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Diversity in Single- and Multiple-Component Crystals. The Search for and Prevalence of Polymorphs and Cocrystals

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ABSTRACT: A detailed description of polymorph screening procedures is presented. On the basis of the results of 245 polymorph screens, organic compounds were found to exist in multiple solid forms quite frequently. About 90% exhibited multiple crystalline and noncrystalline forms; about 50% exhibited polymorphism. Cocrystals are defined, and cocrystal screening is discussed. Data from 64 cocrystal screens show that cocrystals were found in 61% of the cases, and the total number of cocrystals found was 192.

1. Introduction

The properties of a solid material depend not only on the identity of its constituents but also on their arrangement. Crystalline solids are those in which the component atoms, molecules, or ions are arranged in a regularly ordered, repeating pattern in three dimensions. It is quite common for a single constituent to be able to exist in more than one crystalline arrangement. Consequently, solids with significantly different physical properties may be constructed from a single atom, ionic compound, or molecule. This behavior in single-component organic crystals is called polymorphism.

Crystals also may contain more than one type of atom, ionic compound, or molecule. Such cocrystals will have different properties than do crystals made from each constituent alone.

It is primarily with organic compounds used as pharmaceuticals that this article is concerned. There is really no reason to classify organic compounds as "pharmaceuticals" or "non-pharmaceuticals" in discussing solid properties. Compounds used in the pharmaceutical industry are quite structurally varied; there is not any specific chemical attribute that renders them pharmaceutically active. The questions that are intended to be addressed are the following: (1) How does one determine if a given organic compound is polymorphic? (2) How common is polymorphism among organic compounds? (3) How does one search for cocrystals? and (4) How frequently can cocrystals be found?

2. Allotropes

The ability of a single chemical substance to exist in different arrangements was first recognized in inorganic materials.[1] When exhibited by elements, this phenomenon is called allotropism, a term introduced by Berzelius in 1844.[2] It has been reported that 54−55 elements are allotropic, but this count encompasses allotropes in solid, liquid, and gas phases.[3] Descriptions of the elements in CRC's *Handbook of Chemistry and Physic*s contain references to solid allotropes for 29 elements.[4] Included are commonly cited examples such as carbon (graphite, diamond, fullerenes, amorphous) and phosphorus (stable red form used for matches and unstable white form), along with examples less likely to be encountered by the average scientist. Promethium, for example, does not appear to exist naturally on earth, but enough has been produced by atomic reactions to study its properties and it was found to exist in two allotropic forms.[4]

A particularly interesting example of allotropism occurs in elemental tin. It exists in two forms: a white, cubic, more-dense form that is stable above 13 °C (56 °F) and a gray, tetragonal, less-dense form that is stable below that temperature. Many things have been made from white tin or its alloys, but on extended exposure to cold temperatures such things can disintegrate as conversion from the more-dense to the less-dense allotrope results in crumbing of the metal into powder. This behavior is known as "tin disease" or the "tin pest". The disease has claimed European organ pipes,[5] historically valuable pewter pieces,[6] military computers in Afghanistan,[7] and perhaps even contributed to the loss of Robert Scott and his crew during their 1910 expedition to the South pole.[8] In the last case, a cache of kerosene cans that had been soldered with tin were found to be empty.

It is important to realize that elements can exist in different structures in any phase (gas, liquid, or solid) when the structures differ in the number and type of relatively strong bonds. For example, sulfur exists in S_2, S_6, or S_8 allotropes, structures that are maintained in both the solid and the gaseous states. The structures differ in their covalent bonding patterns, and covalent bonds are strong enough to endure vaporization temperatures.

3. Polymorphs

The accepted description of polymorphism as applied to organic compounds is that it is exhibited only in the solid state. On melting, vaporization, or dissolution, polymorphic structures are lost. The reason is that relatively weak hydrogen bonds, ionic interactions, and van der Waals attractions hold crystals together that are made of discreet, covalently bonded, organic molecules. Energies necessary to cause melting, vaporization, or dissolution are sufficient to disrupt the weak intermolecular interactions but not the strong intramolecular covalent bonds. Thus, organic polymorphism has some boundaries that make it a unique area of study.

The pharmaceutical industry recognized the importance of polymorphism only recently. A review published in 1969 by the eminent microscopist Walter McCrone entitled *Pharmaceutical Applications of Polymorphism*[9] seems to define the beginning of that recognition. A culminating event was the temporary removal from the market of the life-saving protease inhibitor Norvir in 1998, which occurred because of the appearance of a previously unknown polymorph of the active ingredient ritonavir.[10] The marketed dosage form of Norvir consisted of gel-caps filled with a solution containing ritonavir. The new crystalline form is more stable, and therefore less

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Table 1. Polymorph Screens

goal	screen type	material requirement
determine the propensity for polymorphism	preliminary	<0.5 g
find the thermodynamically stable form	stable form screen	1−2 g
confirm the selected form can be produced with GMP material[a]	focused	1−2 g
find the best form for development	solid form selection	2−5 g
widest experimental scope to find all forms possible	comprehensive	variable

[a] Material made under good manufacturing practices (GMP) conditions.

soluble, than the old form and crystallized out of solution inside the gel-caps, rendering the formulation unmanufacturable.

The Food and Drug Administration (FDA), the U.S. regulatory agency that oversees the pharmaceutical industry, published a guidance for drug developers in 2000 that states:[11] "Some new drug substances exist in different crystalline forms that differ in their physical properties. Polymorphism may also include solvation or hydration products (also known as pseudopolymorphs) and amorphous forms. Differences in these forms could, in some cases, affect the quality or performance of the new drug products. In cases in which differences exist that have been shown to affect drug product performance, bioavailability, or stability, then the appropriate solid state should be specified."

That provision, along with the potential human and commercial damage that can occur as illustrated by Norvir, has resulted in most pharmaceutical companies incorporating a process to identify and characterize polymorphic forms of an active pharmaceutical ingredient (API) during the development of a drug product.

3.1. Polymorph Screening. Polymorph screening will be considered as it applies to the pharmaceutical industry, although the methods discussed are applicable to all organic molecules. Polymorph screening is an effort to determine if a given compound exists in polymorphic forms. The practice of screening should be differentiated from that of selection. In the former, polymorphic forms and their identities are sought, while in the latter, the properties of forms found in the screen are investigated to determine which has the best property set for a particular use. In industry, it is polymorph selection that is practiced rather than simple screening. The practical implication of this distinction is that certain polymorphic forms found in a screen may immediately be known to be of little interest from a selection point of view and therefore need not be completely characterized.

3.1.1. Goal of a Screen. The first consideration in planning a polymorph screen is the goal. Screens can vary appreciably in scope, and the scope should fit the goal. The most common types of screens carried out during pharmaceutical development are shown in Table 1. Early screens can be conducted with a minimum amount of material, as little as 100−200 mg. Although all of the properties of forms found cannot be determined experimentally if only this much material is available, an estimation of whether the test compound exists in few or many polymorphic forms can be made. This type of screen is valuable during late stages of drug discovery, where selection among potential clinical candidates can be aided by estimation of the "developability" of each based on the complexity of their solid-state chemistries.

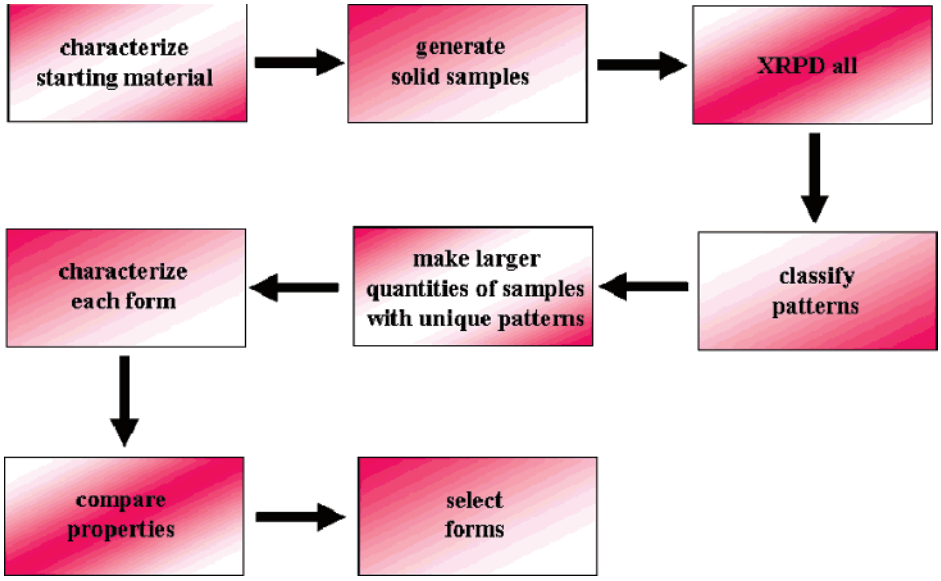
Stable form screens and solid form selections are used to select the proper form of an API for development. These projects require enough material so that relevant forms found can be made in large enough quantities for determination of their properties. One of the most important properties in form selection is the relative thermodynamic stability of the forms found, and knowledge of those thermodynamic relationships is critical to development of a crystallization process that yields a selected solid form consistently. In some cases, a screen designed to find and identify the most thermodynamically stable forms (anhydrate and hydrate) makes sense. For example, early in the development process of a highly water-soluble API it is advisable to identify the most stable form so that good manufacturing practices (GMP) material can be easily made in that single form. For a highly water-soluble API it is unlikely that different aqueous dissolution rates exhibited by different polymorphic forms will result in different bioavailabilities. It is likely in this specific instance that the most thermodynamically stable form will be the best choice for development, since safety and efficacy will not be likely to depend on the form selected. However, for a poorly or even moderately soluble API different polymorphs can have different bioavailabilities.[12]

A focused screen can be carried out to show that a polymorph selected can be made from material synthesized under GMP conditions. Impurities are known to affect crystallizations. It is generally found that they inhibit crystallization, but sometimes they can have a controlling influence on the polymorphic form produced. In the case of ritanovir, there is evidence that an impurity crystallized from a solution of the API and acted as a seed on which the previously unknown form II grew.[13] Both the impurity, a product of ritanovir degradation, and form II have the same conformation in a critical part of the molecule in the crystalline state. If material used in initial screening was not synthesized by the same procedure ultimately chosen for GMP production, it will likely have a different impurity profile than does GMP material. Ideally, a focused screen should be designed to show that impurities in GMP material will not lead to new forms or loss of crystallization control.

A comprehensive screen is a search for every solid form that can be found. In principle, the maximum number of techniques should be used to encompass the widest experimental space possible. However, it is important to realize that polymorph screening is currently an empirical exercise. The ability to predict whether a given compound will exist in multiple crystal forms does not yet exist, although not for lack of effort.[14] Thus, it is impossible to know when a screen is "finished". Given the current state of the science of organic crystals, no amount of screening can guarantee that all polymorphs of a given substance have been found. The scope of a comprehensive screen, therefore, is essentially limited by budgetary constraints rather than by lack of experimental techniques. To plan the most effective comprehensive screen possible, the availability and physical properties of the substance to be screened should be considered and the appropriate experimental techniques should be selected. There is no single screening protocol that fits all molecules.

A review of procedures suggested for systematic polymorph screening recently appeared.[15] It illustrates that although screening is approached differently by different organizations, the same basic techniques are used by all. The screening/selection process used at SSCI is shown in Scheme 1. Material to be used in the screen should be completely characterized using the standard analytical techniques such as X-ray powder diffraction (XRPD),

Scheme 1. Process of Polymorph Screening and Selection



differential scanning calorimetry (DSC), thermogravimetry (TG), thermomicroscopy, infrared (IR) spectroscopy, Raman spectroscopy, solid-state nuclear magnetic resonance (ssNMR) spectroscopy, and dynamic vapor sorption (DVS) analysis. Those techniques have been reviewed.[16] DSC, TG, thermomicroscopy, and DVS can indicate the possibility of polymorph or hydrate formation, and in total the data constitute a baseline set to which data generated during the screen can be compared. A means to assess the chemical integrity of samples generated during the screen is needed, so a proton NMR spectrum or similar data should be obtained for future comparisons.

SSCI is often asked what chemical purity of material should be used for screening. If material made under GMP conditions is available, it is recommended. Otherwise, the most pure material available should be used.

