Polymorphism—A Critical Consideration in Pharmaceutical Development, Manufacturing, and Stability

Welcome to "Pharmaceutical Solids."

This column discusses scientific principles associated with pharmaceutical solids useful to practitioners in validation and compliance. This column has been developed with the intention to help readers understands the principles associated with pharmaceutical solids, and to be a useful resource for daily work applications. Enhanced process understanding is an important objective of the quality by design initiative. The key objective for this column: Usefulness.

The topic of pharmaceutical solids is broad and complex. Its importance is unquestioned. Understanding the basic properties of pharmaceutical solids is fundamental to pharmaceutical discovery, development, clinical studies, manufacturing, processing, problem investigations, and stability. Unfortunately this topic often requires understanding the higher level of principles of chemistry, physics, and mathematics. These may include thermodynamics, crystallization, analytical DSC, X-Ray diffraction, and other research methods. Finally, the language of pharmaceutical solids may be esoteric and intimidating.

These considerations make discussion of pharmaceutical solids a difficult task. This column addresses the various topics of pharmaceutical solids with these considerations in mind. It is our challenge to present these topics in a meaningful way so that our readers will be able to understand and apply the principles discussed in their daily work applications.

This first installment of "Pharmaceutical Solids" addresses the potential solid polymorphic forms of a drug which in turn determine many of the solid physical properties. A thorough understanding of the solid state chemistry of a new drug should be a critical component of pharmaceutical development, and will serve throughout the entire product lifecycle.

Reader comments, questions, and suggestions are needed to help us fulfill our objective for this column. Suggestions for future discussion topics or questions to be addressed are requested. Case studies illustrating principles associated with pharmaceutical solids submitted by readers are also most welcome. We need your help to make "Pharmaceutical Solids" a useful resource. Please send your comments and suggestions to column coordinator John Bauer at consultjb@comcast.net or to journal coordinating editor Susan Haigney at shaigney@advanstar.com.

KEY POINTS

- Pharmaceutical solids may be crystals, crystal solvates or hydrates, crystal desolvated solvates or dehydrated hydrates, or amorphous solids
- All crystal forms described can exist in different forms called polymorphs
- Polymorphs can have significant differences in their physical properties even though they are chemically identical. Physical properties include

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solubility, melting point, particle size, dissolution rate, hygroscopicity, and others.

- Polymorphs may interconvert depending on conditions. Usually the metastable kinetic form converts to the stable thermodynamic form.
- Laboratory studies are key to determining the potential of a compound to form multiple polymorphs, determining under what conditions the polymorphs are formed, what are the physical properties of each polymorph, and what is the stability of each polymorph
- The primary analytical method to characterize polymorphs is x-ray diffraction. Other methods used include solid state NMR, Raman and NIR spectroscopy, and thermal methods such as DSC and TGA.
- Seeding is used to facilitate manufacturing of the desired polymorph
- Polymorph interconversions in pharmaceutical product manufacturing have been reported for grinding, milling, tablet compressing, and other processes involving moisture or other solvents
- ICH Q6A addresses specifications for API and pharmaceutical products and includes several decision trees
- Awareness, knowledge, and understanding of polymorphism are important throughout the product lifecycle. Polymorphism may impact product development, clinical studies, product manufacturing, product quality, and product stability.
- Change management and validation in API manufacturing and product manufacturing should address the potential impact of formulation and process changes on API polymorphism.

INTRODUCTION

In June 1998 at the Geneva International AIDS Conference, ritonavir, the active ingredient in Norvir Capsules (Abbott), was identified as the key component in various protease inhibitor cocktails (combination therapies) used for the successful treatment of HIV infections. This finding enhanced the therapeutic effectiveness of many AIDS therapies, and caused Norvir to be used in combination with many other marketed AIDS products around the world. By that time, 240 lots of the Norvir Capsules had been successfully manufactured. However, in the summer of 1998, a sudden change in physical properties of ritonavir brought production to a halt and eventually led to an interruption of the supply of Norvir capsules to the millions of HIV patients who relied on the product for its therapeutic effects. The crystal form of ritonavir had unexpectedly changed. This change resulted in a solubility change for the drug, which in turn resulted in a bioavailability change and affected the therapeutic effect of the drug. The Norvir product was withdrawn from the market. An intensive research effort was undertaken to understand and solve the problem. A new capsule formulation was eventually introduced that overcame the physical problems. After implementing the new formulation, Norvir Capsules were returned to the marketplace (1).

