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The role of cocrystals in pharmaceutical science

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Pharmaceutical cocrystals, a subset of a long known but little-studied class of compounds, represent an emerging class of crystal forms in the context of pharmaceutical science. They are attractive to pharmaceutical scientists because they can significantly diversify the number of crystal forms that exist for a particular active pharmaceutical ingredient (API), and they can lead to improvements in physical properties of clinical relevance. In this article we address pharmaceutical cocrystals from the perspective of design (crystal engineering) and present a series of case studies that demonstrate how they can enhance the solubility, bioavailability, and/or stability of API crystal forms.

Introduction

The fact that active pharmaceutical ingredients (APIs) are most conveniently developed and delivered as solid dosage forms that contain a single crystalline form of an API means that the selection of a specific crystal form for a given API is a profoundly important step from clinical, legal, and regulatory perspectives:

- Crystalline forms are strongly preferred because they tend to be more stable, reproducible, and amenable to purification than other types of solid forms such as amorphous solids and solid solutions.
- The dissolution rate and intrinsic solubility of different crystal forms are variable and can strongly influence bioavailability.
- Stability regarding temperature and humidity is crucially dependent upon crystal packing.
- The unpredictability (i.e. lack of obviousness) of crystal structures and physical properties means that there are legal issues and challenges in terms of obtaining and maintaining patent protection for an API.

In such a context, scientific developments that afford greater diversity in terms of the number of crystalline forms available for a given compound, which have traditionally been limited to salts, polymorphs, and hydrates/solvates [1,2], (Figure 1) are obviously of relevance to the pharmaceutical industry. This short review highlights the emerging field of pharmaceutical cocrystals with particular emphasis on their history, their design, and their recent impact on preformulation strategies for development of dosage forms of APIs.

The recent and rapid emergence of pharmaceutical cocrystals can be attributed to the following factors:

- *Design*: Cocrystals represent a long-known [3–5] but little-studied (less than 1% of structurally characterized molecular organics are cocrystals) class of compound. However, our scientific understanding of the non-covalent forces that sustain molecular organic crystals, in particular cocrystals, has recently advanced to the extent that control over the stoichiometry and composition of cocrystals can be asserted, that is, by exploiting the strategy of crystal engineering [6–12] in the context of understanding and predicting hydrogen bonding interactions. Crystal engineering is facilitated by the Cambridge Structural Database (CSD) [13] and the nature of APIs, that is, molecules or ions with exterior functional groups that engage in hydrogen bonding; this makes all APIs inherently predisposed to formation of pharmaceutical cocrystals [14–16]. This is not ordinarily the case for polymorphs and solvates, for which HTS (i.e. serendipity) tends to be relied upon rather than design or for salts, which require an ionizable functional group.
- *Discovery*: The fact that mechanochemistry can be utilized to synthesize cocrystals has been known since the first cocrystals were discovered by dry grinding, but it has only recently been

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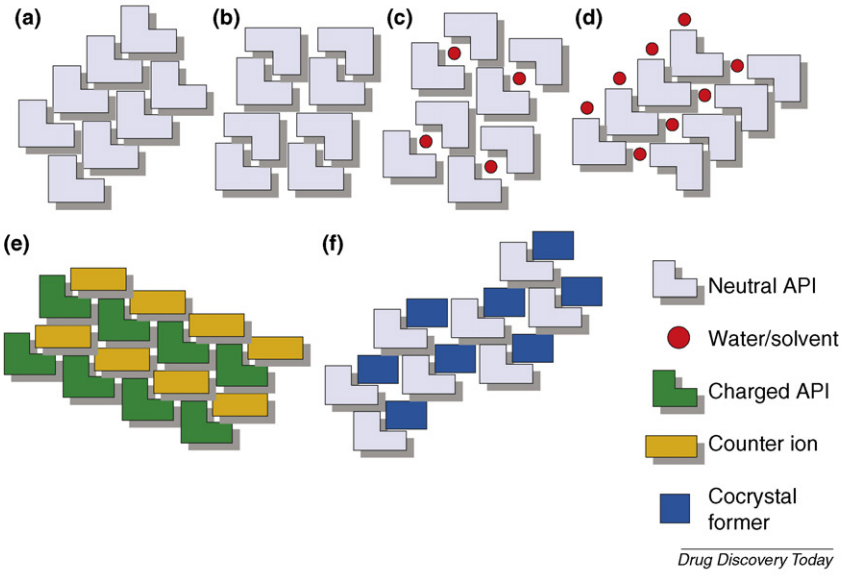