3.1.2. Sample Generation. The next step in a polymorph screen is to generate solid samples under a variety of conditions. There are many techniques available; the most commonly used have been listed by Guillory[17] and Hilfiker.[18] Solvent-based techniques, using solutions or slurries of the test compound, should be carried out. Although many polymorphs have been discovered using thermomicroscopy alone,[19] hydrated and solvated forms can be missed in this way. Hydrates and solvates are important targets in screening of APIs. In some cases, hydrates are the preferred solid form for development, as in the commercial products made from cefadroxil (a monohydrate)[20] and paroxetine hydrochloride (a hemihydrate).[21] Since most APIs are crystallized in the final stage of manufacture, solvates can be an issue. A few commercial products utilize solvates, such as doxycycline hyclate (a hydrochloride hemiethanolate hemihydrate).[22] If an API forms a solvate with the final crystallization solvent, that solvate may be used as an intermediate in production of the final API form. An anhydrous form of paroxetine hydrochloride (form C) can be made by desolvation of the 2-propanol solvate, ethanol solvate, or other solvates.[23]

Solvents used for sample generation should include, but not be restricted to, solvents that can be used for manufacturing (FDA class 3 solvents, for example).[24] Solvents having a wide variety of structures and polarities should be used. Experiments should include evaporation of, cooling of, or antisolvent addition to, solutions, and extended agitation of slurries. Metastable forms can be sought by "kinetic" experiments, such as addition of a solution of the test compound to a large volume of cold antisolvent and immediate harvesting of the resulting solid. However, it must be realized that screening is a hunt for seeds. Without knowing what forms are available, there is no way to plan the appropriate concentration at which to bring about nucleation in order to crystallize one form or another. Rather, the attempt should be to provide a variety of conditions under which nucleation may occur.

A common misconception that is sometimes used to guide sample generation is that solvent controls the polymorph produced. While that is true for solvates and undoubtedly true for unsolvated forms in some cases,[25] in general it is the supersaturation level at which nucleation occurs that controls the polymorph obtained. In my experience, it is the rule, rather than the exception, that a certain form is obtained from a number of different solvents and conditions during a polymorph screen. Similarly, it is common to carry out multiple experiments in the same way, say, evaporations of a common solution in multiple containers, and obtain more than one form among them. The reason for results like that is that nucleation and growth are uncontrolled in polymorph screen experiments, as they must be since the available forms, and their properties, are unknown until the screen is complete.

A second common misconception about sample generation is that crystallization experiments used to produce specific forms may be used in the future to make those forms at will. This is not the case because, as discussed above, screening experiments lack control of the critical crystallization events. The situation where different forms result from apparently the same experiment can be disturbing to a synthetic chemist who is used to obtaining the same result when combining a set of reactants under the same conditions multiple times. SSCI has had clients question the validity of screening results because they cannot obtain a polymorph by repeating an experiment that yielded that polymorph once during a screen. It is important to realize that control of crystal form is based on control of nucleation and growth events. A controlled crystallization process can usually be devised based on the relative solubilities and supersaturation limits of a set of polymorphs. These data can be determined once the available forms in which a test compound can exist have been found by screening, but not before.

The technique of capillary crystallization is useful in that it provides a wide range of supersaturation levels using simple evaporation experiments. The nature of evaporation of small volumes of solutions in capillary spaces can lead to very high supersaturation levels before nucleation occurs. Application of the technique to the highly polymorphic compound 5-methyl-2-[(2-nitrophenyl)amino]-3-thiophenecarbonitrile (ROY) resulted in measured supersaturation levels as high as 60 and clearly showed a correlation between the supersaturation level attained and the polymorph produced.[26] Capillary crystallization of nabumetone solutions produced a new polymorphic form whose appearance was independent of the identity of the solvent.[27] It can also be shown theoretically that as supersaturation increases, the rate of nucleation of metastable forms becomes competitive with the rate of nucleation of stable forms.[28] The important thing to realize is that capillary crystallization allows coverage of a wide range of thermodynamic space in an experimentally simple way. Although a metastable polymorph of nabumetone was obtained in 20% of the capillary crystallization experiments carried out, the stable form was obtained in the other 80%.[27]

Crystallization techniques that do not involve solvent should be utilized during sample preparation. These include thermomicroscopy, grinding, compression, sublimation, vapor and heat stressing of crystalline and noncrystalline forms, and dehydration (desolvation) of hydrates (solvates). For APIs, some of these techniques (grinding and compression, for example) mimic processing steps typically used in converting an API into drug product. Thus, one would want to determine if such steps might be expected to lead to polymorphic conversion.

I agree with Hilfiker that thermomicroscopy is "highly recommended" as a screening technique.[15] Kuhnert-Brandstätter clearly demonstrated its value in screening compounds that are well-behaved thermally.[29] Even for those that decompose during melting, addition of a small amount of organic liquid in which the test compound is soluble at elevated temperatures can allow crystallizations to be carried out between ambient and melting temperatures. Crystallization from the melt can be viewed as occurring under the highest degree of supersaturation possible, and use of the concentrated solutions suggested above provide a close approximation to that. There are some polymorphs that have been made only by melt crystallization in spite of concerted efforts to crystallize them from solution. A case in point is form III of acetaminophen. Acetaminophen is trimorphic. Forms I and II can be prepared from solution.[30] Form III was prepared by Burger in 1982 by crystallization of the melt.[31] In 2002 an iterative, high-throughput polymorphic screening study of acetaminophen was done that consisted of "thermally driven solution crystallization in 7776 samples representing 2592 unique conditions."[32] Form III did not result from any of these experiments and could be prepared only by the melt crystallization technique originally employed by Burger. Thus, polymorphs may be missed if only solution-based experiments are utilized for sample preparation.

Dehydration of hydrates and desolvation of solvates found in a screen are another set of experiments that should not be overlooked. There are cases in which a particular anhydrous polymorph can only be generated in this way. An example is pentamidine isethionate.[33] Crystallization from various solvents afforded an anhydrate (form A) or a trihydrate. Only by dehydrating the trihydrate at elevated temperature or reduced pressure could a second anhydrate (form B) be produced. Another example is an API that was screened at SSCI. That compound forms solvates readily. Solvent-based screening experiments afforded 34 different forms, including solvates, hydrates, and a few anhydrates. However, the thermodynamically most stable anhydrous form (A) was obtained by desolvation of solvates. In this case, additional work was carried out to develop a robust process to make form A. Solid form control in the resulting process was established in the drying step rather than in the crystallization step.

It should be obvious that there are many different crystallization techniques that can be used in polymorph screening. These should be viewed as tools, and the set of tools used for a particular screen should be selected based on the properties of the test compound. Temperatures at which a compound degrades should be avoided. Simple evaporation of solutions using solvents in which a compound is highly soluble will often give oils. Water vapor stress of solids that deliquesce is pointless. The object is to select the appropriate tools and set up experiments to allow nucleation to occur under the widest variety of conditions possible.

To provide the opportunity for various forms to nucleate, sample generation should consist of multiple experiments. But how many? And how many should be conducted under the same conditions? There are no unequivocal answers to these questions. One thing that can be said is that the scope of a polymorph screen is generally related to the number of solid samples generated: the more samples, the greater the scope. However, variation of conditions is the key. A screen with fewer experiments covering a wider experimental space is more likely to find more polymorphs than a screen with a large number of experiments that are performed in a narrow experimental space.

One way to estimate the number of experiments that should be carried out is to look at the percentage of the time various forms are found in published screens. Of course, that will vary based on the nature of the screen and the conditional space it covers, but the numbers are illustrative anyway. In a capillary screen of nabumetone, 150 evaporation experiments yielded a metastable form in 20% and the stable form in 80%.[27] In a capillary screen of metformin hydrochloride, 500 evaporation experiments yielded a metastable form in 45%, mixtures or solids unsuitable for analysis in 16%, and the stable form in 45%.[28] The previously mentioned high-throughput screen of acetaminophen generated 7776 samples under 2592 conditions; 723 (9%) of the experiments provided usable samples, of which 29 (4%) were form II and the remainder were form I.[32] Acetaminophen form III was not found in this screen, as discussed above. An automated screen of carbamazepine was reported by Hilfiker.[34] Of the 85 evaporation and slurry experiments reported, 2% gave form I (as a mixture with other forms), 11% gave form IIa, 24% gave form IIb, 29% gave form III, 12% gave the dehydrate, and the remaining 22% gave solvates or mixtures.

The fact that various forms tend to appear in single or double digit percentages of experiments conducted suggests that screens should incorporate at least few tens of experiments up to a few hundred experiments. The number selected will depend on the goal of the screen. On the basis of the screens conducted at SSCI, I believe that, for an early screen designed to determine the propensity for polymorphism, 50−80 samples are usually sufficient. For a standard polymorph selection, 150−200 samples are recommended. SSCI's SuperScreen, a search for as many forms as can be found, can involve preparation of 600 or more samples. Given the unpredictable nature of the nucleation event, it is advisable in screens of larger scope to carry out the same experiment a few times. However, carrying out the same experiment tens or hundreds of times appears to

provide little value. The key for a successful screen is to vary the conditions as widely as possible.

There is much current interest in high-throughput screening techniques.[35] These techniques involve robotics for sample generation and analysis, and software to sort and display data. There can be considerable gain in efficiency by automating some of the typical screening activities. Systems that carry out standard solvent-based experiments and analyze the resulting samples are excellent tools if properly applied. One of the best applications of this technology is screening where only a small amount of test compound is available, as might be the case in the "early" screen described above.

The automation of sample preparation requires robotics and is probably economically justified only for those who carry out polymorph screening on a regular basis. Most solvent-based sample preparation techniques, such as evaporation and slurry experiments, are amenable to automation. For the occasional screener, use of multichannel pipettes and standard well plates can be quite efficient without requiring a robot. Some techniques that should be used in a screen are probably not worth automating because of the difficulty in doing so and the relatively small number of experiments done using those techniques in a screen. Examples are thermomicroscopy, grinding, and the kinetic type of solvent experiments described above. Perhaps the most efficiency gained from automation is in data analysis. When data sets from a few hundred experiments need to be compared to determine which are alike and which are different, the task is ideally suited to computer support.

It is a mistake, however, to believe that any high-throughput system can increase the merit of a screen simply by its use. Proponents of the technique cite the large number of experiments that can be conducted. However, as discussed above, thousands of experiments are not needed to find polymorphs. As with the other screening tools, automated ones should be applied with discretion. Some sample generation techniques are less amenable to automation than others, and these should not be eliminated from screening in the belief that one technique should supplant all others because it has been described as state-of-the-art. A lesson can be taken from the combinatorial, high-throughput approach to drug discovery, which was the rage in the early 1990s. In 2004, the value of the technology was questioned by many in major pharmaceutical companies.[36] The most ardent critics consider infatuation with high-throughput screening an expensive fiasco that led to the current lack of new products in the pharmaceutical industry. According to the *Wall Street Journal*, "A study led by David Newman of the National Cancer Institute concluded that combinatorial-chemistry machines had failed to create a single FDA-approved drug through the end of 2002."[36] Because of the lack of success, "Bristol-Myers says it has tried to create a better mix of high technology and old-fashioned lab work."[36] The message should be that in searching for new chemicals or new solid forms, diversity in approach has value. New technologies should be added to, not replace, available tools.

3.1.3. Analysis. Once the samples have been generated, the next step is to analyze all the samples using either single or multiple analytical techniques. Full characterization of any solid, or any compound, must involve multiple analytical techniques. However, for a first-pass analysis of screening samples, a single technique may be used. In some robotic screening systems, multiple analyses are performed on each sample and data are correlated by computer,[37] but this is not necessary. The best technique for first-pass analysis will (1) provide data that allow discrimination among various solid forms, (2) be applicable to samples in various configurations (small and large samples, samples contained in well plate or capillaries, etc.), and (3) provide the most structural information possible. Raman spectroscopy has been suggested as an appropriate technique.[34] XRPD is used at SSCI. There are advantages and disadvantages of each. Raman spectroscopy offers easy spatial resolution (identification of multiple forms in a single sample) and does not suffer the effects of sample orientation found in XRPD. However, Raman spectroscopy does not probe three-dimensional (3D) structure directly, and there is the question of miss rate. Miss rate means how often two different forms exhibit the same Raman spectrum or the same XRPD pattern. Since XRPD probes the crystal structure directly and Raman spectroscopy probes the effect of the structure on bond vibrational energies, it would be expected that XRPD is the more specific (lower miss rate) technique. Also, some compounds cannot be analyzed using Raman spectroscopy because they fluoresce or contain impurities that fluoresce. The introduction of near-infrared lasers in 1986 reduced the incidence of fluorescence preventing acquisition of Raman spectra,[38] but some pharmaceutical compounds still cannot be analyzed because of that problem. Nevertheless, Hilfiker states "that the probability of failure to discriminate between solid forms is similar for Raman and X-ray diffraction, provided that the Raman spectra are analyzed carefully."[39] A primary advantage of XRPD is that structural information may be gleaned from the data. With the use of properly configured diffractometers and the appropriate computer software, sample issues like orientation can be dealt with (see below). XRPD is preferred over Raman spectroscopy at SSCI for first-pass evaluation of polymorph screen samples because experience teaches that it has a low miss rate, it can be applied to large and small samples in various containers, it allows easy identification of mixtures, particularly when one component is noncrystalline, and the resulting data can provide structural information.