This unexpected change in physical properties had a dramatic impact on patients, the pharmaceutical manufacturer, and the US Food and Drug Administration. Since this crisis, FDA has become much more aware and concerned about the physical properties of drugs and the measures taken to ensure that physical properties do not change during the product shelf life. The compound that was present in the Norvir formulation before and after the sudden manufacturing problem was chemically the same. So what caused the problem, the inability to produce capsules, and the subsequent global consequences?

PHYSICAL FORMS OF PHARMACEUTICAL SOLIDS

The cause of the ritonavir problem was a change in polymorphic solid form. Most pharmaceuticals are fundamentally organic compounds, and organic compounds can often exist in a variety of solid forms. This means that although a drug will remain as the same chemical entity and have the same chemical properties of stability, reactivity, etc., it may not always act in the same way in the solid state. These differences may or may not cause a difference in pharmacological effect (i.e., how the drug may work in the human body such as inhibiting proteases or reducing blood pressure). In the Norvir example, the change in solid form had a great effect on solubility, which in turn reduced bioavailability.

Pharmaceutical solids can exist in two general forms: Crystalline and non-crystalline forms.

Crystalline Forms

In order to form a solid, a compound must have internal attraction between molecules that is sufficient to restrict the free movement that exists in liquids and gases, but how strong the internal attractions are can vary. There are multiple well-known solid forms that have been identified in pharmaceuticals. A crystalline solid form or crystal exists when the molecules of the drug are arranged in the solid in a three-dimensional repeating pattern or unit cell (see Figure 1).

Crystalline solids are usually highly stable and have a well-established solubility and dissolution rate. Most drugs are used in the crystalline form.

Figure 1: Example of crystal arrangement.

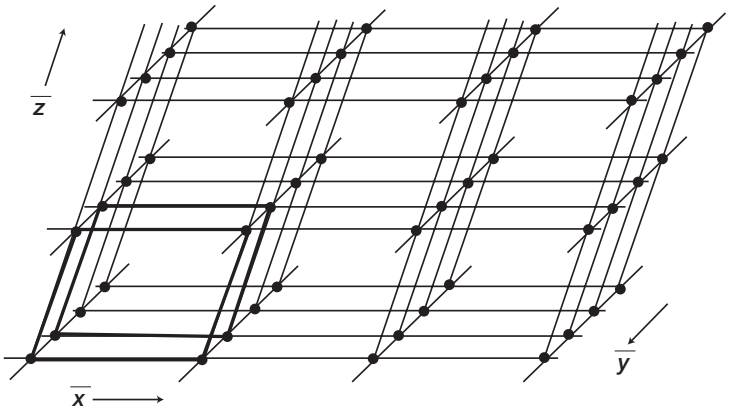
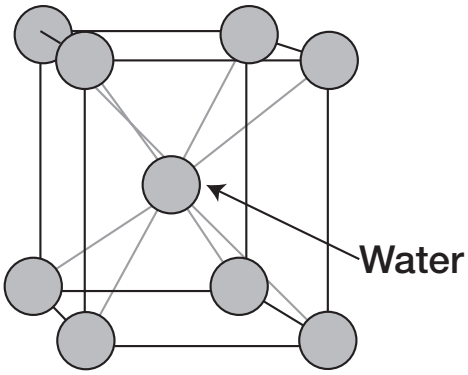


Figure 2: Example of crystal hydrate.



Amorphous Solid

A second type of solid form that is non-crystalline is referred to as the amorphous form. This type of solid is randomly arranged with a high degree of disorder in the molecular arrangement. The amorphous state is usually much faster dissolving than the crystalline state, and has a variable solubility that is usually higher than the crystalline form. The amorphous form is often less stable than the crystalline form and is usually hygroscopic (i.e., the amorphous form will absorb water from the atmosphere under ambient humidity conditions). In actuality, solids can exist on a continuum between amorphous and crystalline whereby they contain varying degrees of disorder—the solid may be partly crystalline and partly amorphous.

