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Specialized Solid Form Screening Techniques

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ABSTRACT: Solid form screening is an integral part of many development plans at various companies and includes polymorph, salt, cocrystal, amorphous, and amorphous dispersion screens. There are a number of traditional solvent- and nonsolvent-based methods that are employed for these screens. Over time, specialized screens have been developed to deal with difficult molecules and situations or to push the limits of traditional experiments. This contribution outlines a variety of specialized screening approaches for polymorphs, salts, cocrystals, and amorphous dispersions. Many techniques are amenable to laboratory equipment and can be incorporated with minimal start-up time, while others are very specific and will need specialized equipment and/or expertise.

1. INTRODUCTION

Screening active pharmaceutical ingredients (APIs) to investigate new solid forms, including polymorphs, salts, cocrystals, and amorphous dispersions, is a common practice for new chemical entities (NCEs) and marketed products. New solid forms will have different properties, such as solubility, crystallinity stability, and bioavailabilty, which can aid in the development of early formulations and later-stage drug products. Different screens can be performed at different points in the development process, depending on the information needed and the goal of the screen. As shown in Figure 1, early development may include a small polymorph, salt, cocrystal, or amorphous dispersion screen.[1] Later in development, new properties may be needed; therefore, an extended screen may be implemented to produce a modified and improved formulation. All of these screens work together to support the formulation goals to produce a product that has acceptable performance.

Polymorph screens focus on finding new forms of an API and can include unsolvated, solvated, hydrated, and even amorphous materials. Salt, cocrystal, and amorphous dispersion screens use additional materials, such as counterions, cocrystal formers, and polymers, respectively. For all solid forms, small screens in early development may lead to medium size screens for phase II or III trials and a more comprehensive screen near launch. It should be noted that, once a new salt or cocrystal is targeted for development, a polymorph screen should be performed on that material to determine the possible forms, the thermodynamically stable form, and how this new form best fits within the development plan.

Techniques used for screening have evolved over time to encompass a wide variety of processes and conditions. A number of specialized screens have been reported in the literature that either expand typical screens or deal with difficult molecules or situations. A summary of various specialized screens is presented. The work described here is not meant to be a comprehensive list but is a sampling of possible scenarios that can be modified or expanded as needed for different situations.

2. POLYMORPH SCREENING

2.1. Traditional Screening. There are a number of excellent reviews on traditional screening techniques,[2−6] so they will be reviewed only briefly here. These techniques can include solvent- and nonsolvent-based methods. When stable forms are desired, thermodynamic conditions are used which employ slower crystallization methods. The formation of metastable forms requires kinetic conditions that cover faster time frames. This concept is illustrated in Figure 2 for a number of crystallization techniques.

Solvent-based methods are the classic approach to polymorph screening due to the diversity of solvents and conditions that can be utilized. They also provide early information for large-scale crystallization of the API. Methods using solvents or solvent mixtures include cooling a solution, evaporation, antisolvent addition, vapor diffusion, and suspensions (slurries). Variations on these methods can include changes in solvent, solvent mixtures, antisolvent, temperature, cooling rate, concentration, rate of addition, and order of mixing, to name a few possibilities. Nonsolvent methods consist of crystallization from the melt, heat-induced transformations, sublimation, desolvation of solvates, salting out, and pH changes. Again, a large number of parameters can be modified for nonsolvent screening experiments.

Manual crystallization methods and automated approaches are both used in polymorph screening. Manual methods usually require more material and may take longer to execute, but a wider variety of conditions can be employed, and multiple techniques can be applied to one sample, if needed. A typical scale for manual experiments can range from ∼20 to 100 mg or more. Automated methods use less material per experiment and can take less time for a larger number of samples, but crystallization conditions are limited, as they are restricted mainly to solvent-based methods.[7] A typical sample size for plate screens is ∼1−3 mg of material. The ideal screen is a

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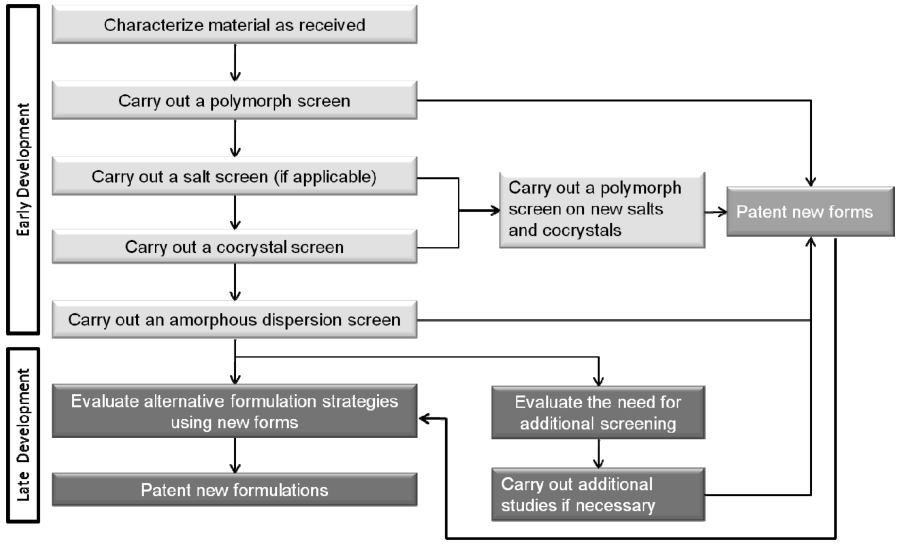

Figure 1. Screening strategies during early and late development (adpated from ref 1).

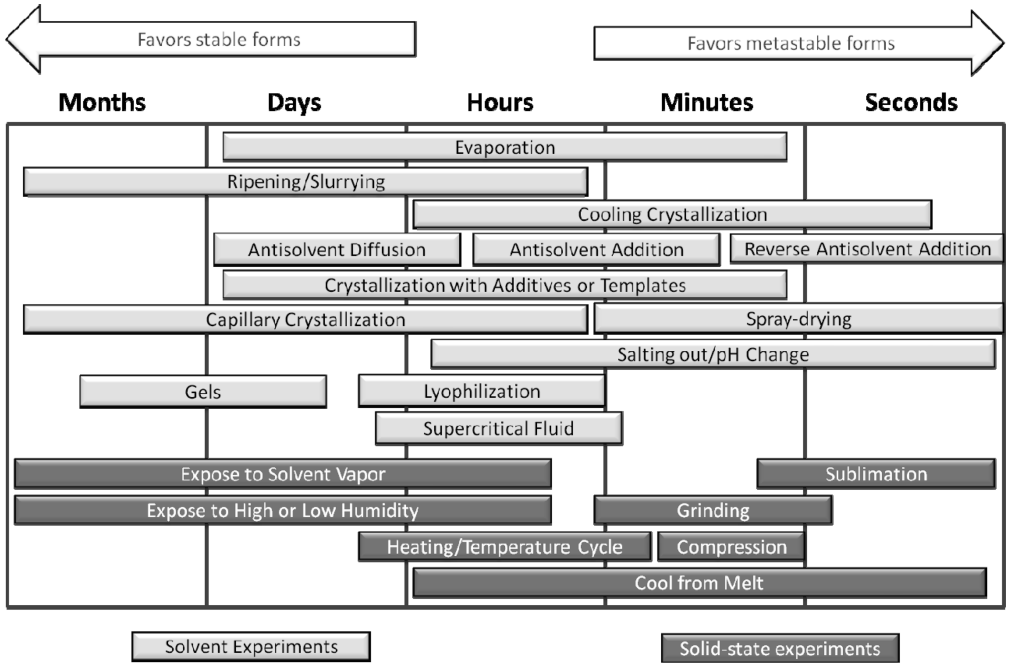

Figure 2. Time frames for common screening experiments (adapted from Anderton *Am. Pharm. Rev.* **2007**, *10*, 24).

combination of solvent, nonsolvent, manual, and automated methods.

While these classic techniques are often adequate to find numerous solid forms for a wide variety of systems, there are always cases where a different approach may be needed for a difficult situation or to expand the crystallization space of the screen. Alternate techniques are discussed in the following sections to diversify common screens.

2.2. Stable Form Screen. One goal for most polymorph screens is to identify the thermodynamically stable form. Finding this form early in development allows its properties and developability to be evaluated while the development plan is being compiled. Most companies prefer to develop the most stable form when possible in order to minimize process induced transformations during storage and drug product manufacturing.[8] The most stable form also exhibits a lower solubility than metastable forms, as seen in the case of ritanovir,[9] so early identification can help avoid problems later in development.