Once all samples have been analyzed by XRPD, the data must be sorted. The appearance of XRPD patterns can be affected by (1) sample particle size, (2) sample orientation (preferred orientation), (3) particle statistics, (4) sample height relative to the diffractometer alignment plane, (5) diffractometer configuration, and (6) data collection parameters. To sort a set of patterns into groups in which each group represents a single structure, these factors must be taken into account. At SSCI we utilize pattern matching software written in-house specifically to do so.[40] The program is very robust and can recognize similar patterns in spite of their alteration by the factors described above. In addition, noncrystalline materials and mixtures are recognized, the latter without having patterns of the pure components for comparison. Other companies have produced proprietary software to sort patterns obtained from analytical testing. A commercial program, PolySNAP, is also available.[41] If computer-based sorting is not available, it can be done by hand. However, for hundreds or even tens of patterns the process can be tedious and time-consuming.

The output from the sorting exercise is groups of patterns, each of which presumably represents a unique solid form. However, without additional analyses the solid structure from which each pattern or set of patterns arises is not known. Whatever classification nomenclature one is using at this step (groups A, B, etc., 1, 2, etc., or other) it is important not to refer to each group as a "form" until it has been established that it is an actual unique solid form. It is not yet known whether the substances responsible for each pattern set are phase pure

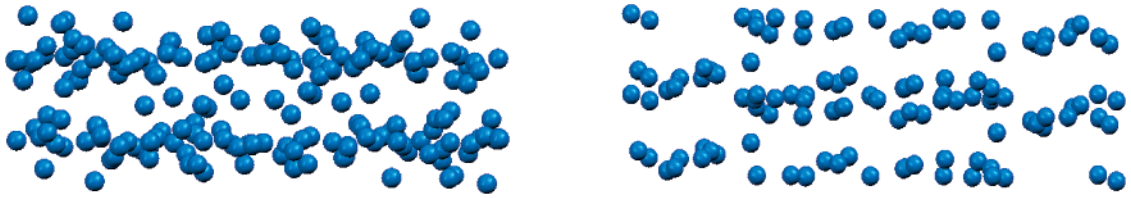


Figure 1. Electron density maps of two polymorphs of buspirone hydrochloride derived from laboratory XRPD data.

or mixtures or even whether they are the same chemical compound that was input into the screen.

For situations where there is insufficient material available to support larger scale production of material having a unique pattern, which is often the case for preliminary screens, XRPD data obtained from screening samples can provide much information. This is an advantage of using XRPD as a first-pass analytical tool in screening studies. The holy grail of this approach would be to solve the crystal structure of each true form from its XRPD pattern. While this is possible some of the time, it is not necessary to go that far to obtain enough knowledge to predict specific material properties. At SSCI, we have developed proprietary software that employs a number of different tactics to glean useful information from XRPD data. A brief overview of that software will be presented here.

It is first important to be able to index XRPD patterns. Indexing involves assigning *hkl* indices to each XRPD peak position, giving a unit cell description of the crystal structure.[42] Accurate peak positions and relatively high quality data are generally required for indexing. To work with typical data that might be collected as part of a screening process, knowledge of the molecule and packing rules derived from the study of known crystal structures can be used to limit the possible solution space. In addition to seeking indexing solutions, electron density can be placed in the unit cells based on symmetry considerations and the measured intensities in the XRPD data. Thus, the process is an iterative one where unit cell parameters and electron density positions are changed until the best solution is reached. The "goodness" of any potential solution is judged by a comparison of the measured XRPD pattern with one calculated from the unit cell; and the correlation between the resulting electron density and allowed molecular packing configurations. The best solution is when the best fit between measured and calculated patterns is achieved and the electron density matches an allowed molecular packing configuration. This approach takes every measured data point as being significant, similar to the Rietveld method,[43] and is grounded in knowledge of the molecule and its packing ability. Ultimately, a final packing of the molecule (API that is being screened) can sometimes be carried out, again using matching of measured and calculated patterns as a guide, to give a crystal structure from powder data. Commercial software, such as Cambridge Crystallographic Data Centre's DASH,[44] are available that can be used to solve structures using indexed XRPD patterns. The keys to writing indexing algorithms that have a high rate of success are to (1) limit in a rational way the infinite number of solutions that need to be searched to find the correct answer and (2) realize that ultimately selecting only one solution from a handful of close possibilities need not be necessary for certain property predictions. In addition, for such programs to work well using standard laboratory XRPD data as input, the source diffractometer has to be properly aligned and the effects on peak shape of diffractometer configuration and data acquisition parameters need to be incorporated in the algorithms.

Successful indexing of XRPD patterns can be extremely helpful in pattern matching. Normally, only the pattern from a pure phase can be indexed; patterns from mixtures will not converge to a realistic solution. Thus, if an XRPD pattern in a group derived from pattern sorting can be indexed with a reasonable unit cell volume, it is evidence that group represents a pure phase. If multiple patterns in a group provide the same indexing solution, it is evidence that the sort is correct.

From indexing results, the unoccupied unit cell volume, and hence the density, of each form can be calculated. The Burger-Ramburger density rule states that the more dense polymorph (at absolute zero) is the more stable.[45] Thus, relative thermodynamic stabilities may be inferred from relative densities, but the rule does not hold in all cases. It has been estimated that about 10% of compounds violate the density rule.[45b] Another caveat related to use of densities is to be sure that compared densities were derived from data obtained at the same temperature.

Beyond indexing, however, the placement of electron density in the unit cell can allow certain property predictions to be made. When some electron density has been placed, but before a total structure solution has been achieved, an electron density map can be created. Simple inspection of these can reveal structural features such as channels that may hold water or solvent. Figure 1 shows electron density maps derived from XRPD patterns of two polymorphs of buspirone hydrochloride.[46] Note spaces in the map on the right, which arose from the XRPD pattern of a desolvated solvate. In addition, predictions of bulk properties such as morphology can be made from electron density maps. That prediction is based upon a modified Bravais-Friedel-Donnay-Harker calculation,[47] where growth rates of individual crystal faces are adjusted according the relative electron density present at each face. The growth rate for the face with the highest electron density is normalized to unity, and growth rates for faces having lower electron densities are proportionately slowed. For example, Figure 2 shows the predicted and exhibited morphologies for two polymorphs of buspirone hydrochloride.[46]

In summary, XRPD data can provide a picture of a solid-state system without having to generate samples over a few milligrams in size. The number of forms, nature of each, thermodynamic relationships, and properties of each can be predicted. Of course, not all relevant properties can be determined in this way. Nevertheless, the approach is valuable when, for example, material is limited or the results of preliminary screening of clinical candidates are included in the candidate selection process.

3.1.4. Scale Up. If sufficient material (1−5 g) can be devoted to the effort, a polymorph selection project should be undertaken. The next step after analysis of first-pass data is to prepare larger quantities (a couple hundred milligrams or so is usually sufficient) of each material that exhibits a unique XRPD pattern. Sometimes this is not as straightforward as it sounds. As a first attempt, it is sufficient to utilize the crystallization technique, or techniques, that yielded each material during the screen. However, because screening experiments are uncontrolled as far as nucleation events (see the discussion above), repeating a

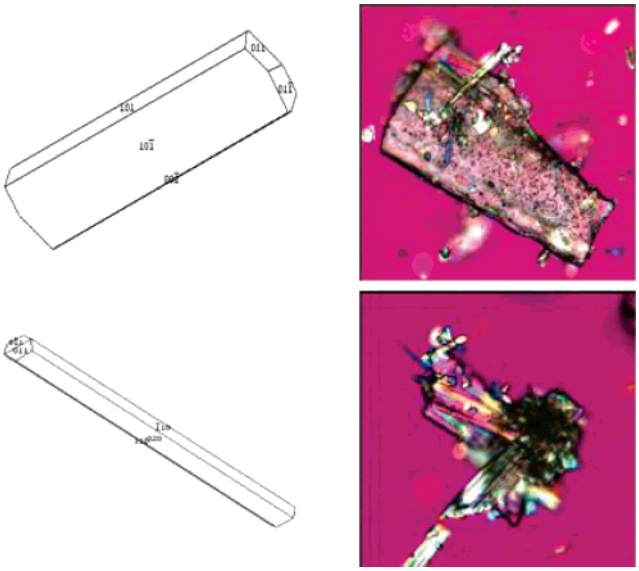


Figure 2. Predicted (left) and observed morphologies (right) for two polymorphs of buspirone hydrochloride.

particular experiment may not yield the same material that was obtained the first time. Other techniques may need to be used.

Clues to technique choice may sometimes be found in the screening results. A table of crystallization techniques and XRPD pattern results should be generated. Then, for example, it is easy to see that a particular XRPD pattern was exhibited only by materials crystallized in the presence of a particular solvent. That would suggest the solid is a solvate, and to make more it is necessary to use that solvent. In another example, observing an XRPD pattern in only a small percentage of experiments but independent of solvent suggests the solid giving the pattern may be metastable. Thus, a kinetic experiment (such as addition of a solution of the test compound to a large volume of cold antisolvent and immediate harvesting of the resulting solid) can be used to try to make a larger sample. Even better in this case would be to employ seeds from the originally generated sample to control crystallization at larger scale. This brings up an important point: always retain some of each sample generated in a screen. It can be used as seed and in some cases will be all of a particular form there is. In a final example, thermodynamic techniques such a slow cooling of solutions or slurrying of a solid for an extended time period (usually a matter of hours or days) in a solvent would be expected to lead to the most thermodynamically stable form. Remember while planning larger-scale crystallizations that both kinetic and thermodynamics play a role. We have encountered several cases in which there was a clear predominance of a form during the screen that turned out to be kinetically favored. To make larger samples of the thermodynamically most-stable form required extended slurrying of the kinetic form in solvents saturated with the test compound. Also be aware of enantiotropism.[48] For systems that are enantiotropic with a transition temperature near ambient, it is common to obtain mixtures no matter what technique is used, including long-term slurrying in hopes of converting all to the stable form. Since enantiotropic forms have the same free energy at the transition temperature, there is little or no driving force to interconvert near or at that temperature.

A situation fairly common in screening is to generate a sample during the initial screen that exhibits a certain XRPD pattern, and then not be able to make a similar sample again. Whether these are cases of disappearing polymorphs,[49] or simply the occasional appearance of a very metastable form, is important or not depending on the goal of the screen. For standard polymorph selection projects, it is usually satisfactory, after several attempts to remake the material have failed, to consider it high-energy and therefore irrelevant to the selection process. On the other hand, if all forms are being sought for patent purposes, it may be wise to make the effort to recover it.[50]

In some cases, a screen will result in a large number of different patterns that may represent different forms. Economic or time restrictions may not allow all of these materials to be prepared and characterized. Thus, relevant materials should be selected for additional investigation. But which are relevant? That depends on the goal of the screen. Certainly for API form selection projects solvates of solvents that cannot be used for manufacturing can be considered irrelevant.

3.1.5. Form Characterization. Each sample of material made at larger scale should be characterized using the standard set of analytical techniques (DSC, TG, thermomicroscopy, IR spectroscopy, Raman spectroscopy, ssNMR spectroscopy, DVS, etc.). A measure of chemical integrity, such as proton NMR spectroscopy, must also be included so that degradation products are not misidentified as polymorphs of the starting material. The data resulting from these tests should allow determination of the nature of each material exhibiting a unique XRPD pattern. That is, which are hydrates, solvates, or water- and solvent-free forms.

One should always be on the lookout for single crystals that appear to be suitable for X-ray analysis among the sample produced. If they are found, successful structure solution using single-crystal X-ray diffraction data will give the precise 3D structure. It is advisable to try to produce suitable single crystals for forms that are ultimately deemed relevant to production of the API and for which such crystals were not produced simply by sample generation. The standard techniques of slow cooling, temperature cycling, vapor diffusion, and so on can be used.[51] Since these techniques stress slow growth to obtain high-quality crystals, they tend to yield thermodynamically more stable forms. Consequently, growing single crystals of metastable polymorphs can be difficult. The use of seeds or non-traditional techniques[27] can be invaluable in these efforts.

A single-crystal structure can be helpful in many ways. Calculation of the XRPD pattern from the single-crystal X-ray data will allow correlation of the structure of bulk material to that of the single crystal. Since the calculated pattern will be free of particle size or orientation effects, it can serve as the reference pattern for a specific structure. Remember when using a calculated pattern that single-crystal X-ray data are often collected at low temperature. A pattern calculated from such data will often fail to match an experimental XRPD pattern obtained at ambient temperature.