FIGURE 1

The range of single crystalline forms that are possible for an API: (a) pure API; (b) polymorph of pure API; (c) clathrate hydrate/solvate of API; (d) hydrate/solvate of API; (e) salt of API; (f) pharmaceutical cocrystal. Salts and cocrystals can also form hydrates, solvates, and polymorphs.

realized and accepted that 'solvent-drop' or 'liquid assisted' grinding are preferred methodologies [17–19]. Indeed, it is fair to assert that cocrystals are most readily accessible through solvent-free or solvent-reduced methods.

- *Diversity*: It has become apparent that pharmaceutical cocrystals exhibit different physical properties compared with the pure crystal form(s) of APIs and that a given API might form cocrystals with dozens or even hundreds of cocrystal formers and that some of these cocrystals might exhibit enhanced solubility [20–33] or stability to hydration [34–35]. Therefore, pharmaceutical cocrystals represent an opportunity to significantly diversify the number of crystal forms of an API and in turn fine tune its bioavailability without the need for chemical (covalent) modification.
- *Development*: Whereas pharmaceutical cocrystals can be designed using crystal engineering strategies this does not mean that details of their crystal structures or physical properties can be predicted before they have been measured. Therefore, pharmaceutical cocrystals of existing APIs can be patented as new crystal forms, and if they exhibit clinical advantages, then they can be developed as new drugs [36]. This has potentially important implications for drug development because it abbreviates some aspects of the drug development timelines (i.e. those related to discovery and toxicology).

What are cocrystals?

The issue of how one defines a cocrystal is a matter of recent debate [37–39]. Whereas everyone can agree that a cocrystal is a crystalline form that contains more than one compound in the crystal, in our research groups we have been using a more restrictive operating definition: 'A cocrystal is a multiple component crystal in which all components are solid under ambient conditions when in their pure form. These components co-exist as a stoichiometric ratio of a target molecule or ion and a neutral molecular cocrystal former(s)'. It can be argued that liquids and gases can also serve as cocrystal formers, and this is appropriate from a supramolecular perspective. However, that all components are solid under ambient conditions has important practical considerations: cocrystals are amenable to being discovered and prepared via solid-state approaches; they tend to be more stable to heat than, for example, solvates or hydrates; there is a design or crystal engineering aspect of cocrystals that distinguishes them from solvates and single component molecular solids. Nevertheless, it should be noted that focusing upon solids is not really a limitation because the vast majority of molecular compounds exist as solids under ambient conditions [40]. If one accepts this definition then cocrystals represent a long-known class of compounds: a prototypal example is quinhydrone, which was prepared by grinding at least as early as 1844 [3] and was further studied during the late 1800s [4]. Cocrystals were subsequently described as organic molecular compounds [5]. However, structural information on cocrystals was largely absent until the 1960s, when the term 'complexes' was coined, primarily in the context of molecular recognition between nucleic bases [41–43]. Figure 2 illustrates the crystal structure of the cocrystal that forms when 9-methyladenine is crystallized in the presence of 1-methylthymine. This cocrystal illustrates how molecular recognition (i.e. 2-point hydrogen bonding) can govern the existence of a cocrystal. It is therefore somewhat surprising, especially given the broad relevance of interactions between nucleobases [44], that even today there is relatively little structural information on base pairing (<100 crystal structures involving nucleobases). The situation with nucleobases represents a microcosm of cocrystals in general since there is not a great deal of structural information in the CSD on cocrystals. There are only a few entries before 1960, and even today there are only ca. 1950 (ca. 0.45% of the 4 36 384 structures in the January 2008 release of the