Early development screens targeting the most stable form are becoming more common for new chemical entities (NCEs). A small stable form screen at the pre-IND stage can provide important information to help guide API crystallization and early formulation process development. More advanced screens can be performed to find additional forms if the stable form cannot be easily developed or as the compound moves further into development.

A stable form screen typically employs slow crystallization conditions under thermodynamic rather than kinetic conditions.[10] Experiments can include slurrying, slow evaporation, slow cooling, slow antisolvent addition, or a combination of these methods. Solvent-mediated polymorphic transformations using slurries is a common screening method to produce the

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most stable form at ambient temperature, and a stable form screen using this approach has been reported.[11] Suspensions were made using 18−20 solvents with a wide range of dielectric constants as a measure of polarity (see Table 1 for common solvents and their dielectric constants). One set of suspensions was stirred for 2 days and the other for 2 weeks. The fastest transformations occurred in solvents with the highest solubilities, and a minimum solubility of approximately 3 mg/mL was found to be a reasonable cutoff to minimize the time of the experiment. The screen was used for 43 development compounds. For 26% of the compounds a more stable form was found using the screen. A more stable form was not observed later in development for any of the 43 compounds used in the study.

Table 1. Common solvents and dielectric constants for use in a stable form screen (adapted from refs 11a, b)

solvent	dielectric constant
water	78
N,N-dimethylformamide (DMF)	37
nitromethane	36
acetonitrile	36
methanol	33
ethanol	25
acetone	21
2-propanol (isopropyl alcohol, IPA)	20
1-butanol	18
2-butanone (methyl ethyl ketone, MEK)	18
1-pentanol	14
1-octanol	10
tetrahydrofuran (THF)	7.6
1,2-dimethoxyethane	7.3
methyl acetate	6.7
acetic acid	6.2
ethyl acetate	6.1
propyl acetate	6.0
chloroform	4.9
methyl *tert*-butyl ether (MTBE)	4.3
1,2-xylene	2.6
toluene	2.4
1,4,-dioxane	2.2
hexanes	1.9

The slurry methodology does have limitations that need to be considered. Slurries equilibrated at ambient temperature will provide the most stable form at this temperature; if the system is enantiotropic, it is important to determine the transition temperature where the thermodynamic stability will change. The presence of trace amounts of impurities may prevent nucleation and transformation to the most stable form. Minimal solubility of the API in organic solvents can also prohibit transformation to the stable form. To remedy this, solvent mixtures can be used to achieve the necessary solubility. High solubilities (>200 mg/mL) are not ideal for slurries due to the large amount of material needed to produce a saturated solution. It is also important to determine if an intermediate solvate has been produced that may desolvate to an unsolvated form upon drying. This situation will not result in a thermodynamic ranking of the forms, even though it appears that an unsolvated form was obtained. Comparing data for both the wet cake and the dried material will help determine if an intermediate solvated material is involved.

2.3. Hydrate Screen. In many cases, an acceptable anhydrous form is not available, and other forms, such as a hydrate, may need to be targeted. Specific conditions can be used to produce hydrated forms in a screen.[2] A sampling of these conditions is given in Table 2. These include aqueous crystallizations, as well as exposure to water vapor and crystallization with solvent systems containing water.

Table 2. Experimental conditions to produce hydrates

method	comments
exposure to RH	dynamic vapor isotherm including sorption/desorption cycling, humidity chambers
slurry in water	suspension, various temperatures
temperature cycling of aqueous suspension	different heating and cooling rates, different water activities
mixed-solvent system	dependent on water activity
vapor diffusion	water activity will change over time
solvent/antisolvent	use water as solvent or antisolvent
heating	dry higher hydrates incrementally to form lower hydrates
solvent exchange	exchange solvent for water by stressing at elevated RH or slurrying in water or aqueous solvent
wet−drying	dry in oven at elevated temperature with controlled RH stream over sample
wet grinding	use water as solvent
wet granulate	use water and various excipients, different drying temperatures

Exposure to different relative humidities (RH) is a common method to look for hydrates. An automated moisture balance system covering a range of 5−95% RH is an efficient method to determine the RH conditions where a hydrate may form. This can then be confirmed by equilibrating samples in an RH chamber and analyzing the solid by various methods to characterize the hydrate that has formed. Multiple sorption/desorption cycles in an automated system can also provide information on hydrate formation and dehydration.

Aqueous solvent systems can be used to obtain a variety of water activities which can be used to tailor a crystallization process to a specific hydrate. Water activities will be constant when using different organic solvents, but will correspond to different water levels in different solvents, as shown in Figure 3a.[12] It is important to understand the water content of the organic solvent being used and how it relates to the water activity. Having a water content of 0.2 mol fraction of water in methanol will give a water activity around 0.25; however, the same amount of water in isopropanol will give a water activity around 0.45, which could result in an entirely different hydrate (Figure 3a). This is illustrated in Figure 3b for theophylline which exists as the anhydrate below a water activity of approximately 0.25 and a monohydrate above a water activity of approximately 0.25.[12] A water value of 0.1 mol fraction of water in IPA gives a water activity of 0.3, resulting in the monohydrate, whereas the same mole fraction of water in methanol gives a water activity of 0.15, producing the anhydrous material. It is important to determine the water activity where hydrates form, and this can be accomplished with screening experiments covering a large range of water activities.

A hydrate screen has been reported using five different methods (exposure to RH, water slurry, temperature cycling of aqueous suspensions, mixed-solvent systems, and vapor diffusion) and 10 hydrate-forming compounds exhibiting both low and high aqueous solubilities.[13] Compounds included

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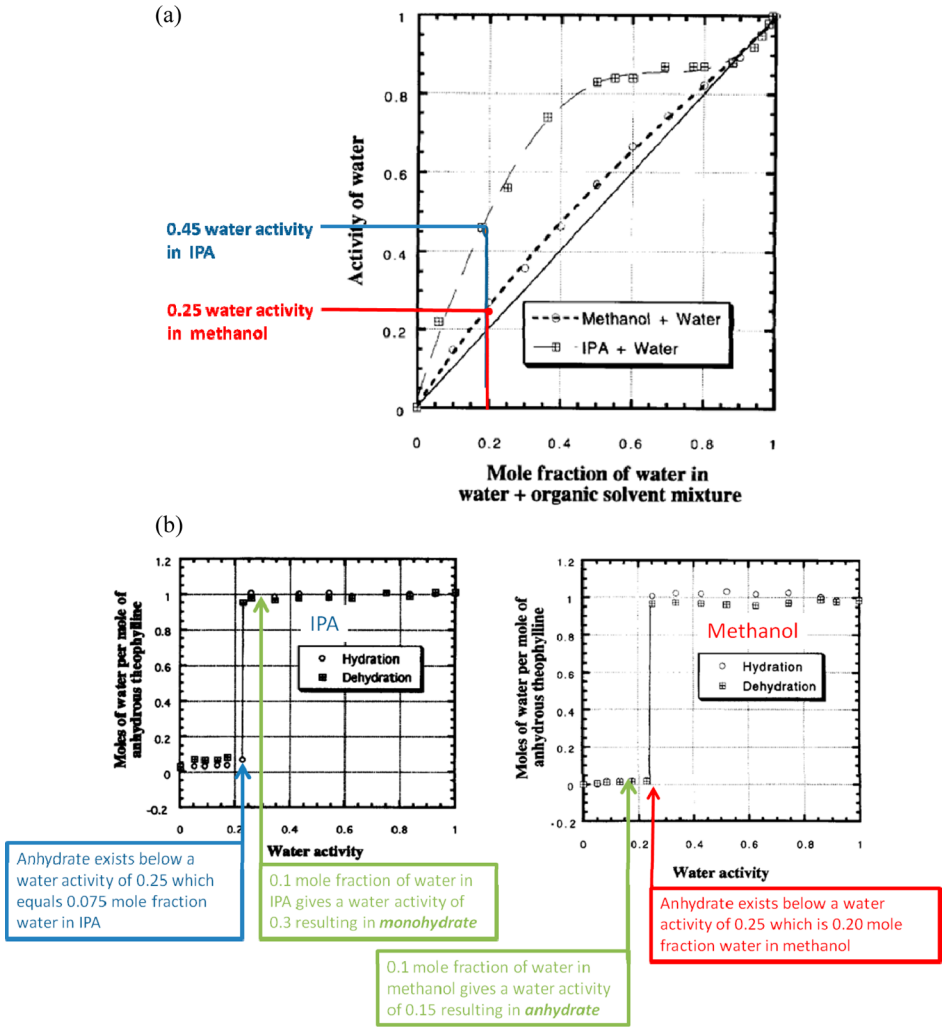

Figure 3. (a) Water activity curves for methanol/water and isopropanol(IPA)/water. (b) Effect of water activity and mole fraction of water on the crystallization of theophylline (adapted from ref 12).

caffeine, carbamazepine, fluconazole, naproxen sodium, niclosamide, prazosin, theophylline, and tranilast. It was found that a combination of slurry or temperature cycling along with a mixed-solvent system provided a screening strategy with a success rate of about 90% for the cases studied.