Packing diagrams generated from single-crystal data aid in understanding of physical properties such as hygroscopicity or habit. Variable hydrates frequently contain open spaces (channels or tunnels) in the structure that are populated with amounts of water that depend on the humidity of the environment.[52] These types of features are readily recognized by inspection of packing diagrams. In some cases, the XRPD patterns of channeled or layered structures change slightly with varying amounts of water or solvent present in the channels or between the layers. This situation can lead to confusion in pattern sorting during screening. The patterns in a group may appear basically the same, but certain peaks are shifted (occur at different °2θ positions) among them. When this happens the question of whether the group represents a single phase, mixtures of phases,

or multiple pure phases is paramount. If a single-crystal structure obtained from a crystal that exhibits a pattern in the group shows, for example, layers in the structure that can accommodate small molecules, it can be used to answer the question. The directions that would be expected to undergo expansion with increasing occupancy of the layers can be identified from a packing diagram. With appropriate software, the unit cell dimensions of the structure can be artificially changed to mimic the expansion expected as the interlayer spaces are filled. XRPD patterns can be calculated at various levels of expansion based on the new structural dimensions and compared to the patterns in the group. Agreement between the calculated and the observed patterns indicates that only a single structure is represented by the set, but the differences among the members of the set are due to varying populations of water or solvent between the layers. It is also possible to use approaches similar to this even if a single-crystal structure is not available. Indexing of, electron density mapping from, and property prediction from XRPD data can provide sufficient structural information to solve such problems.

Having collected analytical information on each material, it is usually possible to establish the nature of each material exhibiting a unique XRPD pattern. Sometimes there are problem cases in which more advanced analytical techniques (TG coupled to IR spectroscopy, variable temperature or humidity XRPD or Raman spectroscopy, for example) need to be employed. Again, the derivation of structural information from XRPD patterns can be most helpful in form characterization. At this point, knowing that different solid forms of the test compound have indeed been found and identified, it is reasonable to assign each form a designation (form A, B, etc., 1, 2, etc.).

3.1.6. Property Comparison. The final step in the selection process is to compare the properties of the forms found. Some of the properties that can depend on polymorphic form include solubility, dissolution rate, bioavailability, chemical and physical stability, hygroscopicity, melting point, crystal habit, and powder handling characteristics.[53] Which of these should be determined depend on various factors. For poorly water soluble compounds, aqueous dissolution rate is probably the most important. For highly water soluble compounds, that is usually not an issue. Remember that there is a simple relationship between dissolution rate and solubility,[54] so a highly water soluble compound will have a high rate of dissolution in water. However, most APIs coming from current discovery programs tend to have poor water solubility, so in many cases the rate of dissolution can be a critical factor in determining bioavailability. If formulation is to be in a solution, solubility in the vehicle is key. Certainly chemical and physical stability must always be considered, and these can be estimated by subjecting materials to accelerated stability conditions.[55]

For solid form control purposes, the most important property is the thermodynamic stability relationship of the forms found. It is absolutely critical to know that in order to devise a crystallization process that provides the selected form consistently. A primary relationship that needs to be established is which polymorph is the most thermodynamically stable in the temperature range anticipated for generation of the API, and generation, storage, and use of the drug product. In some cases, finding the most stable form is the goal of the screen (Table 1), but the stable form should be identified in any selection process carried out. The thermodynamic relationships of polymorphs can be monotropic or enantiotropic, and these relationships should also be established. If relevant forms are enantiotropically related and the transition temperature is within the temperature range of production and use, it must be known to establish form control in the product. If possible, the most thermodynamically stable polymorph should be selected as the form of the API to make and include in the drug product. In this way, there is no driving force for form interconversion, an event that can cause major problems in formulation and product stability. If a polymorph is selected for use because it is more soluble than another polymorph, it must be realized that the former will be less thermodynamically stable than the latter. This situation is viable, but only with that foreknowledge since control of the crystallization, formulation, and product manufacturing processes will usually be more difficult than if the most stable form were used.

If hydrates were found during the screen, they must be assessed against anhydrous forms to determine which is more stable. This is not strictly a relative thermodynamic stability issue since different entities are involved. The idea is to determine under what conditions of temperature and humidity will the hydrate exist instead of the anhydrate. To evaluate the relationships of hydrated and anhydrous forms, solids can be kept under elevated humidity conditions and slurried in water or organic solvents containing water at different activities.[56] Again, the effect of temperature needs to be evaluated. In some cases, a hydrated form is so preferred over anhydrous forms that not only is it selected for drug product, but it is difficult to prevent conversion of solid anhydrates to the hydrate under standard conditions. An example of this is paroxetine hydrochloride, the active ingredient in the antidepressant Paxil. A hemihydrate of paroxetine hydrochloride is in Paxil,[21] and it was established during litigations surrounding introduction of a generic version that it is difficult to avoid the hemihydrate even when concerted efforts are undertaken to do so.[57]

There are several techniques that can be used to assess relative thermodynamic stabilities. For compounds that melt without decomposition, melting point and heat of fusion data can be used along with certain of the Burger-Ramburger rules.[45] A higher-melting polymorph is not always the most stable at all temperatures but is only the most stable at the melting temperature. Considering two polymorphs, if the first has a higher melting point and heat of fusion than the second, the first is more thermodynamically stable at all temperatures. If the first has a higher melting point but a lower heat of fusion than the second, then there is a transition temperature below the melting point at which the relative stabilities switch (enantiotropy). Above the transition temperature the first is more stable; below the transition temperature the second is more stable. In many of those cases, the transition temperature is not apparent from the DSC data that provide the melting points and heats of fusion. Thus, more work will be required to determine if the transition temperature is in the relevant temperature range. Also, crystal densities can be obtained from single-crystal structure data or from XRPD data using the approaches described above, and relative thermodynamic stabilities may be inferred from the relative densities.[45]

A simple technique to determine relative thermodynamic stabilities is competitive slurry evaluation. This involves suspending solids in a solvent that is saturated with the test compound. If the solids consist of two different polymorphs of the test compound, and the resulting slurry is agitated until equilibrium is reached, the more stable polymorph will be the only solid phase remaining. That can be carried out with two or more forms in each experiment. The solvent provides a low-energy pathway, dissolution/recrystallization, for form inter-

conversion to take. Identification of the solids in such an experiment can be by any technique that differentiates the polymorphs. Solids can be removed from the slurry by filtration and subjected to XRPD analysis, for example, or can be analyzed in situ using immersible or noncontact Raman or IR probes.

The results of competitive slurry experiments will be independent of solvent, since the property being evaluated is a thermodynamic one. However, kinetic effects can lead to confusion.[58] The rate of interconversion, thus the amount of time it takes to reach equilibrium, can vary based on the solvent.[59] Normally, the more soluble the test compound is in a solvent, the faster interconversion occurs. A downside of using a solvent in which the test compound is highly soluble is the amount of material required to saturate that solvent. Normally, solvents in which the test compound has a solubility of a few tens of milligrams per milliliter are preferred. It is usually not known ahead of time how long a particular slurry interconversion experiment should be allowed to proceed. At SSCI, they are usually allowed to proceed for a few days before the initial pull of solids for analysis. If time is critical then dynamic analysis (using, for example, Raman or IR immersion probes) or daily withdrawal of samples for analysis can be carried out. It is usually important in these experiments to start with at least a little of all the forms to be tested in the solid phase. That provides seeds of each form, so one does not have to await a nucleation event on the road to equilibrium. For slow-nucleating forms, lack of a seed can result in long and inconsistent experiment durations. If a solvate is formed that readily desolvates to give an anhydrous form during recovery and identification of solids, results can appear nonsensical. It is advisable to analyze solids in a still-wet condition if that is suspected. Remember that in most cases a solvate will be the most stable form in the presence of the solvent incorporated. Another situation that can provide confusing results is when polymorphs are very similar in energy. That can be because experiments are being conducted at or near the transition temperature of enantiotropes, or because monotropes are simply energetically similar to each other (isoenergetic polymorphs[60]). Results will appear random in such instances. A change in slurry temperature can sometimes be used to resolve relative stabilities in those cases, since the free energy difference between forms can vary with temperature (that is always the case for enantiotropes). In fact, competitive slurry experiments should always be carried out temperatures that span the normal range in which APIs are prepared and used; from about 0 °C at the low end to about 60 or 80 °C at the high end is typical. If an enantiotropic relationship is suggested by results (one form is obtained at low temperature and another at high temperature), competitive slurry experiments can be done at converging temperatures to bracket the transition temperature. Having reached this point in a polymorph selection project, it should be possible to recommend the best form for development. There will not always be a clear winner, as the number of important properties necessitates choosing the form having the optimum set. As in many things, the choice is often a compromise. Selecting the most thermodynamically stable polymorph will alleviate some potential problems, but what if that form crystallizes into thin needles that filter and flow poorly? It is helpful to involve a multidisciplinary team in final form selection. In that way, options to handle problems envisioned by the different technical areas arising from properties of the API can be discussed, and the form having the greatest chance of success can be selected. Maybe isolation of a hydrate that is dried to give the final form could overcome poor filterability in the example above, for instance.

3.2. How Common Is Polymorphism among Organic Compounds? Current thinking about the prevalence of organic polymorphism was well summarized by Bernstein in his book *Polymorphism in Molecular Crystals*.[61] Although some authors have gone so far as to state that polymorphism is characteristic of all substances,[3] there are compounds that have been made many times that are only known to exist in one crystal form. Ibuprofen (2-(4-isobutylphenyl)propionic acid) is an example. It was first introduced in the UK in 1969, approved by the FDA as an over-the-counter drug in 1984, and is the most widely prescribed nonsteroidal anti-inflammatory (NSAID) in the world. Millions of kilograms are produced annually, and the compound is widely used in research laboratories. Yet, only one crystal form has been reported.[62] On the other hand, there are many reports in the literature of organic compounds that are polymorphic. Included are compendia of compounds that have been found to be polymorphic by research specific to that goal, such as the ones by Deffet,[63] Kuhnert-Brandstätter,[29] and Giron.[64] Bernstein wrote specifically about the occurrence of polymorphism in pharmaceuticals, noting that several compilations have appeared that contain references to several hundred compounds.[65]

Attempts to estimate the frequency of polymorphism in organic compounds (what percentage display the property) have been sporadic. A search of the Cambridge Structural Database (CSD) in 1995 found 163 entries in which multiple crystal structures were reported for a single organic compound (compounds considered contained C, H, N, O, F, Cl, and S in any combination).[66] On the basis of statistics provided on the Cambridge Crystallographic Data Centre (CCDC) website, the database contained 52,450 organic compounds in 1990 and 112,-113 in 2001,[67] so 163 polymorphic systems represents less than 0.5%. A search of the Merck Index (12th ed., 1996) for entries specifically described as polymorphic, hydrated, or solvated revealed that out of 10,330 compounds 140 (1.4%) were polymorphic, 540 (5%) were hydrated, and 55 (0.5%) were solvated.[68] Statistics posted on the CCDC web site show that as of January 1, 2006, 12,392 of the 366,866 structures in the CSD (3.4%) are polymorphic.[67] Note that all compounds, organic and otherwise, are included in that analysis.

Compilations such as the CSD and Merck Index have purposes other than assessing polymorphism, so whether a compound is described as polymorphic in these will depend on things like whether the compound happened to appear in polymorphic forms and whether the scientists who made the compound noticed and reported it. There have been some reports of the frequency of polymorphism based on other sources. From 1948 to 1961, McCrone studied 140 organic compounds by microscopy and found that 25% of them exhibited polymorphism.[69] All literature references to each compound in the 1999 European Pharmacopoeia were collected and examined for mentions of polymorphism.[70] For 135 compounds, 58% were polymorphic, 57% formed hydrates, and 20% formed solvates. A survey of 62 APIs developed at Bayer AG showed 80% to be polymorphic.[71] References cited in a recent publication suggest that "Approximately one-third of organic compounds and about 80% of marketed pharmaceuticals exhibit polymorphism under experimentally accessible conditions."[72]

SSCI carries out polymorph screening on a contract basis. This puts the company in a unique position to amass data related to the frequency of polymorphism, since a wide structural variety

Table 2. Percentages of Forms from Polymorph Screening

	all compounds [count (%)]	salts [count (%)]	non-salts [count (%)]
multiple forms[a]	220 (89)	86 (91)	116 (91)
multiple crystalline forms[b]	200 (82)	77 (81)	105 (82)
polymorphs[c]	118 (48)	37 (39)	71 (55)
hydrates	94 (38)	46 (48)	38 (30)
solvates	78 (32)	34 (36)	36 (28)
noncrystalline	118 (48)	51 (54)	55 (43)
total compounds	245	95	128

[a] Crystalline polymorphs, hydrates, and solvates plus noncrystalline forms. [b] Crystalline polymorphs, hydrates, and solvates. [c] Crystalline polymorphs.

of compounds are screened specifically for the existence of polymorphs. In a typical polymorph screen conducted at SSCI solid forms of interest include polymorphs, hydrates, solvates, and noncrystalline materials. Screens to find salts and cocrystals of APIs are also carried out. Similarly then, the frequency with which cocrystals occur can be probed.