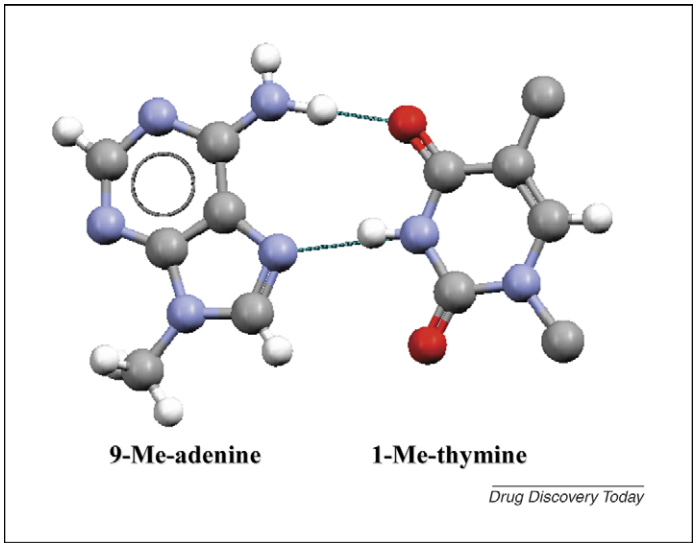

FIGURE 2

The Hoogsteen base pairing that occurs in the cocrystal of 9-methyladenine and 1-methylthymine represents an early example of a cocrystal that has broad scientific relevance.

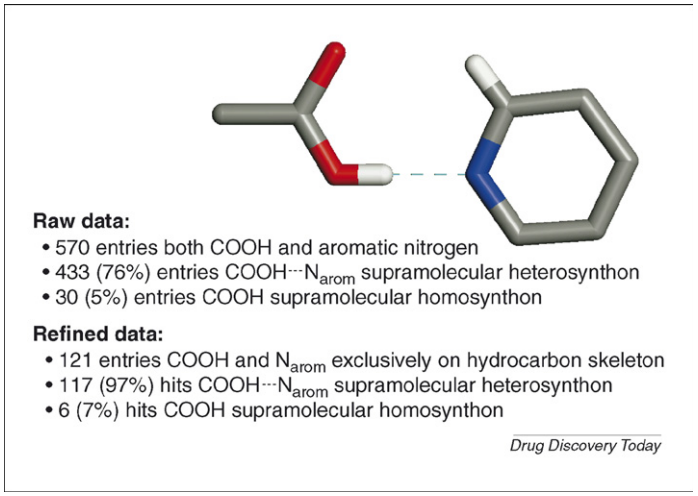

FIGURE 3

A comparison of the CSD statistics associated with the carboxylic acid–carboxylic acid supramolecular homosynthon vs. the carboxylic acid–aromatic nitrogen supramolecular heterosynthon reveals that the heterosynthon dominates and is therefore a reliable predictor of cocrystal formation. The 'raw data' refer to all compounds that contain both functional groups rather than just cocrystals, and the 'refined data' refer to compounds that do not contain additional hydrogen-bond donors or acceptors.

CSD) hydrogen bonded cocrystals vs. 47 021 hydrates (10.8% of the CSD). Therefore, it would be fair to summarize cocrystals as being a long-known but little-studied class of compounds, and even the term cocrystal only became popular in small molecule solid-state chemistry in the late 1980s thanks to the work of Etter [6].

