Application Note

November 2023

A Comprehensive Approach for Solid Form Selection in Preclinical Development and Beyond.

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Different solid forms (polymorphs, salts, cocrystals) of an active pharmaceutical ingredient (API) can have very different physico-chemical properties. Those differences can impact bioavailability, solubility, dissolution rate, side effect incidence, stability, API and drug product manufacturability, and other important parameters. Most APIs can exist in multiple solid forms, including polymorphs, hydrates, solvates, salts, cocrystals, and non-crystalline forms. The goal in screening and selection is to produce an optimal solid form based on parameters such as crystallinity, stability, solubility, hygroscopicity, and ease of production ("manufacturability"). Understanding the process chemistry is paramount for reproducibility during drug development and manufacturing. Here we discuss various solid forms and a comprehensive way to approach solid form screening for regulatory, manufacturing, financial, and intellectual property needs.

Keywords: *Polymorphism, pharmaceutical salt, pharmaceutical cocrystal, amorphous materials, solid-state intellectual property.*

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Introduction

Most active pharmaceutical ingredients (API) can exist in multiple solid forms, including polymorphs, hydrates, solvates, salts, cocrystals, and amorphous non-crystalline forms. Over 90% of naturally occurring and man-made solids are crystalline. Most solids form with an orderly, repeating arrangement of molecules driven by intermolecular interactions, such as van der Waals, hydrogen bonds, and ionic bonds (for salts), in such a way that minimizes the crystal-free energy. The crystalline arrangement at a molecular level is often reflected at a macroscopic level as different particle morphologies (also described as crystalline shapes or habits). However, crystal habits can be modified for the same crystalline form with various additives or changes in process chemistry.

Different crystalline solid forms (Figure 1) can have very different physico-chemical properties. Those differences can impact bioavailability, solubility, dissolution rate, side effect incidence, stability, API and drug product manufacturability, and other important parameters. For example, crystal habits generally affect the manufacturability of the molecule, such as filterability and flowability. The goal in screening and selection is twofold: to produce an optimal solid form for drug development based on parameters such as crystallinity, stability, solubility, hygroscopicity, and ease of control and production ("manufacturability"), and to generate intellectual property around the primary molecule. Additionally, understanding the process chemistry is paramount for reproducibility during drug development and manufacturing and is a requirement in regulatory filings. Much of the Chemistry, Manufacturing, and Controls (CMC) requirements in FDA submissions can be satisfied with a comprehensive understanding of a molecule’s solid-state behavior.

It is desirable when developing a pharmaceutical drug substance to evaluate its propensity to produce solid forms. Those forms include:

- **Polymorphs (including hydrates and solvates)**
- **Salts**
- **Cocrystals**
- **Amorphous Materials**