Crystal Solvate/Hydrate

The solubility that is of the most importance as far as pharmaceuticals are concerned is the aqueous solubility. Some drugs can dissolve rapidly in water but then incorporate water molecules into a different solid form that has water systematically distributed within the molecular arrangement (see Figure 2). This solid form is known as a hydrate. Depending on the number of molecules of water incorporated, this crystal can be a monohydrate, dihydrate, trihydrate, etc. These hydrates will have reduced solubility in water and often precipitate out of an aqueous solution of drug. It is critical to know if a particular drug substance can form hydrates because this reduced solubility in water can also lead to reduced bioavailability and to manufacturing problems. Finally, it is also possible for some drugs to form solid forms analogous to hydrates but that incorporate other solvents such as ethanol or ethyl acetate into the solid rather than water. These are known as solvates. Solvates and hydrates can be very stable solid forms and may have definite benefits in regard to manufacturing.

Crystal Desolvated Solvate/Dehydrated Hydrate

Although hydrates can have benefits in manufacturing, they can also present a significant problem from the standpoint of drying. Many hydrates will dehydrate or lose the water from the crystal under normal drying conditions forming a dehydrated hydrate. This creates what amounts to an activated hole in the crystal, and the active sites exposed have a tendency to either reabsorb water or to bind to other available moieties. Over drying erythromycin dihydrate can cause it to dehydrate and bind to an excipient. This binding slows the dissolution rate sufficiently to causes stability failures and notification of FDA (2). If the crystal loses solvent such as ethanol or other solvent other than water, the resulting crystal is called a desolvated solvate.

All solid forms described above can have significant differences in their physical properties even though they are chemically identical. Physical properties include solubility, melting point, particle size, dissolution rate, hygroscopicity and others. All of these properties can have a dramatic impact on manufacturability, stability, and sometimes bioavailability of the commercial formulation.

POLYMORPHISM

The ritonavir problem was caused by a change in the solubility of ritonavir that caused the drug to precipitate from the capsule formulation, and reduced its bioavailability to less than 5%. The reason for this change is a phenomenon known as polymorphism. As described previously, solids can exist as crystalline, amorphous, solvate (hydrate), and desolvated (dehydrated) forms. Complicating this situation is the fact that crystalline solids (and solvates/hydrates and

desolvated/dehydrated solvates/hydrates) can exist in what are known as polymorphs. Crystals exist with the molecules arranged in a repeating pattern with an identifiable symmetry. However, there can be more than one possible repeating pattern for many drugs. This can be demonstrated by visualizing a number of identical Lego pieces of a specific shape. Each Lego piece represents a drug molecule. These individual Lego pieces can be assembled in several different ways to form different symmetrical patterns. Each of the different patterns contains the same number and type of individual Lego pieces.

Each of these different patterns would represent a different polymorph of the drug. These various polymorphs are chemically identical but can have significantly different physical properties. Because the molecules are arranged differently in the different polymorphs, it is possible to have different portions or functional groups of the molecule exposed at the surfaces of the crystal. These differences, especially when they involve hydrogen bonding groups, can cause the crystal to interact differently with solvents and therefore change the solubility of the drug. This was the case with ritonavir. A much less soluble polymorph having five times lower solubility was formed. The significantly different solubility of the new ritonavir polymorph made it impossible to manufacture the original Norvir formulations.

Different crystal arrangements or crystal lattices are possible for any particular compound. Under particular temperature, pressure, and humidity conditions, the various polymorphs of a drug have different energies. There is one polymorph that has the lowest energy and is considered the most stable. All other forms are referred to as metastable, although they may be quite stable under that particular combination of temperature, pressure, and humidity. Theoretically any metastable form will convert to the stable form under particular conditions. However, this conversion will be extraordinarily slow unless mediated by a solvent. In the case of ritonavir, the solvent system in the capsule mediated the crystal form change. The stability referred to here is the ease with which one solid form converts to another solid form, for example, conversion of amorphous solid to crystalline form or one polymorph to another. Crystal polymorphs can also differ in chemical stability because the groups present on the surface of the molecule will be more or less labile or reactive. The tendency of a compound to attract water from the atmosphere (i.e., hygroscopicity) is also the result of surface groups.