The data presented below are based on 245 polymorph screens conducted at SSCI.[73] It must be realized that the scope of these screens varied (see the polymorph screening discussion above). Some were cursory, and others were extensive, depending on the goals, financial restraints, and material availability for each project. Thus, not all forms found were characterized to the same extent, and some were not characterized at all.

Compounds screened were of a wide variety of structural types, including 10 steroids, 7 peptide-based structures, 5 cephalosporins, 4 organometallics, and 2 macrolide antibiotics. Of the 245, 128 (52%) were non-salts, 95 (39%) were salts, and the structures of 22 (9%) were unknown to SSCI. The molecular weights of the compounds ranged from 139 to 1099. The raw data are available as Supporting Information.

Table 2 shows the data in terms of percentages of compounds that exist in multiple forms. The counts of the number of compounds that were found to exist in multiple forms and multiple crystalline forms include crystalline materials that were observed but not characterized. The counts of the number of compounds that were found to exist in multiple polymorphs, hydrates, solvates, and noncrystalline forms include only characterized materials.

The numbers in Table 2 show that about 90% of the compounds screened exist in multiple solid crystalline and noncrystalline forms. About half of the compounds screened were polymorphic. This number is about the magnitude of that found from the search of the 1999 European Pharmacopoeia.[71] About a third of the compounds exist in hydrated and solvated forms. It is interesting to compare the propensity of salts and non-salts to occur in different solid forms (Figure 3). The percentage of compounds that exist in multiple solid forms was the same for salts and non-salts (91%). Non-salts were more frequently polymorphic than were salts (55% compared to 39%). Salts were found to exist as hydrates more frequently than did non-salts (48% compared to 30%). The latter is explainable based on the known ability of water to bind to ionic sites.[74]

Figure 4 shows plots of the number of compounds against the total number of forms found and against the number of anhydrous, non-solvated, crystalline forms found. Thus, from the plot on the left 25 compounds were found to have 1 form, 54 were found to have 2 forms, 44 were found to have 3 forms, etc. Note that the plot on the left does not include two compounds that were found to have 28 and 34 solid forms each. Both of these plots have the same basic shape, which is a decrease in the number of compounds as the number of forms

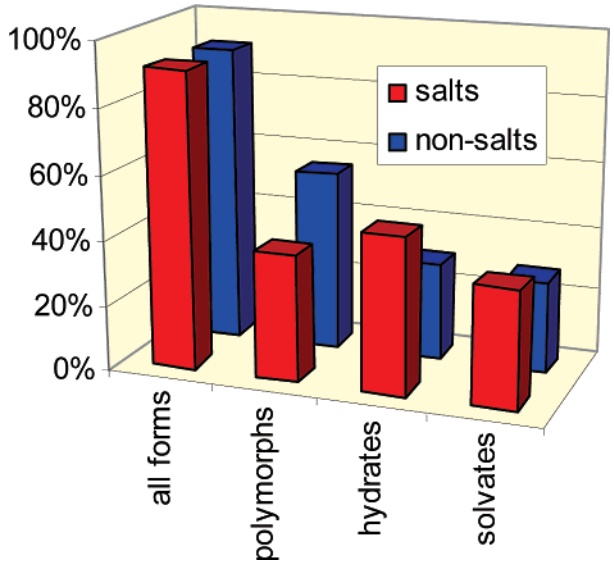


Figure 3. Comparison of the propensity of salts and non-salts to occur in different solid forms.

(or polymorphs) increase. This seems a reasonable outcome; some compounds can exist in many crystal forms, some can exist in only one, and there are many situations in between.

There are more structural data relative to the compounds screened at SSCI than are presented here. Confidentiality necessitates this. To date no correlations have been found between any structural features and the number of forms observed. Searching has involved consideration of such features as numbers and types of atoms as well as use of statistical software that could identify multivariate correlations. A typical outcome is illustrated by the plot in Figure 5 of molecular weight against number of forms (the two compounds that exhibited 28 and 34 solid forms each are omitted).

4. Cocrystals. To discuss cocrystals, it is necessary to understand what they are. Single-component solids can be of various types. The definition of the term "polymorph" has already been mentioned. Organic polymorphs are different crystalline structures that have the same empirical formula and are indistinguishable in the liquid, gaseous, or dissolved states. Polymorphs are a subset of the term "form", which encompasses all crystallographically distinct solids attainable by a compound. Both noncrystalline and crystalline forms are possible. Although it is common to refer to "amorphous" organic solids, it is generally the case that organic molecules, being anisotropic in shape, have at least short-range order in their noncrystalline forms.[75] In general, cocrystals can be considered unique crystalline solids containing multiple components.

4.1. Nomenclature. There is currently a controversy in the literature regarding naming conventions for crystals that contain more than one component (multicomponent crystals). Common materials of this type are hydrates and solvates, which contain the "host" molecule (the API for pharmaceuticals) and water or solvent as a "guest". In either case, the guest can be a structural piece of the crystal or simply fill space. For hydrates, the latter situation often results in a nonstoichiometric (or variable) hydrate, wherein the amount of water in the crystal depends on the relative humidity of the surroundings.[76] Morris called the two types of structures in hydrates "isolated lattice sites" (structural guest) and "water forming lattice channels" (space-filling guest).[74] In their study of sulfathiazole solvates, Bingham and co-workers called them "cocrystals" (structural guest) and "clathrates" (space-filling guest).[77] In my view, all

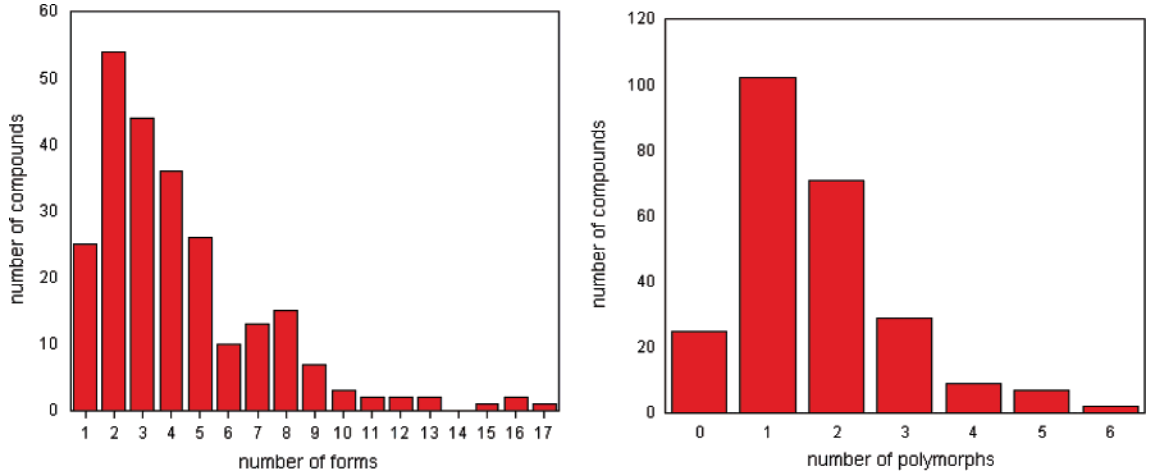


Figure 4. Plot of the number of compounds against the total number of crystalline and noncrystalline forms found (left) and against the number of anhydrous, non-solvated, crystalline forms found (right).

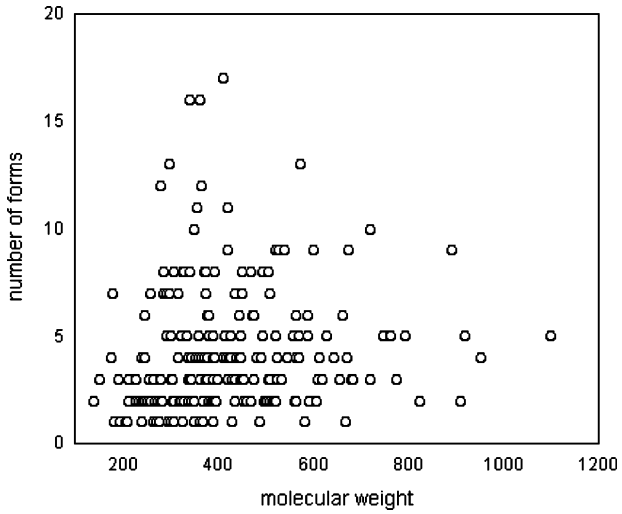


Figure 5. Plot of molecular weight against number of forms.

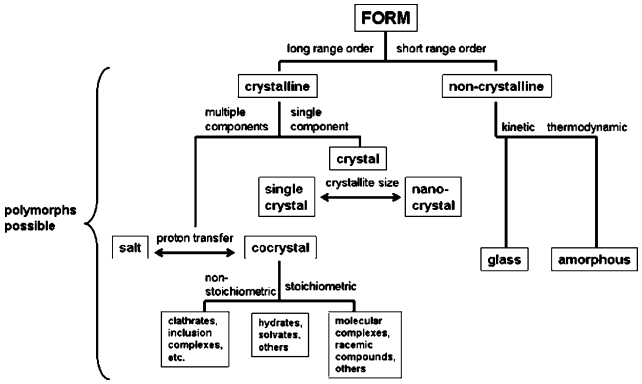
of these structural types are best considered to be subsets of the classification termed "cocrystals". The terms hydrate and solvate are entrenched in the literature and afford easy communication of commonly encountered structural types, so should certainly be retained. However, I agree wholeheartedly with Seddon[78] and Bernstein[79] that the term "pseudopolymorph", sometimes used to describe hydrates and solvates, should be abandoned (for an opposing view see the letters of Desiraju[80] and Nangia[81]). Proposed terms like "solvatomorph",[82] "hydratomorph,"[83] and "pseudopolymorphic solvate"[84] are not necessary and do not seem to have gained acceptance.

Cocrystals were well defined by Dunitz, who wrote "the word [co-crystal] provides a succinct though possibly inelegant definition of what it is intended to describe, a crystal containing two or more components together. Thus cocrystal encompasses molecular compounds, molecular complexes, hydrates, solvates, inclusion compounds, channel compounds, clathrates, and possibly other types of multi-component crystals."[85] The word is certainly succinct, which is an undeniable advantage over the term molecular complex.[86] Personally, the term does not strike me as inelegant, but this aside to personal taste should not be a criterion that carries much weight in selection of a descriptive scientific term. I do not agree with Dunitz in his assertion that "... the hyphen is essential: co-crystal, but under no circumstances cocrystal."[85] There is no more need for a hyphen in cocrystal than there is for a hyphen in coenzyme, coplanar, or cosine. To quote from *The Columbia Guide to Standard American English*, "How should the co- prefix be attached to the base word, with a hyphen or without? Answer: usually without a space or hyphen.." The exceptions are when "the base word begins with o (co-opt)... or when a word is so new as to look odd and risk misreading."[87] In any case, a scientific classification of multicomponent crystals that is based on structure is superior to one based on frequency of observance or the nature of one of the components. Thus, solvates and hydrates must, as multicomponent crystals, be subsets of the cocrystal classification rather than differentiated from it. Clearly, these designations arose because of the frequency with which they are encountered, water being ubiquitous and many solids being recrystallized from the relatively small number of organic compounds typically used as solvents. The terms hydrate and solvate are descriptive, in wide use, and should be preserved but with the realization that solvates and hydrates are part of, rather than separate from, the general category of cocrystals.

There seems to be little scientific value in creating designations based on the state of one of the components under standard conditions, such as Aakeröy's suggestion that cocrystals should only be those composed of components that are solids at ambient temperature,[88] or based on whether the structure in question was found by accident or intent, as in the suggestion that cocrystals of current interest encompass an "element of design."[89] Similarly, recent suggestions that "pharmaceutical cocrystals" should be a subset of multicomponent crystals, similar to hydrates, solvates, clathrates, and inclusion crystals,[90] would perpetuate classifications based on some randomly selected property of one of the components (is it used as a solvent? is it solid under STP conditions? is it an advantageously bioactive molecule?). Such systems are unnecessarily complicated. It is suggested that nomenclature be based on unambiguous properties of the multicomponent crystals themselves, not on some unrelated property of one of the components. The critical and important distinction that must be made is between crystals containing one component from all of the various types of molecular crystals that contain more than one component.

I think the best way to describe these various structures is outlined in Scheme 2. The term "form" can be considered to include cocrystals if one takes the position that there is one molecule of specific interest; the API in a pharmaceutical development program, for example. Single-component crystals or cocrystals can be polymorphic. In that scheme, cocrystals

Scheme 2. Classification Scheme for Organic Solids



consist of two or more components that form a unique crystalline structure having unique properties. That definition requires clarification of the meaning of "component". If a component is defined as being an atom, ionic compound, or molecule, then a cocrystal becomes more specifically either (1) a crystal that contains two or more different atoms or molecules or (2) a crystal that contains an ionic compound plus additional atoms, ionic compounds, or molecules. Note that salts can also exist in noncrystalline form.