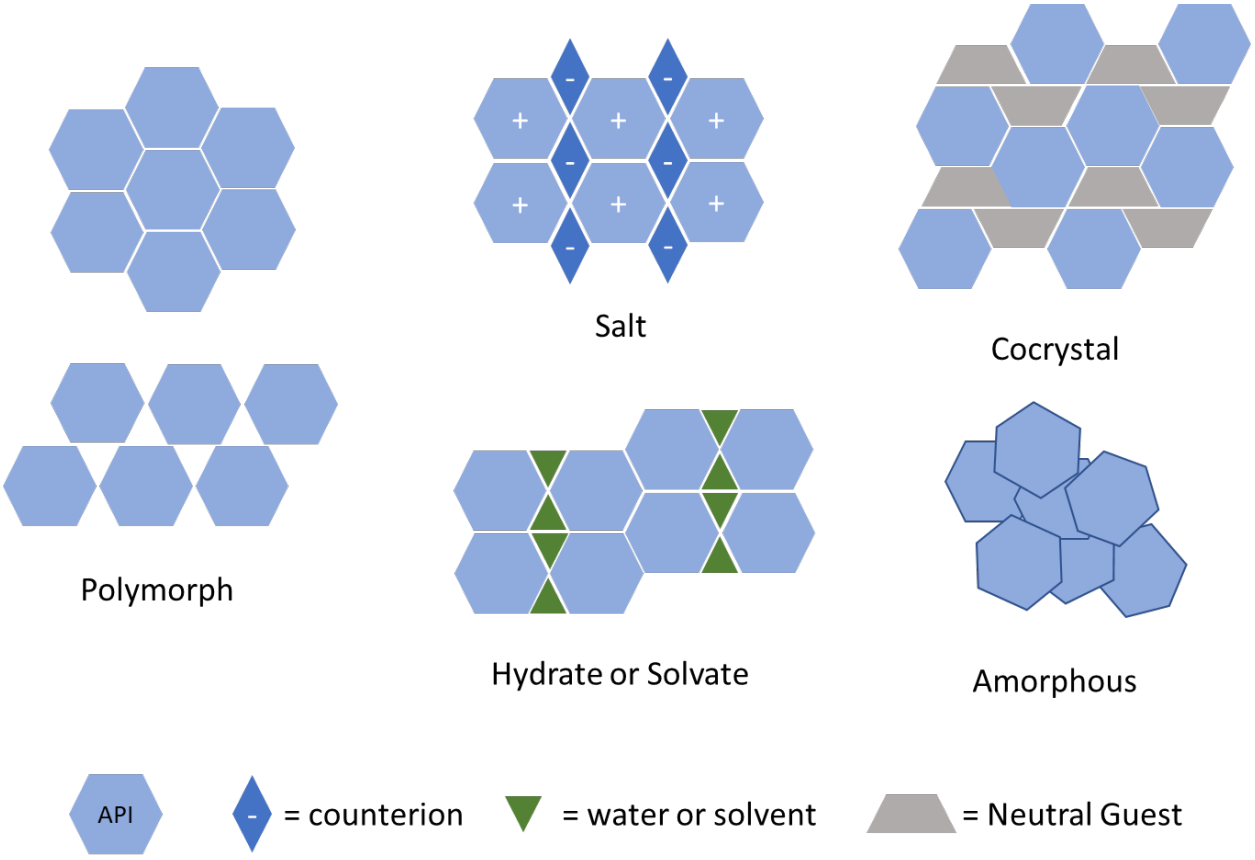

Figure 1. Illustration of the solid-state arrangement of different solid forms that are discussed. This illustration is not comprehensive, as polymorphs of salts and cocrystals may also exist.

While there is no guarantee that your chemical will be polymorphic or be able to generate a usable salt solid form, data collected by Dr. Pat Stahly at Triclinic Labs [1] indicates the prevalence of alternate solid forms is likely:

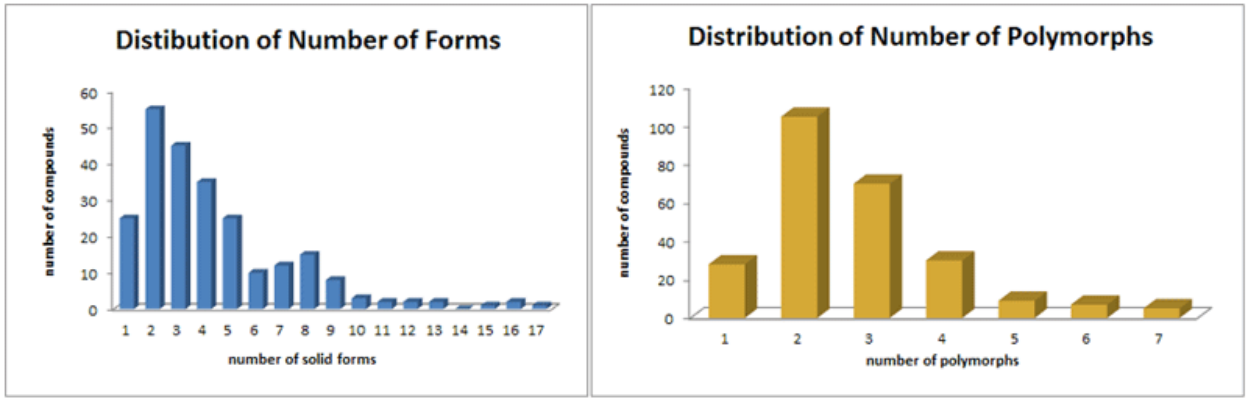

Figure 2. On the basis of the results of 245 solid-form screens, organic compounds were found to exist in **multiple solid forms** quite frequently. About 90% exhibited multiple crystalline and non crystalline forms; **a majority exhibited polymorphism**.

Properties that can differ among solid forms of molecules include:

- Color
- Compressibility
- Crystal shape (habit)
- Density
- Filterability
- Flow
- Hygroscopicity
- Organoleptic Attributes
- Solubility
- Stability

Variations in solid-form properties can lead to observed differences in dissolution rate, absorption, bioavailability, toxicology and can affect both the safety and efficacy of the API. **Each solid form is discussed in detail below.**

An Overview of Solid Form Screening and Selection

Polymorphism.

Polymorphism refers to the existence of two or more crystalline phases with the same chemical composition that have different three-dimensional arrangements and/or confirmations in the crystal lattice. In general, a polymorph screening study is a search for those distinct crystalline phases and the determination of their relative physical stabilities at relevant conditions. Herein, the term polymorph is used to encompass both true polymorphs, with molecules arranged in different crystal lattice arrangements, and pseudo-polymorphs, such as solvates and hydrates where solvent or water molecules are incorporated in the crystal lattice, respectively. The physical and chemical properties of each solid form (polymorph) of an API can vary dramatically and have a significant impact on the pharmacokinetics, consistency, and ease of manufacturing, and overall product stability. In many cases, one of the goals of a polymorph study may be a robust crystallization process that consistently produces the desired polymorphic form of the API during all manufacturing phases. If a suitable polymorph is unavailable, alternative solid forms may be developed with suitable properties.

