Pharmaceutical Cocrystals: An Emerging Approach to Physical Property Enhancement

William Jones, W.D. Samuel Motherwell, and Andrew V. Trask

Abstract

Pharmaceutical cocrystals are crystalline molecular complexes containing therapeutic molecules. They represent an emerging class of pharmaceutical materials offering the prospect of optimized physical properties. This article highlights important opportunities and challenges associated with the design and synthesis of pharmaceutical cocrystals. Cocrystallization is first placed into context with the more established approaches to physical property optimization of polymorph, hydrate, and salt selection. A directed, intermolecular-interaction-based approach to cocrystal design is described. The enhancement of specific physical properties, such as dissolution rate and physical stability, is illustrated by summarizing several recent reports. Synthetic approaches to cocrystallization are considered; in particular, the selectivity and screening-related opportunities afforded by solid-state grinding and solvent-drop grinding methods are discussed. Finally, an outlook on future developments summarizes the growth potential in this field, especially with regard to targeted, informatics-driven cocrystal screening approaches.

Keywords: *biomedical, crystal growth, crystalline.*

Introduction

On average, about a decade of research and development is expended in the discovery and commercialization of a new pharmaceutical product. Initial R&D efforts center on the identification of a suitable molecular structure, physical form, and formulation. Whereas the molecular structure of the active pharmaceutical ingredient (API) of a drug substance is selected to optimize therapeutic properties, selecting the physical form of an API represents a strategic opportunity for optimizing such physical properties as solubility, dissolution rate, hygroscopicity, physical stability, and chemical stability.[1]

Most APIs are dosed as solids, and most solid APIs exist in the crystalline form. Frequently, however, the API does not crystallize on its own or it crystallizes into one or more crystal forms that possess undesirable physical properties. In either case, an alternative crystal form is typically sought. Various options include single-component and multiple-component modifications of an API, including polymorphs, salts, solvates, and hydrates. In addition to these established crystalline API modifications, pharmaceutical cocrystals, or crystalline molecular complexes involving an API, have recently attracted interest as an alternative approach.

This article outlines how pharmaceutical cocrystals offer an alternative approach to physical property optimization during crystal form selection. Important design strategies for making cocrystals are described, along with some recent examples of using cocrystals to enhance specific physical properties. Cocrystal screening and synthesis are also covered, particularly using solid-state grinding and solvent-drop selective cocrystal synthesis.

Solid-State Modifications of APIs

Polymorphs

A polymorph is "a solid crystalline phase of a given compound resulting from the possibility of at least two different arrangements of the molecules of that compound in the solid state."[2] Different polymorphs of a given compound each possess a unique set of physicochemical properties, and many, if not most, compounds exhibit polymorphism to some extent.[1,3,4] Some compounds exist in more than ten crystal form modifications.[5] At present, it is not generally possible to computationally predict the number of observable polymorphs of even the simplest molecules,[6] and as a result, the use of high-throughput screening methods to search for new polymorphic forms has become an important tool in form screening.[5]

Hydrates and Solvates

Frequently during crystallization, solvent may be taken up and incorporated as part of the crystal structure. Most solvents, however, are biologically toxic; as a result, most solvate-containing crystals are avoided in the development of the solid form of an API.

An important exception is the subclass of API hydrates, which are well known in pharmaceutical products.[7,8] It has been estimated that one-third of pharmaceutical molecules are capable of forming hydrates.[9,10] As a result of process-induced stresses, such as changes in temperature, pressure, or relative humidity, hydrates often convert into anhydrous crystal forms. This conversion from hydrate to anhydrate can result in significant changes in physical properties and can present major issues, for example, during storage, where hydrate conversion can compromise dosage form appearance and integrity.

Pharmaceutical Salts

Salt formation is a common approach to modifying the properties of an API.[11–13] Salt formation is an acid–base reaction between the API and an acidic or basic substance. It is an attractive strategy, because most pharmaceutical compounds possess either acidic or basic functionality, and the widespread use of salt formation is evidenced by the large number of marketed crystalline salts of APIs.[14]

Pharmaceutical Cocrystals

A more recent approach to pharmaceutical physical property optimization is pharmaceutical cocrystal formation. A cocrystal may be thought of as a crystalline complex of two or more neutral molecular constituents bound together in the crystal lattice through noncovalent interactions, often including hydrogen bonding.