Design of cocrystals

Pepinsky introduced the concept of crystal engineering in 1955 [8], and it was implemented by Schmidt in the context of organic solid-state photochemical reactions [9]. Desiraju subsequently defined crystal engineering as 'the understanding of intermolecular interactions in the context of crystal packing and in the utilization of such understanding in the design of new solids with desired physical and chemical properties' [10]. Crystal engineering has now matured into a paradigm for the preparation or supramolecular synthesis of new compounds. A crystal engineering experiment typically involves CSD surveys followed by experimental work to prepare and characterize new compounds that are sustained by molecular recognition events or supramolecular synthons [12]. A detailed understanding of the supramolecular chemistry of the functional groups present in a given molecule is a prerequisite for designing a cocrystal because it facilitates selection of appropriate cocrystal formers. We [45–48] and others [49–53] have addressed the hierarchy of the supramolecular synthons that can occur for a range of common functional groups in order to design new cocrystals and certain functional groups such as carboxylic acids, amides, and alcohols are particularly amenable to formation of supramolecular heterosynthons (i.e. non-covalent bonds between different but complementary functional groups). It is becoming evident that such interactions are the key to implementing a design strategy for cocrystals in which a target molecule forms cocrystals with a series of cocrystal formers that are carefully selected for their ability to form supramolecular heterosynthons with the target molecule. Figure 3 illustrates how the CSD provides statistics that suggest that the carboxylic–pyridine supramolecular heterosynthon is statistically much more likely to occur than the acid–acid supramolecular homosynthon. This is the type of database mining that makes cocrystals designable because if the acid and pyridine moieties are in different molecules then it follows that a cocrystal is the likely outcome.

How are cocrystals prepared?

Supramolecular heterosynthons that seem to favor formation of cocrystals are now well documented and exemplified by carboxylic acid–aromatic nitrogen (Figure 3), carboxylic acid–amide, and alcohol–pyridine. Cocrystals involving these supramolecular synthons can be synthesized by slow evaporation from a solution containing stoichiometric amounts of the components (cocrystal formers); however, sublimation, growth from the melt, or grinding of two or more solid cocrystal formers in a ball mill are also suitable methodologies. Indeed, dry grinding was used in the 1840s [3] and, as suggested earlier, the recently developed technique of solvent-drop grinding appears to be a particularly effective preparation method [17–19]. More often than not, the phase that is obtained is independent of the synthetic methodology.

Why are cocrystals relevant?

Cocrystals offer opportunities to modify the composition of matter and the chemical and/or physical properties of a molecular species without the need to make or break covalent bonds. This has already resulted in two applications for cocrystals:

1. The term 'non-covalent derivatization' was coined in the context of enhancing the stability of Polaroid film [54].
2. Solid-state synthesis offers great potential in the context of green chemistry (high yield, regio/stereospecificity, no solvent or by-products). However, although almost all common chemical transformations have been effected in the solid-state, the lack of generality caused by the fact that there has been little ability (or attempt) to control the alignment of

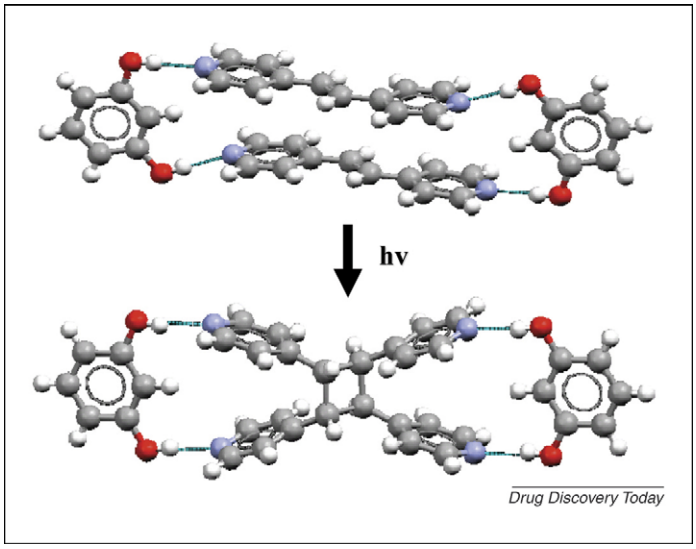

FIGURE 4

An example of a single-crystal to single-crystal photodimerization that occurs in a cocrystal. In this example the cocrystal former is not involved in reaction; it serves to align the reactive groups.

substrates means that processes tend to be only valid for a small proportion of substrates. There is now a catalog of research that demonstrates how non-covalent interactions [55] or coordination bonds [56] can afford control over alignment of reactants and topochemistry. Photodimerization is perhaps the most widely studied reaction in such a context, an example of which is presented in Figure 4 [55]. However, even though photodimerization is established in solid-state chemistry, there is less literature on the subject of reactions between two or more substrates [57].