Energy differences between forms are usually relatively small, and as such, form interconversion is common and can occur during routine API manufacturing operations, drug product formulation, storage, and use. Polymorphic forms of the drug substance can undergo phase conversion when exposed to a range of manufacturing processes, such as drying, milling, micronization, wet granulation, spray drying, and compaction. Exposure to environmental conditions such as humidity and temperature can also induce polymorph conversion. The extent of conversion generally depends on the relative stability of the polymorphs, kinetic barriers to phase conversion, and applied stress.[2] Stability of the molecule is of particular concern because manufacturing conditions often produce an unintentional and incorrect form due to the introduction of thermal and mechanical energy. Scale-up of a process often leads to encountering new forms inadvertently in the later stages of development. This can delay clinical trials, manufacturing campaigns, and regulatory submissions. A thorough understanding of the polymorphic landscape of an API and the relationships between different polymorphs is critical to the identification and mitigation of potential solid form conversions and avoiding costly development delays downstream. Another advantage of having multiple polymorphs is that it provides alternative crystallization avenues, which may be useful when poor impurity rejection is encountered with the initial crystallization route.

Polymorphs have intellectual property advantages, and a comprehensive screening study should be done to ensure franchise protection, extension, and a complete portfolio for optimal asset valuation. There is also significant consideration in claims construction with

respect to polymorphism and solid form characterization. Regulatory and legal approaches change constantly in patent prosecution, and a firm familiar with solid form claim construction should be used.

Polymorph screens are often conducted at various stages of development, and the amount of material available and the stage of development often dictate the scope and approach. Screening and selection timing and goals are discussed in a later section. Polymorphs have been shown to have an impact on safety. For example, a new lot of drug substance tested in a four-week tox study was more toxic than previously demonstrated with earlier lots. The sponsor decided to put the clinical trial on hold. It was later found that all previous toxicology was done with the crystalline form of the drug, whereas the new batches were amorphous. Approximately one year of development time was lost.[3]

Hydrates And Solvates:

How common is hydrate formation?

A compilation showed that of 245 compounds that were subjected to solid form screening, 94 (**38%**) formed hydrates

How common is solvate formation?

A compilation showed that of 245 compounds that were subjected to solid form screening, 78 (**32%**) formed solvates

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Salt Screening and Selection

If usable polymorphs of the chemical asset do not exist, the form does not have the desired properties for development (e.g. solubility, stability, crystallinity), and the molecule is ionizable, a pharmaceutical salt screen can be conducted to ameliorate these issues. Pharmaceutically acceptable counterions are selected for screening along with knowledge of the molecule. Screening projects are designed in a tiered manner and with a variety of techniques in an attempt to improve on the properties of the API that are problematic.

Counterion selection is based on:

- pKa of the API
- Physical properties
- Previous clinical and market use
- Toxicology data
- Past use and success in screening studies
- ICH Guidelines

Ionic salts are common materials used in pharmaceuticals. Over 50% of all approved drug molecules exist as salts, most frequently as the hydrochloride, sodium, or sulfate salts. It is not uncommon for pharmaceutical salts to also exhibit polymorphism. Thus, a polymorph screen is recommended once a salt candidate is selected.

The Top 15 Most Common Drug Salts as of publication*

- hydrochloride (15.5%)
- sodium (9%)
- sulfate (4%)
- acetate (2.5%)
- phosphate or diphosphate (1.9%)
- chloride (1.8%)
- potassium (1.6%)
- maleate (1.4%)
- calcium (1.3%)
- citrate (1.2%)
- mesylate (1%)
- nitrate (0.9%)
- tartrate (0.8%)
- aluminum (0.7%)
- gluconate (0.7%)

*https://www.drugs.com/article/pharmaceutical-salts.html
*https://pubs.acs.org/doi/10.1021/jm701032y

Cocrystal Screening and Selection

Like salt screening, cocrystal screening is usually undertaken when another suitable solid form cannot be found and/or the molecule is non-ionizable. Cocrystals take advantage of guest molecules in a crystal lattice along with the API, and often the solubility of the guest enhances the cocrystal's overall solubility. Guests are selected from a wide variety of sources, such as pharmaceutically acceptable and Generally Recognized As Safe (GRAS) lists. Triclinic has more than 200 guest molecules available for screening. Cocrystals are often used for purification and stabilization as well as intellectual property improvement. Existing pharmaceuticals with physical or chemical property issues can be improved as well.

For example, McNamara, et. al.[4] found that the bioavailability of a development candidate API was very low after oral dosing in dogs. In order to improve bioavailability, they sought to increase the dissolution rate of the solid form of the API. When traditional methods of forming salts and amorphous material failed to produce a viable solid form for continued development, they turned to cocrystallization. Several carboxylic acid guest molecules were tested for cocrystal formation with the API, and a cocrystal containing the API and glutaric acid in a 1:1 molecular ratio was identified. The use of the cocrystal increased the aqueous dissolution rate by 18 times as compared to the homomeric crystalline form of the drug (Figure 3). Single-dose dog exposure studies confirmed that the cocrystal increased plasma AUC values by three times at two different dose levels (Figure 4). APIs that are non-ionizable or demonstrate poor salt-forming ability traditionally have been viewed to present few opportunities for creating cocrystalline solid forms with desired physical properties. Cocrystals are an additional class of crystalline solids that can provide options for improved properties. In this case, a cocrystal of glutaric acid and an API was identified and used to demonstrate an improvement in the oral bioavailability of the API in dogs.