LABORATORY STUDIES TO DETERMINE POLYMORPHISM

Which polymorph of a crystalline drug will form under certain conditions cannot be predicted. However, laboratory experiments can be conducted that will determine the potential for formation of multiple polymorphs. These studies are performed by crystallizing the drug from multiple solvents of differing polarities, different solvent combinations, at different temperatures, at different rates of cooling, and other experimental conditions. These studies are conducted in solid state laboratories using a laboratory robot system.

The crystal form that will be easiest to form is the one closest in arrangement to the drug in solution under the same environmental conditions. This transition requires the least energy, and the form produced is called the kinetic form. There may also be other forms that are not as closely related to the dissolved drug but can also form under the specific environmental conditions. The form that has the strongest internal attractions within the crystal is the most stable form under these conditions and is referred to as the thermodynamic form. Given enough time and especially if solvent mediated, the thermodynamic form of the crystal would be the final and most stable polymorphic crystal form produced. When different temperatures are involved, more complexity may be introduced. For example, the simplest situations are those in which a single polymorph is always the most stable polymorph regardless of temperature; these systems are called monotropic systems. However, there may be situations in which a different polymorph is the most stable polymorph at a higher temperature; these systems are called enantiotropic systems.

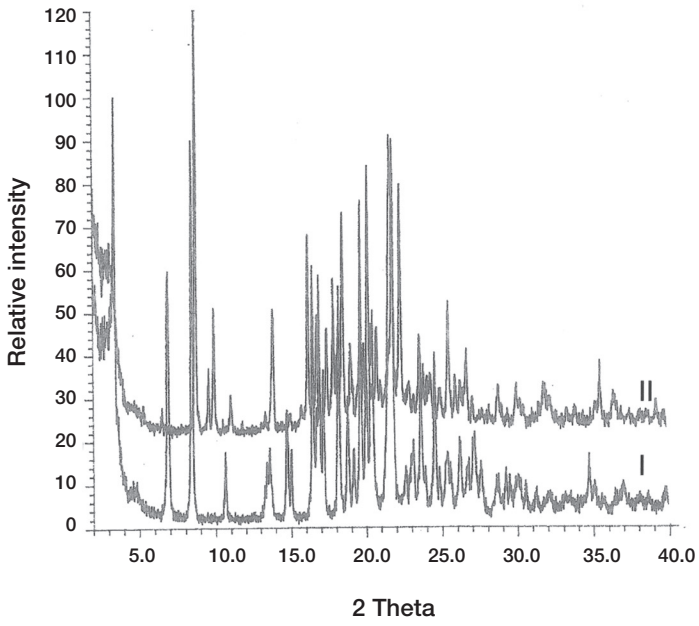
When multiple polymorphs of a drug are formed it is necessary to understand their conditions of formation and the physical properties associated with each form. Polymorphic interconversions have been reported in the solid state, caused by mechanical stress and/or high temperature. The stability of each form must be studied. The information learned in these studies is used in the selection of the appropriate form for development. Thereafter, laboratory information is useful for development of the active pharmaceutical ingredient (API) manufacturing process. When multiple polymorphic forms are possible, it is critical to understand the conditions under which they can interconvert. In many cases the forms do not differ enough to affect the manufacture, stability, and/or efficacy of the compound. However, this information is only known through appropriate laboratory investigations.

One other important benefit of understanding the various polymorphs and methods of preparation of different polymorphs is that polymorphs are patentable. This knowledge may thus provide commercial benefit for the organization.

CHARACTERIZING POLYMORPHS

Polymorphs are characterized by techniques and methods that provide particulate level characterization of pharmaceutical solids. The "gold standard" for this type of investigation is X-ray diffraction. The x-ray beam is diffracted or reflected as it collides with atoms in the crystal. The different atoms will bend the x-rays at different angles that indicate the distances between the atoms. The exiting beams can be detected. This can be plotted as a graph of intensity versus angle that represents a unique fingerprint for a particular crystal form of a drug. Amorphous solids are not crystalline and do not give a characteristic x-ray pattern. Figure 3 illustrates an X-ray diffraction pattern for two different crystal polymorphs of the same drug—chemically identical but having two different polymorphic crystal forms.