Another approach uses a small-scale crystallizer with temperature cycling to look for hydrates.[14] The method requires about 15−20 mg of material per experiment, and the solvent system and cycling sequence need to be determined for each system. Both solutions and suspensions can be investigated with this technique and related directly to larger-scale processing. This study screened nine compounds; seven compounds were known to form hydrates (caffeine, niclosamide, cimetidine, carbamazepine, theophylline, and two proprietary compounds), and two compounds exhibited no known hydrates (chlorthiazide and indomethacin). The screen resulted in hydrates for the seven compounds known to have hydrates and no changes for the two compounds without known hydrates.

These types of screens can also be performed on salts and cocrystals. Care must be taken, for certain salts may dissociate in aqueous solutions and precipitate the parent compound (free acid or base). Characterization of the solid after the experiment with elemental analysis and comparison to known free acid and free base forms will determine if dissociation has occurred.

2.4. Processing Stresses. While it is helpful to discover forms during a standard screen, it is also important to understand how these forms and conditions relate back to processing stresses that the API will encounter during development.[15] Screening experiments around formulation processes can include compaction with Carver press, milling in a mortar and pestle or Wig-L-Bug, and wet granulation with water alone or with excipients.

One screening approach to investigate processing stresses utilized a well-plate chassis that incorporates different attachments to mimic wet massing (100 mg), compaction, milling (30 mg), drying (50 mg), and crystallization (2.5 mL).[16] Theophylline and nifedipine were used as model compounds in the study. Phase changes were observed during all four simulated manufacturing steps (wet massing, drying, milling, and compaction).

This approach can be very helpful in determining parameters for formulation processes, especially for metastable forms. APIs can also be combined with excipients to determine any issues with processing mixtures or granulations.

2.5. Polymers. Using different surfaces to act as nucleation sites is another screening approach to produce new forms. A

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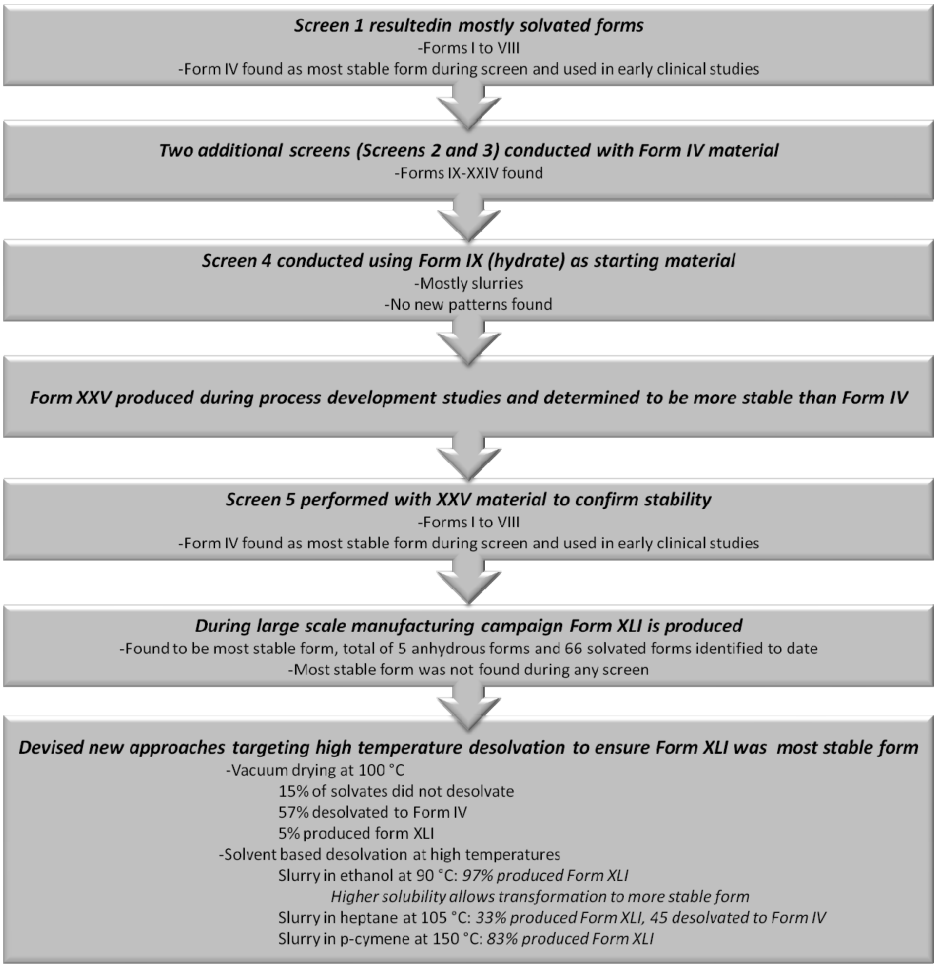

Figure 4. Summary of axitinib screening studies.[21]

variety of glass (borosilcate, silanized, acid- or base-washed) or polymer vials can be used for screening experiments; however, it is important to determine which solvents may be used with the polymer vials. Different surfaces can nucleate different forms during a screen, providing a wider crystallization space.

A related methodology is to add a solid insoluble polymer to polymorph screen experiments to act as a heteronucleation site and promote the crystallization of different forms.[17] Commercially available polymers as well as specially synthesized cross-linked polymers have been used in high-throughput screens by placing the polymers in the wells, and a similar procedure can be employed on a larger scale using vials or other laboratory equipment. Once new crystalline forms are found, the polymers can also be used to identify functional groups that are selective for a particular polymorph to guarantee production of that form on a larger scale. A number of model systems have been tested with this screen, including acetaminophen, sulfamethoxazole, carbamazepine, and sulindac. The screens produced the two stable forms of acetaminophen, while a new form of carbamazepine, two new forms of sulfamethoxazle, and two new forms of sulindac were found by using the heteronucleation screening procedure. In the case of sulindac, a polymer was also used to direct the crystallization of pure metastable Form III in bulk quantities and to grow single crystals for structure determination.[18] Heteronucleation can be a useful alternative for pharmaceutical compounds that are difficult to initially crystallize in early development.

2.6. Highly Solvating API. Some compounds have a propensity to form solvates when using traditional screening techniques.[19] In many cases, new stable forms will appear during process changes, which can result in significant delays later in development. Another issue with highly solvating APIs is the difficulty in finding unsolvated forms to move forward in development. One example is sulfathiazole, which is reported to have five unsolvated forms, over 100 solvates, and numerous adducts with single-crystal structures solved for more than 60 of these compounds.[20] Polymorphs of the solvates have also been observed for this system, which increases the complexity of the solid form landscape.

Another example of a highly solvating API is axitinib, which is reported to have 71 forms comprising five unsolvated forms, two hydrates, and the 64 solvates.[21] A total of six polymorph screens were performed throughout development, and new forms were produced from various large-scale crystallization processes that were not found in the screens (Figure 4). Five unsolvated forms were found (Forms I, IV, VI, XXV, and XLI), but due to the unexpected occurrence of more stable forms later in development, a screen was put in place to try to identify the unsolvated forms and ensure that Form XLI was the thermodynamically most stable form. The two main methods of desolvating the materials in the screen were vacuum drying at 100 °C and solvent-based desolvations at elevated temperatures. Three different solvent systems and temperatures were used for the solvent desolvations: ethanol at 90 °C, heptanes at

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105 °C, and *p*-cymene at 150 °C. These solvent-mediated experiments at elevated temperatures may allow a larger number of conformations of the API, resulting in the formation of the most stable form. Many of the solvates (57%) converted to Form IV upon heating under vacuum. When the single-crystal structures of the solvates and Form IV were analyzed, it was evident that a similar packing motif was present in both sets of structures, providing a low-energy route to Form IV, rather than the more stable Form XLI which exhibited an entirely different structure than Form IV. The high-temperature slurry in heptane produced the more stable XLI in 33% of the experiments, whereas the slurries in ethanol and *p*-cymene produced Form XLI in 97 and 83% of the cases, respectively. The lower conversion in heptanes can be explained by the lower solubility in this solvent compared to solubilities in ethanol and *p*-cymene. Full conversion to Form XLI was not possible in the time frame used for the experiment, but extended times would likely lead to full conversion. No new unsolvated forms were obtained from the screen, providing confidence that Form XLI was the thermodynamically stable form.