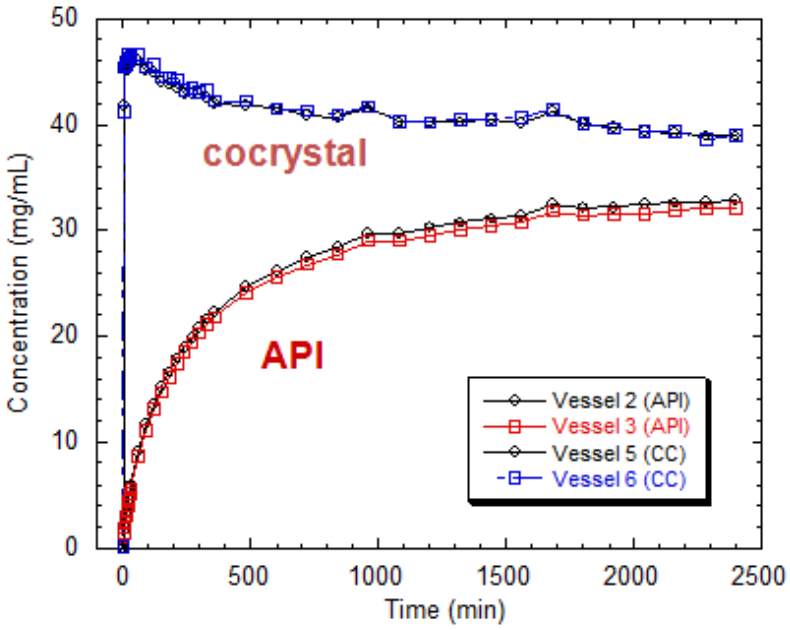

Figure 3: Intrinsic Dissolution (37 °C in water), The cocrystal dissolves 18× faster than API

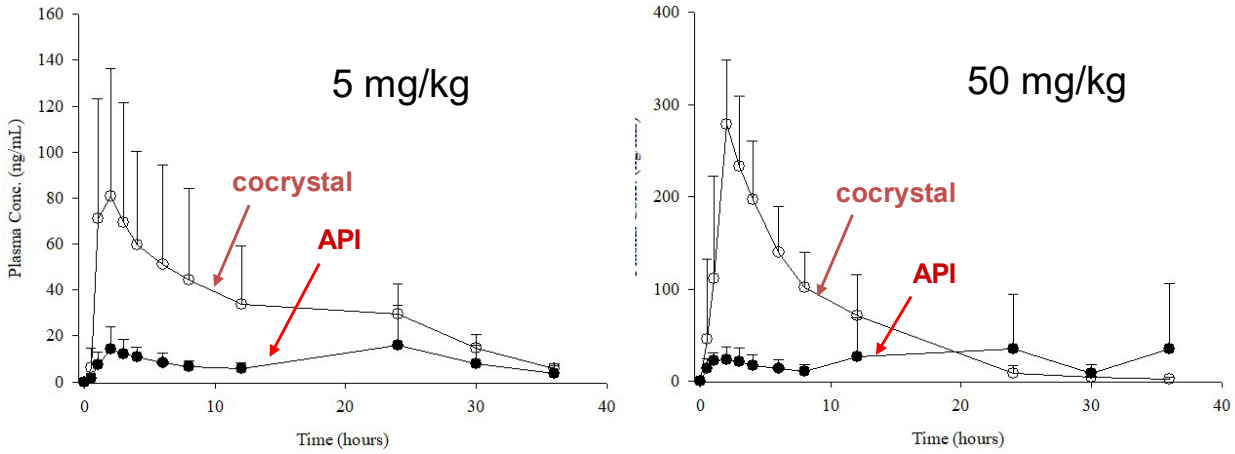

Figure 4: Bioavailability study in dogs demonstrates ~4X AUC increase.

Cocrystals represent not only an alternative for solid form development but also an intellectual property opportunity. Some examples of approved cocrystals are shown below:

Examples of Approved Cocrystals:

- **Steglatro®** - 2017 (ertugliflozin/L-pyroglutamic acid)
- **Entresto®** - 2015 (hemi-pentahydrate of the cocrystal comprising the sodium salt of sacubitril and the di-sodium salt of valsartan)
- **Odomzo®** - 2015 (sonidegib phosphate/phosphoric acid)
- **Lexapro®** - 2009 (partial hydrate of the cocrystal comprising escitalopram oxalate and oxalic acid)
- **Dramamine** - Dimenhydrinate® - 1977 (diphenhydramine is an antiemetic but causes drowsiness, 8-chlorotheophylline is a stimulant)

Amorphous (Non-Crystalline) Material Development and Solid Dispersion Development

Amorphous materials are generally much more soluble than their crystalline counterparts due to the lack of solute-solute interaction in the solid state. Literature[5,6] suggests between a two - to fifty-fold increase in solubility may be observed when amorphous materials are used. However, this increase in solubility is generally accompanied with poor physical stability as the amorphous phase tends to crystallize over time. Thus, stabilization of the amorphous phase against crystallization, which is accomplished typically using an amorphous solid dispersion (ASD), is one of the critical attributes for successful development.