The application of cocrystallization to the pharmaceutical industry provides inherent benefits as compared with salt formation in at least two ways. The first is that, at least in theory, all types of molecules can form cocrystals, including weakly ionizable and non-ionizable APIs, which are traditionally considered to present a higher risk in terms of physical property optimization because they have either limited or no capacity for salt formation.

A second benefit is that, whereas for toxicological reasons only 12 or so acidic or basic counterions are explored in a typical API salt screen,[12,15] there are many potential counter-molecules that may be used in cocrystal synthesis. (A counter-molecule may be defined as the species cocrystallized with the API.) The U.S. Food and Drug Administration manages several lists of substances that have precedence as food ingredients (e.g., the FDA's GRAS list, a list of substances "generally recognized as safe"), with the total amount of substances numbering in the thousands. Although the increased scope of cocrystals is a benefit in that it suggests a greater likelihood of achieving a desirable physical property profile for an API physical form, it also presents a challenge in terms of screening efforts, even with high-throughput screening.

To maximize efficiency in screening for cocrystals, therefore, improved rational cocrystal design and more efficient cocrystal screening protocols are needed.

Synthon Approach to Cocrystal Design

The formation of cocrystals has been studied for some time in academic research, and various important studies aimed at understanding cocrystal design have been published.

In early studies, Etter and co-workers proposed several "hydrogen-bond rules," including the observations that (1) all good proton donors and acceptors are used in hydrogen bonding, and (2) the best donor typically pairs with the best acceptor in a given crystal structure.[16] The combined use of the hydrogen-bond rules with a geometric analysis (known as graph-set analysis[17]) assisted Etter and co-workers in implementing rational cocrystal design in the synthesis of many new supramolecular structures.

Allen et al. demonstrated a quantification of the "robustness" of a certain class of intermolecular arrangements (commonly called motifs, or synthons) involving strong hydrogen-bonded bimolecular ring motifs. Their analysis involved examining trends within the Cambridge Structural Database (CSD), a searchable repository containing more than 300,000 small-molecule crystal structures.[18] They assessed the robustness of a motif in terms of its "formation probability," that is, the observed frequency of motif formation among all structures containing the necessary functional group components. A higher formation probability suggested a greater utility in a cocrystal design scheme.

By relying on robust intermolecular interactions with demonstrated solid-state reproducibility, synthon-based cocrystal design has become increasingly important to the synthesis of new cocrystal materials. In the future, automated searches for formation probabilities pertaining to the molecular structure of an API of interest will be an important step toward rational pharmaceutical cocrystal design.

Pharmaceutical Cocrystals and Physical Property Enhancement

During the past few years, the focus on pharmaceutical cocrystals has increased significantly.[19] In 2002, Oswald et al. demonstrated cocrystallization of the analgesic drug paracetamol (acetaminophen) with six different counter-molecules, each of which was capable of acting as a hydrogen-bond acceptor.[20] Shortly thereafter, Zaworotko and co-workers reported cocrystals of the APIs ibuprofen, flurbiprofen, and aspirin with several hydrogen-bond acceptors.[21] These examples served as early proof that a series of cocrystals with common hydrogen-bonding features may be obtained with APIs. Aside from melting point data, however, these reports focused essentially on structural features without addressing the functional properties that these cocrystals might offer. Additionally, from an industrial standpoint, these were only model systems, in that the non-API components were, in most cases, not known to be safe for human ingestion.

In a subsequent paper, Zaworotko and co-workers reported on a series of cocrystals of the API carbamazepine, a drug used in the treatment of epilepsy, with a variety of different counter-molecules, including several that are biologically nontoxic, including acetic acid, nicotinamide (vitamin B_3), and the well-known sweetener saccharin.[22] The report brought to light the variety of possible counter-molecules that may form cocrystals with a single API.

Despite the increase in reports containing new pharmaceutical cocrystal structures, however, only a limited number of studies have directly addressed the realization of physical property modification. One report of a pharmaceutical cocrystal with enhanced dissolution properties involved cocrystals of several nontoxic C_4 (four-carbon) 1,4-dicarboxylic acids with itraconazole, an antifungal drug with very low aqueous solubility in its crystalline free base form.[23] The cocrystals reportedly resulted from a high-throughput crystal form screen of itraconazole, and the acids in the study were known to be biologically nontoxic at common pharmaceutical dosage levels.[15] Single-crystal data were reported for one of the cocrystals, a 2:1 itraconazole:succinic acid cocrystal (Figure 1), where it was observed that the diacid spanned two itraconazole molecules via OH···N hydrogen bonds. All of the cocrystals demonstrated an enhanced dissolution profile as compared with itraconazole free base, and in some cases the dissolution profiles of the cocrystals approached that of amorphous itraconazole, which itself had been developed for the specific aim of enhancing the dissolution rate of the API.