A salt contains a single ionic compound, but multiple ions. Formation of salts of organic compounds involves proton transfer from an acid to a base. It is enlightening to think of organic salts as multicomponent species where the components are individual ions. Studies of crystal structures revealed that whether a proton is transferred from one component to another in a crystalline solid is dependent on the crystalline environment and cannot be predicted from ΔpK_a values alone.[91] Thus, it is reasonable to consider crystalline salts and cocrystals as species that exist at either end of a continuum of multicomponent crystal structures. At the salt end proton transfer is complete, and at the cocrystal end proton transfer is absent. When a pair of ionizable components crystallize, both the ΔpK_a value and the crystalline environment determine the extent of proton transfer and therefore the placement of the structure on the continuum. An interesting example is aminophylline, which is a compound composed of 2 mol of theophylline and 1 mol of ethylenediamine.[92] SSCI scientists have solved crystal structures of an anhydrous form and a monohydrate form of aminophylline. In one structure, there is proton transfer and in the other there is proton sharing (Figure 6).[93] Can it be said when these two components cocrystallize they form a salt? I believe the classification of such structures is not so simple as defining them as salts or not salts. Details of the aminophylline data and an analysis of the salt−cocrystal continuum will be presented in a forthcoming manuscript from SSCI.[93]

From a practical perspective, what a particular solid is called makes little difference. In selecting the solid form of an API for development into a drug product, for example, it should be the pharmaceutical acceptability of the components and the properties of the candidate solids that guide the selection process rather than the classification of each. However, in the highly regulated pharmaceutical industry it is desirable to classify materials to determine what testing may be required to meet guidelines. It must be realized, though, that it is often not possible to make hard divisions in science, and that is the case for organic solids. In particular, the difference between salts and cocrystals mentioned above is not easily defined.

4.2. Examples of Cocrystals from the Literature. Having defined cocrystals, a few examples from the literature will be presented. The examples do not include hydrates or solvates. Cocrystals, however they have been named, have been known for a long time. A study of quinhydrone and derivatives, called molecular compounds by the authors, was reported in 1893.[94] Quinhydrone is a 1:1 cocrystal of quinone and quinol.

Kofler used the contact thermomicroscopic method that bears his name to investigate cocrystals in the 1940s. The contact method involves melting two compounds and allowing the melts to come into contact. On cooling a contact preparation, cocrystals, if they can form, will do so at the contact interface. It is usually easy to differentiate a cocrystal from the starting crystalline components visually. An example is shown in Figure 7. The melting point of a cocrystal formed in this way can be determined by reheating the preparation.

Note that Kofler used the term molekülverbindungen (molecular compound) rather than cocrystal. He found that nicotinamide forms cocrystals with a number of different compounds, including azelaic (nonanedioic) acid, diallylbarbituric acid, and pyrocatechol.[19] Similarly, he found a series of cocrystals containing polyaromatic compounds and trinitroaromatic compounds.[95]

Organic and inorganic compounds can cocrystallize, examples being cocrystals of 2,5-*O*-methylene-D-mannitol with sodium chloride (1:1)[96] and carbamazepine with ammonium chloride (1:1).[97] A cocrystal of cyclotetramethylenetetranitramine (HMX) and ammonium perchlorate (3:2 molar ratio of HMX/NH_4ClO_4) was found, which has utility as a rocket propellant.[98] Ammonium perchlorate is a widely used oxidant in propellant systems, but its high degree of water solubility necessitates the use of desiccants and motor seals. The cocrystal, being water insoluble, can be used in lieu of those precautions.

4-*tert*-Butylcalix[4]arene forms cocrystals with various substances wherein the guests occupy space inside the bowl-shaped calixarene (clathrates). Cocrystals containing materials that are gaseous under ambient conditions (air, NO, SO_2, and Xe) were found to be stable at ambient temperature, releasing the guests on heating.[99] Thus, the calixarene was suggested to be useful as a thermally programmable gas storage and release system.

Triphenylphosphine oxide (TPPO) was found to cocrystallize with a variety of different organic compounds, including *N*-acetyl-*p*-toluenesulfonamide, acetanilide, triphenylcarbinol, saccharin, and phenol.[100] That behavior was attributed to the fact that TPPO is a good hydrogen bond acceptor. In addition, the bulky shape of TPPO inhibits the formation of layered structures. Thus, the compounds mentioned above crystallize as needles, but their cocrystals with TPPO are equant (blocky). At least one benefit that can be derived from the ability to convert needles into blocks is that single-crystal X-ray structure solutions can be achieved where the original needles lacked sufficient three-dimensionality for such analysis.

The structure of a three-component cocrystal containing aspirin, β-cyclodextrin, and succinic acid was determined by single-crystal X-ray analysis.[101] The purpose of generating the cocrystal was to slow aspirin hydrolysis in aqueous media, since cyclodextrin inclusion complexes are maintained in solution. Apparently, inclusion of succinic acid in the crystalline complex was unexpected, and the paper is silent relative to potential utility of the three-component cocrystal.

Recovery of expensive cephalosporins was achieved by crystallization of cocrystals. Cefaclor, cephalexin, cepfradine, and loracarbef form cocrystals with parabens (*para*-hydroxybenzoate esters) and related compounds.[102] Those cocrystals allow isolation of the cephalosporins from dilute solutions such as mother liquors remaining after direct crystallization. Crystal-

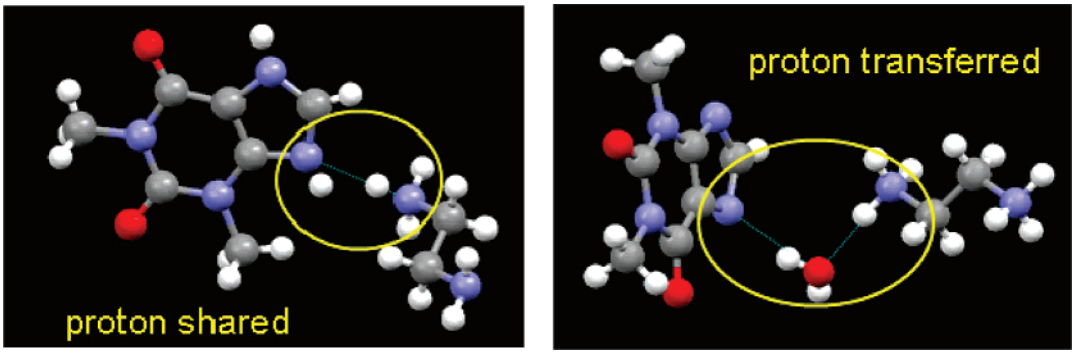


Figure 6. Diagrams from single-crystal structure analyses of aminophylline crystals. An anhydrous structure is on the left, and a monohydrated structure is on the right. In both cases, the acidic proton of theophylline was located using electron density maps. In the anhydrate, proton electron density was found to be disordered, some on the acidic theophylline nitrogen atom and some on the basic ethylenediamine atom. In the monohydrate, the proton is completely transferred to the ethylenediamine nitrogen atom.

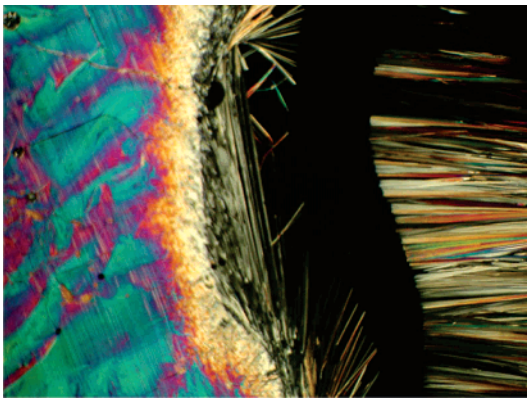


Figure 7. An optical microphotograph of a cocrystal formed using the contact method. Cooling of the contacted melts is underway. Crystalline nabumetone (mp 80 °C) is the birefringent material on the left, crystalline 2,3-naphthalenediol (mp 162 °C) is the horizontally striated material on the right, the black area is melted material, and the cocrystal (mp about 98 °C) is clearly visible as the needles in the center.

lization of the cocrystals was followed by pH-mediated precipitation of the purified cephalosporins under conditions which leave the parabens in solution.

Racemic mixtures are composed of equimolar mixtures of R and S enantiomers. Crystalline racemic mixtures exist more often than not as cocrystals. Approximately 90% of racemic mixtures crystallize as racemic compounds, in which equal numbers of R and S isomers occupy a single-crystal lattice.[103] A racemic compound is a distinct solid entity whose properties differ from crystals of the pure enantiomers. For example, ibuprofen crystals consist of stacked, hydrogen-bonded, carboxylic acid dimers. In the racemic compound, each dimer is composed of one S and one R enantiomer;[104] crystals of either pure enantiomer necessarily contain dimers composed of only one enantiomer (Figure 8).[105] That seemingly small structural difference results in significant physical property differences (Table 3).[106]

Sometimes, but not often, chiral compounds crystallize as solid solutions. In these, either enantiomer may equally well occupy a position in the crystal structure. Usually solid solutions exist only over a specific composition range, and the concentration of each enantiomer in the crystal is determined by the concentrations present in the solution or melt from which the crystal was produced. Thus, these types of solid solutions are non-stoichiometric cocrystals. In rare cases, the composition range is so narrow that a specific enantiomer stoichiometry other than 1:1 is maintained. For example, naringenin (2,3-dihydro-5,6-dihydroxy-2-(4-hydroxyphenyl)-4H-1-benzopyran-4-one) crystallizes as a solid solution that contains 75% of one enantiomer and 25% of the other.[107]

The use of cocrystals to alter the properties of pharmaceutically active compounds was reported as early as 1946, when Krantz et al. found that the stoichiometric (1:1) cocrystal containing the sodium salt of theophylline and glycine increased the water solubility of the API.[108] A clinical study using the cocrystal showed that it was tolerated in "unusually large amounts in man" and elicited the "typical theophylline response."[108] In the 1950s, Higuchi used solubility measurements to search for complex formation in solution between caffeine and a number of pharmaceutically active or acceptable compounds such as benzoic acid, benzoate ion,[109] aspirin, 4-hydroxybenzoic acid, 3-hydroxybenzoic acid, salicylic acid, salicylate ion, butyl paraben,[110] sulfathiazole, sulfadiazine, 4-aminobenzoic acid, benzocaine, phenobarbital, and barbital.[111] Ultimately, he found and isolated cocrystals of caffeine and gentisic acid that had stoichiometries of 1:1 and 1:2 (caffeine/gentisic acid).[112] Those materials altered the pharmaceutically important property of dissolution rate, reducing the rate of dissolution of caffeine. Higuchi wrote, "These complexes thus present a potentially useful way of formulating caffeine in dosage forms such as chewable tablets that are intended to linger in the mouth. Such dosage forms would only release caffeine slowly and should, consequently, have an improved taste factor over ones containing pure caffeine."[112]

Some other cocrystals containing pharmaceutically active molecules that were reported between 1940 and 1970 are theophylline/phenobarbital,[113] caffeine/5-chlorosalicylic acid,[114] adenine/phenobarbital,[115] and caffeine/barbital.[116]

In many cases, cocrystals are discovered empirically. In contrast, cocrystal design is also possible. One of the most active researchers in the field to date was Dr. Margaret Etter. She viewed hydrogen bonds as design elements in organic solids, similar to the role of covalent bonds as design elements in organic molecules.[117] By studying hydrogen-bonding patterns in crystal structures reported in the Cambridge Crystallographic Database, Etter devised a series of rules that govern hydrogen bond formation. Subsequently, application of the rules and a growing understanding of crystal structures has led to an increasing number of designed cocrystals. Examples are cocrystals of peptides,[118] cocrystals containing the sunscreen *para*-aminobenzoic acid,[119] cocrystals containing nucleotide bases,[120] and cocrystals showing promise as nonlinear optical materials.[121]