Case studies of pharmaceutical cocrystals

Perhaps the earliest example of pharmaceutical cocrystals in the context of APIs relates to a series of studies conducted in the 1950s by Higuchi and Roy [58,59]. They studied complex formation between macromolecules and certain pharmaceuticals. For example, complexes of polyvinylpyrrolidone (PVP) with sulfathiazole, procaine hydrochloride, sodium salicylate, benzylpenicillin, chloramphenicol, mandelic acid, caffeine, theophylline, and cortisone were isolated [58,59]. However, these would not be classified as pharmaceutical cocrystals according to the criteria applied herein. Perhaps the first application of crystal engineering to the generation of pharmaceutical cocrystals was a series of studies reported by Zerkowski *et al*. [28] concerning the use of substituted barbituric acid, including barbital and melamine derivatives, to generate supramolecular 'linear tape', 'crinkled tape', and 'rosette' motifs sustained by robust supramolecular synthons with three-point hydrogen bonding [28]. Despite their success in cocrystal formation, the focus of these studies was not so much the physical properties of the resulting cocrystals but rather the supramolecular functionality of barbitals and their complementarities with melamine. Nevertheless, these studies illustrated very well the potential diversity of forms that can exist for a particular API as more than 60 cocrystals were structurally characterized in this series of studies. Clearly, such a diversity of forms could offer an exciting opportunity to novel and improved crystalline forms of APIs. Herein, we have chosen to focus upon several case studies that involve the formation of pharmaceutical cocrystals with altered physical properties of clinical relevance.

Pharmaceutical cocrystals of carbamazepine (Tegretol®)

Carbamazepine (CBZ) is an important anti-epileptic drug that has been in use for over three decades. Oral administration of CBZ encounters multiple challenges, including low water solubility with high dosage required for therapeutic effect (i.e. >100 mg/day), dissolution-limited bioavailability and autoinduction for metabolism. In contrast to its simple molecular structure, CBZ exhibits complexity in its crystal forms [22,27]. To date, four anhydrous polymorphs, a dihydrate, an acetone solvate, and two ammonium salts of CBZ have been identified. It is noted that, in the crystal structures of all these forms, the self-complementary nature of the amide group manifests itself in a predictable manner. Therefore, CBZ has been used as an ideal candidate to demonstrate how APIs can be converted to pharmaceutical cocrystals, and how these cocrystals could offer optimized physicochemical properties over existing forms of an API [27,48]. Two strategies have been adopted for cocrystal formation of CBZ. One crystal engineering strategy is to employ the peripheral hydrogen bonding capabilities that are not engaged in the pure form of CBZ. A second strategy for cocrystallization of CBZ involves breakage of the CBZ amide–amide dimer and formation of a supramolecular heterosynthon between CBZ and a cocrystal former [48]. Both strategies are successful and have afforded a number of CBZ cocrystals that exhibit improved physicochemical properties. For example, the CBZ:saccharin cocrystal shows significantly improved physical stability (i.e. only one cocrystal form with equivalent chemical stability to the anhydrous polymorph has been identified after sophisticated form screening) [27]. In addition, the CBZ:saccharin cocrystal possesses favorable dissolution properties, suspension stability, and pharmacokinetics using dog models. The pharmacokinetic study reveals that the CBZ:saccharin cocrystal exhibits a higher C_{max} and comparable T_{max} when compared with the marketed form, Tegretol® [27]. In short, the CBZ:saccharin cocrystal appears to be superior to existing crystal forms of CBZ in the following respects: stability relative to the anhydrous polymorph of CBZ; favorable dissolution and suspension stability; favorable oral absorption profile in dogs.