The same study also emphasized the value of performing high-throughput cocrystal screening in addition to implementing rational design methodology. In the itraconazole:succinic acid cocrystal, the diacid formed a hydrogen bond with the five-membered triazole ring rather than with the most basic site on the drug molecule, the nitrogen of the six-membered piperazine ($pK_a = 3.7$). This example appeared to violate the best-donor–best-acceptor hydrogen-bond rule in preference for what may have been a geometric consideration: attempts to cocrystallize itraconazole with dicarboxylic acid chain lengths other than C_4, including malonic (C_3), glutaric (C_5), and adipic (C_6) acids, were reportedly unsuccessful. Until it becomes possible to confidently predict which counter-molecules will form cocrystals with a given API, high-throughput screening will continue to be of tremendous value to this research field.

A second demonstration of dissolution rate enhancement via cocrystallization involved three pharmaceutical cocrystals of the API fluoxetine, the active ingredient in the antidepressant drug Prozac.[24] This case was of particular interest from the standpoint of cocrystal design: the researchers formed cocrystals by combining a carboxylic acid with the hydrochloric acid (HCl) salt of fluoxetine, generating three novel cocrystals of salts. For example,

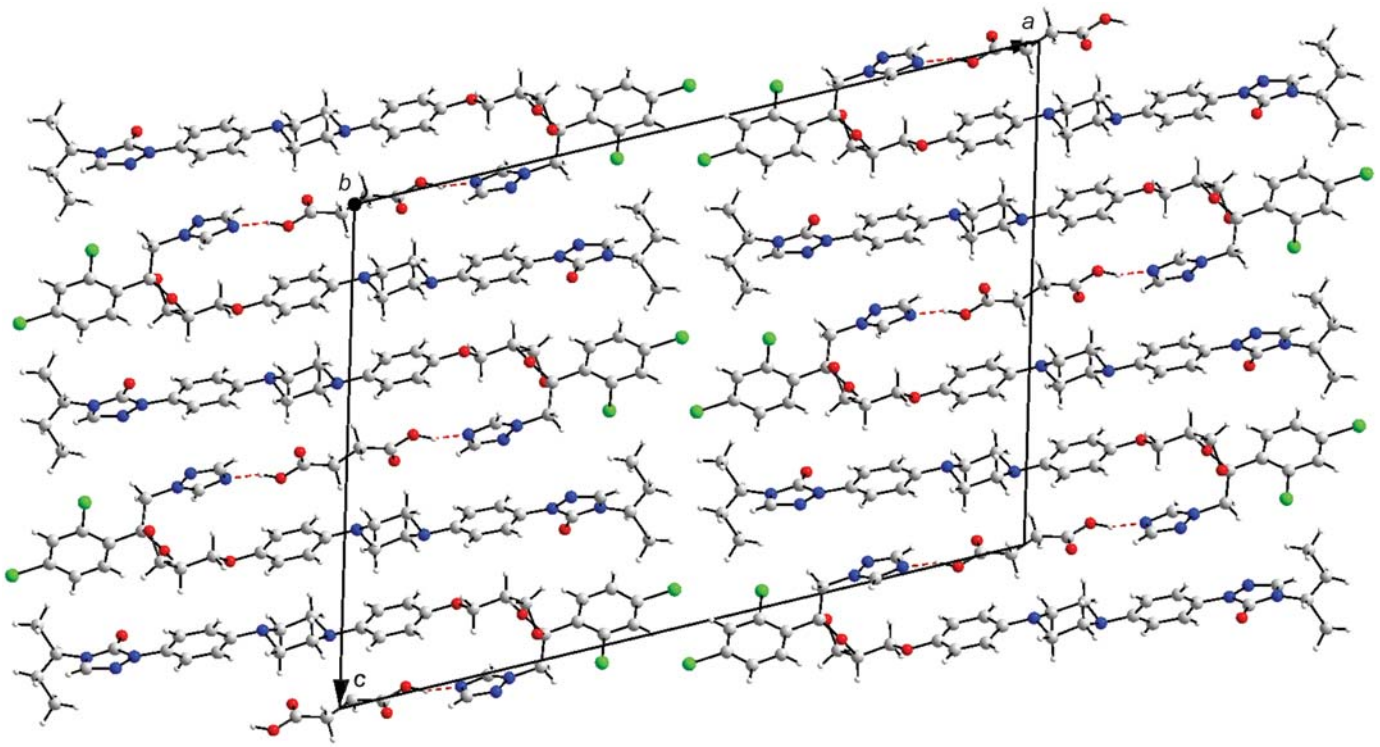


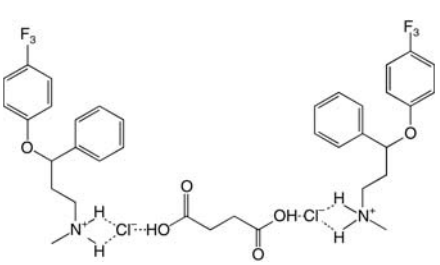
Figure 1. Crystal packing diagram and corresponding unit cell of the 2:1 itraconazole:succinic acid cocrystal.[23] Carbon atoms are large and gray, hydrogen atoms are small and white, nitrogen atoms are blue, oxygen atoms are red, and chlorine atoms are green.

fluoxetine:HCl salt was cocrystallized with succinic acid to form a succinic acid cocrystal of the fluoxetine:HCl salt, with a stoichiometry of 2:2:1 fluoxetine:chloride:succinic acid (see Structure **1**). Significant differences in the measured dissolution rates of each of the three cocrystals were observed, such that individual cocrystals were found to exhibit rates above, below, and comparable with that of the crystalline HCl salt. In general, multiple-component cocrystals (and cocrystals of salts) with more than two components are evidence of the wide supramolecular diversity that may be achieved via cocrystal design.