A number of solvents with high boiling points are available for these types of experiments including *tert*-amyl alcohol (102 °C), *n*-butanol (118 °C), 2-methoxyethanol (124 °C), anisole (155 °C), *o*-cymene, *p*-cymene, *m*-cymene (175 °C), *o*-cresol, *p*-cresol (200 °C), and benzyl alcohol (205 °C). The high-temperature slurry experiments need to be performed on materials that have adequate chemical stability under these conditions as well as acceptable solubility in the solvents chosen.

2.7. Ionic Liquids. Ionic liquids are finding a niche in pharmaceutical form screening. They are purely ionic, salt-like materials that are liquid at unusually low temperatures. Ionic liquids have been defined as salts with melting points below 100 °C, while salts with melting points below room temperature (25 °C) are classified as room temperature ionic liquids (RTIL). The RTILs are most often used in screening studies. General properties include thermal stability, low vapor pressure, high heat capacity, and nonflammability. These materials are commercially available, and the number of reported ionic liquids continues to increase. They can be used as-is or mixed with organic solvents to produce new solutions for polymorph screening experiments or synthesis and crystallization.[22]

An example of using ionic liquids for polymorphs screens was reported for adefovir dipivoxil.[23] Six polymorphs of adefovir dipivoxil have been identified using traditional organic and aqueous solvents. A polymorph screen using the ionic liquid AElmBF$_4$ (1-ally-3-ethylimidazolium tetrafluoroborate) as a solvent and water as an antisolvent was also performed. The temperature and volume ratio of water to ionic liquid used for crystallization were varied to control the polymorphism and resulted in two new forms. A high ionic liquid fraction (greater than 50 vol %) in the solvent mixture and a high crystallization temperature (greater than 85 °C) produced a new anhydrous form (N-II), while a temperature of 80 °C produced a new hemihydrate crystal (N-I). The addition of the ionic liquid also improved the chemical thermostability of the API in a 50/50 vol % ionic liquid/water mixture compared to a methanol/water mixture.

As with all solvents, solubility and chemical stability need to be evaluated for the API in the ionic liquids or in the solvent/ionic liquid mixtures chosen for the polymorph screen. Ionic liquids can also be used at elevated temperatures which could expand the possible crystallization conditions in a screening study.

2.8. Gels. Crystal growth in gels has been used for many years in a variety of applications.[24,25] Hydrogels are commonly used for crystal growth and comprise a liquid phase in a microporous solid phase, such as a polymer. Physical gels use a physical parameter, such as cooling, to produce a gel, whereas chemical gels undergo a polymerization reaction. Examples of gels include silica[24] and polyacrylamide.[26] Due to the slow diffusion of the dissolved molecules in the gel, they have been used for single-crystal growth or hard to crystallize compounds. Variations include placing compounds in the gel, on top of the gel, or using a U-tube configuration with two solutions.[24] One of the drawbacks has been isolation of the crystals from the gel which in many cases is done by physically removing the crystals by hand and attempting to wash the excess gel off the crystals. Another isolation method is to add another compound to promote the gel to solution transition so that the crystals can be easily filtered, but this can be problematic if the API is sensitive to the acid or base used for this phase change.

Gels can be used in polymorph screens if the solids can be easily isolated for characterization. A thermogel system that gels at 18−25 °C and liquefies at a lower temperature for easy isolation has been reported, with the study using lactose as the model compound.[27] Poloxamer (also known as Pluronic) is a copolymer of polyethylene oxide (PEO)−propylene oxide-(PPO)−polyethylene oxide(PEO) and was used as the gel matrix. The polymer was dissolved in water and ethanol, and the gel set when the temperature was raised to its gel point. The gel point temperature changed on the basis of a number of factors such as the polaxamer PEO/PPO ratio and concentration, the solvent, and concentration of other materials, such as dissolved API. When the gels were placed in an ice bath, the gels liquefied allowing easy isolation of the API crystals by filtration. Characterization of the isolated lactose crystals showed that most experiments resulted in the α-form monohydrate, but mixtures of amorphous and the α-form were also obtained.

The use of gels in polymorph screens provides a different nucleation mechanism from that found in solutions. The API supersaturation levels will also be different in the gel matrices which will influence the crystal form and particle size produced, especially over time. These differences can be used to compile a diverse screening strategy for difficult compounds or for more comprehensive screens.

2.9. Impurities. Impurities can direct nucleation and crystallization of different forms by acting as nucleation templates or can prevent nucleation of certain forms by acting as crystallization inhibitors. A change in process will very often change the impurity profile which can then lead to different crystalline forms. Small amounts of related compounds can influence the metastable zone width of a system, resulting in the crystallization of a different form.[28] Polymorph screens are commonly performed with one lot of material with a specific impurity profile, and it is not known how these impurities may affect the polymorph screens. There are reports where impurities can affect the induction time of crystallization[29] and the form produced.[30]

Sulfamerazine forms are enantiotropically related with a reported transition temperature of 52 °C. For this system, Form II is more thermodynamically stable (less soluble) below the transition temperature, and Form I is thermodynamically more stable above this temperature. A stable form screen of

sulfamerazine using solution-mediated transformation determined that certain lots of metastable Form I failed to convert to stable Form II under normal room temperature slurry conditions.[31] The Form I lots that failed to convert were found to contain a minor amount (less than 0.5%) of an acetyl derivative impurity that prevented the transition to the more stable form. The impurity was found to have a structure similar to that of Form II which likely disrupted the crystallization by substituting into the lattice. Modifications were made to the stable form screening experiments to successfully convert the impure Form I samples to the stable form by (1) changing the solvent or solvent mixtures to increase solubility, (2) minimizing the level of impurity in the slurries by preparing the slurries as dilute as would be practical, (3) pretreating the solid to quickly reach maximum supersaturation by reducing the particle size, adding surface defects, or adding amorphous content, and (4) using temperatures below the transition temperature that optimized the thermodynamics. It is understood that there can be complications in early development, such as unidentified impurities and unknown crystallization inhibition; however, adding the above experimental changes to a stable form screen can help reduce the risk of missing the most stable form.

For polymorph screens it is helpful to use the lot with the highest purity, but using several lots from different processes with varied impurity profiles can be very helpful. Crystallization will commonly purify material, so using recrystallized material, even if it is produced during the screen, is another option for producing materials with a varied purity profile. When crude material is going to be used in a final crystallization, it is important to use that material in screening and crystallization development programs in order to understand of the role of the impurities in producing various crystalline forms.

2.10. Conformations in Solution. It is known that different crystalline forms can be produced from different solvents, but the function of the solvent is not always understood. A combination of solubility and supersaturation can play a role in the form that is crystallized, but other factors can also be involved. Prenucleation aggregates formed in solution can contain different conformers of the molecule, which proceed to produce nuclei which can then convert to different crystalline forms of a molecule.[32] A mixture of conformers can be produced which may then compete to produce one crystal form or a mixture of forms.

A computational method to predict the conformers present in different solvents could help direct a polymorph screen by using solvents that may produce a variety of forms. A recent study calculated the percentage of different conformers in solvents for a number of APIs including ibuprofen, *N*-phenylhydroxamic acid, taltireline, famotidine, and ritanovir.[33] The data were then compared with the forms produced experimentally from the solvents and with the known single-crystal structures when available. It was demonstrated that relative conformational population predicted by computational methods can correlate with experimental results.

More work is needed to test this screening methodology, but one possible use is to help direct and produce new forms during screening and larger-scale crystallization experiments by controlling the conformer population. When a polymorph screen is being planned, this type of information can be used to help direct experiments, but other factors such as solubility and stability still need to be assessed.

2.11. Design of Experiments (DOE). Design of experiments (DOE) is commonly used for a number of development functions including polymorph screens. The aim is to predict the polymorphic form from crystallization conditions. Input variables, the crystallization parameters, would be analyzed against the output response, the polymorphic form. This provides a better understanding of crystallization parameters on the final form produced.