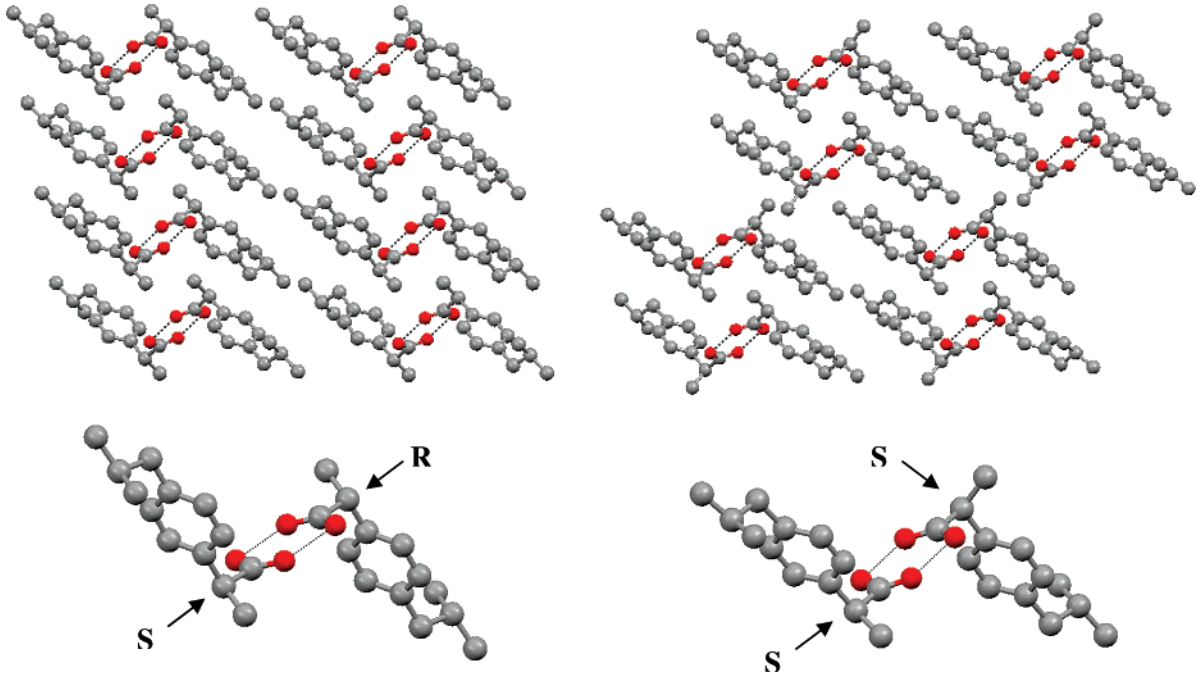


Figure 8. Packing diagrams (top) and dimer structures (bottom) of racemic ibuprofen (left) and *S*-ibuprofen (right) crystals.

Table 3. Properties of Racemic and *S*-Ibuprofen

property	*R,S*-ibuprofen (racemic compound)	*S*-ibuprofen
melting point (°C)	71	46
heat of fusion (kJ/mol)	26.9 ± 1.0	19.9 ± 0.8
solubility in aqueous KCl−HCl at 25 °C (M)	0.943×10^{-3}	1.79×10^{-3}

The implications of the early work on cocrystals containing bioactive components on pharmaceutical development seem to have been unrealized until only recently. Drug development, particularly when directed to a solid oral dosage formulation, is critically dependent on the physicochemical properties of the API. Important properties include solubility, dissolution rate, bioavailability, chemical and physical stability, hygroscopicity, melting point, crystal habit, and powder handling characteristics.[53] For ionizable APIs with undesirable properties, salts may be generated in a search for a better solid.[122] But where salts fail, or for non-ionizable APIs, traditional approaches are exhausted. Cocrystals provide expanded opportunities to alter API properties. For example, it has been demonstrated that cocrystals containing carboxylic acid guests alter the dissolution rates of itraconazole (antifungal),[123] fluoxetine hydrochloride (antidepressant),[124] and an API investigated by the Purdue Pharma company. The latter cocrystal, containing 2-[4-(4-chloro-2-fluorophenoxy)phenyl]pyrimidine-4-carboxamide and glutaric acid (Figure 9), afforded a 4-fold bioavailability increase in dogs.[125] Cocrystals have also been used to overcome undesirable physical properties, an example being that a cocrystal of caffeine with oxalic acid is non-hygroscopic, in contrast to crystalline caffeine, which absorbs atmospheric water to produce a hydrate.[126]

4.3. Cocrystal Screening. The process of cocrystal screening is much like polymorph or salt screening. Approaches to the latter have been described in several publications.[127] All of these screens follow the same general outline presented in Scheme 1; samples need to be made, characterized, and their properties determined. As in polymorph screening, the differentiation between screening (finding cocrystals) and selection (property evaluation of cocrystals) should be recognized. In this section, some of the primary differences between polymorph and cocrystal screening will be discussed.

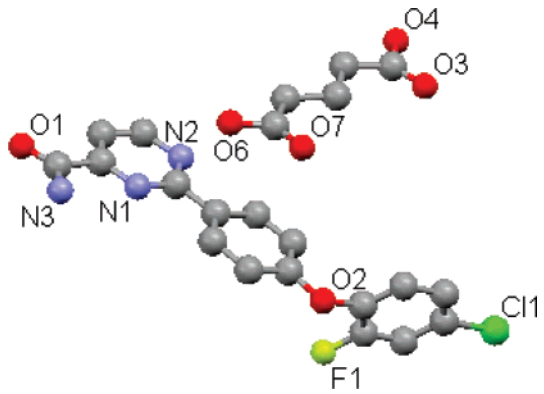


Figure 9. The structure of a glutaric acid cocrystal of 2-[4-(4-chloro-2-fluorophenoxy)phenyl]pyrimidine-4-carboxamide.[125] Chlorine atoms are green, fluorine atoms are yellow, nitrogen atoms are blue, oxygen atoms are red, and carbon atoms are gray; hydrogen atoms are omitted for clarity.

4.3.1. Sample Generation. Cocrystal screening differs from polymorph screening in that two (or more) components are mixed to generate each sample. Thus, selection of potential cocrystal guests (the API is the host) is the first step. The process is similar to salt screening, in which counterion sources need to be selected to use in salt formation experiments. Counterions are typically selected based on the following criteria:

(i) they have been used in commercial drug products and are thus known to be pharmaceutically acceptable (the greater the frequency of appearance the better);

(ii) they are nontoxic;

(iii) there is at least a separation of 2 or 3 pK_a units between the acid and the base;

(iv) the size of the counterion relative to the API loading in the drug product.

The same criteria should be used for selection of guests in a cocrystal screen, with the exception of number (iii). Since cocrystals can consist of un-ionized components, and

since ΔpK_a values have little predictive value relative to crystalline environment, as discussed above, eliminating experiments based on pK_a values can only lead to missed cocrystals.

There are various sources in which pharmaceutically acceptable guest molecules can be found. Foremost are listings of counterion sources for salt selection, such as those compiled by Stahl and Wermuth.[122] Also, the Generally Recognized as Safe (GRAS) list[128] and the Everything Added to Food in the US (EAFUS) list[129] are useful. Not everything in the latter two lists is pharmaceutically acceptable; the toxicological profile of any potential guest needs to be considered. At SSCI, we have compiled a master guest list that currently contains approximately 230 compounds.

Although pharmaceuticals present a significant opportunity for the practical application of crystal engineering, that opportunity comes with a few limitations. Perhaps the most significant is that the guest compounds used as cocrystal formers must meet a restrictive set of requirements, as do the acids and bases that are commonly used as API salt formers. There are only about 100 salt formers that are in drug products approved by regulatory agencies and therefore are considered to be pharmaceutically acceptable.[122] Pharmaceutical companies prefer to develop salts containing pharmaceutically acceptable ions to avoid the risk that the non-API portion of the salts will adversely affect safety and efficacy behavior. Fortunately, many pharmaceutically acceptable salt formers are also suitable cocrystal formers. With time, it is likely that companies will consider using a wider range of nontoxic cocrystal guests and consequently GRAS compounds, food additives, and other nontoxic compounds will become accepted as guest compounds in cocrystal dosage forms.

Cocrystal screening could be done in a completely empirical manner, conducting experiments using every combination of API and guest. This is not the most efficient approach, however. Because of the large number of potential guests and the various experimental techniques that should be considered (see below), many experiments are possible. The number becomes even greater if the API is ionizable and cocrystals are sought that contain the salt of the API and a guest molecule. It is preferable to select guests, at least for initial experiments, based on structural features of the API and guest. While cocrystal structures cannot be predicted and the screening exercise is ultimately an empirical one, often a rational guest selection process leads to cocrystals with a minimum number of experiments.

Structural features of the API that should be assessed are the number, arrangement, and types of groups that can participate in hydrogen bonding as well as symmetry and conformational flexibility. If a single-crystal structure of the API is available it should be examined. Hydrogen bonds are often the primary directors of organic crystalline structure. By evaluating the disposition of hydrogen bond donors and acceptors, and applying general rules such as those developed by Etter and Görbitz,[117,130] it is sometimes possible to predict interactions that suggest the use of certain guests. For example, Etter's general rules are particularly useful:[117]

(i) All good proton donors and acceptors are used in hydrogen bonding.

(ii) Six-membered-ring intramolecular hydrogen bonds form in preference to intermolecular hydrogen bonds.

(iii) The best proton donors and acceptors remaining after intramolecular hydrogen-bond formation form intermolecular hydrogen bonds to one another.

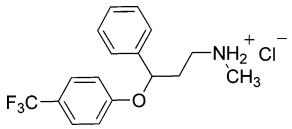


Figure 10. The structure of fluoxetine hydrochloride.

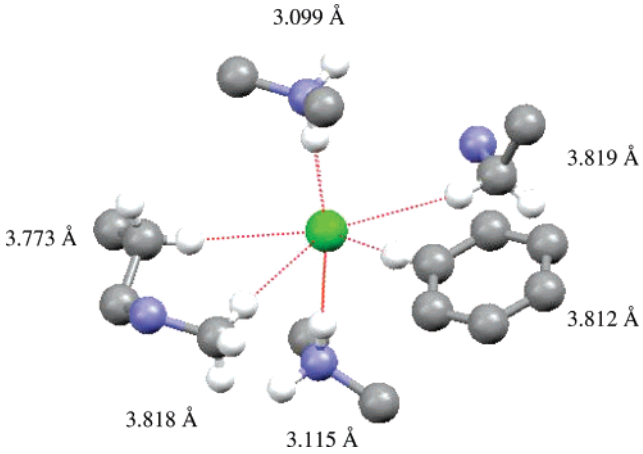


Figure 11. The coordination sphere of the chloride ion in the crystal structure of fluoxetine hydrochloride (Cl−N and Cl−C distances shown). The chloride ion is green, nitrogen atoms are blue, carbon atoms are gray, and hydrogen atoms are white. Close contacts are shown by dotted red lines.

Also, mining of the Cambridge Structural Database, particularly using the Isostar search program,[131] allows discovery of common hydrogen bonding arrangements in crystals.

The value of such analyses is illustrated by the generation of cocrystals of fluoxetine hydrochloride, the API in the antidepressant Prozac (Figure 10).[124] Inspection of the published crystal structure of fluoxetine hydrochloride[132] revealed that the chloride ion, a good hydrogen bond acceptor, is coordinated by two types of hydrogen bond donors (Figure 11). The axial donors are NH groups and the equatorial donors are CH groups. It is not uncommon for weak CH donors to occupy acceptor sites on the strong chloride ion acceptor.[133] Steiner noted that hydrogen bonding to halogen anions is "one of the largest contributors to crystal stability."[134] Thus, pharmaceutically acceptable guests were sought that would be expected to form stronger hydrogen bonds to chloride than do CH groups. The idea was that Etter's third rule might drive cocrystal formation, in that the strongest donor and acceptor (one on each molecule) would form a strong intermolecular hydrogen bond. Carboxylic acids were selected based on their known ability to form strong hydrogen bonds to chloride ion,[135] and indeed cocrystals were found that contained fluoxetine hydrochloride and the pharmaceutically acceptable benzoic, fumaric, and succinic acids.[124] While the anticipated hydrogen bond between the COOH group of the guest and the chloride ion were present in each of the cocrystal structures, it should be noted that other, unanticipated hydrogen bond motifs are also present and important to the overall stability of the structures (exemplified by the succinic acid cocrystal shown in Figure 12).[124] The point is that, even though the chloride ion was used in this case as the focus of efforts to establish new cocrystal structures, it was still not possible to predict exactly the structures and hydrogen bond motifs that eventually resulted. In fact, not all pharmaceutically acceptable carboxylic acids that were used with fluoxetine hydrochloride in screening experiments provided cocrystals,

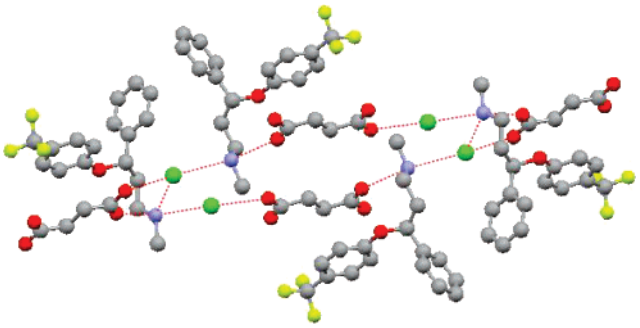


Figure 12. The crystal structure of a 1:1 fluoxetine HCl/succinic acid cocrystal. The chloride ion is green, fluorine atoms are yellow, nitrogen atoms are blue, oxygen atoms are red, and carbon atoms are gray; hydrogen atoms are omitted for clarity. Hydrogen bonds are shown by dotted red lines.

confirming that hydrogen bonding between the acid group and the chloride ion is not a sufficient condition for cocrystal formation.