Pharmaceutical cocrystals of fluoxetine hydrochloride (Prozac®)

The availability and marketability of a variety of APIs as chloride salts is well recognized, and, recently, an approach to utilize such chloride salts, specifically fluoxetine hydrochloride (fluoxetine HCl), to generate cocrystals of an amine hydrochloride salt via a chloride-mediated carboxylic acid supramolecular synthon has been reported [21]. Fluoxetine HCl is the active pharmaceutical ingredient found in the common antidepressant drug Prozac®. It is a solid under ambient conditions, only one crystalline phase is known, and it is available in the salt form. It has been demonstrated that cocrystallization of this API modifies the physical properties of fluoxetine HCl while still retaining the hydrochloride salt of the API [21]. Fluoxetine HCl was cocrystallized with benzoic acid (1:1), succinic acid (2:1), and fumaric acid (2:1) via traditional evaporation techniques. For all three cocrystals, the carboxylic acid was found to hydrogen bond to the chloride ion, which in

turn interacted with the protonated amine, thus generating, in all three cases, an amine hydrochloride salt hydrogen bonding to an additional neutral molecule [21]. Powder dissolution experiments were carried out in water for the three novel cocrystals resulting in a spread of dissolution profiles (Figure 5). The fluoxetine HCl:benzoic acid cocrystal was found to have a decrease in aqueous solubility by ca. 50%, and the fluoxetine HCl:fumaric acid cocrystal had only a slight increase in aqueous solubility. However, the fluoxetine HCl:succinic acid cocrystal exhibited an approximately twofold increase in aqueous solubility after only 5 min. The complex formed between succinic acid and fluoxetine HCl falls apart in solution to generate its pure components after about 1 h. An intriguing aspect of this study is that by simply hydrogen bonding a hydrochloride salt of an API with similar cocrystal formers one can generate distinctively different dissolution profiles [21].

Pharmaceutical cocrystals of itraconazole (Sporanox®)

Itraconazole is a triazole antifungal agent that is prescribed to patients with fungal infections. Itraconazole is extremely water insoluble and administered both orally and intravenously [20]. In order to achieve the required oral bioavailability, the oral formulation of itraconazole is the amorphous form coated on the surfaces of sucrose beads, and marketed as the Sporanox® capsule. In addition, co-administration of acidified HP-β-cyclodextrin beverages with Sporanox® capsules is required to achieve the maximal absorption of the API, even though such a co-administration can cause diarrhea [20,30]. Interestingly, no crystalline salt of itraconazole has been reported in the patent literature, even though salt formation using itraconazole and an acidic salt former would seem to be a logical approach to improve the absorption properties of the API. In order to improve the absorption of the API and maintain the form crystallinity and stability, the pharmaceutical cocrystal approach has been evaluated in the formulation of itraconazole. Crystalline phases of itraconazole can be engineered by introduction of additional molecules to match hydrogen-bond donors and acceptors [20,30]. A number of stable pharmaceutical cocrystals of itraconazole and 1,4-dicarboxylic acids were synthesized and crystallographically characterized [20]. Each cocrystal contains two API molecules and one acid cocrystal former, hydrogen-bonded through carboxylic acid–triazole supramolecular synthons, to form a trimeric assembly. The aqueous dissolution of itraconazole cocrystals was studied in order to assess their potential impact on bioavailability of the API. The dissolution of itraconazole cocrystals was observed to behave more akin to the Sporanox® form than to the crystalline form of the pure API. In particular, it was noted that the itraconazole:L-malic acid cocrystal exhibits a similar dissolution profile to that of the marketed formulation [20]. In a further pharmacokinetic study of itraconazole cocrystals, it was revealed that cocrystal formulation of the API gives similar oral bioavailability to the Sporanox® form in the animal trial using a dog model [30]. In short, this study demonstrates the use of pharmaceutical cocrystals for the improvement of solubility and bioavailability without compromising crystallinity and stability.

