POLYMORPHIC CRYSTAL FORMS AND COCRYSTALS IN DRUG DELIVERY (CRYSTAL ENGINEERING)

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Active pharmaceutical ingredients, APIs, are most conveniently developed and delivered orally as solid dosage forms that contain a defined crystalline form of an API. This means that the pharmacokinetic profile of a dosage form is at the very least linked to the physicochemical properties of the crystal form that is selected for development. Furthermore, that crystal forms of new chemical entities are novel, lack obviousness, and have utility makes them patentable. Therefore, selection of a specific crystal form for a given API is a profoundly important step in drug development from clinical, legal, and regulatory perspectives. In this context, scientific developments that afford greater understanding of and diversity in the number of crystalline forms available for a given API, which have traditionally been limited to salts, polymorphs, and hydrates/solvates [1], are obviously of relevance to the pharmaceutical industry. The science of *crystal engineering* [2] focuses upon self-assembly of existing molecules or ions and it has evolved in such a manner that a wide range of new crystal forms can be generated without the need to invoke covalent-bond breakage or formation. This contribution will address the impact of crystal engineering upon our fundamental understanding of crystal form diversity and how physical properties of crystals can be customized via the emerging class of crystal forms that have been termed *pharmaceutical cocrystals* [3].

1. INTRODUCTION

The importance of crystallization and crystal forms to pharmaceutical science is the result of multiple practical considerations. In terms of processing, crystallizations tend to afford highly pure products, they are typically reproducible and scalable, and they are generally stable when compared to amorphous solids or solutions. They are therefore preferred by developers and regulatory bodies. Furthermore, although crystallization has been widely studied scientifically since at least the early nineteenth century, this does not mean that crystallization is predictable [4] or even controllable [5]. New crystal forms are therefore likely to be patentable in their own right since they meet the primary criteria for patentability: novelty, lack of obviousness and utility. Finally, it has been known for over 100 years that rate of dissolution of a solid is at least partly determined by thermodynamic solubility of a compound [6] and it is well recognized that solubility can significantly influence the bioavailability and pharmacokinetics of an API. Given that the majority of APIs currently under development fall into Biopharmaceutical Classification Scheme [7] (BCS) classification II (low solubility, high permeability), the importance of API crystal form screening and selection is, if anything, increasing in scope and importance. In short, the existence of multiple crystal forms of an API affords both challenges and opportunities to the pharmaceutical industry. In this context, the emergence of the concept of crystal engineering is timely and relevant.

Crystal engineering [2] was coined by R. Pepinsky [2c] in 1955 and brought to practice by G.M.J. Schmidt in the context of topochemical reactions [2d]. Crystal engineering has more recently matured into a paradigm for the understanding of existing crystalline solids and the design of new compounds with customized composition and physical properties. Indeed, crystal engineered materials have been studied in the context of host–guest compounds, nonlinear optical materials, organic conductors, and coordination polymers [8–11]. However, given that APIs are perhaps the most valuable crystalline substances known and their very nature (i.e., the presence of hydrogen-bonding functionality at their periphery) makes them predisposed toward crystal engineering, it is perhaps unsurprising that crystal engineering concepts are increasingly being applied to pharmaceutical

Burger's Medicinal Chemistry, Drug Discovery, and Development, Seventh Edition,
edited by Donald J. Abraham and David P. Rotella

science by both industrial and academic researchers [12–23]. It can be asserted that crystal engineering is finally realizing Desiraju's vision that crystal engineering is "the understanding of intermolecular interactions in the context of crystal packing and utilization of such understanding in the design of new solids with desired physical and chemical properties" [2e].

The range of crystal forms that are typically exhibited by APIs represents a microcosm of organic compounds although it would be fair to assert that APIs are more promiscuous than "typical" organic compounds because they contain multiple hydrogen-bonding sites and/or torsional flexibility. It is hydrogen bonding sites or, more specifically, the detailed understanding of the supramolecular chemistry of these hydrogen-bonding sites that is the key to understanding the structure–property relationships in crystal forms. The existence of multiple crystal forms for an API is therefore to be expected and they are typically categorized as follows: polymorphs, salts, solvates, hydrates, and cocrystals (Fig. 1).

- *Polymorphs*: Polymorphism, the existence of more than one crystal form for a compound, has been described as "the nemesis of crystal design" by one of the pioneers of crystal engineering, G.R. Desiraju. Indeed, there are probably many researchers in the pharmaceutical industry who would regard polymorphism as the nemesis of crystal form selection since the unpredictability of polymorphism complicates all aspects of crystallization from laboratory scale discovery through to industrial scale processing.
- *Salts*: Salts have long been an integral part of crystal form selection because they offer diversity of composition and can therefore exhibit a wide range of physicochemical properties. However, salts, especially chloride salts, tend to be prone to exist as hydrates, there are a

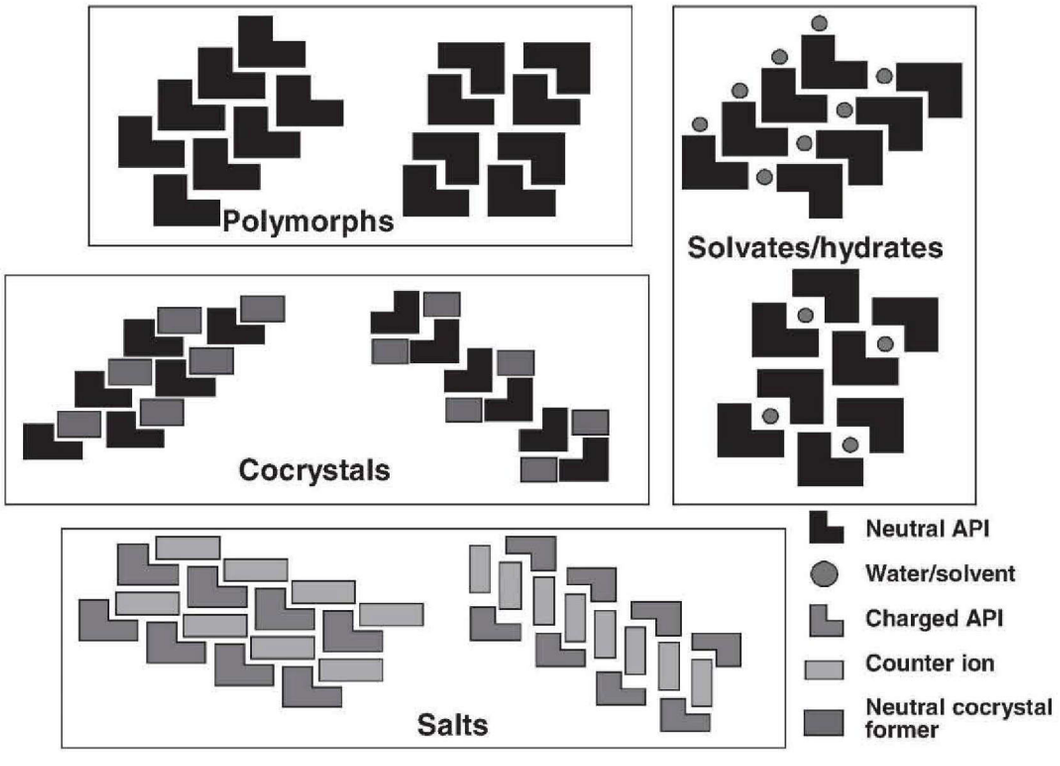

Figure 1. Crystal forms typically exhibited by molecular organics.

limited number of pharmaceutically acceptable counterions, and not all APIs are acidic or basic enough to form salts [24].

- *Hydrates and Solvates*: Solvates are crystalline compounds in which solute and solvent molecules coexist, normally but not always through interaction of noncovalent bonds such as hydrogen bonds. Likewise, hydrates are compounds that contain water bound within the crystal lattice. One might think that hydrates are typically prepared using water as a solvent but the ubiquitous presence of water means that they are most typically isolated through the presence of adventitious water molecules. Indeed, they represent more than 10% of the >500,000 crystalline organic compounds that have been archived in the Cambridge Structural Database, CSD. However, just as polymorphs are unpredictable, so are solvates and hydrates. Furthermore, solvates and hydrates are less likely to be selected as dosage forms because they tend to be prone to desolvation or dehydration in dry conditions.
- *Cocrystals*: Cocrystals represent a class of compounds that could reasonably be described as long known but little studied [25]. Indeed, to our knowledge the term cocrystal was not coined until 1967 [26] and it was not popularized in the context of small molecules until M.C. Etter used the term extensively in the 1980s [2a]. Furthermore, even today the term cocrystal is poorly defined and represents ambiguity or even controversy [27]. We define a cocrystal as following: a multiple component crystalline solid formed in a stoichiometric ratio between two compounds that are crystalline solids under ambient conditions. At least one of these compounds is molecular (the cocrystal former) and forms supramolecular synthons(s) with the remaining component(s) [3a–3e]. If one uses this definition then the first cocrystals were reported in the 1800s [25] and they have had various terms applied to them: addition compounds, organic molecular compounds, complexes, and heteromolecular crystals [28–35]. Cocrystals are also distinct from solvates, salts and inclusion compounds if one employs this definition. Nevertheless, the term pharmaceutical cocrystal, that is, a cocrystal between an API and a molecular cocrystal former, was not widely used until recent years. Pharmaceutical cocrystals were reported as far back in the 1930s [36], yet only in recent years has their diversity in terms of crystal form and physical properties been fully recognized in the context APIs.