Triclinic has pioneered rapid materials modeling approaches for amorphous materials and can provide insight in how to improve the manufacturing process, formulation process, and predicted shelf life of solid dispersions manufactured in a wide variety of ways. At Triclinic, the material amorphous solubility and stability is assessed prior to strategically screening for polymers useful for ASDs. The amorphous solubility is evaluated by determining the concentration at which liquid-liquid phase separation (LLPS) occurs (Figure 5). Following the material initial assessment, a rapid thermal screen is conducted to determine lead polymers exhibiting the highest miscibility. In some instances, it is worthwhile to determine the solid "solubility" of the API in the lead polymers. For example, in the case of nifedipine, its solubility in PVP at room temperature was found to be 34% w/w (Figure 6). This indicates that a nifedipine-PVP ASD can be developed at 34% without any risk of crystallization (albeit protection against moisture and residual solvent during processing is necessary for this to remain valid). When solubility of API is low in screened polymers, the composite glass transition temperature (T_g) becomes the dictating factor of ASD development. While there are several techniques available, spray

drying is the main technique to generate ASDs at Triclinic. Generally, sufficient solubility in spray drying solvents is required but recent research[8] shows that a secondary solvent, such as volatile acetic or hydrochloric acid, or elevated temperature can be used to expand the utility of spray drying in ASD generation. In our hands a spray drying process can be done very efficiently with a yield of up to 90%. Thus, an ASD screening process can be done with as low as 100-200 mg of materials, which is very useful for a compound in the early development phase. Once a lead ASD is selected, its performance is evaluated on the basis of LLPS generation in biorelevant media and the kinetics of crystallization. The potential advantages of LLPS during dissolution of an ASD in the gastrointestinal tract are illustrated in Figure 7, where maximum supersaturation is achieved and particle drifting through the mucosa membrane is observed.

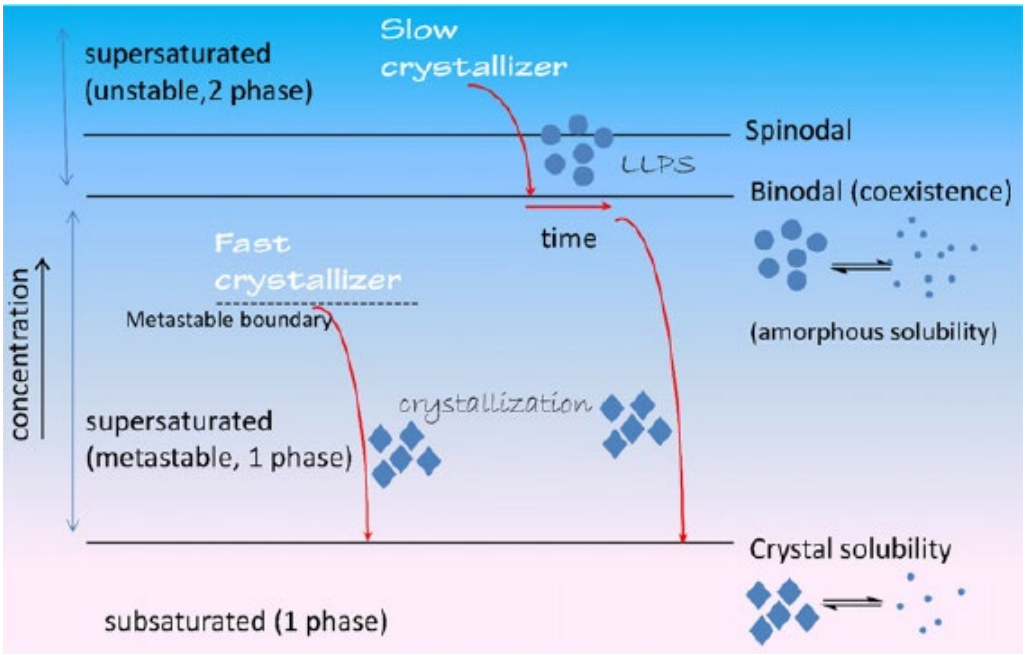

Figure 5. Phase behavior of slow and fast crystallizers in the context of crystalline and amorphous solubility boundaries (adapted from Taylor[7]).

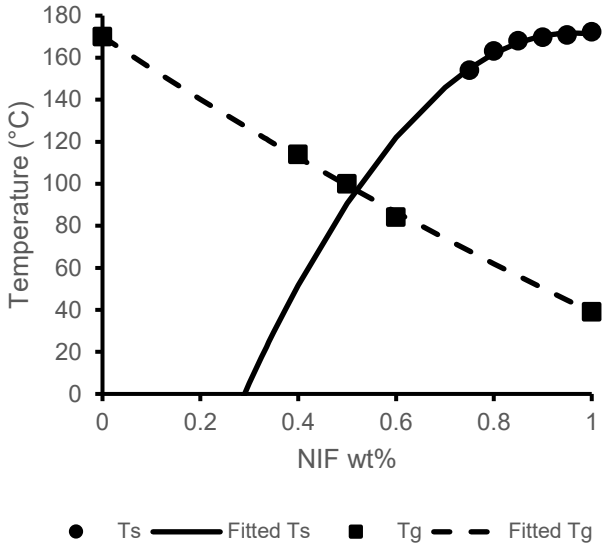

Figure 6. Nifedipine solubility and glass transition (T_g) in a mixture with polyvinylpyrrolidone (PVP) as a function of drug load.