Pharmaceutical cocrystals of sildenafil (Viagra®)

Sildenafil is a drug used in the treatment of pulmonary arterial hypertension, congestive heart failure, atherosclerosis, conditions of reduced blood vessel patency and peripheral vascular disease, as well as male erectile dysfunction and female sexual disorders [31]. Sildenafil selectively inhibits cyclic guanosine monophosphate (cGMP)-specific phosphodiesterase type 5 that is responsible for degradation of cGMP in the corpus cavernosum, leading to smooth muscle relaxation in the corpus cavernosum, and resulting in increased inflow of blood and an erection. Sildenafil citrate, with moderate water solubility, has been commercially developed

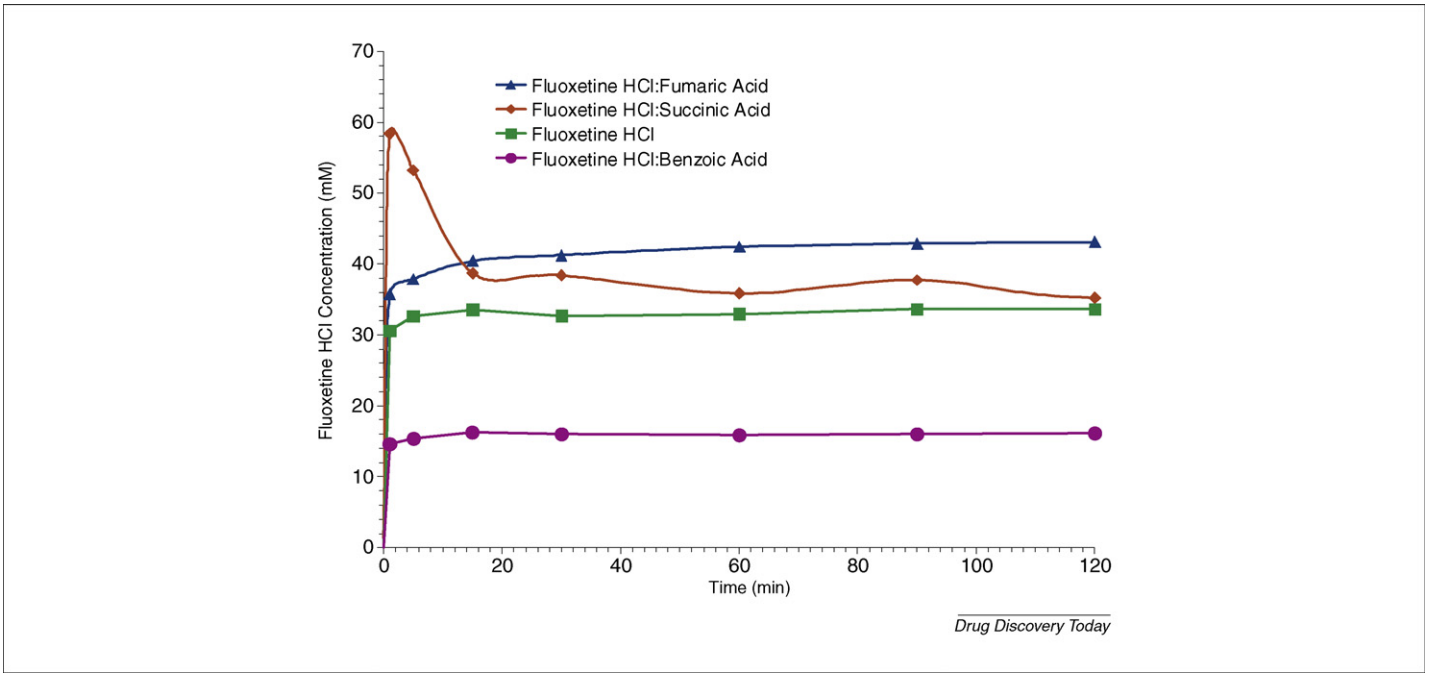

FIGURE 5

Dissolution profiles for novel cocrystal forms of fluoxetine HCl reveal how intrinsic dissolution can be modified through cocrystallization.