Salt screening and selection is covered in a different chapter and solvates and hydrates tend to exhibit lower stability than polymorphs or pharmaceutical cocrystals. This chapter will therefore focus upon polymorphs and cocrystals with emphasis upon how they can be subjected to rationalization through crystal engineering. The key to crystal engineering in the context of APIs lies with understanding the hydrogen-bonding groups present in the API. Two approaches have been developed to analyze existing crystal structures with the view to utilize the structural knowledge thereby gained to rationalize and even control the composition or even structure of new crystal forms. These related and compatible approaches, *graph sets* and *supramolecular synthons*, were developed by Etter [2a] and Desiraju [2i], respectively. In both instances, there is reliance upon utilizing the Cambridge Structural Database [37], to gather statistical information about crystal packing and intermolecular interactions. We shall focus herein upon supramolecular synthons, which are defined as "a structural unit within the supermolecule that can be formed and/or assembled by known or conceivable intermolecular interactions." Supramolecular synthons focus upon functional groups rather than molecules and exist in two distinct categories: *supramolecular homosynthons* that are composed of identical complementary functional groups, for example, carboxylic acid dimers [38], amide dimers [39] (Fig. 2a and b); *supramolecular heterosynthons* composed of different but complementary functional groups such as acid-amide [40] and acid-aromatic

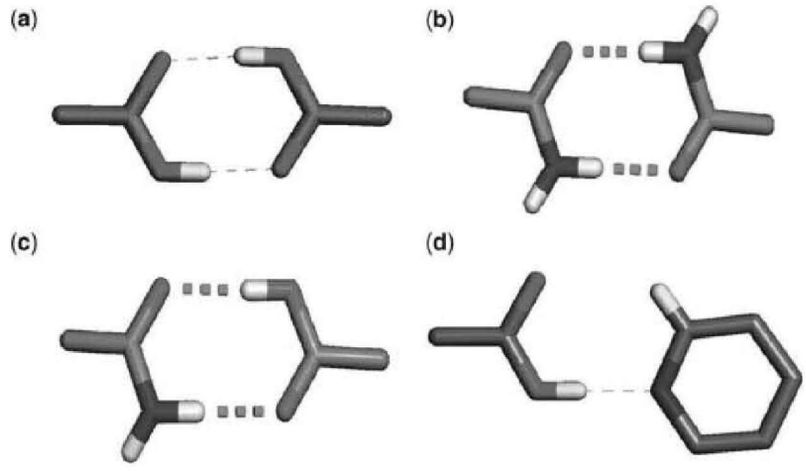

Figure 2. Prototypal supramolecular homosynthons (a) and (b) and supramolecular heterosynthons (c) and (d).

nitrogen [41] (Fig. 2c and d). The aforementioned supramolecular synthons are particularly salient because carboxylic acids are present in 25 of the top 100 most prescribed drugs in the United States. Furthermore, they are frequently encountered in pharmaceutical excipients, salt formers and cocrystal formers.

2. CRYSTAL FORM TYPES

2.1. Polymorphs

The first observation of polymorphism can be attributed to Wöhler and von Liebig, who in 1832 reported that upon cooling a boiling solution of benzamide, needle-shaped crystals would initially form [42]. However, upon standing the needle-shaped crystals would slowly be replaced by rhombic crystals. This observation is a manifestation of Ostwald's step rule, that is, that the crystal form first obtained upon crystallization of a substance from a solution or a melt will be a metastable polymorph, a long recognized [43] and qualitative generalization about crystallization. However, despite a long history, it would be fair to say that, until recently, polymorphism has been more of a scientific curiosity than an urgent challenge of commercial relevance. Pharmaceutical science has been largely responsible for a change in this situation since most orally delivered APIs receive regulatory approval for a single crystal form or polymorph and novel crystal forms are patentable. Awareness of the matter heightened following a now classic patent litigation between Glaxo and Novopharm in which Glaxo defended its patent for the form II polymorph of ranitidine hydrochloride, the API in Zantac®. The Glaxo patent on form I of ranitidine hydrochloride (US patent 4,128,658) expired on December 5 1995, but the form II patent (US patent 4,521,431) did not expire until 2002. Although Novopharm ultimately prevailed, Glaxo retained exclusivity beyond the patent expiration of form I for several years on what was at the time the top-selling drug in the world. In addition to legal, regulatory and commercial considerations, polymorphism in drug substances can also have direct clinical implications since dissolution rates are sometimes impacted by polymorphism. However, although polymorphism might be long recognized and topically relevant to pharmaceutical science [44], this does not mean that polymorphs are predictable or that their discovery is routine despite McCrone's statement on the subject in 1965 [45]: "Every compound has different polymorphic forms and the number of forms known for a given compound is proportional to the time and energy spent in research on that compound." This provocative

statement has often been debated and many solid-state scientists would be inclined to support such an assertion. However, McCrone's statement cannot realistically be proved through experiment and even today the number of publicly disclosed cases of polymorphism in organic compounds remains quite low based upon CSD statistics: only 8525 out of 195,222 organic compounds archived are polymorphic and since there must be at least two entries for each compound this represents $\leq$2.2% of organic compounds; only 667 out of 11,501 compounds with biological or pharmacological activity are polymorphic (selected using keywords "activity," "agent," "biological," "drug," "pharmaceutical," "pharmacological"), representing just $\leq$2.9% of this subset. One must also bear in mind that the CSD is unlikely to be representative in the context of polymorphs since entries are biased by the compounds that have been of interest to crystallographers at particular points in time. The focus until recently has been upon molecular structure rather than crystal structure and many polymorphs probably remain unpublished.

Although polymorphism might remain largely unpredictable it can be rationalized and categorized through understanding the molecular and supramolecular structure of the compound in question, allowing us to define at least two classes of polymorphism [45]: *conformational polymorphism* is the consequence of more than one conformer in the solid state (i.e., the shape of the molecule is different); *packing polymorphism* occurs when rigid molecules exhibit more than one packing arrangement. Packing polymorphs might be caused by different supramolecular synthons (i.e., the intermolecular connectivity is different) or they might retain their supramolecular synthons but exhibit different crystal packing. Such a situation might be termed *supramolecular synthon polymorphism*. Conformational polymorphism is exemplified by what is thus far the most promiscuous molecule in terms of the number of structurally characterized polymorphs, 5-methyl-2-[(2-nitrophenyl)amino]-3-thiophenecarbonitrile, a pharmaceutical intermediate that has been called ROY because its eight crystallographically characterized polymorphs are red, orange, or yellow in color [46,47]: ROY is illustrated in Fig. 3, which highlights the portion of ROY that is responsible for its conformational flexibility. Six room temperature polymorphs of ROY were reported by Yu et al. in 2000 [46] and two additional polymorphs, Y04 and YT04, were reported in 2005 [47]. Y04 was prepared from a melt at room temperature, and YT04 was obtained via solid-state transformation of Y04. Y04 and YT04 exemplify polymorphs that would likely be missed by solvent-based screening, highlighting the experimental

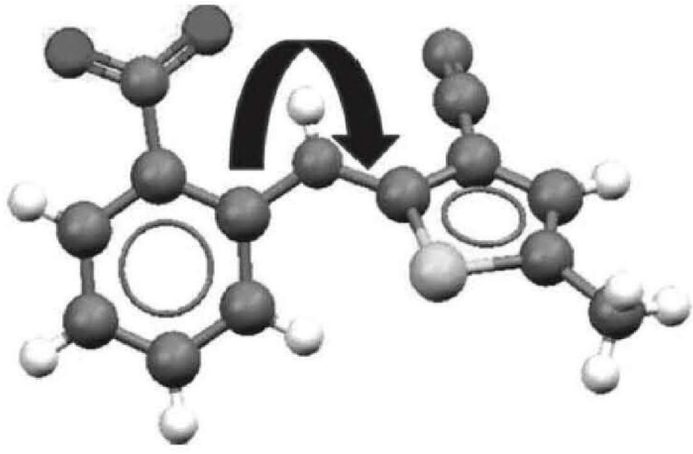

Figure 3. The molecular structure of the ON polymorph of 5-methyl-2-[(2-nitrophenyl)amino]-3-thiophenecarbonitrile, ROY (CSD refcode = QAXMEH) indicating the region of torsional flexibility.

challenge of polymorph discovery. Packing polymorphism is exhibited by numerous APIs and exemplified herein by Piracetam and Aspirin. Piracetam, 2-oxo-pyrrolidineacetamide, is a nootropic drug that improves cognitive ability and it exhibits five structurally characterized polymorphs [48]. Although one of these polymorphs, the high-pressure form IV, is a conformational polymorph, forms I and II are examples of packing polymorphism caused by different supramolecular heterosynthons. Form I exists as a cyclic tetramer whereas form II forms infinite tapes in which amide–amide dimers are hydrogen bonded to adjacent dimers through amide-carboxamide N—H . . . O hydrogen bonds. Aspirin had long been considered to represent an example of a compound that does not exhibit polymorphism. However, in 2005, metastable form II of aspirin was discovered during an attempted cocrystallization reaction [49] Forms I [50] and II are illustrated in Fig. 4, which reveal that both crystal forms of aspirin contain dimers that are sustained by the carboxylic acid supramolecular homosynthon. However, C—H . . . O interactions between adjacent dimers are different and in turn cause different crystal packing. Subsequent work has suggested that forms I and II might coexist within the same crystal (Fig. 5) [51].

In conclusion, polymorphs can generally be rationalized through supramolecular concepts such as crystal engineering but this does not mean that they can yet be predicted from first principles. However, although one should not confuse crystal engineering with crystal structure prediction, crystal structure prediction using computer modeling has advanced considerably within the past decade [52].

2.2. Cocrystals

2.2.1. What is a Cocrystal? That there is not yet a recognized definition of the term "cocrystal" has engendered debate on the subject [27]. We have been using the following operating definition: a multiple component crystalline solid formed in a stoichiometric ratio between two compounds that are crystalline solids under ambient conditions. At least one of these compounds is molecular (the cocrystal former) and forms supramolecular synthons(s) with the remaining component (s) [3a–3e]. That all components are solids under ambient conditions has important practical considerations since synthesis of cocrystals can be achieved via solid-state methods (e.g., mechanochemistry) and chemists can execute a certain degree of control over the composition of a cocrystal since they can invoke molecular recognition, especially hydrogen bonding, during the selection of cocrystal formers. These features distinguish cocrystals from solvates and despite restrictions they still represent a broad range of compounds since most molecular compounds exist as solids under ambient conditions [53].

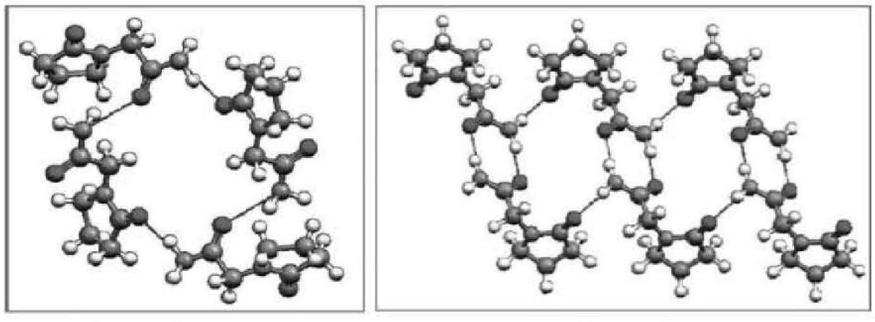

Figure 4. Forms I and II of piracetam exhibit packing polymorphism because they exhibit different supramolecular synthons. Form I exists as a cyclic tetramer whereas form II forms infinite tapes.