The issue of physical stability enhancement via cocrystallization was addressed using caffeine as a model API. Caffeine is known to exhibit solid-state physical instability as a function of relative humidity (RH); its stable anhydrous polymorph undergoes conversion to a crystalline hydrate upon exposure to high RH, and the hydrate loses water below a critical RH and reverts to the anhydrate. This form of physical instability limits the processing and storage conditions of an API in development. Caffeine also has a limited salt-forming capacity attributable to its weak basicity (its conjugate acid has a reported pK_a of 3.6), meaning that it is capable of forming salts only with strong acids. Only one pharmaceutically acceptable salt of caffeine had been reported in the CSD, a caffeine HCl salt that existed as a dihydrate.

A cocrystallization study was initiated to obtain a series of cocrystals of caffeine that could be measured with regard to RH stability.[25] A strategy was devised whereby caffeine cocrystallization was attempted with several pharmaceutically acceptable dicarboxylic acids of various chain lengths. The strategy relied upon a caffeine-acid hydrogen-bond interaction that satisfied the hydrogen-bond rules, forming a motif that exhibited a good degree of robustness in the CSD.

Six caffeine:dicarboxylic acid cocrystals were reported, and the results of storing cocrystal materials at several RH conditions were described. One cocrystal (the 2:1 caffeine:oxalic acid cocrystal, Figure 2), was physically stable at all RH conditions and all time points across the study. This cocrystal material was also fully stable upon slurrying in water. The stability of the caffeine:oxalic acid cocrystal is particularly remarkable given that both caffeine and oxalic acid, as pure materials, are known to convert to crystalline hydrates. The reason for this stability is currently being studied.



*Structure **1**. Hydrogen-bond arrangement in the crystal structure of succinic acid cocrystal of fluoxetine:HCl salt; taken from crystal structure data.[24]*

Supramolecular Synthesis via Solid-State Grinding

Solid-state grinding is the act of mixing, pressing, and crushing materials manually

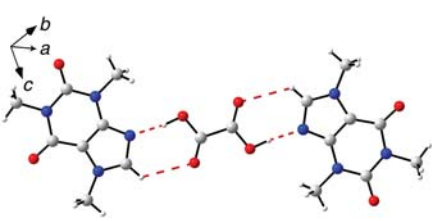


Figure 2. Hydrogen bonding in a 2:1 caffeine:oxalic acid cocrystal. Carbon atoms are large and gray, hydrogen atoms are small and white, nitrogen atoms are blue, and oxygen atoms are red.

with a mortar and pestle or mechanically in a mill. A common means of particle size reduction, solid-state grinding may also be performed on a mixture of materials to induce covalent or supramolecular reactivity. In the context of pharmaceutical cocrystals, solid-state grinding has emerged recently as a viable synthetic alternative to solution-based crystallization methods. In certain cases, pharmaceutical cocrystal synthesis by solid-state grinding offers enhanced selectivity as compared with that of solution crystallization. Moreover, the simplicity of the technique in revealing the cocrystallization potential between two molecular species suggests application in cocrystal screening efforts.