A screen incorporating DOE methodology used carbamazepine as a model compound due its diverse and well studied polymorphism.[34] Carbamazepine has a number of forms including three anhydrous forms (Forms I, II, and III), a dihydrate, and multiple solvates.[35] The purpose of the study was to determine if a medium-throughput screening methodology is suitable for late discovery/early development and to apply DOE in a screen to provide information on crystallization conditions to selectively produce the desired form. It was set up in three stages:

1. A medium-throughput screen was performed with a range of solvents with varied properties using evaporation and crash cooling crystallizations using plates and *in situ* XRPD. A total of 180 experiments were performed. The three anhydrous forms, the dihydrate, and three solvates were found (1,4-dioxane, NMP, and metastable nitromethane).
2. A fractional factorial design for temperature and cooling rates were used for the crystallization parameters. Fourteen solvents/mixtures, four elevated temperatures, and three cooling rates resulted in 42 experiments. The three anhydrous forms, the dihydrate, and the NMP solvate were obtained.
3. An experimental design that included evaporation, cooling, antisolvent addition, and suspension experiments using nine solvents was performed. Input variables included temperature, cooling/evaporation rate, water content/activity, and solvent properties; upper and lower values were chosen for each variable. The measured response was the solid form produced. The 76 experiments were set up in an iterative fashion dependent on the results from the initial conditions. The three anhydrous forms, the dihydrate, and the acetone solvate were obtained.

It was concluded that a medium-throughput screen is suitable for late discovery/early development to determine the propensity of polymorphism and find readily available forms. From the second and third study it was found that, by controlling the input variables, the factors for producing a specific solid form can be understood and used for crystallization process development. Several analysis approaches (parallel coordinate geometry, neuro fuzzy logic, and artificial neural network models) gave consistent results with each other. This example provides alternative approaches for setting up more controlled polymorph experiments that can be directly related to crystal form control in the last API step.

2.12. High Potency Compounds. Many drug substances fall under the category of high potency compounds, which are materials that produce a pharmacological response with small quantities. Special handling is needed for these compounds to reduce exposure due to their toxicity, carcinogenicity, teratogenicity, mutagenicity, or reproductive toxicity. Screening of these materials requires modifications to normal procedures to limit exposure.

One report on polymorph and salt screening of high potency compounds uses plates to perform the experiments on a small scale.[36] Solubilities in different solvents were used to determine the type of experiment to be performed, such as crystallization by controlled evaporation, cooling crystallization, or antisolvent addition. Special enclosed evaporation racks for the well plates were used during the screen. Custom made glass boxes were employed to contain samples during the optical and Raman microscopic analyses used to identify the new forms. An automated microscope with motorized stage allowed microscopic screening of the full well plate in a few minutes, as well as the ability to take photographs at different depths in the wells to look for crystalline material. Using these same coordinates, Raman microscopy spectra were collected for crystals 5 μm and smaller to identify the presence of new forms or salts, depending on the screen.

While it is possible to screen highly potent compounds, it is important to have procedures in place to protect the scientists performing the screens. Modifications to common screening procedures are possible while still maintaining a rigorous experimental plan. Analysis of the samples also needs to be modified in many cases to keep all samples enclosed during data collection, as shown with the glass box for the Raman microscopy analysis. Samples in well plates can be isolated during XRPD analysis by being covered with a material, such as a polymer, that will not interfere/overlap with the XRPD data. Closed DSC pans will minimize exposure for thermal data collection, and closed DSC pans with a pinhole in the lid can be used to collect thermogravimetric data when needed.

2.13. Substrates. Specialized substrates can be used to nucleate and template certain forms, similar to the polymers discussed previously. Some of these methods are much more specialized and API-specific, and may not be routine for early screening studies.

Self-assembled monolayers (SAMs) on gold have been developed as templates for screening studies to control the form with the added ability to control the particle size of the crystals.[37] Gold is deposited onto glass slides using an electron beam evaporator, and a mask is used to produce a specific grid pattern with islands ranging from 25 to 725 μm. The size of the islands controls the size of the crystals produced. The glass slides are then immersed in solutions of organic molecules to produce the SAMs. A variety of compounds can be used to produce the SAMs. For example, using 4-mercaptobenzoic acid results in hydrophilic regions on the gold islands that are surrounded by hydrophobic regions containing octadecyltrischlorsilane (OTS). The prepared slides are then immersed and slowly withdrawn from undersaturated API solutions, resulting in crystallization on the square islands containing the SAMs. A screen can be performed by varying the size of the island, the concentration of the API solution, the rate of evaporation, and even the type of SAM used. Due to the small crystals produced, initial characterization is limited, and Raman microscopy is commonly used as a first-pass characterization technique. If a new form is found, in many cases the crystals produced are suitable for single-crystal structure determination and seeding experiments.

Crystallization of glycine polymorphs using SAMs has been reported,[37] and it was found that the form produced was dependent on the supersaturation level and the solvent used to dissolve and deposit the API onto the glass slide. High supersaturation favored the unstable β-form in organic solvents, but using aqueous solvents usually resulted in the more stable α-form. Chiral SAMs have also been used to crystallize pure enantiomers of valine from racemic solutions.[38]

While the specialized substrates are not a routine screening method at this point, further work may lead to a variety of substrates, including and beyond SAMs, that may able to template and direct compounds during the screening process to produce new forms.

3. SALT SCREENING

3.1. Traditional Salt Screening. There are a number of excellent references on salts and screening[39−41] so a brief overview will be given here. Most salt experiments are solvent-based crystallizations. Salt formation depends on the pK_a difference between the acid and base, with a difference of two units usually resulting in salt formation in solution. It should be noted that most pK_a values used for this calculation are based on water, and many salt-screening experiments are performed in organic solvents, which will change the pK_a difference.[42] The pK_a difference is an initial starting point when choosing counterions for a screen but other parameters should also be considered, such size, shape, solubility, frequency in marketed products, compatibility with dosage form or disease state, acute vs chronic dosing, and toxicity. For screening experiments, a variety of solvents or solvent mixtures need to be found where both the acid and base have adequate solubility. Once the acid and base are dissolved, precipitation of the solid is achieved using techniques such as concentrating the solution, cooling, or adding antisolvent. Evaporation to dryness can often lead to a mixture of starting materials if the conditions are not optimal for salt formation; therefore, precipitation from solution is usually preferred over evaporation. A number of parameters can be investigated in a salt screen including solvent, concentration, stoichiometry, cooling rates, order of addition, and evaporation rates. Different methods of crystallization can result in different stoichiometries or solid forms of the salts produced.[43]

Manual and automated screens are both available for salts. More parameters can be changed with manual screens giving more variability, but they usually require larger quantities of API. Automated screens again use less material and may take less time overall, but the experimental parameters are more limited. Kumara et al[44] summarized a number of automated salt screens, with one study reporting 18 crystalline salts for sertraline HCl and 10 crystalline salts for sulfathiazole. Well-plate or high-throughput salt screening has been used and is becoming common practice but variations on this type of screen continue to be reported.

It is important to note that once a salt is produced, it should undergo a polymorph screen to determine what possible crystalline, amorphous, solvated, and hydrated forms exist, as well as the most thermodynamically stable form. This information will help guide API crystallization, formulation processing, and storage.

Other methods and strategies continue to be reported to help increase the success of salt formation or to manage the amount of screening needed during development. Even though a variety of parameters are considered when compiling the screening experiments, most salt screens are still empirical in nature.

3.2. Grinding. Grinding, also known as mechanochemistry, is a common process for polymorph screens in order to assess the propensity of the API to change form or become amorphous. It has also been used to make salts and cocrystals. Two methods are reported: (1) neat grinding, where both dry

components are added to a mortar and pestle or mill and mixed, and (2) solvent drop grinding (also known as liquid-assisted grinding, or wet cogrinding), where both dry components and a small amount of solvent are added to a mortar and pestle or mill and mixed. This technique not only reduces the use of solvents, but also provides a different crystallization route for salt production which does not involve the standard solution crystallization techniques described above. Using an entirely different method for salt production can influence the forms that are found by expanding the crystallization space.

A salt screen using mechanochemistry compared both neat and solvent drop grinding methods using trimethoprim and pyrimethamine as model compounds.[45] Seven counterions were used in the study based on known single-crystal structures for pyrimethamine salts (formate, acetate, maleate, fumarate, xuccinate, glutarate, and salicylate). Neat grinding resulted in the formation of a salt in about 40% of the experiments performed, and new salt forms were found for four salts. In comparison, solvent drop grinding using only methanol resulted in salt formation in 100% of the experiments and 10 new salt forms were found. This study shows that grinding may be an easy way to find new forms with a small amount of material. Amorphous salts can also be produced by grinding reactants together, as reported for vinpocetine citrate.[46]

The above study shows that solvent drop grinding can be used as part of a larger screen involving traditional solvent-based methods in order to expand the possible crystallization parameters that will result in new salts and salt forms. Using different solvents or stoichiometries in the solvent drop grinding experiments could lead to more variation in polymorphic forms and stoichiometries for the salts that are formed. As with any screening technique, variations in the parameters will help increase the number of salts/forms obtained.