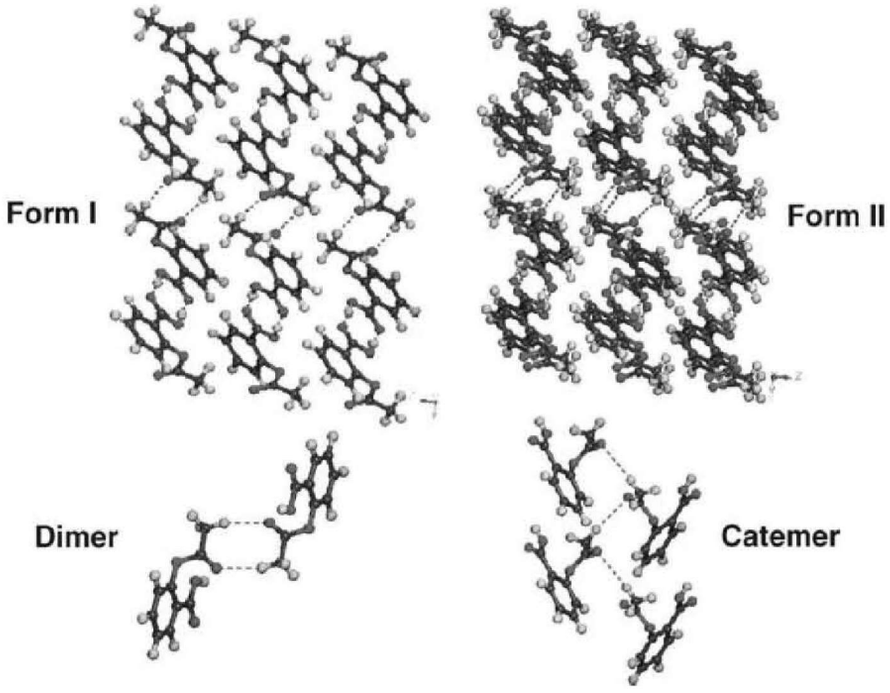

Figure 5. The two polymorphs of aspirin are both based upon carboxylic dimer supramolecular homosynthons. However, they differ in the manner in which adjacent dimers interact. In form I C—H . . . O dimers are formed whereas in form II the structure is sustained by C—H . . . O catemers.

2.2.2. Why are Cocrystals of Interest to the Pharmaceutical Industry? Pharmaceutical cocrystals, that is, cocrystals in which the target molecule or ion is an active pharmaceutical ingredient, API, and the cocrystal former is a pharmaceutically acceptable molecule or ion, are emerging rapidly because of a number of factors including the following:

- *Design*: Our scientific understanding of the noncovalent forces that sustain molecular organic crystals has advanced to the extent that control over the stoichiometry and composition of cocrystals can be asserted. This is not ordinarily the case for polymorphs and solvates for which high-throughput screening, which to a certain extent practices serendipity, tends to be relied upon rather than design, or for salts, which require an ionizable functional group.
- *Discovery*: That mechanochemistry can be utilized to synthesize cocrystals has been known since the first cocrystals were discovered in the 1840s by dry grinding [25a], but it has only recently been realized and accepted that "solvent-drop" or "liquid assisted" grinding are preferred methodologies [54]. Indeed, it is fair to assert that cocrystals are most readily accessible through solvent-free or solvent-reduced methods although other techniques such as slurrying [55] and solution [56] are complementary.
- *Diversity*: It has become apparent that pharmaceutical cocrystals always exhibit different physicochemical properties compared to the pure crystal form(s) of APIs, that a given API might form cocrystals with dozens of cocrystal formers and that some of these cocrystals might exhibit enhanced solubility or stability to

hydration. Therefore, pharmaceutical cocrystals represent an opportunity to diversify the number of crystal forms of a given API and in turn fine-tune or even customize its physicochemical properties 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, one might assume that it will be possible for pharmaceutical cocrystals of existing APIs to be patented as new crystal forms and, if they exhibit clinical advantages, developed as new drugs. This has implications for drug development because it abbreviates some aspects of drug development timelines and mitigates costs and risks related to discovery and toxicology of new APIs.
- *Delivery*: As mentioned earlier, being able to fine-tune solubility can be a critical factor that influences the clinical performance of an API if its bioavailability is affected by rate of dissolution. This is generally considered to be important for BCS Class II APIs [57], perhaps the most common classification for the current generation of APIs.

The August 2008 release of the CSD contains structural information on 456,628 organic, metal–organic, and organometallic crystal structures, but there is not a great deal of structural information on cocrystals. There are only two cocrystal entries prior to 1960 and even today there are only ca. 2083 (0.46% of the CSD) hydrogen-bonded cocrystals versus 50,019 hydrates (10.95% of the CSD). Therefore, it would be fair to summarize cocrystals as being a long known but little studied class of compounds. Nevertheless, the realization that there will be multiple cocrystal formers for a given API makes pharmaceutical cocrystals somewhat diverse in terms of their composition. The scope of available cocrystal formers is not yet set but even if it is limited to "generally regarded as safe" (GRAS) compounds or compounds that have already been approved by the federally mandated Food and Drug Administration (FDA) for use in formulation such as a "salt formers," there could be 100 or more possible pharmaceutically acceptable cocrystal formers for an API.

In terms of the pharmaceutical industry, perhaps the earliest example of a pharmaceutical cocrystal was reported in a 1934 French patent that disclosed cocrystals of barbiturates with 4-oxy-5-nitropyridine, 2-ethoxy-5-acetaminopyridine, *N*-methyl-α-pyridone, and α-aminopyridine [36]. In 1995, Eli Lilly and Co. patented complexes of cephalosporins and carbacephalosporins, a class of β-lactam antibiotics, with parabens and related compounds [57]. In terms of the scientific literature, there were few reports of pharmaceutical cocrystals until the past decade. However, Caira demonstrated that "old" drugs such as sulfonamides can form cocrystals [58] and also emphasized their potential in drug development.

2.2.3. Design of Cocrystals A crystal engineering experiment typically involves CSD surveys followed by experimental work to prepare and characterize new compounds that are sustained by *supramolecular synthons*. Supramolecular synthons facilitate understanding of the supramolecular chemistry of the functional groups present in a given molecule and are prerequisites for designing a cocrystal since they facilitate selection of an appropriate cocrystal former(s). However, when multiple functional groups are present in a molecule, the CSD rarely contains enough information to address the hierarchy of the possible supramolecular synthons. Fortunately, the hierarchy of the supramolecular synthons that can occur for common functional groups such as carboxylic acids, amides, and alcohols with emphasis upon *supramolecular heterosynthons* is becoming better defined [12d,e]. Furthermore, it is becoming evident that such interactions are key to implementing a design strategy for cocrystals in which a target molecule forms cocrystals with cocrystal formers that are carefully selected for their ability to form supramolecular heterosynthons with the target molecule.

The design aspect of cocrystals is illustrated if one focuses upon carboxylic acids, perhaps the most important and widely studied functional group in the context of pharmaceutical cocrystals since carboxylic acids represent ca. 25% of marketed drugs and carboxylic acids are commonly used as salt formers or excipients. The CSD enables statistical surveys of intermolecular contacts as well as intramolecular connectivity and it is therefore a powerful tool for addressing supramolecular chemistry in the solid state. A survey of the CSD revealed that there were 8154 organic carboxylic acids in the CSD as of August 2008. However, an analysis of intermolecular contacts in this subset revealed that only 1926 of these carboxylic acids exhibit the carboxylic acid dimer supramolecular homosynthon (Fig. 6) and that only 143 exhibit the carboxylic acid catemer motif. So what about the remaining 75% of carboxylic acids that have been crystallographically characterized? As revealed by Fig. 7, there is a tendency for carboxylic acids to form supramolecular heterosynthons with, for example, chloride anions and aromatic nitrogen moieties. Furthermore, the statistics seem to strongly favor these supramolecular heterosynthons over the corresponding supramolecular homosynthons. For example, there are 277 crystal structures that contain both a carboxylic acid and a chloride anion and 180 of them exhibit the carboxylic acid chloride supramolecular heterosynthon. In only one of this subset of 277 crystal structures does the carboxylic dimer exist. The statistics are similar for the carboxylic acid—pyridyl supramolecular heterosynthon. There are 606 crystal structures that contain both a carboxylic acid and a pyridyl moiety and 415 of them exhibit the carboxylic acid—pyridyl supramolecular heterosynthon. In only 25 of this subset of 606 crystal structures does the carboxylic dimer exist. In short, although these data are raw and une-

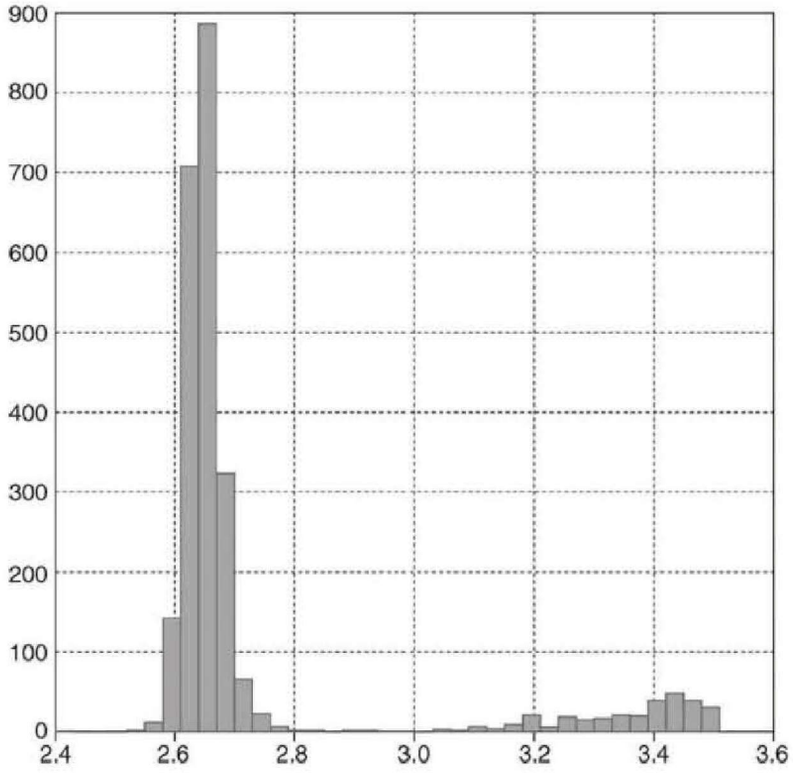

Figure 6. Distribution of carboxylic dimer contacts between 2.4 and 3.6 Å in organic only carboxylic acid crystal structures in the CSD. The distribution reveals 1926 H-bonded contacts between 2.55 and 2.80 Å.

