of analysis of co-crystal systems. By investigating co-crystals, we can begin to design drugs using a bottom-up approach that starts from the molecular-level building blocks, thus leading to an enhanced product.

Declaration of interest

The authors declare no conflict of interest and have received no funding in support of this manuscript.

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