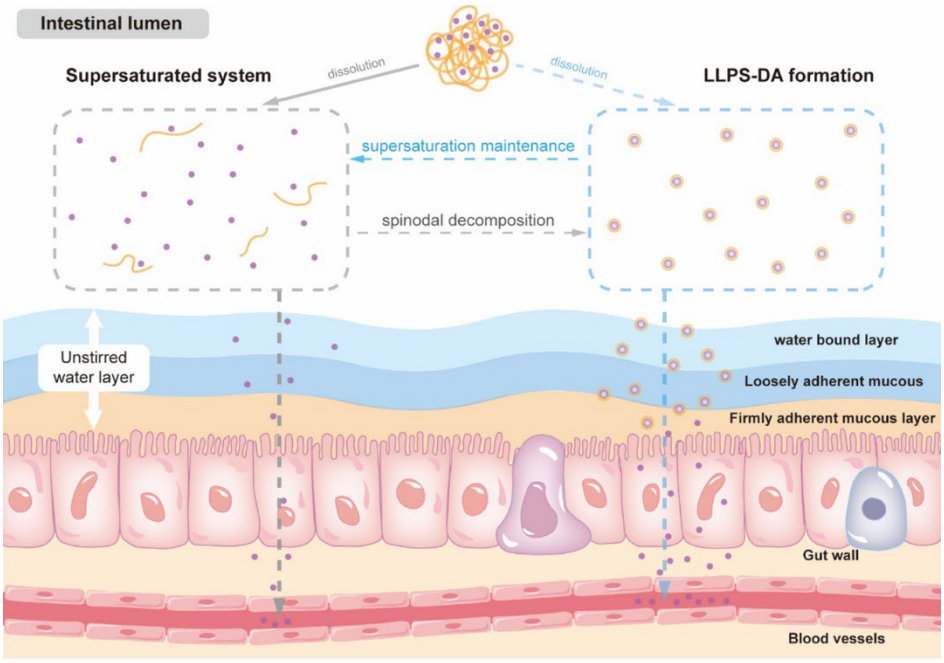

Figure 7. Illustration of potential advantages of LLPS-generating ASDs (adapted from Zhao et al[9]).

Screening and Selection Timing.

CMC regulatory requirements mandate an understanding of an API's polymorphism. Indeed, The US Food and Drug Administration (FDA) requires submitters of an Investigational New Drug Application (INDA) to submit information regarding a compound's polymorphic landscape. In addition, the International Conference on Harmonization of Technical Requirements of Pharmaceuticals for Human Use (ICH harmonized Tripartite Guideline - For more info, see:

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4544148/)

ICHQ6A states that the following is required: Evidence that polymorphism is or is not exhibited by a new drug substance. If polymorphism is exhibited, whether the different polymorphic forms can affect the performance of the drug product, what the potential for change is, and how it might be controlled must be determined.

The table below describes a variety of screens based not only on scope but also the desired outcome and where it is usually done along the drug development continuum.

Type of Screen/Selection	Application	Usual Stage When Conducted
Preliminary Solid-Form Screen	• Gives an indication of polymorphism • Excellent for instances where little API exists (<500mg)	• Early Preclinical Development
Abbreviated Solid-Form Screen	• High probability of determining polymorphism and a better chance of understanding the extent of polymorphism	• Early Preclinical Development
Standard Solid-Form Screen	• Attempt to identify the most stable form • Good for assessing the complexity of the solid-form landscape	• Prior To Toxicology Studies
Extensive Solid Form Screen	• The most complete analysis of your API • Ideal for determination of manufacturability, patent protection, and solubility optimization	• Prior to Commercialization and for intellectual property protection/generation

Salt or Cocrystal Screen/Selection	• Ideal for property improvement, IP, or developability	• Usually, the properties of the crystalline material are not ideal or well controlled. • Searching for additional Intellectual Property
Amorphous Material Development/Characterization	• Amorphous Stability and Performance Evaluation • Screening for dispersions with pharmaceutically acceptable polymers	• Usually, when a suitable crystalline material has not been found or when crystalline API cannot be obtained
Scale Up of Desired Form	• Attempt to find conditions to prepare the desired form, at will	• Prior to cGMP Batch Production

Table 1. Timing and Goals of Solid-Form Screening.

Screening and Selection Strategy

Below is a graphic describing Triclinic Labs' approach to solid form screening and selection. This process prioritizes the client's needs, intelligent experimental design, and high-quality data rather than a high throughput approach.