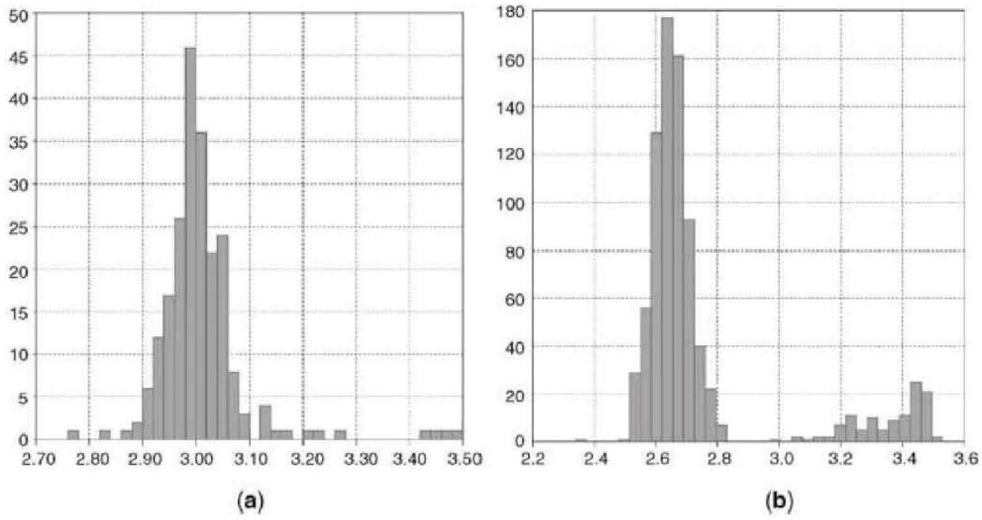

Figure 7. (a) Distribution of carboxylic acid—chloride anion contacts between 2.4 and 3.6 Å in organic only carboxylic acid crystal structures that also contain chloride anions. There are 180 short contacts between 2.7 and 3.3 Å. (b) Distribution of carboxylic acid—aromatic nitrogen contacts between 2.4 and 3.5 Å in organic only carboxylic acid crystal structures that also contain aromatic nitrogen moieties.

dited, it strongly suggests that if the relevant functional groups are in different molecules then a cocrystal involving supramolecular heterosynthons is likely to occur over the corresponding single component structures that would be sustained by supramolecular homosynthons. This principle is exemplified by several of the case studies presented herein.

2.2.4. Polymorphs, Solvates, and Hydrates of Cocrystals There remains a dearth of systematic structure and property information on cocrystals. However, at this point there is no reason to believe that pharmaceutical cocrystals will be more or less promiscuous than single component APIs when it comes to crystal form diversity. For example, both conformational and packing polymorphs have been observed in cocrystals. Figure 8 reveals that rotation around the central C—C bond in 4,4′-biphenol can afford conformational polymorphism in the 2 : 1 cocrystal of 4-cyanopyridine and 4,4′-biphenol [59]. Figure 9 reveals how a model cocrystal based upon the pyridine-carboxylic acid supramolecular synthons [60], a supramolecular synthons that is particularly relevant to APIs, exhibits packing polymorphism. In this case, packing polymorphism manifests itself through networks and interpenetration in the polymorphs of the 3 : 2 cocrystal of 4,4′-bipyridylethane and trimesic acid [61].

3. CASE STUDIES THAT DEMONSTRATE HOW CRYSTAL FORMS CAN IMPACT PHYSICOCHEMICAL PROPERTIES AND/OR BIOAVAILABILITY

3.1. Case Studies of Polymorphs

The impact of polymorphism on solubility was addressed by Pudipeddi and Serajuddin, who collated data on 81 polymorphic pairs [62]. The majority of these polymorphs (63/81) were observed to exhibit a solubility ratio of ≤ 2 and only one pair of polymorphs exhibits a solubility ratio of >10. This outlier, premafloxacin (Fig. 10), is a broad-spectrum antibiotic initially developed for veterinary use by Pharmacia and Upjohn, Inc. and it is chemically known as [*S*-(*R**,*S**)]-1-cyclopropyl-6-fluoro-1,4-dihydro-8-methoxy-7-{3-[1-methylamino) ethyl]-1-pyrrolidinyl}-4-oxo-3-quinolinecarbo-

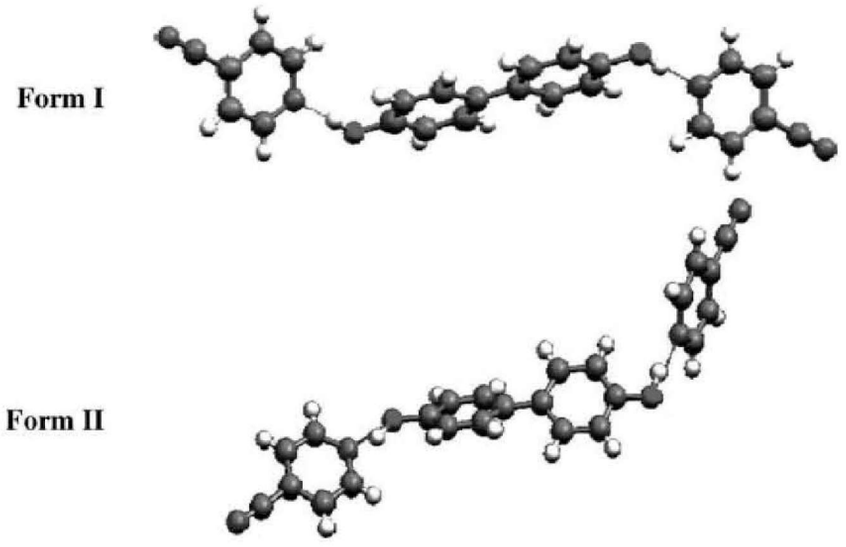

Figure 8. The conformational polymorphs exhibited by the 2:1 cocrystal of 4-cyanopyridine and 4,4′-biphenol.

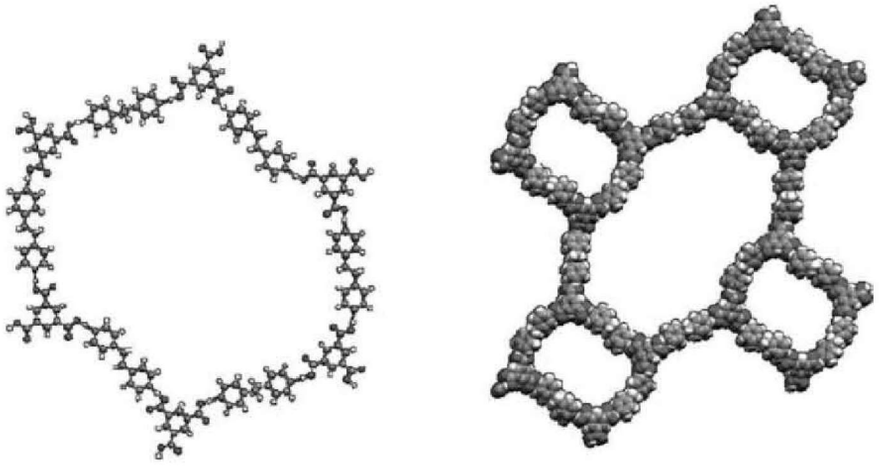

Figure 9. The 3:2 cocrystal of 4,4′ bipyridylethane and trimesic acid exhibits two packing polymorphs: a (6,3) honeycomb network that with 3-fold parallel interpenetration and a (10,3)-*a* 3D network with 18-fold interpenetration.

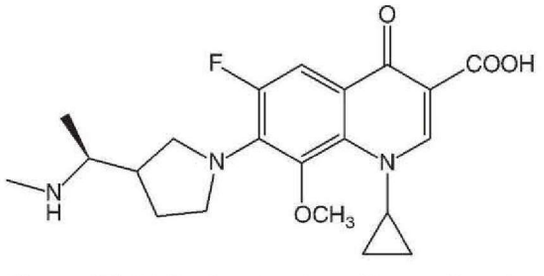

Figure 10. Molecular structure of premafloxacin.

xylic acid. This fluoroquinolone derivative has activity against a wide range of veterinary pathogens with equivalent activity to similar antibiotics such as ciprofloxacin against Gram-negative bacteria but enhanced MICs (minimum inhibitory concentration) against Gram-positive bacteria [63]. This API exhibits polymorphism and five crystal forms have been reported although they are not yet

archived in the CSD [64]. Schinzer et al. analyzed interconversion of these crystal forms through PXRD, thermomicroscopy, DSC, isothermal calorimetry, and dynamic moisture sorption gravimetry [64]. It was concluded that three anhydrous forms, a hydrate and a methanol solvate exist. Form I was made by desolvating the methanol solvate and form II was a metastable form that occurred through a melt-recrystallization process at 140–150 °C. When heated further, another phase transition occurred at 165–180 °C and resulted in form III. The hydrate was formed by exposing form I to 80% relative humidity (RH). Form III can be grown directly from ethylacetate but not from methanol, which results in the methanol solvate. Form I was observed to convert to form III at temperatures as low as 40 °C in the presence of moisture but at a RH of 51%, the rate of conversion was almost two orders of magnitude lower than at 75% RH. Form III is the most stable form and it sorbed less water than form I at all humidity conditions tested. Solubility in ethyl acetate was determined to be 3.23 mg/mL for form I and 0.14 mg/mL for form III (i.e., solubility ratio between the most soluble form and least soluble form is 23.1), easily the largest solubility ratio difference of the 81 polymorphic pairs analyzed [62].

3.2. Case Studies of Pharmaceutical Cocrystals

Perhaps, the earliest examples of pharmaceutical cocrystals were described in a series of studies conducted in the 1950s by Higuchi and his coworkers [65,66], who studied complex formation between macromolecules and certain pharmaceuticals; for example, complexes of polyvinylpyrrolidone (PVP) with sulfathiazole, procaine hydrochloride, sodium salicylate, benzylphenicillin, chloramphenicol, mandelic acid, caffeine, theophylline, and cortisone were isolated [65,66]. However, these compounds 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 described in a series of papers by Zerkowski et al. [67], who reported the use of substituted barbituric acids, 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 [67]. In spite of 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 complementarity with melamine. Nevertheless, these studies highlighted 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. Undoubtedly, such a diversity of forms could offer an exciting opportunity to produce, patent and market novel API crystalline forms with improved physical properties of clinical relevance. Herein we have selected a series of case studies (Table 1) that illustrate how pharmaceutical cocrystals can significantly alter the physicochemical properties of APIs.