3.3. BCS Classification. The Biopharmaceutics Classification System (BCS)[47] and Biopharmaceutics Drug Disposition Classification System (BDDCS)[48] (Figure 5a) are used in early development to help determine the best development path for a new chemical entity based on its properties. By moving screening studies earlier in the process, it is important to consider how the BCS or BDDCS properties can affect screening decisions and the details of the screen.

Salt forms are routinely used to increase the solubility of poorly soluble molecules, and if used for this purpose, they need to be identified early so the same material will be used in early toxicology and pharmacokinetic (PK) studies, as well as the initial clinical trials. Preliminary BCS data on a molecule is determined from the discovery pharmaceutical profiling and is usually available at the early screening stage. This information can be used to help direct the appropriate form of screening, and a decision tree has been reported to help determine when a salt screen is required.[49] The strategy is to perform screens on the candidates that need them the most in order to obtain relevant data in early animal studies and reduce the number of repeat studies due to form changes. For example, Figure 5b shows that a form screen for a BCS 1 compound is probably not necessary in most cases since the form will not directly impact bioavailability. If other properties, such as melting point or stability, need to be improved, then it is possible that a salt screen would still be a viable option in early development. For a Class 2 or 4 compound, finding a salt early in development may significantly increase the bioavailability and would be an asset

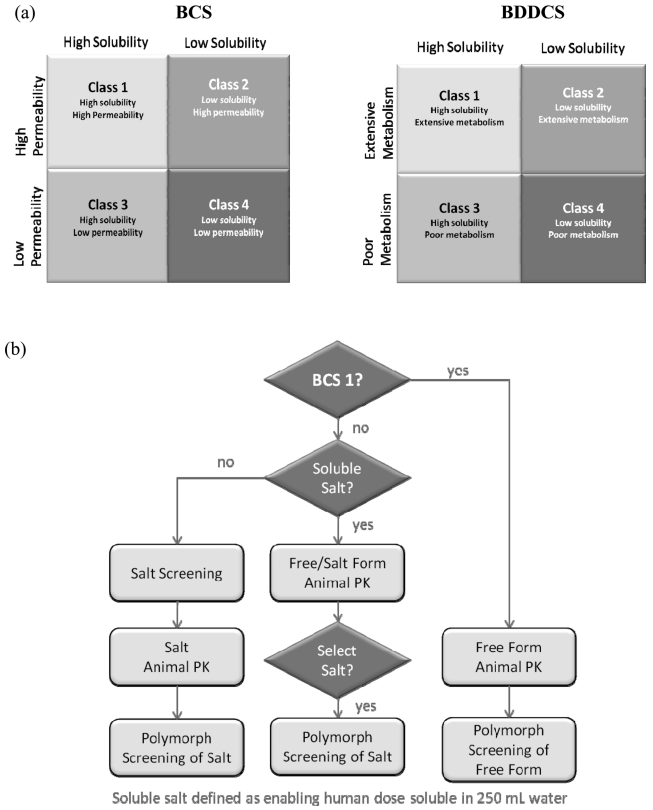

Figure 5. (a) Biopharmaceutics Classification System (BCS)[47] (right), Biopharmaceutics Drug Disposition Classification System (BDDCS)[48] (left). (b) BCS-based decision tree for salt/polymorph screens (adapted from ref 49).

for early animal studies. It should be noted that the type of early formulation also needs to be assessed and included in the decision-making process when selecting a solid form.[50]

Although this approach is not directly related to the detailed experimental parameters of a salt screen, the strategy for the type of screen to be performed and the timing for that work is an important decision in early development and needs to be a consideration for all departments using the bioavailability data.

3.4. Ionic liquids. While ionic liquids can be used as possible solvents for polymorph screening, using them to screen for polymorphs of salts could cause complications. A different strategy has been adopted where the ionic liquids are produced directly from the APIs for use in early development studies.[51] As with any other salt screen, the properties of the ionic liquids can be tailored by choosing different cations and anions; these properties could include hydrophobicity/hydrophilicity, acidity/basicity, solubility, stability, and viscosity. Early studies[52] suggest that ionic liquids do not dissolve as separate ions but maintain a nanostructured system in aqueous media. Oligomeric species are also possible with these materials when there is an excess of one of the components.[51] Different types of concentrated liquid delivery methods could then be explored, such as patches, aerosols, etc. A number of ionic liquids from APIs have been reported, as summarized in Table 3.

Screening studies for ionic liquids focus on preparing a salt that is a liquid or glass (not a supercooled liquid) in the temperature range of interest which is around room temperature for most pharmaceutical applications. One screen proposed an "anti-crystal engineering" approach based on

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Table 3. Examples of ionic liquids made with APIs

ionic liquid	crystalline API	melting point (°C)	ref
1-methylhexylammonium salicylate	1-methylhexylammonium salicylic acid	5	51
propantheline acesulfamate	propantheline Br	−20[a]	53
propantheline *p*-toluenesulfonate	propantheline Br	7	53
ranitidine docusate	ranitidine HCl	−12	51
benzethonium saccharinate	benzethonium Cl	−4	53

[a]No observable melting point and passes into glassy state at −20 °C.

identifying and avoiding combinations that would result in common supramolecular synthons.[53] Five active ingredients (pyridostigmine, benzethonium, propantheline, mepenzolate, and phenytoin) were paired with five compounds on the GRAS list (choline, *p*-toluenesulfonic acid, saccharin, acesulfamate, and cyclamate). All cations contained tetra-alkylated ammonium or alkylpyridinium moieties commonly found in ionic liquids, and all anions, except phenytoin, were previously used to prepare ionic liquids. Four cation/anion combinations contained no opportunity for hydrogen-bond formation due to the lack of donor groups, and three of those combinations produced ionic liquids (see Table 3). The fourth combination, propantheline saccharinate, did form poor crystals, and a single-crystal structure shows offset $\pi-\pi$ interactions between the propantheline cations as the primary crystallization mechanism.

As described above, ionic liquids are another possibility when searching for usable forms for development. As more information is obtained on these systems, screening techniques can become more refined to increase the chance of successfully producing these materials as an option for development.

4. COCRYSTAL SREENING

Cocrystal screening is similar to salt screening in many aspects. The counterions used for salts are usually the same compounds used as the guests, also known as coformers, in cocrystal screens. Rather than the pK_a values used for salts, hydrogen-bonding networks and other interactions are used to choose the guests.[54,55] Early cocrystal screens used stoichiometric amounts of API and guest, similar to salt screens. Recent studies have shown that an excess of one component is usually more successful in producing corystals.[56] Ternary phase diagrams have also been useful in understanding cocrystal formation in solvent systems.[57]

Manual and high-throughput cocrystal screens have been reported, and conditions similar to those used for salts are used in these studies as well.[58,59] Once a cocrystal is found and selected, it is important to perform a second screen to identify the thermodynamically stable form as well as solvated or amorphous forms. As more is learned about the nucleation and crystallization of cocrystals, the number of possible screening techniques will continue to increase to improve the success rate of the screens.

4.1. Slurry. Slurries are a common method employed in polymorph screening, and the technique has been extended to cocrystals. Slurry conversion for polymorphs is a dynamic process where the more soluble (less stable) form dissolves and the less soluble (more stable) form precipitates out of the solution. In the case of cocrystals, a critical coformer or API activity is needed in solution; when the concentration is above this activity, the cocrystal will form.[60] When using a slurry method, the solid components are suspended in a solvent, and partial dissolution occurs, resulting in activity values of one for both components; therefore the activity of the slurries will always be greater than the critical coformer activity needed for cocrystal formation, and this will result in precipitation of the cocrystal.

This concept was tested with 16 systems known to form cocrystals.[60] The APIs included caffeine, itraconazole, sulfamethazine, paracetamol, aspirin, flurbiprofen, ibuprofen, carbamazepine, and piroxicam. The coformers used in the study were oxalic acid, maleic acid, malonic acid, glutaric acid, succinic acid, sulfamethoxypyridazine, benzoic acid, 4,4′-dipyridyl, nicotinamide, and saccharin. Known stoichiometries (1:1 and 2:1 API:coformer) were slurried for 12 h to eight days with most cocrystals forming in an hour. Cocrystals were obtained for all 16 compounds. The technique produced known cocrystals for 13 of the systems, new unsolvated cocrystals for two systems, and two new solvated cocrystals for one system. Studies with caffeine,[61] stanolone,[62] and mestanolone[62] have also shown successful cocrystal production using this technique.