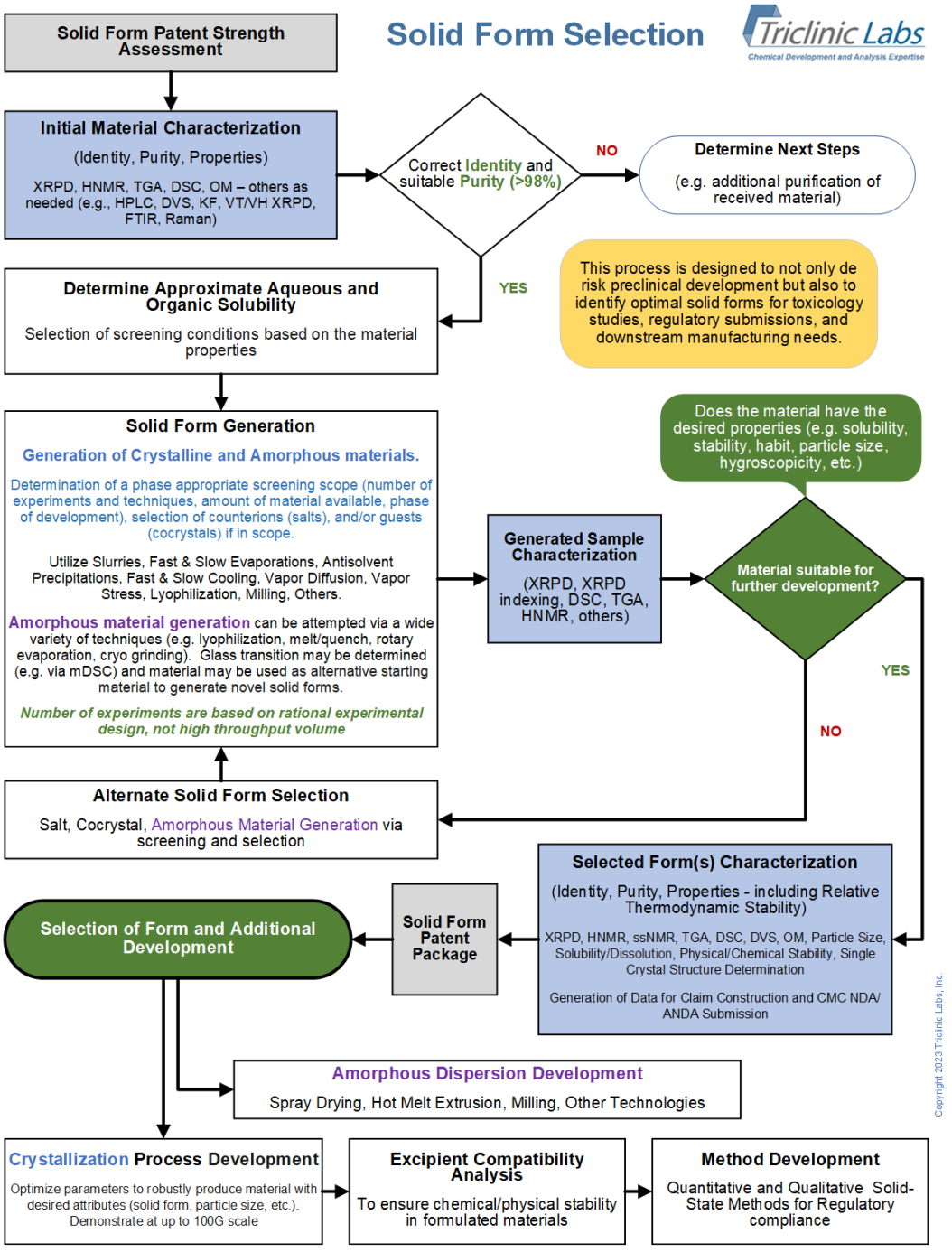

Figure 8. A comprehensive approach to solid form screening, selection, and characterization.

Solid Forms as Intellectual Property.

The FDA issued a guidance on cocrystals in 2013, which considered cocrystals as drug product intermediates. The original authors clearly did not fully understand what cocrystals are. After many comments from the scientific community, a new guidance was issued in 2016 that assigned cocrystals a regulatory classification similar to that assigned to polymorphs.
Different salt forms of the same active moiety are considered different active pharmaceutical ingredients (APIs), but polymorphs and cocrystals of an API are not.
The guidance was finalized in 2018. For more information on the FDA's approach to cocrystals as intellectual property, please see our White Paper: Cocrystals, A Regulatory Rebirth at:

https://triclinic labs.com/reference-material/downloadable-documents/whitepapers-pubs/COCRYSTAL-WHITEPAPER-TRICLINIC-LABS.pdf

High Throughput Screening or Not?

The number of usable samples that can be generated in a screen depends somewhat on the physical properties - particularly solubility - of the test compound. Therefore, it is difficult to plan a screen without knowing those properties. For example, if the test compound exhibits poor solubility in a wide range of solvents, it is likely not worthwhile to attempt generation of 150 samples, as the techniques available for sample generation are limited. One could always slurry a compound in various solvents in which it is insoluble to attain a target number of samples, but such experiments are quite unlikely to yield new solid forms.

Based on reports in the literature, isolable solid polymorphs tend to be created in at least single-digit percentages of samples made. Thus, it is reasonable to target less than 100 experiments, or maybe between 100-200 experiments, in a polymorph screen. **The variety of sample generation conditions is more important than the number of experiments.** For salt and cocrystal screening, the number of experiments it makes sense to generate is related to the number of counter-ion sources or coformers that are used. Typically two or three experiments with each counter-ion source/coformer are all that are attempted in order to determine the propensity for the API to form a crystalline salt or cocrystal.

The cost and time requirements for screening depend on the number of experiments and the number of usable samples analyzed. Scale-up and characterization of a solid form found during screening adds additional cost and time.