3.2.1. Pharmaceutical Cocrystals of Carbamazepine (Tegretol®) Carbamazepine (CBZ) has been used as an important anti-epileptic drug for over three decades. The oral administration of CBZ encounters multiple challenges, including low water solubility with high dosage for therapeutic effect (i.e., >100 mg/day), dissolution-limited bioavailability, and autoinduction for metabolism. In contrast to its simple molecular structure, CBZ exhibits complex behavior in the context of its crystal forms [15b,68]. A CSD analysis on CBZ reveals that it has four fully characterized polymorphs [69], a dihydrate [70], 14 solvates (i.e., acetone, furfural, dimethyl sulfoxide, trifluoroethanol, dimethylformamide, *N*-methylpyrrolidone, nitromethane, acetic acid, formic acid, butyric acid, formamide, trifluroacetic acid, tetrahydrofuran, *N*,*N*′-dimethyl acetamide) [12b,71], two ammonium salts [72], and a solid solution with dihydrocarbamazepine [73]. In addition, Hilfiker et al. [74] have identified three new polymorphic forms and a dioxane solvate using high-throughput screening. It is noted that, in the crystal structures of all CBZ polymorphs and solvates, the self-complementary nature of the amide group manifests itself in a predictable manner.

Table 1. A Summary of Pharmaceutical Cocrystals in the Patent and Scientific Literature by February 2009

	API	Cocrystal Former	Solubility Study	Stability Study	Pharmacokinetic Study	References
1	(2R-*trans*)-6-Chloro-5-[[4-[(4-fluorophenyl) methyl] -2,5-dimethyl-1-piperazinyl]carbonyl] -*N*,*N*,1-trimethyl-alpha-oxo-1 *H*-indole-3-acetamide	HCl form: urea, arginine Free base form: salicylic acid, 4-aminosalicylic acid, benzoic acid				Chiarella RA. WO 2008013823 A2.
2	5,5′-Diphenylhydantoin	1-(4-Bromophenyl)-4-dimethylamino-2,3-dimethyl-3-pyrazolin-5-one				Uno T. Shimizu N. *Acta Crystallogr* 1980; B36:2794.
3	5-Methoxysulfadiazine	Acetylsalicylic acid				Caira MRJ. *Chem Crystallogr* 1994;24:695.
4	AMG 517	Benzoic acid, *trans*-cinnamic acid, 2,5-dihydroxybenzoic acid, glutaric acid, glycolic acid, *trans*-2-hexanoic acid, 2-hydroxycaproic acid, L-lactic acid, sorbic acid, L-tartaric acid	Dissolution		Pharmacokinetic study	[80a] [80b]
5	Aspirin	4,4′-Bipyridine				Walsh RBD, Bradner MW, Fleishman S, Morales LA, Moulton B, Rodriquez-Hornedo N, Zaworotko MJ. *Chem Commun* 2003;186.
6	Barbiturates	5,5′-Diethylbarbituric acid:*N*,*N*′-bis(4-t-butylphenyl)melamine 5,5′-Dimethylbarbituric acid:*N*,*N*′-bis(4-*t*-butylphenyl)melamine				[67]
7	Barbiturates	5,5′-Diethylbarbituric acid:acridine 5,5′-Diethylbarbituric acid:1,10-phenanthroline				Vishweshwar P, Thaimattam R, Jaskolski M, Desiraju GR. *Chem Commun* 2002;1830.

(*continued*)

Table 1 (*continued*)

	API	Cocrystal Former	Solubility Study	Stability Study	Pharmacokinetic Study	References
8	Barbiturates	5,5-Diethylbarbituric acid:2,4-diamino-5-(3,4,5-trimethoxybenzyl) pyrimidine				Shimizu N, Nishigaki S, Nakai Y, Osaki Y. *Acta Crystallogr* 1982;B38:2309.
9	Barbiturates	5,5-Diethylbarbituric acid: *N,N′*-diphenylmelamine				Zerkowski JA, Seto CT, Wierda DA, Whitesides GM. *J Am Chem Soc* 1990;112:9025.
		Barbituric acid:melamine				
10	Barbiturates	Amobarbital:salicylamide				Hsu IN, Craven BM. *Acta Crystallogr* 1974; B30:843.
11	Barbiturates	Barbital *N′*-(*p*-cyanophenyl)-*N*-(*p*-iodophenyl) melamine				Zerkowski JA, McDonald JC, Whitesides GM. *Chem Mater* 1994;6:1250.
		5,5-Dimethylbarbituric acid:*N,N′*-diphenylmelamine				
		Barbital 2-amino-4-(m-bromophenylamino)-6-chloro-1,3,5-triazine				
		5,5-Dibromobarbituric acid: melamine				
		Barbituric acid:melamine				
12	Barbiturates	Barbital:2-aminopyrine				Kiryu S. *J Pharm Sci* 1971;60:699.
13	Barbiturates	Barbital:9-ethyladenine				Voet DJ. *Am Chem Soc* 1972;94:8213.
14	Barbiturates	Phenobarbital:(4,4′-bipyridine-*N,N′*-dioxide)$_{0.5}$				Reddy LS, Babu NJ, Nangia A. *Chem Commun* 2006;1369.
		Barbituric acid:4,4′-bipyridine-*N,N′*-dioxide:H_2O				
15	Barbiturates	Phenobarbital:8-bromo-9-ethyladenine				Kim SH, Rich A. *Proc Natl Acad Sci USA* 1968;60:402.

16	Beta-lactam compounds	Cephalexin:methyl paraben:H_2O Cephradine:Methyl Paraben:H_2O Cefaclor:methyl paraben:$3H_2O$ Loracarbef:methyl 3-hydroxybenzoate:$5H_2O$ Loracarbef:methyl paraben Loracarbef:ethyl paraben Loracarbef:propyl paraben Loracarbef:butyl paraben	Amos JG, Indelicato JM, Pasini CE, Reutzel SM. EP0637587	
17	Bicalutamide (Casodex)	4,4′-Bipyridine, *trans*-1,2-bis(4-pyridyl)ethylene	Bis JA, Vishweshwar P, Weyna D, Zaworotko M. *J Mol Pharm* 2007;4:401.	[54b]
18	Caffeine	Formic acid, acetic acid, trifluoroacetic acid, adipic acid	Trask AV, van de Streek J, Motherwell WDS, Jones W. *Cryst Growth Des* 2005;5(6):2233.	[54b]
19	Caffeine	Glutaric acid, saccharin, salicylic acid	Lu E, Rodriguez-Hornedo N, Suryanarayanan R. *CrystEngComm* 2008;10(6):665.	
20	Caffeine	Methyl gallate	Sun CC, Hou H. *Cryst Growth Des* 2008;8(5):1575.	Mechanical stability
21	Caffeine	Oxalic acid, malonic acid, maleic acid, glutaric acid		[16d] Stability
22	Carbamazepine	4,4′-bipyridine, 4-aminobenzoic acid, 2,6-pyridinedicarboxylic acid		[76]
23	Carbamazepine	Aspirin		[49]
24	Carbamazepine	Benzoquinone, terephthalaldehyde, saccharin, nicotinamide, butyric acid, trimesic acid, 5-nitroisophthalic acid, adamantane-1,3,5,7-tetracarboxylic acid		[12b]

(*continued*)

Table 1 (*continued*)

	API	Cocrystal Former	Solubility Study	Stability Study	Pharmacokinetic Study	References
25	Carbamazepine	Glutaric acid, salicylic acid, urea.				Lu E, Rodriguez-Hornedo N, Suryanarayanan R. *CrystEngComm* 2008;10(6):665.
26	Carbamazepine	Glycolamide, lactamide				Ras E. WO 2008108639 A1.
27	Carbamazepine	Nicotinamide and saccharin (cocrystal form II)				[75]
28	Carbamazepine	*p*-Phthalaldehyde				[12c]
29	Carbamazepine	Quinoxaline *N*,*N*′-dioxide, pyrazine *N*,*N*′-dioxide				[13b]
30	Carbamazepine	Saccharin	Dissolution		Pharmacokinetic study	[68]
31	Carbamazepine	Succinic acid, benzoic acid, ketoglutaric acid, maleic acid, glutaric acid, malonic acid, oxalic acid, adipic acid, (+)-camphoric acid, 4-hydroxybenzoic acid, salicylic acid, 1-hydroxy-2-naphthoic acid, DL-tartaric acid, L-tartaric acid, glycolic acid, fumaric acid, DL-malic 2 acid, L-malic acid (total of 27 forms)	Dissolution	Stability in water		[55]
32	Celecoxib	Nicotinamide, 18-crown-6	Dissolution	Stability		[12c] Remenar JF, Peterson ML, Stephens PW, Zhang Z, Zimenkov Y, Hickey MB. *Mol Pharm* 2007;4(3):386.
33	C-glycoside (1*S*)-1,5-anhydro-1-[3-(1-benzothien-2-ylmethyl)-4-fluorophenyl]-D-glucitol	L-proline		Stability	Pharmacokinetic study	[83a]

34	Fenbufen	Nicotinamide			Berry DJ, Seaton CC, Clegg W, Harrington RW, Coles SJ, Horton PN, Hursthouse MB, Storey R, Jones W, Friscic T, Blagden N. *Cryst Growth Des* 2008;8(5):1697.
35	Fluconazole maleate	Maleic acid hydrate			McMahon J, Peterson M, Zaworotko MJ, Shattock T, Bourghol Hickey M. WO 2006007448 A2.
36	Fluoxetine HCl	Fumaric acid, succinic acid, benzoic acid	Dissolution		[14c]
37	Flurbiprofen	4,4′-Bipyridine, 1,2-bis(4-pyridyl)ethylene			Walsh RBD, Bradner MW, Fleishman S, Morales LA, Moulton B, Rodriquez-Hornedo N, Zaworotko MJ. *Chem Commun* 2003;186.
38	Flurbiprofen	Nicotinamide			Berry DJ, Seaton CC, Clegg W, Harrington RW, Coles SJ, Horton PN, Hursthouse MB, Storey R, Jones W, Friscic T, Blagden N. *Cryst Growth Des* 2008;8(5):1697.
39	Gabapentin	3-hydroxybenzoic acid	Solubility	Stability	Reddy LS, Bethune SJ, Kampf JW, Rodriguez-Hornedo N. *Cryst Growth Des* 2009;9(1):378.
40	Gemfibrozil	Hydroxy derivatives of t-butylamine			Cheung EY, David SE, Harris KDM, Conway BR, Timmins P. *J Solid State Chem* 2007;180:1068.
41	Gossypol	C1–8 carboxylic acid, C1–8 sulfonic acid (example only shows acetic acid solvate)			Wang S, Chen S. WO 2005094804 A1.
42	Ibuprofen	4,4′-bipyridine			Walsh RBD, Bradner MW, Fleishman S, Morales LA, Moulton B, Rodriquez-Hornedo N, Zaworotko MJ. *Chem Commun* 2003;186.
43	Ibuprofen	Nicotinamide			Berry DJ, Seaton CC, Clegg W, Harrington RW, Coles SJ, Horton PN, Hursthouse MB, Storey R, Jones W, Friscic T, Blagden N. *Cryst Growth Des* 2008;8(5):1697.
44	Imipramine HCl	(+)-Camphoric acid, fumaric acid, 1-hydroxy-2-naphthoic acid	Dissolution		Childs SL. WO 2007067727 A2.
45	Indomethacin	Saccharin	Dissolution	Stability	Basavoju S, Bostroem D, Velaga SP. *Pharm Res* 2008;25(3):530.