and marketed by Pfizer and is available under the trademark Viagra® [31]. It has been observed that sildenafil in a pharmaceutical cocrystal form could provide an improved solubility of the API under acidic conditions. In addition, such an improvement of solubility of sildenafil could be particularly advantageous for its orally administrable formulation. Sildenafil has been successfully cocrystallized with acetylsalicylic acid (1:1 molar ratio) by slurry or under reflux conditions [31]. The crystal structure of the cocrystal of sildenafil and acetylsalicylic acid has been determined by single-crystal X-ray diffraction [31], and in addition, the composition of matter was confirmed by powder X-ray diffraction and infrared spectrometry. Moreover, the differential scanning calorimetry and thermogravimetric analyses indicate that the melting point of the cocrystal is approximately 143 °C, and it remains thermodynamically stable up to ca. 165 °C [31]. An intrinsic dissolution study in simulated gastric body fluid (pH 1.2) shows that the sildenafil:acetylsalicylic acid cocrystal exhibits an intrinsic dissolution rate (IDR) of ca. 11.75 mg min^{-1} cm^{-2} vs. 6.64 mg min^{-1} cm^{-2} for sildenafil citrate under the same conditions [31].

Cocrystal of melamine and cyanuric acid

In early 2007, the FDA received complaints from owners of more than 4000 pets regarding the deaths of animals after taking food that was later recalled; it was reported that majority of those deadly incidents were caused by acute renal failure [33]. At first, melamine, which was observed in the tainted products, was the suspected contaminant, since this particular chemical could be intentionally added to raise the apparent protein content of the food. However, melamine is considered relatively nontoxic [i.e. the acute toxicity of melamine in rats was reported with oral lethal doses 50 (LD_{50}s) of 3100 mg/kg (male) and 3900 mg/kg (female)] [33]. Also, the quantity of melamine observed in those incidents was not at levels that would normally kill. In the course of the pet food recall investigation, cyanuric acid, another relatively nontoxic compound, was also identified in the pet food as a co-contaminant. Although melamine and cyanuric acid are relatively safe individually, no data could be found in the literature that could determine the potential toxicity of melamine and cyanuric acid in combination [33]. From the crystal engineering viewpoint, melamine and cyanuric acid (1:1 molar ratio) form an extensive two-dimensional networks in the solid-state based on the robust three-point molecular recognition, and it was observed that the resulting melamine:cyanuric acid cocrystal is highly insoluble in water [32–33]. As reported by a recent investigation, the combination of melamine and cyanuric acid can result in the intratubular precipitation of melamine:cyanuric acid cocrystals in the kidney, even though the mechanism associated with renal damage is not fully understood to date [33]. A study conducted at the Bergh Memorial Animal Hospital in New York revealed that cocrystals blocked the tubes leading from the kidneys to the bladder in one cat [33], and a toxicology assessment of melamine and cyanuric acid indicated that a single oral exposure of cats to the melamine:cyanuric acid cocrystal at a concentration of 32 mg/kg body weight can result in acute renal failure. It seems clear that the formation of a low solubility cocrystal of melamine and cyanuric acid is responsible for these incidents. Perhaps this case study of melamine:cyanuric acid cocrystals is the first example showing how cocrystals can significantly alter the relevant physical properties in a negative manner.

Concluding remarks

In summary, the importance of crystal form selection during development of APIs has probably never been higher, and pharmaceutical cocrystals have become an important part of a landscape that was previously occupied only by polymorphs, salts, and solvates/hydrates. Nevertheless, whereas there is a clear need for better understanding and control of crystalline forms in the context of pharmaceutical development, the concepts of supramolecular synthesis [60] and crystal engineering remain largely underexploited, and there are many basic questions about pharmaceutical cocrystals that remain unanswered, including their tendency to form polymorphs [61]. This contribution highlights how crystal engineering can afford opportunities to diversify the number of crystal forms known for an API and to improve their physical properties of clinical relevance. One might claim that it is now fair to assert that the issue no longer centers around whether cocrystals are designable or if pharmaceutical cocrystals will impact pharmaceutical form and formulation; the issue now is when it will happen, who will benefit, and whether the changes will be evolutionary or revolutionary.

Conflict of Interest

MZ serves as a scientific advisor to Thar Pharmaceuticals.

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