Caira and co-workers provided an early demonstration of the application of solid-state grinding to pharmaceutical cocrystal synthesis in a study of six cocrystals of the sulfa drug sulfadimidine with various carboxylic acids, including anthranilic acid (AA) and salicylic acid (SA).[26] Additionally, a remarkable preference was demonstrated for one particular cocrystal, the sulfadimidine:AA cocrystal. In a grinding competition experiment, a sulfadimidine:SA cocrystal, for which the crystal structure had been previously determined, was ground in the presence of AA. The result was a displacement of SA by AA as the cocrystal partner of sulfadimidine. Because of the common hydrogen-bonding pattern in both cocrystals, the authors based their explanation for the preference on the relative strengths of hydrogen bonding in the ingoing homomeric acid crystals. In extending these results to pharmaceutical processing considerations, it can be imagined that a grinding competition experiment such as the one just described might be used to assess the stability of a given pharmaceutical cocrystal material in the presence of excipients (i.e., substances other than the pharmacologically active drug in the final drug product) that may be encountered in the course of a formulation process.

With regard to the caffeine cocrystals described in the previous section, whereas single crystals were obtained by solution growth, it was reported that most cocrystals could also be prepared by grinding together the reactants in a ball mill. This finding was not unexpected: solid-state grinding has been repeatedly relied upon as a viable synthetic method for organic cocrystals. Solid-state grinding was often used by Etter and co-workers as a means of preparing cocrystal materials for the investigation of hydrogen-bond preferences. Furthermore, in a number of instances they reported that certain cocrystal modifications could be formed only by the grinding method. These and other examples of this phenomenon were recently summarized.[27]

The ability of solid-state grinding to reveal alternative cocrystal modifications would be particularly useful in pharmaceuticals, where unforeseen polymorphic transformations can bring disastrous consequences, including the withdrawal of a pharmaceutical product from the market.[28] For example, in a model system of cocrystals with caffeine and several monocarboxylic acids, solid-state grinding generated crystal forms which were initially inaccessible from solution. In experiments involving caffeine and trifluoroacetic acid, cocrystal material synthesis was initially found to be possible only via grinding. Two 1:1 polymorphs were identified and could be prepared separately depending upon the quantity of starting material in the grinding jars. The structure of each was solved from powder x-ray diffraction (PXRD) data. Subsequently, by using seeds obtained by grinding, cocrystal material of each polymorph was prepared by solution growth methods. This seeding method was used to obtain a single crystal for one of the structures, which confirmed the initial PXRD structure solution of that polymorph.[29]

Enhanced Supramolecular Selectivity via Solvent-Drop Grinding

A modification to the solid-state grinding experiment has enabled enhanced supramolecular selectivity in certain cocrystal systems. Termed "solvent-drop" grinding, this method allows for stoichiometric and polymorphic selectivity in two model cocrystal systems.

Solvent-drop grinding involves the grinding of two materials together, as with solid-state grinding, but with the addition of a minor quantity of solvent (typically a few tenths of one equivalent of solvent per mole of starting material). The added solvent acts in what may be described as a catalytic role, in that the quantities employed are small and the solvent is not a component of the final cocrystal product.

The usefulness of solvent-drop grinding was first demonstrated in the context of cocrystallization rate enhancement in a system involving several cocrystals of nitrogenous bases with a cyclohexanetricarboxylic acid derivative, all of which were initially prepared by solution growth. It was found that some cocrystals could be readily prepared by solid-state grinding, whereas others exhibited only minor cocrystal content after grinding together starting materials for a significant time. For those that did not proceed to completion upon solid-state grinding, it was found that solvent-drop grinding could be used to prepare an essentially phase-pure cocrystal material after significantly reduced periods of time.[30]