(*continued*)

Table 1 (*continued*)

	API	Cocrystal Former	Solubility Study	Stability Study	Pharmacokinetic Study	References
46	Isovaleramide	Citric acid, gentisic acid, glutaric acid, maleic acid, mandelic acid				Oliveira M, Peterson M. WO 2006116655 A2.
47	Itraconazole	Fumaric acid, L-tartaric acid, succinic acid, D-tartaric acid, L-malic acid, DL-tartaric acid	Dissolution		Pharmacokinetic study	[15a]
48	Lamivudine	Zidovudine, 3,5-dinitrosalicylic acid, 4-quinolinone				Bhatt PM, Azim Y, Thakur TS, Desiraju GR. *Cryst Growth Des* 2009;9:951–957.
49	Merck compound I N-{(1*S*)-1-[2-(1-{[(3*S*,4*R*)-1-*tert*-butyl-4-(2,4-difluorophenyl)pyrrolidin-3-yl] carbonyl}piperidin-4-yl)-5-chlorophenyl]ethyl} acetamide	HCl cocrystal of HCl salt (rigorously not a cocrystal)	Solubility			Peresypkin A., Variankaval N, Ferlita R, Wenslow R, Smitrovich J, Thompson K, Murry J, Crocker L, Mathre D, Wang J, Harmon P, Ellison M, Song S, Makarov A, Helmy R. *J Pharm Sci* 2008;97(9):3721.
50	Merck monophosphate salt	Phosphoric acid	Solubility	Stability	Pharmacokinetic study	[84]
51	Mestanolone	Salicylic acid				Takata N, Shiraki K, Takano R, Hayashi Y, Terada K. *Cryst Growth Des* 2008;8(8):3032.
52	Metronidazole	Gentisic acid, gallic acid	Dissolution			Childs SL. WO 2007067727 A2.
53	Modafinil	Malonic acid, succinic acid, fumaric acid	Dissolution		Pharmacokinetic study	[12c] Peterson M, Bourghol Hickey M, Oliveira M, Almarsson O, Remenar J. US Patent 2,005,267,209 A1.
54	Naproxen	*trans*-1,2-bis(4-Pyridyl) ethylene, 1,2,4,5-tetracyanobenzene				Weyna DR, Zaworotko MJ. Abstracts, 59th Southeast Regional Meeting of the American Chemical Society, 2007, GEN-015. Koshima H, Ding K, Chisaka Y, Matsuura T. *Tetrahedron* 1995;6:101.
55	Norflaxacin	Isonicotinamide (salts formed with malonic acid, and maleic acid)	Solubility			Basavoju S, Bostroem D, Velaga SP. *Cryst Growth Des* 2006;6:2699.

56	Norfloxacin	Norfloxacin saccharinate-saccharin dihydrate cocrystal	Velaga SP, Basavoju S, Bostroem D. *J Mol Struct* 2008;889(1–3):150.
57	Olanzapine	Nicotinamide	[12c]
58	Ornidazole	3,5-Dinitrobenzoic acid	Anderson KM, Probert MR, Whiteley CN, Rowland AM, Goeta AE, Steed JW. *Cryst Growth Des* 2009; 9:1082.
59	Paracetamol	Morpholine	Oswald IDH, Motherwell WDS, Parsons S, Pulham CR, *Acta Crystallogr* 2002;E58(11): o1290.
60	Phosphodiesterase-IV Inhibitor	L-Tartaric acid	Variankaval N, Wenslow R, Murry J, Hartman R, Helmy R, Kwong E, Clas S-D, Dalton C, Santos I. *Cryst Growth Des* 2006;6:690.
61	Piracetam	Gentisic acid, 4-hydroxy-benzoic acid	[12a]
62	Piroxicam	L-Tartaric acid, citric acid, fumaric acid, adipic acid, succinic acid, L-malic acid, glutaric acid, DL-malic acid, oxalic acid, (+)-camphoric acid, ketoglu-taric acid, benzoic acid, 4-hydroxybenzoic acid, malonic acid, salicylic acid, glycolic acid, 1-hydroxy-2-naphthoic acid, gentisic acid, DL-tartaric acid, maleic acid, caprylic acid, hippuric acid, L-pyroglu-tamic acid (50 cocrystals)	[14a]
63	Piroxicam	Saccharin Solubility	Bhatt PM, Ravindra NV, Banerjee R, Desiraju, GR. *Chem Commun* 2005;1073.
64	Pyrazinamide	2,5-Dihydroxybenzoic acid	[76]
65	Quercetin	Isonicotinamide Solubility	Zaworotko MJ, Clarke H, Kapildev A, Kavuru P, Shytle Roland D, Pujari T, Marshall L Ong TT. WO 2008153945 A2.

(*continued*)

Table 1 (*continued*)

	API	Cocrystal Former	Solubility Study	Stability Study	Pharmacokinetic Study	References
66	Salicylic acid	Nicotinamide				Berry DJ, Seaton CC, Clegg W, Harrington RW, Coles SJ, Horton PN, Hursthouse MB, Storey R, Jones W, Friscic T, Blagden N. *Cryst Growth Des* 2008;8(5):1697.
67	Sildenafil	Aspirin	Solubility			Zegarac M, Mestrovic E, Dumbovic A, Devcic M, Tudja P. WO 2007080362 A1.
68	Sodium-channel blocker [4-(4-chloro-2-flourophenoxy)phenyl]pyrimidine-4-carboxamide	2-Glutaric acid	Dissolution		Pharmacokinetic study	[79]
69	Stanolone	L-Tartaric acid				Takata N, Shiraki K, Takano R, Hayashi Y, Terada K. *Cryst Growth Des* 2008;8(8):3032.
70	Sulfadimidine	2-Aminobenzoic acids, 4-aminobenzoic acid				Caira MR. *J Crystallogr Spectrosc Res* 1991;21:641.
71	Sulfadimidine	Aspirin, 4-aminosalicylic acid				Caira MR. *J Crystallogr Spectrosc Res*1992;22:193.
72	Sulfadimidine	*p*-Chlorobenzoic acid				Lucaciu R, Ionescu C, Wildervanck A. Caira MR. *Analytical Sciences: X-Ray Structure Analysis Online* 2008;24(5):87.
73	Sulfadimidine	Trimethoprim, 2-aminobenzoic acid, 4-aminobenzoic acid, aspirin, 4-aminosalicylic acid, 2-aminobenzoic acid				58
74	Sulfamethazine	Indole-2-carboxylic acid, 2,4-dinitrobenzoic acid				Lynch DE, Sandhu P, Parsons S. *Aust J Chem* 2000;53:383.
75	Sulfamethazine	Nicotinamide, saccharin, salicylic acid				Lu E, Rodriguez-Hornedo N, Suryanarayanan R. *CrystEngComm* 2008;10(6):665.
76	Sulfamethoxypyridazine	Trimethoprim				58
77	Sulfathiazole	Sulfanilamide				Shefter E, Sackman P. *J Pharm Sci* 1971;60:282.

78	Sulfathiazole	Trimethoprim			Giordano F, Bettinetti GP, La Manna A, Ferloni P. *Farmaco Ed Sci* 1977;*32*:889.
79	Temozolomide	4,4′-Bipyridine-*N*,*N*′-dioxide Carbamazepine, 3-hydroxypyridine-*N*-oxide			Babu NJ, Reddy LS, Aitipamula S, Nangia A. *Chem An Asian J* 2008;3(7):1122.
80	Tenofovir disoproxil	Hemi-fumaric acid		Pharmacokinetic study	Dova E, Mazurek JM, Anker J. WO 2008143500 A1.
81	Theophylline	5-Chlorosalicylic acid			Shefter E. *J Pharm Sci*.1969;58:710.
82	Theophylline	Glutaric acid, nicotinamide, saccharin, salicylic acid and urea			Lu E, Rodriguez-Hornedo N, Suryanarayanan R. *CrystEngComm* 2008;10(6):665.
83	Theophylline	L-Tartaric acid, DL-tartaric acid			Friscic T, Fabian L, Burley JC, Jones W, Motherwell MDS. *Chem Commun* 2006;5009.
84	Theophylline	Malonic acid, glutaric acid, maleic acid, oxalic acid	Stability		[16c]
85	Theophylline	Phenobarbital			Nakao S, Fujii S, Sakaki T, Tomita K. *Acta Crystallogr* 1977;B33:1373.
86	Theophylline	*p*-Nitrophenol			Aoki K, Ichikawa T, Koinuma Y, Iitaka Y. *Acta Crystallogr* 1978;B34:2333.
87	Theophylline	Sulfathiazole			Shefter E, Sackman P. *J Pharm Sci* 1971;60:282.
88	Trimethoprim	5,5′-Diethylbarbituric acid			Shimizu N, Nishigaki S, Nakai Y, Osaki K. *Acta Crystallogr* 1982;B38:2309.
89	VX-950	Salicylic acid, 4-aminosalicylic acid, oxalic acid	Solubility Suspension stability		Connelly PR. WO 2007098270 A2.
		4-Hydroxybenzoic acid, 4-amino salicylic acid, phenylalanine, threonine, tartaric acid, adipic acid, succinic acetate, proline, me 4-hydroxybenzoate, anthranilic acid, and D-biotin			Connelly PR, Kadiyala I, Stavropolus K, Zhang Y, Johnston S, Bhisetti GR, Jurkauskas V, Rose P. WO 2008106151 A2.
90	Zidovudine	2,4,6-Triaminopyrimidine			Bhatt PM, Azim Y, Thakur TS, Desiraju GR. *Cryst Growth Des* 2009:9:951–957.