The slurry technique can be easily implemented in the laboratory as another way to screen for cocrystals. If mixtures of cocrystals and API or coformer are produced then a different stoichiometry should be tried. Adding diversity to the experiments by varying the stoichiometry and solvents may also produce different polymorphs or solvates of the cocrystals.

4.2. Thermal. Thermal methods available for screening cocrystals include binary melting using a hot stage microscope (Kofler technique) and differential scanning calorimetry (DSC). Heating the components above the melting temperature allows interactions to occur in the melt, potentially nucleating cocrystals which then crystallize out of the molten phase. In the case of the Kofler technique, the two compounds are melted adjacent to each other on a glass slide and are mixed by adding a cover slide. In some cases, high-boiling organic solvents can also be used to create a highly concentrated solution which reduces the melting point of the API.[63] Varying the liquid composition and ratio of the API and cocrystal can lead to different forms. The compounds will mix at the melt interface, and a positive reaction is the formation of crystalline material at the melt interface. A negative reaction may result in a eutectic region where no crystallization is observed. The crystals can be characterized using Raman spectroscopy to determine if a cocrystal has formed. For DSC, the two components are placed in a DSC pan and heated past the melt, cooled, and reheated. The endotherms are compared to the pure materials to see if a new transition has occurred that may be due to a cocrystal. Both thermal methods require additional characterization to confirm cocrystal formation.

Screens using the Kofler method have been reported for a number of systems.[63,64] In the first example,[63] a development candidate with low solubility and bioavailability was screened using 26 guests resulting in five cocrystals (benzoic acid, fumaric acid, gentisic acid, glutaric acid, and salicylic acid). Raman spectroscopy was used for initial characterization to determine cocrystal formation. Cocrystals were scaled up using solution methods with seeds from the thermal experiments. In a second screen using the Kofler method,[64] the guest nicotinamide was paired with a number of drug substances (ibuprofen, fenbufen, flurbiprofen, ketoprofen, paracetamol, piracetam, and salicylic acid). Five cocrystals were found in this study. Seeded solutions were used to grow single crystals of the

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new phases in order to elucidate the structures and compare the bonding motifs. A rapid DSC cocrystal screen has also been reported[65] using four APIs (caffeine, carbamazepine, sulfamethazine, and theophylline) and five conformers (glutaric acid, nicotinamide, saccharin, salicylic acid, and urea). Eight new cocrystals and eight reported cocrystals were found in this screen. In all cases, an endotherm for the eutectic was found in the DSC scan below the cocrystal melting temperature. Advantages to the DSC screen include the following: (1) rapid screening, (2) amenable to automation and high-throughput screening, (3) small amount of material needed for each experiment, and (4) no solvent required, making it a "green" technique.

Thermal methods are a way to focus cocrystal experiments or expand the crystallization space by including them with other screening methods. They use a small amount of material, so that a larger number of experiments can be performed when material is limited. These methods are not suitable for thermally labile or volatile systems; therefore, the initial thermal information needs to be collected on the API and guest molecules. For the DSC method, thermal transitions for polymorphic transformations or desolvations may complicate the scan, making the approach unsuitable for some systems.

4.3. Grinding. Neat grinding and solvent drop grinding for cocrystals are the same as described for salts. The advantages of solvent drop grinding over solution crystallization are that dissolution of both cocrystal formers is not required and solvent interactions that might interfere with solute−solute interactions are limited. It has also been shown that this technique can help control cocrystal polymorphs, as described for caffeine:glutaric acid cocrystals.[66]

There are a couple of variations that have been reported for screening studies. An early development compound initially used neat grinding with a mixer ball mill.[67] Twenty-five conformers were used for this stage of the study, and equimolar ratios of the drug (~60 mg) and coformer were ground for 20 min. Solids were analyzed, and those that showed a different DSC trace and XRPD pattern were classified as leads. Five cocrystals were found (fumaric acid, salicylic acid, succinic acid, maleic acid, and piperazine). In the second stage of the screen, the leads were produced from solution crystallization or slurry interconversion to get information on scale-up of the materials. In a second study, both neat and solvent drop methods using a mixer mill were investigated to find cocrystal hydrates.[68] Neat milling was performed with hydrated APIs and coformers and the solvent drop grinding used water as a solvent. Theophylline was found to readily form a cocrystal hydrate with citric acid; however, caffeine only produced an anhydrous citric acid cocrystal. On the basis of the results, solvent drop grinding appears to be a more efficient method of screening for cocrystal and API hydrates over neat grinding of hydrated materials.

A slightly different approach was taken with a carbamazepine cocrystal screen that initially used a mortar and pestle to grind the reactants for 4 min.[69] If partial conversion was observed, a solvent drop method using a mixer/mill was employed with eight solvents and eight guests. Cocrystals were produced with all the guests, and it was found that dimethylformamide (DMF) and dimethylsulfoxide (DMSO) produced the most cocrystals. It was also suggested that higher guest solubility would lead to cocrystal formation. A recent report[70] compared both neat and solvent drop grinding using a novel planetary mixing system which grinds 48 samples simultaneously in 2-mL glass vials. One carbamazepine and three caffeine cocrystals were used as model systems with grinding times of 0.5, 2, and 4 h. All mixtures showed some degree of cocrystallization, and the solvent drop grinding was more effective than the neat grinding. The known forms were found for four systems, and the caffeine:maleic cocrystal samples resulted in three solid forms identified as 1:1 and 2:1 cocrystals, as well as a new unsolvated form.

Grinding experiments have been found to successfully produce cocrystals with solvent drop grinding resulting in more positive results when compared to neat grinding. Different stoichiometries and grinding times are variables that can lead to different cocrystals and possibly different forms. The use of different solvents in solvent drop grinding experiments also increases the crystallization space and can be more focused by using acceptable solvents to produce hydrates and other acceptable solvates when needed for development. Scale-up of cocrystals originally found by grinding are usually performed by using solution crystallization methods and seeds from the grinding studies. Additional work, such as constructing ternary phase diagrams,[57] may be needed to determine the best solvent(s) and concentrations to readily crystallize the desired form at scale.

4.4. Supercritical Fluid. Supercritical fluid crystallization has been used in designing particles and generating polymorphs of APIs. Carbon dioxide is the most common supercritical fluid used for pharmaceutical applications, and it can be used as a solvent or antisolvent, depending on the process used. Reports of cocrystals produced using this method include indomethacin:saccharin cocrystals prepared by supercritical antisolvent (SAS) or supercritical atomization.[71]

A recent study demonstrates how supercritical enhanced atomization (SEA) can be used for cocrystal screening.[72] The SEA process also produces submicrometer particles, which can further enhance bioavailability for poorly soluble drugs. Saccharin was used as the cocrystal former with six APIs (indomethacin, aspirin, carbamazepine, theophylline, caffeine, and sulfamethazine). A 1:1 ratio was used for all APIs along with a 1:2 theophylline:saccharin ratio. The components were dissolved in ethanol which was then mixed with the supercritical fluid before depressurization into the precipitation vessel. Known cocrystals of all the APIs were successfully produced, and a new form of the theophylline:saccharin cocrystal was also found. A narrow size distribution of 0.3−10 μm was observed for all systems, showing that this process can also readily control particle size.

Supercritical fluid crystallization is a more specialized cocrystal screening technique that requires specific equipment, but it can significantly expand the crystallization space into areas that may not be accessible by other more conventional methods. Particle design is an added benefit to this technique where narrow submicrometer particle size ranges could help early formulations. Large-scale production using this method would need to be investigated, or conventional methods using seeding would need to be explored.

4.5. Sonochemistry. Sonochemistry involves the use of ultrasound during the cocrystal formation. The components are usually added in stoichiometric amounts to an appropriate solvent to form a slurry which is then sonicated. The solvent is used to mediate the reaction between the components to form a cocrystal, while sonication can help promote nucleation of different forms of the cocrystals.