Solvent-drop grinding was then found to enable selective polymorphic synthesis between two 1:1 caffeine:glutaric acid cocrystals (Forms I and II).[31] The two polymorphs, which shared an identical sheet-like hydrogen-bonding arrangement and differed primarily in terms of the stacking of sheets, were first found to precipitate concomitantly from solution. In an effort to prepare each polymorphic modification separately, grinding was explored as a method of cocrystal synthesis. It was found that solid-state grinding of caffeine and glutaric acid produced predominantly Form I and that solvent-drop grinding with polar solvents (cyclohexane, hexane, and heptane) also produced Form I in the absence of Form II. Alternatively, phase-pure Form II could be prepared by the grinding of starting materials in the presence of more polar solvents (acetonitrile, chloroform, and water). A possible factor that may have had a role in this observed selectivity was the observation of a potential nonpolar cleavage plane in the Form I polymorph. Examples have also been reported of stoichiometric selectivity via solvent-drop grinding.[25]

In addition to the ability of solvent-drop grinding to provide for polymorphic and stoichiometric selectivity in cocrystallization, the technique has also been demonstrated as a way of interconverting crystal forms of polymorphic organic materials, such as succinic acid and anthranilic acid.[32] In the case of succinic acid, grinding of the stable polymorph in the presence of nonpolar solvents was found to result in significant quantities of the metastable polymorph, hitherto known to crystallize only at high temperatures. AA, a trimorphic system, underwent interconversions between the three different polymorphs depending upon the solvent that was added in minor quantities to the grinding experiment. A schematic depicting the interconversions among AA polymorphs is provided as Figure 3.

Solvent-drop grinding has also found application with regard to crystalline salt synthesis with pharmaceuticals.[33] Salt screening is an important aspect of physical property optimization, as well as intellectual property protection, for many API candidates. Much effort, increasingly using high-throughput robotics, is expended in revealing all potential salts (and polymorphs of salts) to ensure that the salt selection is made from the widest knowledge of potential candidates.[5]

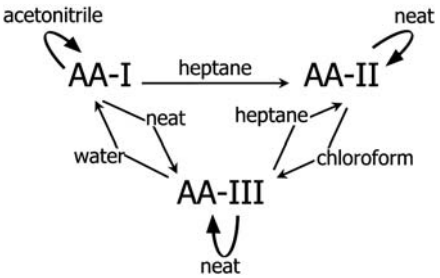


Figure 3. Interconversions among anthranilic acid (AA) polymorphs via solvent-drop grinding.

Conclusions and Outlook

Physical property improvement via cocrystallization will be of increasing importance in the area of pharmaceutical solid form selection in the near future. Several hurdles remain, however, before this technique can become fully implemented in the industry.

The wide number and variety of possible counter-molecules that may be considered in a cocrystal screen with an API is a significant benefit of this approach, but offers challenges in terms of screening efforts. There is a tremendous number of potential counter-molecule combinations to be explored in a given cocrystal screen, especially if ternary systems are to be considered (e.g., three-component cocrystals and cocrystals of salts). Current crystal form screening methodology, to a certain extent, applies a predetermined set of crystallization variables to any system under study. This unguided approach could generate an insurmountable number of different cocrystal synthetic possibilities.

In screening for cocrystals, it is therefore necessary to develop a guided screening methodology. This approach may include an initial stage during which potential counter-molecules for an API are automatically pre-screened and ranked using informatics tools such as the CSD, described in the earlier section Synthon Approach to Cocrystal Design. Counter-molecules that are capable of forming more robust hydrogen-bond motifs with the API may be ranked higher in terms of likelihood of cocrystal formation. In subsequent experimental efforts, higher-ranking cocrystal counter-molecules might justify increased experimental screening resources with the API of interest.

In consideration of the typically small quantity of material available during the development stages of an API, it also appears necessary to improve experimental screening methodology to facilitate cocrystal screening efforts. Solution-based techniques, which are most common in current polymorph and salt screens, require a small amount of sample per experiment, but entail a large number of experiments to cover variables such as solvent system choice, concentration, and heating or cooling profiles, among others. Techniques such as solid-state grinding, as well as the developing approach of solvent-drop grinding, appear to offer a highly efficient alternative for offering evidence of whether two materials will cocrystallize. Other techniques, such as crystallization from the melt using techniques such as thermal microscopy and differential scanning calorimetry, may also offer the opportunity to screen for cocrystals with minimal expenditure of API material and reduced experimental effort.

This two-step cocrystal screening approach, involving an informatics-based ranking of counter-molecules followed by targeted, efficient cocrystal screening methodology, remains to be fully demonstrated. Nonetheless, as examples mount that indicate the ability of cocrystals to overcome the physical property shortcomings of API candidates, a guided approach to pharmaceutical cocrystal screening should become increasingly important for the successful implementation of cocrystallization in the pharmaceutical industry.

Acknowledgments

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