Once guests have been selected, the physical properties of the API of interest should be evaluated to aid in selection of experimental techniques. The techniques used may be somewhat different than those used for polymorph screening since two compounds are involved in a cocrystal experiment, and thus conditions must be found where a cocrystal, if one can form, will crystallize instead of the individual compounds.

To carry out solvent-based experiments (evaporation or cooling of solutions, for example) solvents or solvent mixtures must be found in which both components dissolve sufficiently. Thus, the solubility of the API in various solvents need to be estimated. If the solubility of the potential guests in the same solvents in which the API is soluble are not known, they must be determined also. Since the cocrystals sought will typically contain a stoichiometric ratio of components, such ratios should be used, particularly in experiments where solvent is completely evaporated. For cooling or other experiments where solvents will not be completely removed, there need not be a stoichiometric ratio of the concentrations of the components. In fact, Rodríguez-Hornedo et al. recently described the method of obtaining cocrystals from solution using the common cocrystal component effect, which operates as does the common ion effect.[136] By increasing the concentration of one cocrystal component, the solubility of the cocrystal decreases to a level below the solubility of either component. This provides a means of achieving cocrystal supersaturation other than cooling, solvent removal, or antisolvent addition. For screening, then, solvent systems should be sought where one component can be dissolved in excess relative to the second component. In the absence of such a solvent system, however, addition of a solution of the more-soluble component to a slurry of the less-soluble component can also bring about the desired concentration ratio and lead to a conversion of the undissolved solid to a cocrystal.[136]

Another property of the API that should be evaluated is its thermal behavior. In particular, its melting point and whether it melts without decomposition are important. For well-behaved compounds, thermomicroscopic methods provide a convenient and often-successful route to cocrystals. Thermomicroscopic techniques have been described in detail,[29] and their application to cocrystal screening was discussed above.

A technique that can be used that is relatively independent of the properties of the API is grinding. Preparation of cocrystals in this way was reported as early as 1893, where quinhydrone derivatives were made by grinding solid quinones and quinols together in a mortar and pestle, with or without solvent.[94] Subsequent work showed that some cocrystals could be prepared by grinding but not from solution. For example, in a study of cocrystal formation between imides and a variety of guest molecules, it was found that many cocrystals could be obtained both by grinding and from solution, but others, such as the 1:1 cocrystals of diacetamide with acetamide, benzamide, and 3,4-dinitrobenzoic acid, could only be prepared by grinding.[137] Conversely, cocrystals of 9-ethylguanine and 1-methylcytosine can be prepared from solution but not by grinding in spite of repeated attempts.[138] Trask and co-workers compared grinding and solvent-based cocrystal preparation methods using caffeine as a model API.[139] They found, similar to previous work, that some cocrystals could first be prepared only by grinding, but subsequent addition of seeds of those cocrystals to solutions of the components provided the cocrystal from solution. They made some interesting observations, such as the fact that a 1:1 cocrystal of caffeine and trifluoroacetic acid, which could be prepared only by grinding (not from solution), could be made in two polymorphic forms depending on the total quantity of material in the grinding jar. One polymorph resulted from grinding 140 mg of a stoichiometric mixture of caffeine and trifluoroacetic acid, a second polymorph resulted from grinding 320 mg of the same mixture. A variant of the standard grinding techniques is solvent drop grinding. Selection of the polymorph of a caffeine/glutaric acid cocrystal was possible by inclusion of small amounts of specific solvents during grinding.[140] The results discussed above clearly demonstrate the need for multiple techniques when carrying out a cocrystal screen and specifically the value of grinding experiments.

At SSCI, we are investigating sonication as an alternative to grinding. That technique may be applied to wet or dry solid mixtures and has been effective in producing cocrystals that previously were found only by grinding or only from solution.[46,141] An added advantage to sonication over grinding is the ability to easily carry out the former on multiple samples at once using commercially available equipment. Results from SSCI studies will be published in due course.

4.3.2. Additional Cocrystal Screening Steps. Once samples have been generated, a cocrystal screen is no different than a polymorph screen. The samples must be analyzed, the data sorted, cocrystals that are found made in larger scale, and the properties of relevant cocrystals determined. Producing cocrystals at scale can be somewhat more challenging than crystallization of a single substance for the reasons described above. However, the factors that need to be known to control crystallizations of polymorphs, such as solubilities, metastable zone widths, rates of nucleation and growth, are the same factors that need to be known to control cocrystal crystallizations.

4.4. How Often Do Organic Compounds Form Cocrystals? There are fewer reports in the literature about the frequency with which organic compounds can form cocrystals than there are reports about the frequency of polymorphism. That is not surprising when one considers that organic compounds are frequently crystallized and recrystallized for purification, providing multiple opportunities for polymorph formation but purposely reducing the presence of other components (impurities) that would be necessary for cocrystal formation. Crystallizations are most often carried out from the relatively small number of compounds used as organic solvents, so the frequency of solvate formation gives some idea of the frequency with which cocrystals might be expected to form if a wider search

Table 4. Percentages of Compounds that Formed Cocrystals

	no. that formed cocrystals	total compounds	percent that formed cocrystals
all compounds	39	64	61
salts	15	24	63
non-salts	24	40	60

were conducted. Thirty-eight percent of the compounds subjected to polymorph screening at SSCI cocrystallized with water and 32% cocrystallized with other solvents (Table 2). Those percentages seem quite high considering that the test compounds were exposed only to water and solvents during screening. A recent review of the data in the CSD showed that 1.1% of the crystal structures of organic compounds were cocrystals, using that author's definition of the term.[90b] This number is certainly smaller than the percentage of compounds that can form cocrystals, but again does not represent the results of an intentional search. If one were to look for cocrystals other than hydrates or solvates, how frequently might they be found?

Where cocrystals are of potential use, deliberate searches for them will be carried out. This is the case at SSCI, where projects whose goal is to find cocrystals are increasing in frequency. There is some reluctance in the pharmaceutical industry to embrace cocrystals as development candidates because of the uncertainty of the response from regulatory agencies. However, the FDA's definition of an "active moiety" appears to allow consideration of such species:[142] "the molecule or ion, excluding those appended portions of the molecule that cause the drug to be an ester, salt (including a salt with hydrogen or coordination bonds), *or other noncovalent derivative (such as a complex, chelate, or clathrate) of the molecule,* [italics added] responsible for the physiological or pharmacological action of the drug substance."

A number of cocrystal screens have been carried out at SSCI. Data from these can be used to provide a sense of the likelihood of finding cocrystals when they are purposely sought, and in particular the likelihood of finding cocrystals that might be used as APIs. Note that in this discussion I refer only to cocrystals that are not hydrates or solvates. Rather, the cocrystals sought and found contain organic molecules as guests which are not solvents and are, with only a few exceptions, pharmaceutically acceptable. The cocrystal screens carried out differed from traditional salt screens in that the salt of an API was the host, the API was non-ionizable, or the API and guest were not expected to form a salt because of their pK_a values. The cocrystals found may be classified according to those criteria, as follows.

Type 1 cocrystals are defined as those in which the host is the salt of an API and the guest is a covalent compound. Those cocrystals, which are exemplified by the cocrystal containing fluoxetine hydrochloride and succinic acid (Figure 12),[124] contain an API ion, a counterion, and a non-ionized guest.

In cocrystals of types 2, 3, and 4 both the host and the guest are covalent compounds. Those are designated as type 2, 3, or 4 based on the pK_a values of the components. The relevant pK_a values represent the following reactions. Note that all pK_a values were calculated.[143]

$$\text{(host most basic center)H}^+ \rightarrow \text{(host most basic center)} + \text{H}^+ \qquad \text{p}K_a\ 1$$

$$\text{(host most acidic center)H} \rightarrow \text{(host most acidic center)}^- + \text{H}^+ \qquad \text{p}K_a\ 2$$

$$\text{(guest most basic center)H}^+ \rightarrow \text{(guest most basic center)} + \text{H}^+ \qquad \text{p}K_a\ 3$$

$$\text{(guest most acidic center)H} \rightarrow \text{(guest most acidic center)}^- + \text{H}^+ \qquad \text{p}K_a\ 4$$

When pK_a values are expressed as shown above (acid on the left of the equation and base on the right) and listed in order of lower to higher, an acid will only react with a base below it on the list.[144] When the pK_a value of the most basic site of the host−guest pair is smaller than the pK_a of the acidic site on the other component, the cocrystal is designated type 2. For example, a cocrystal is type 2 if the host is the most basic of the pair (pK_a 1 > pK_a 3), and pK_a 4 is greater than pK_a 1. In such cases, salt formation would not be expected because the acid (guest) would be below the base (host) in the list, and the components would therefore not even be expected to react.

Type 3 cocrystals are those in which the pK_a value of the most basic site of the host−guest pair is larger than the pK_a of the acidic site on the other component, but is less than 2 pK_a units larger. For example, a cocrystal is type 3 if the host is the most basic of the pair (pK_a 1 > pK_a 3), and pK_a 1 is less than 2 units greater than pK_a 4. The value of 2 was selected because a common criterion in pharmaceutical salt selection is that the pK_a of the base is at least 2 units greater than the pK_a of the acid,[145] the belief being that a lesser separation will not result in formation of a stable salt. Thus, type 3 cocrystals would not normally be expected to be stable salts. In nearly, all cases the extent of proton transfer in the type 3 cocrystals was not investigated, so the placement of those materials on the salt−cocrystal continuum is unknown.

When either the host or guest component is not ionizable under normal conditions, or both are acidic, the cocrystal is designated as type 4. Not ionizable is defined when the pK_a values for the most basic and acidic sites are <-5 and >12, respectively. Thus, a cocrystal is type 4 if pK_a 1 is <-5 and pK_a 2 is >12, or if pK_a 3 is <-5 and pK_a 4 is >12.

As of the time this is being written, SSCI has completed cocrystal screens for 53 APIs, or 64 different compounds when different salts of a given API are counted as different compounds. The raw data from the screens are available as Supporting Information.

The results in terms of percentages of compounds that yielded cocrystals are shown in Table 4. Significantly, around 60% of the structurally diverse set of 64 compounds (53 APIs) provided cocrystals. This unexpectedly high success rate indicates that cocrystals should be viable targets of API solid form selection projects.

A total of 192 cocrystals were found containing the 39 compounds that functioned as hosts, because 32 of the compounds formed cocrystals with more than one guest. Of the 192 cocrystals, 48 are type 1 (the host is the salt of an API and the guest is a covalent compound), 101 are type 2 (the pK_a value of the most basic site of the host−guest pair is smaller than the pK_a of the acidic site on the other component), 32 are type 3 (the pK_a value of the most basic site of the host−guest pair is larger than the pK_a of the acidic site on the other component, but is less than 2 pK_a units larger, and 11 are type 4 (the host or guest component is not ionizable under normal conditions, or both are acidic).

As with the polymorph screens discussed above, the cocrystal screens varied in scope. Different numbers of potential guests were tested under different experimental conditions. Not all

cocrystals found were made in bulk and fully characterized. Those that were not characterized are believed to be cocrystals based on X-ray powder diffraction (XRPD) analysis, spectroscopic analysis, or, in the case of thermomicroscopic experiments, visual assessment.

5. Conclusions

Solid form selection is an important component of drug development. Although polymorph screening is an expected, in fact required, preformulation activity, the scopes and experimental breadths of screens vary. To carry out an effective polymorph screen, it is important to cover as much experimental space as possible during sample generation, obtain the maximum amount of information in a first-pass analytical evaluation, use multiple analytical techniques for characterization of forms found, and determine relevant properties of selected forms. Data from screens carried out in this way indicate that 80−90% of organic compounds can exist in multiple crystalline forms (polymorphs, hydrates, solvates).

Cocrystals are underutilized solids that greatly expand the possibilities for finding a developable solid form of an API. The term "cocrystal" is preferred over recently suggested terms such as "molecular complex", "pharmaceutical co-crystal", and "co-crystal", from both scientific and brevity standpoints. Cocrystals can be thought of as representing a continuum of structure with salts at one end and crystals containing multiple, non-ionized components at the other. Cocrystals are quite common; they have been found at SSCI for about 60% of the APIs screened. To find cocrystals, it is most efficient to use a combination of structural evaluation (for potential guest selection) and physical evaluation (for experimental technique selection), followed by a screening procedure similar to that used for polymorph screening.

Solid-state chemistry has much greater potential than currently realized by the pharmaceutical industry. Not only useful in development of new chemical entities, new technologies, such as cocrystals, provide means for product line extensions and rescue of APIs that were abandoned because of development problems.

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