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 [12b,68], Two strategies have been adopted for cocrystal formation of CBZ. One crystal engineering strategy is to employ the peripheral H-bonding capabilities that are not engaged in the pure form of CBZ. A second strategy for cocrystallization of CBZ involves breakage of CBZ amide–amide dimer and formation of a supramolecular heterosynthon between CBZ and a cocrystal former [12b]. Both strategies have proven to be successful and have afforded a number of CBZ cocrystals that exhibit improved physicochemical properties. Crystal structures of 16 CBZ cocrystals including cocrystal hydrate/solvates and cocrystal polymorphs [12b,13b, 49,75,76] have been determined and deposited in the CSD. As further crystal form studies of CBZ continue, Childs et al. [55] have demonstrated the preparation of 27 unique solid phases of CBZ utilizing 18 carboxylic acids as cocrystal formers together with four different screening methods.

CBZ perhaps has more reported cocrystals than any other API and some of these cocrystals have also been studied in terms of their dissolution and bioavailability. For example, the CBZ:saccharin cocrystal shows significantly improved physical stability, that is, between two polymorphic cocrystal forms [68,75] that have been identified, the stable form I [68] can be reliably prepared and have equivalent chemical stability to the anhydrous polymorph. In addition, the CBZ:saccharin cocrystal form I possesses favorable dissolution properties and suspension stability. One dissolution study shows that, within the initial 10 min, the API concentration in water solution generated by slurry of the CBZ:saccharin cocrystal form I is twice as much by slurry of the pure CBZ. In the further study of pharmacokinetics using dog models, the CBZ:saccharin cocrystal form I prototype exhibits comparable oral absorption profile with the marketed immediate release formulation [68]. In summary, the CBZ:saccharin cocrystal form I appears to be superior to existing crystal forms of CBZ in many respects.

3.2.2. Pharmaceutical Cocrystals of Fluoxetine Hydrochloride (Prozac®) The availability and marketability of a variety of APIs as chloride salts is long known 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 [14c]. That chloride is perhaps the most preferred anion for salts APIs makes generating cocrystals of fluoxetine HCl prototypal for many other APIs. 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 is available in the salt form. Childs et al. have demonstrated the preparation of cocrystals of fluoxetine HCl using pharmaceutically acceptable carboxylic acids that form hydrogen bonds with the chloride ions. In addition, the resulting cocrystals of fluoxetine HCl, while still retaining the hydrochloride salt of the API, exhibit dramatically different physical properties compared to the original API [14c]. Fluoxetine HCl cocrystals are the first cocrystal examples of an HCl salt.

Fluoxetine HCl was cocrystallized with benzoic acid (1 : 1), succinic acid (2 : 1), and fumaric acid (2 : 1) from solution evaporation. For all three cocrystals, the carboxylic acid was found to hydrogen bond to the chloride ion that in turn interacted with the protonated amine, thus generating, in all three cases, an amine hydrochloride salt hydrogen bonding to an additional neutral molecule [14c]. Powder dissolution experiments were carried out in water for these three novel cocrystals resulting in a spread of dissolution profiles (Fig. 11). 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 2-fold increase in aqueous solubility after only 5 min. The complex formed between succinic acid and fluoxetine

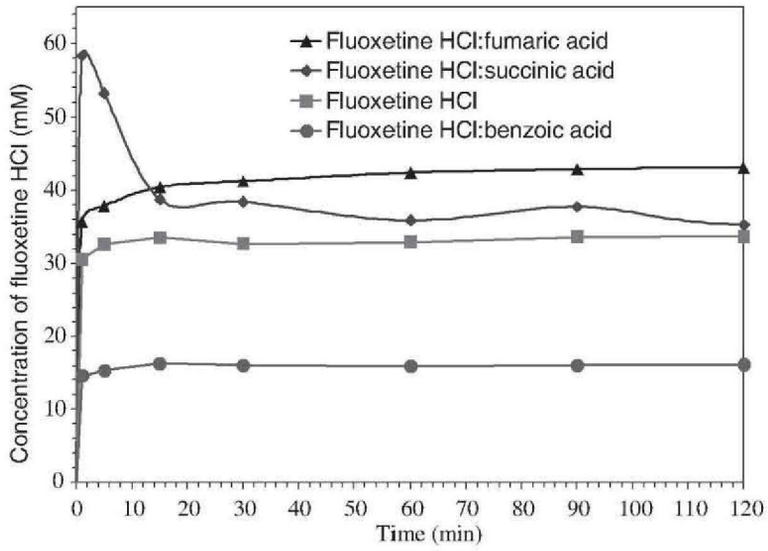

Figure 11. Dissolution profiles for novel forms of fluoxetine HCl.

HCl falls apart in solution to generate its pure components after about 1 h. The intriguing factor in this study is that by simply hydrogen bonding a hydrochloride salt of an API with similar cocrystal formers one can generate such distinctively different dissolution profiles [14c].

3.2.3. Pharmaceutical Cocrystals of Itraconazole (Sporanox®) Itraconazole is a triazole antifungal agent that is extremely water insoluble, that is, aqueous solubility of itraconazole is estimated to be ca. 1 ng/mL at neutral pH and ca. 4 µg/mL at pH 1 [77]. It is administered both orally and intravenously for patients with fungal infections [15a]. 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, coadministration of acidified beverages with Sporanox capsules is required to achieve the maximal absorption of the API, even though such a coadministration could cause diarrhea [15a,78]. Interestingly, no crystalline salt of itraconazole has been reported in the patent literature, despite that salt formation using itraconazole and an acidic salt former seems to be a logical approach to improve the absorption properties of the API. To improve the absorption of the API and maintain the form crystallinity/stability, the pharmaceutical cocrystal approach has been evaluated in the formulation of itraconazole. As successfully demonstrated in the previous examples, crystalline phases of itraconazole can be engineered by introduction of additional molecules to match hydrogen-bond donors and acceptors [15a,78]. A number of stable pharmaceutical cocrystals of itraconazole and 1,4-dicarboxylic acids were synthesized and characterized [15a]. The cocrystals each contain two API molecules and one acid cocrystal former hydrogen bonded together to form a trimeric assembly. The aqueous dissolution of itraconazole cocrystals was studied to assess their potential impact on bioavailability of the API. The dissolution of itraconazole cocrystals was observed to behave more similarly to 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 [15a]. In a further pharmacokinetic study of itraconazole cocrystals, it was revealed that cocrystal for-

mulation of the API gives similar oral bioavailability to the Sporanox form in the animal trial using a dog model [78]. In short, this study demonstrates the use of pharmaceutical cocrystals for the improvement of solubility and bioavailability without compromising crystallinity and stability.

3.2.4. Pharmaceutical Cocrystals of 2-[4-(4-Chloro-2-Fluorophenoxy)Phenyl]Pyrimidine-4-Carboxamide, a Sodium-Channel Blocker 2-[4-(4-Chloro-2-fluorophenoxy)phenyl]pyrimidine-4-carboxamide (CFPPC) is an active pharmaceutical compound that belongs to the pharmacologic class of sodium-channel blockers; CFPPC was developed as a potential drug candidate useful for treating or preventing surgical, chronic, and neuropathic pain [79]. The pharmacokinetic study in dogs shows that the oral bioavailability of CFPPC is very low due to its extremely low aqueous solubility (i.e., <0.1 μg/mL). Based on the calculated octanol/water partition coefficient ($c \log P$ 2.9), it is suspected that CFPPC is a compound of BCS Class II. To identify a solid form with better bioavailability, both pharmaceutical salts and amorphous materials of CFPPC have been investigated, yet the attempt was proven to be unsuccessful. As an alternative choice of development, the potential of forming CFPPC pharmaceutical cocrystals with higher dissolution rate has been examined [79].

A cocrystal screening was carried out employing both melt crystallization and supersaturated solution crystallization. A total of 26 carboxylic acids has been used in the screening while cocrystals of CFPPC and glutaric acid with 1 : 1 molecular ratio was successfully obtained and characterized. The CFPPC:glutaric acid cocrystal that can be scaled up in gram quantities, is nonhygroscopic and chemically and physically stable to thermal stress. An additional dissolution study revealed that the intrinsic dissolution rate of CFPPC in the cocrystal form showed an 18-fold increase compared to that of the original API in water at 37 °C. Single-dose pharmacokinetic evaluations for the CFPPC:glutaric acid cocrystal has also been performed. At the 5 mg/kg dose, the use of cocrystal significantly improved *in vivo* exposure in dogs, as the cocrystal achieved a mean plasma AUC (i.e., area under curve) of 1234 ng·h/mL from an original value of 374 ng·h/mL for the free base. In addition, the use of CFPPC:glutaric acid cocrystal also exhibits a significant increase of the AUC value using a dosage of 50 mg/kg CFPPC equivalent. Clearly, this case study exhibits how *in vivo* exposure of the original API could be significantly increased by the pharmaceutical cocrystal approach [79].

3.2.5. Pharmaceutical Cocrystal of AMG 517 AMG 517 is a transient receptor potential vanilloid 1 antagonist that was developed by Amgen, Inc. for the treatment of acute and chronic pain [80]. It is observed that AMG 517 has several isolated crystal forms, that is, two polymorphs and a number of crystalline solvates including a monohydrate that is stable for at least 3 years at ambient conditions. The free base of AMG 517 is practically insoluble in water and in physiological pH buffer solutions. Naturally, development of pharmaceutical salts for AMG 517 has been attempted whilst the resulting forms were found unstable in aqueous solutions, that is, they either converted to the monohydrate or decomposed at lower pH conditions. As a result, AMG 517 was formulated as a suspension in 10% (w/v) Pluronic F108 in the OraPlus® at lower doses and satisfying *in vivo* exposure in animal studies have been observed. However, absorption at higher doses was limited by the low solubility of AMG 517. Interestingly, a further investigation of the AMG 517 suspension revealed the unexpected *in situ* formation of AMG 517:sorbic acid cocrystals. Physical characterization including a solubility study was carried out for the cocrystal of AMG 517 and sorbic acid. The solubility study in FaSSIF (fasted state simulated intestinal fluid, pH 6.8) [81] showed that the AMG 517:sorbic acid cocrystal achieved an API concentration almost 10 times that of AMG 517 free base at 1.1 h. After prolonged slurry, it was observed that the cocrystal converted back to the free base monohydrate form. The pharmacokinetic study using Sprague-Dawley rats was also carried out. At 500 mg dose, the peak plasma concentration (C_{max}) of AMG 517 achieved by oral administration of the cocrys-

tal was approximately 7.7 times that of the free base. Meanwhile, the *in vivo* exposure of the cocrystal formulation, as indicated by $AUC_{0\text{-inf}}$, increased almost 10 times compared to that of the free base formulation. In reality, the 30 mg/kg dose AMG 517:sorbic acid cocrystal formulation has a comparable exposure to a 500 mg/kg dose free base formulation. AMG 517 has also been found to be capable of cocrystallizing with 10 additional carboxylic acids, that is, benzoic acid, *trans*-cinnamic acid, 2,5-dihydroxybenzoic acid, fumaric acid, glutaric acid, glycolic acid, *trans*-2-hexanoic acid, 2-hydroxycaproic acid, L-lactic acid, and L-tartaric acid. The physicochemical properties such as particle size, solubility, stability, hygroscopicity, thermal behavior, and structural characteristics of these cocrystals were studied in details. Good correlation between the melting point of cocrystal formers and AMG 517 cocrystals has been observed; while no direct correlation was found between melting point and solubility of the AMG 517 cocrystals [80].