Instrument and Methods

Numerous analytical techniques can be used to characterize solids. Characterization often provides insight into three-dimensional structure, chemical/physical stability, reactivity, solubility, water- and chemosorption, active compound release, and bioavailability. X-ray powder diffraction (XRPD) is a powerful tool for determining polymorphism or salt/cocrystal formation, as each new material typically displays a unique pattern, similar to a fingerprint for that particular solid form. Additionally, by indexing patterns, XRPD can facilitate the identification of a mixture of forms. A prime question to address is, “Which phases are stable at what composition and at what stoichiometry?” Other methods, including Differential Scanning Calorimetry (DSC), Thermogravimetric Analysis (TGA), Hot-Stage Microscopy (HSM), as well as Raman spectroscopy (Dispersive and Low Frequency), Single Crystal X-ray Diffraction (SCXRD), IR spectroscopy, and Dynamic Vapor Sorption/Desorption (DVS) analysis as well. are useful to further characterize polymorphic forms.

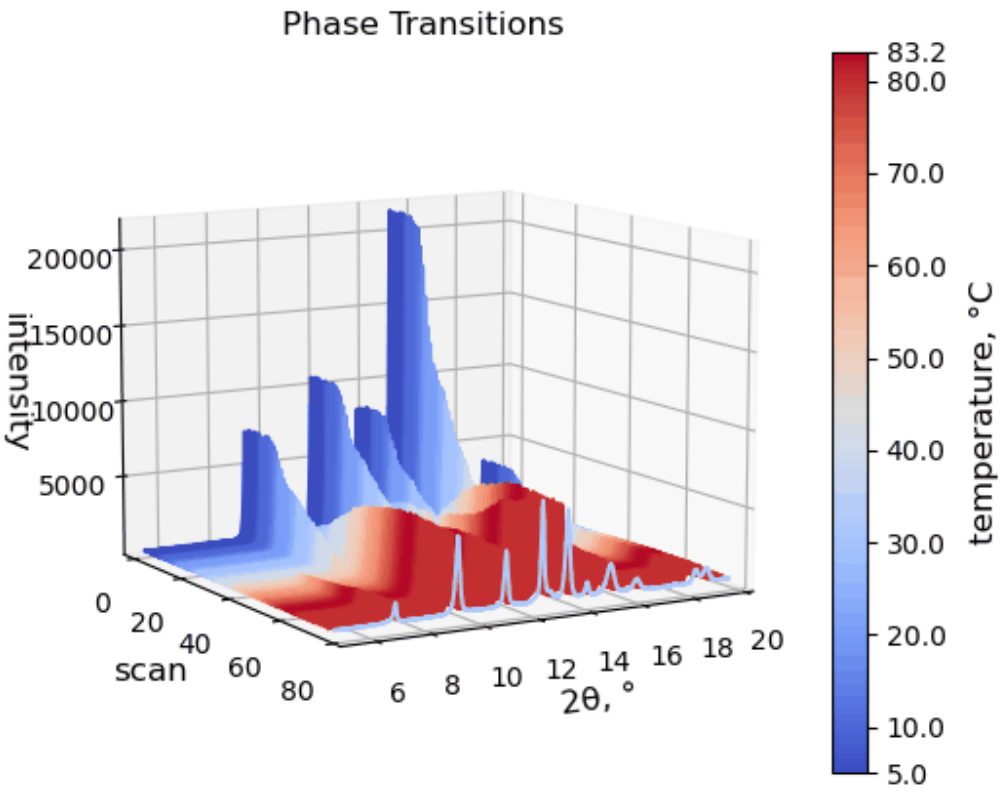

Figure 9. Use of Variable Temperature Variable Humidity Powder X-ray Diffraction for determination of polymorphic conversion: Theophylline was heated from 5 to 80 °C under constant relative humidities of 5%, 50%, and 75%. PXRD patterns were collected in the 2θ range of 5° to 20° every seven minutes. The animation shows a waterfall plot of the heating experiment at 5% RH. The onset temperature at which each form was first observed is indicated on the right. The experiment started with pure Theophylline. At 10 °C a set of peaks was observed to emerge at 2θ angles of 9.4°, 12.5°, 13.7°, and 15.3°. This set of peaks matches the dehydrated-hydrate form I. At 30 °C, a new set of peaks emerged that could be attributed to form III. At 50 °C, the peaks attributed to the stable anhydrous form II started to appear. Before the final temperature of 80 °C was reached, the peaks of form I had completely diminished, resulting in a mixture of forms II and III at the end of the experiment. This approach is useful for time-course studies under normal and modified conditions (e.g. stability, scale-up, formulation) to determine if polymorphic change arises. Infringement determination cases and process control experiments benefit from this approach as well.

Conclusion

Different crystalline solid forms (polymorphs, salts, cocrystals, and amorphous materials) of an active pharmaceutical ingredient (API) can have very different physico-chemical properties. A comprehensive understanding of the solid form landscape is necessary not only to select the optimal solid forms for development but also to maximize intellectual property value and satisfy regulatory requirements. Many common issues that result later in development could have been avoided with a better understanding of solid form dynamics and an effective strategy to mitigate those potential problems. In this Application Note, we discussed the various solid forms of an organic API and a timeline for screening and selection to produce a solid form with the optimal physical, chemical, and intellectual properties. Triclinic Labs offers comprehensive and individually planned solid-form studies tailored to our client's needs and assets, all designed to maximize your development potential.

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