A report using sonochemistry for a cocrystal screen compared it to the solvent drop grinding approach to

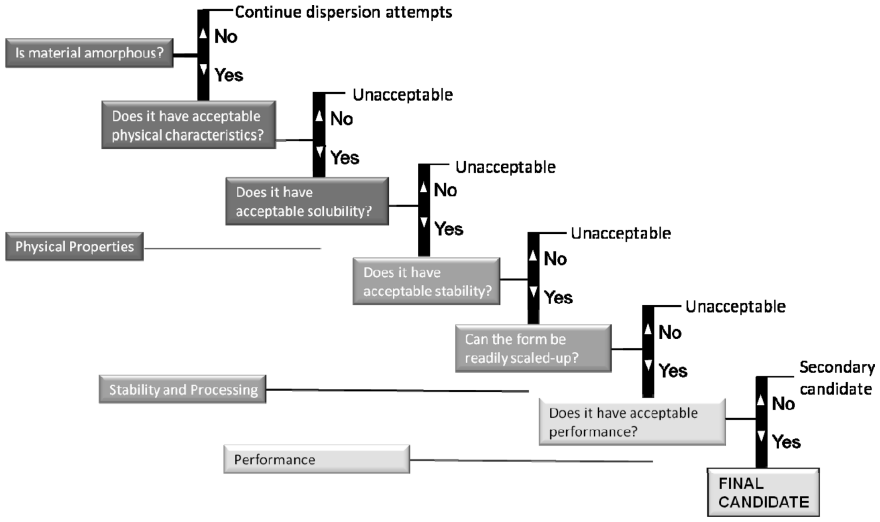

Figure 6. Decision tree for amorphous solid dispersions (adapted from ref 77).

investigate the role of the solvent in these experiments.[73] Theophylline and caffeine were used as the model compounds, and L-malic or L-tartaric acid were used as the guests. The API and guest (about 100 mg total solid) were combined in stoichiometric amounts in a suitable solvent to produce a slurry. Four different solvents were used for each API−coformer pair, and three different concentrations of the solution were prepared to vary the supersaturation of the API and coformer. The reactants were then subjected to an ultrasonic probe at a frequency of 20 kHz and a variable power setting between 0.1 and 100 W. Short pulses over the course of 2−5 min were used to avoid heating the sample. Formation of the cocrystal was reported to be dependent on the saturation level of both the API and coformer. Extremes of high and low supersaturations did not result in cocrystals, and a method to find suitable conditions for cocrystal formation is proposed.

Using sonication in a screen can be implemented with an ultrasonic probe with direct control of the energy input or more simply by using an ultrasonic bath that has less control but may have sufficient energy to effect nucleation compared to no sonication. A number of parameters can be varied, such as solvent, sonication time, sonication power, and supersaturation, in order to make new cocrystals and unique cocrystal forms.

5. AMORPHOUS SOLID DISPERSION SCREENING

Amorphous dispersion screening is relatively new compared to other forms of screens that have been discussed. The API and a polymer, and sometimes a surfactant, need to be molecularly mixed to form binary or tertiary systems. Common laboratory practices include solvent evaporation, melting, comilling, or lyophilization. The solvent methods used can give information on large-scale processes such as spray drying if the screening experiments are designed with relatively fast evaporation. It must be determined if there is sufficient solubility of both components in the solvent chosen. The melt techniques provide details on using melt extrusion for large-scale production. For any preparation method, it needs to be determined if a miscible system or a physical mixture of the amorphous API and the excipients is obtained.[74] The preparation method has also been found to influence the properties of amorphous solid dispersions,[75] suggesting that a screen with a variety of methods will provide a larger range of options for these types of materials.

One reported screen for a development compound used an approach that is amenable for melt extrusion.[76] A solvent casting screen in well plates was employed for the initial experiments and included 14 binary mixtures and 48 ternary mixtures based on six polymers and eight surfactants. This was followed by a small-scale melt−press method for dispersions that showed an increase in apparent solubility, involving 13 ternary formulations and dissolution testing in this second stage. Scale-up using melt extrusion was then used to produce material for five ternary formulations that were tested in animal bioavailability studies. A dispersion containing HPMCP/Vit ETPGS (vitamin E/*d*-α-tocopheryl polyethylene glycol 1000 succinate) showed a bioavailability similar to that of an oral solution in dog studies. Limitations to this particular screen were the lack of physical characterization to determine if the material was amorphous and physical stability testing. Even with the limitations, the study showed that automated screening was an efficient tool to rapidly survey a large number of combinations with minimal sample. A second study used manual experiments involving evaporation and lyophilization using itraconazole as a model compound.[77] Six polymers (including three grades of PVP) and four API:polymer ratios were included in the study. Physical characterization and stability data were used to select a 1:2 itraconazole:HPMC-P dispersion for scale-up, formulation, and bioavailability studies.

Selection for amorphous dispersions depends on a number of factors specific to the development of the compound and can be aided by a decision tree. An example of a decision tree for amorphous solid dispersions is given in Figure 6. This figure includes physical properties, stability and processing, and performance as decision points, but it can be modified as needed to fit individual systems.

6. COMPUTATIONAL APPROACHES

Predicting structures of organic compounds using computational approaches, including pharmaceutical polymorphs, salts, and cocrystals, is an active area of research. The Cambridge Crystallographic Data Centre has conducted five blind tests since 1999 to evaluate current computational methods and their ability to predict crystal structures, with the latest held in

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Table 4. Summary of Specialized Screening Methods

method	application	incorporation into screen
gels	polymorphs, salts, cocrystals	need materials to make gels; can be easily incorporated once gels are made
grinding	polymorphs, salts, cocrystals	both neat and solvent drop grinding can be easily incorporated into traditional screens
highly solvating screen	polymorphs, salts, cocrystals	extension of traditional screening experiments
hydrate screen	polymorphs, salts, cocrystals	extension of traditional screening experiments
impurities	polymorphs, salts, cocrystals	can be an extension of traditional screen if APIs of different purities are used, can be more involved if computational studies and spiking of different impurities is performed
ionic liquids	polymorphs, salts	can be an extension for traditional polymorph screening, new liquid form for salts that would need determination of toxicological properties for ionic liquid counterion
polymers	polymorphs, salts, cocrystals	extension of tradtional screening experiments
processing stresses	all solid forms	can be an extension of traditional screening experiments (grinding, compression, granulation); or specialized small equipment can be used
sonochemistry	polymorphs, salts, cocrystals	can be an extension of traditional screens if ultrasonic bath is sufficient; will need special ultrasonic probe for more controlled experiments
stable form screen (slurries)	polymorphs, salts, cocrystals	extension of traditional slurry experiments
supercritical fluid	all solid forms	special equipment and expertise needed
substrates	polymorphs	substrates such as sams need specialized equipment and expertise
thermal/melt	all solid forms	extension of traditional screen experiments in most cases

2010.[78] The compounds included in the most recent study were two rigid molecules, one semiflexible molecule, a 1:1 salt, a large flexible molecule, and a hydrate with more than one polymorph. While there were successes, especially for the small molecules, the study also highlighted a number of challenges that still need to be overcome for large pharmaceutical compounds and more complex structures such as salts.

Computational approaches have also been used for other solid state forms. Structure prediction of cocrystals has been studied using a lattice energy approach[79] and consideration of proton position.[80] Both approaches provide valuable insight into predicting cocrystals, but they do not work for all model systems, suggesting that a number of factors need to be considered when performing these calculations, making the studies more complex and requiring significant computer resources. Another study takes a different approach and uses modeling to find additives to prevent crystallization of amorphous drugs.[81] In the case of salicylamide, salicylic acid, and sulfanilamide, computationally prescreened additives were tested experimentally and found to decrease the nucleation and crystal growth rates for the amorphous materials.

At this point in time, computational approaches are not a substitute for experimental screening to find new forms. Coupling an experimental screen with computational studies can help assess the possibility of polymorphism for many systems. The structures predicted from computational methods can also be used to help interpret data from screening studies. The simulated powder patterns for computational hits can be compared to the experimental powder patterns to determine if pure forms have been made and to determine structural aspects of these new materials that may be translated to other properties to help further understanding of the solid system during development. Indexing of experimental patterns to determine lattice parameters can also provide information about the structure and help determine if the experimental powder pattern represents a pure phase (pattern can be indexed) or a possible mixture (pattern cannot be indexed).

7. CONCLUSIONS

Many of the specialized screening methods discussed in this review are easily incorporated into most screening studies, as outlined in Table 4. Others, such as SAMs and supercritical fluid, will require specialized equipment or will need to be outsourced to a contract or academic laboratory. The incorporation of new molecules, such as the ionic liquids, will need to be evaluated for toxicity based on literature values or new studies. Examples of every technique for each type of solid form were not presented, but extensions into other areas are feasible.

Routine screening of pharmaceutical compounds is currently a largely empirical process where different conditions are used to try to cover a wide crystallization space. Physical properties of the API such as solubility, thermal stability, and types of functional groups present are used to guide the experimental process, but there are no guarantees that the entire space has been covered. Computational studies can help provide information and supplement experimental screening, but at this point they are not a replacement for an experimental screen. As the number of screening and computational studies increases, new methods and techniques will continue to evolve and provide a broader array of technologies to choose from in order to maximize or focus conditions as needed to find new solid state forms of pharmaceutical compounds.

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Notes

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