3.2.6. 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 [82]. 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 and marketed by Pfizer, Inc. and is available under the trademark Viagra [82]. 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 [82]. The crystal structure of the cocrystal of sildenafil and acetylsalicylic acid has been determined by single-crystal X-ray diffraction [82] 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 [82]. An intrinsic dissolution study in simulated gastric fluid (pH 1.2) shows that the sildenafil:acetylsalicylic acid cocrystal exhibits an intrinsic dissolution rate (IDR) of ca. 11.75 mg/min·cm^2. Within just 10 min, the IDR of sildenafil:acetylsalicylic acid cocrystal exhibits approximately twice that of sildenafil citrate under the same conditions [82].

3.2.7. Pharmaceutical Cocrystal of a C-Glycoside Derivative Recently a *C*-glycoside derivative, (1*S*)-1,5-anhydro-1-[3-(1-benzothien-2-ylmethyl)-4-fluorophenyl]-D-glucitol (ABYFG), has been developed as an active pharmaceutical compound to inhibit Na^+-glucose cotransporter for the treatment and prevention of diabetes, such as insulin-dependent diabetes (type 1 diabetes) and non-insulin-dependent diabetes (type 2 diabetes), insulin resistance diseases, and obesity [83]. The crystal of ABYFG forms a clathrate hydrate that reversibly transform from an anhydrous compound to a nonstoichiometric hydrate depending on hygrothermal condition. Because of its physical instability, ABYFG is difficult to retain a constant quality as a drug substance used for preparing pharmaceuticals. To avoid the formation of clathrate hydrate, investigation of novel crystal forms of ABYFG has been attempted using various solvents or solvent mixtures. It was observed that, while some solvents still produced the clathrate, others led to the formation of solvates that contain hazardous solvents in the crystal lattices. Pharmaceutical salt formation was also considered. Given the fact that ABYFG is present as a nonionic compound in an ordinary pH range, however, preparation of a pharmaceutically acceptable salt of ABYFG is impossible. As a result, pharmaceutical cocrystal approach has been used to explore for novel crystal forms of ABYFG with consistent quality and superior storage stability.

Thirty-five amino acids were used in the cocrystal form screening with ABYFG. Consequently, cocrystals of ABYFG and L-proline form at a 1 : 1 molar ratio from water/alcoholic solutions. It is noted that the ABYFG:L-proline cocrystal is one of the first pharmaceutical cocrystals comprising a sugar derivative and a zwitterions [82]. In the storage stability test, the ABYFG:L-proline cocrystal showed no form transformation in the condition of no less than 7 days at 25 °C at 63.5–84% RH. The cocrystal was also physically stable for at least 2 months at 40 °C (75% RH, open vial), 60 °C (uncontrolled humidity) or 80 °C (uncontrolled humidity). In addition, the cocrystal, with only of 0.7% or less moisture contents, showed no moisture absorption between 5% and 95% RH range. Moreover, the *in vivo* pharmacological study using nonfasted mice as test animals showed that oral administration of the ABYFG:L-proline cocrystal with a 1 mg/kg dose enabled a strong antihypoglycemic action. In summary, this case study demonstrates the use of a zwitterion as a coformer in the pharmaceutical cocrystallization such that consistent quality and superior storage stability can be achieved in a crystalline form of the original API [83].

3.2.8. Pharmaceutical Cocrystal of a Monophosphate Salt I Compound **I** was in the drug development pipeline of Merck, Inc. As the development of a crystalline form of compound **I** was not successful, an amorphous bis-HCl salt was initially selected for early development. Such an amorphous form, however, was proven unsuitable for further development as an oral dosage form due to its hygroscopicity and chemical instability [84]. After 1 week storage at 40 °C and 80 °C (both at ambient RH), the amorphous HCl salt exhibits 7 and 40% degradation, respectively. Extensive efforts have been taken to identify a crystalline form for compound **I**. As a result of the high-throughput screening, the only crystalline form produced was compound **I** with two phosphoric acids. A more careful analysis of the crystal structure revealed that, in such a crystal structure, half of phosphoric acids are ionized while the other half remain neutral; clearly this molecular complex is a cocrystal of compound **I** monophosphate salt and phosphoric acid (Fig. 12) [84].

The physicochemical properties of this cocrystal were characterized. It was observed that the cocrystal exhibited a high melting point of ca. 235 °C, plate-like morphology and good powder flow properties. No degradation has been detected for the cocrystal within 8 weeks of storage at 40 °C/75% RH and 60 °C. In addition, the cocrystal was found highly soluble in water and showed an excellent *in vivo* performance. The cocrystal structure was proven to be stable as no cocrystal polymorph was obtained from high-throughput screening. Naturally, this cocrystal was selected as the optimal solid form for further development. Cocrystal of compound **I** monophosphate salt and phosphoric acid is the first example of pharmaceutical cocrystals formed between an API phosphate and a phosphoric acid. Such an example sheds light on the use of

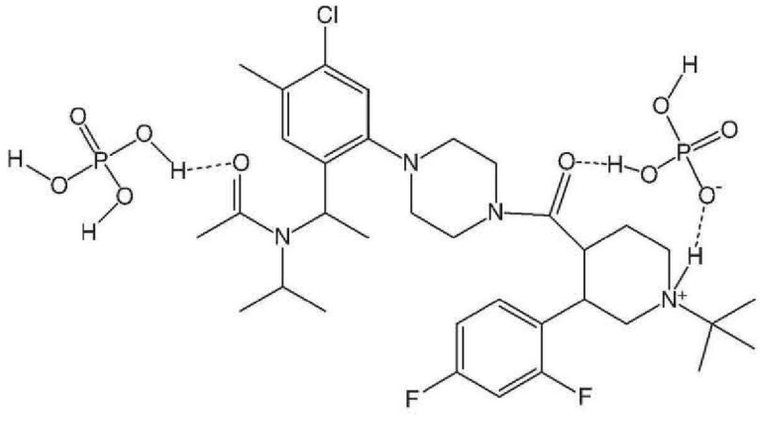

Figure 12. Phosphoric acid cocrystal of compound **I** phosphate salt.

an inorganic acid as a coformer in the pharmaceutical cocrystal approach for exploring suitable solid dosage forms in pharmaceutical development [84].

3.2.9. 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 [85]. At first, melamine that 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, that is, the acute toxicity of melamine in rats has reported oral lethal doses 50 (LD_{50}) of 3100 mg/kg (male) and 3900 mg/kg (female) [85]. 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 cocontaminant. Although melamine and cyanuric acid are relatively safe individually, no data could be found in the literature that has determined the potential toxicity of melamine and cyanuric acid in combination [85]. From the crystal engineering viewpoint, melamine and cyanuric acid (1 : 1 molar ratio) form extensive two-dimensional network in the solid state based on robust three-point molecular recognition, and it was observed that the resulting melamine:cyanuric acid cocrystal is highly insoluble in water [85,86]. 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 are not fully understood to date [85]. 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 [85] 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 cocrystal is the first example showing how cocrystals can significantly alter the relevant physical properties in a negative manner.

4. CONCLUSION

The science of crystal structure prediction continues to evolve [52] and the legal and regulatory aspects of API crystal forms are also moving targets. Nevertheless, the relevance of crystal forms to oral delivery, intellectual property and regulatory control is unlikely to diminish when one considers the impact of pharmaceutical cocrystals upon crystal form diversity and the resulting opportunity to customize the physicochemical properties of APIs. In this context, the "state of the art" concerning pharmaceutical cocrystals can be summarized as follows:

- Cocrystals were discovered at least as early as 1844 but they are underrepresented in the CSD (ca. 0.5% of structures). In short, they might be long known but they are little studied.
- In principle, the range of cocrystal formers for an API can include excipients, salt formers, food products, and nutraceuticals, that is, pharmaceutical cocrystals will ultimately offer more crystal form diversity than polymorphs, solvates, hydrates, and salts combined.
- Unlike polymorphs, solvates, hydrates. and salts, pharmaceutical cocrystals are amenable to a level of design from first principles, that is, by exploiting the supramolecular heterosynthon strategy.
- Pharmaceutical cocrystals can profoundly change the physicochemical properties of an API by using noncovalent bonds only, that is, without making derivatives of the API.
- Although there are limited data on solubility and bioavailability, it is becoming apparent that pharmaceutical cocrystals

can afford unique pharmacokinetic profiles because of the complex mechanisms of dissolution.

- Pharmaceutical cocrystals can be prepared via multiple methods (e.g., supercritical fluids, solution, mechanochemistry, melt, slurry) and their discovery is not as amenable to high-throughput screening as, for example, polymorphs and solvates.
- There remain a number of legal and regulatory uncertainties because there are few if any precedents.

The overall situation is that pharmaceutical cocrystals represent a vehicle to fine-tune the physicochemical properties of APIs, especially in terms of solubility and stability. It should therefore be unsurprising that they are being studied extensively by pharmaceutical companies in preclinical research and their more commonplace usage in drug products seems to be imminent. From a crystal engineering perspective it is now feasible to view pharmaceutical cocrystals as a mechanism to address control and/or customization of properties to a particular need, that is, we are now able to "engineer crystals." The almost 50-year old dream of physicist and Nobel Laureate Richard Feynman is therefore being realized: "I can hardly doubt that when we have some control of the arrangement of things on a small scale we will get an enormously greater range of possible properties that substances can have, and of different things that we can do" (Richard P. Feynman lectures, December 29, 1959).

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