Figure 3: X-ray of forms I and II of a drug.



Other techniques that can be used to distinguish and identify crystal forms are solid state nuclear magnetic resonance (ssNMR), Raman spectroscopy, and near-infrared spectroscopy (NIR). Of these techniques, Raman and NIR spectroscopy are adaptable to process analytical technology (PAT). These techniques are useful for in process monitoring of the manufacturing process (i.e., the formation of the actual desired or undesired polymorph can be detected during the manufacturing process and appropriate controlling adjustments can be made).

MANUFACTURING THE DESIRED API POLYMORPH

Laboratory studies provide information regarding desired polymorph solubility, preferred crystallization solvent, optimized concentrations in mixed solvent systems, crystallization conditions, and other processing parameters. One very important phenomenon related to solid form manufacturing control is seeding. As mentioned previously, the various solid forms possible for a compound include polymorphs, solvates, and amorphous. As also mentioned, the surfaces of these various forms can have different functional groups or active portions of the molecule exposed. The mechanism for crystal growth is for further molecules to attach themselves to the surface of existing crystals and continue the crystal symmetry. This mechanism can be exploited by providing crystals of the desired solid polymorphic form to a supersaturated solution of the drug to act as a template or starting point for further crystallization. Such crystals are called seeds and in many instances can be used to direct the crystallization to the desired solid form. This technique, known as seeding, is commonly used in bulk drug synthesis. In these cases, the seeding is intentional and controlled. It is possible, however, to inadvertently seed processes, producing undesired solid forms. In some cases, such as the aforementioned ritonavir example, it is possible for an undesired polymorphic form to be seeded by a compound different from the drug itself. In the case of ritonavir, the less soluble polymorph (called Form 2) was never seen in laboratory studies. It was inadvertently seeded by a degradation product with a similar crystal structure to Form 2 ritonavir.

POLYMORPHS IN PHARMACEUTICAL PRODUCT MANUFACTURING

There are many reported examples of changes in solid form due to conditions typical of product manufacturing processes. Examples of processing that may cause polymorphic changes including grinding, milling, heating, and compressing. Manufacturing conditions that include a solvent (e.g., wet granulation, polymorphs in solution, polymorphs in suspension) may also facilitate conversion to the thermodynamic polymorph. An often-cited article entitled "Disappearing Polymorphs" (3) describes multiple cases where a crystal form was developed and even

patented and marketed when a new polymorph suddenly appeared, and the first form could no longer be produced. The extreme example of ritonavir (Norvir) exemplifies the criticality of solid state investigations during the development of a new drug entity and manufacturing process development. This has been an important area of concern and emphasis by FDA and International Conference on Harmonisation (ICH) in recent years.

REGULATORY DOCUMENTS ADDRESSING POLYMORPHISM

The following are several regulatory documents addressing polymorphs and changes in polymorphs:

- FDA ANDAs: *Pharmaceutical Solid Polymorphism* (4)
- ICH *Q6A Specifications:* "Test procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances" (5)
- ICH Guideline Q6A has also been published in the FDA *Federal Register* (6).

The FDA and ICH guidelines both provide a series of decision trees that can be followed in determining if a specification is required to confirm the nature of the polymorph present in both bulk substance and product. These decision trees are very useful and reflect the current approach to evaluating the concern that should exist around polymorphs for any particular product. The decisions trees are built on information gathered in the initial laboratory studies on the drug crystal form (see Figure 4).

The important questions to be answered in the decision trees either eliminate potential solid form changes as a concern (i.e., changes have no effect on product) or demonstrate that the manufacturer has control of the solid form throughout the process. The analytical methodology to detect undesirable solid forms in the presence of the desired form must be validated.

The Norvir polymorph example discussed previously suggests an additional concern in the formulation of liquid solution products. Conventional wisdom suggests that since the drug is in solution, polymorphic forms should be of no concern. However, extraneous materials can sometimes seed new thermodynamic crystal forms that may precipitate from solution. When solution products are formulated, the drug concentrations should be well below the saturation concentrations of any of the known drug product polymorphs.

PRACTICAL IMPLICATIONS OF POLYMORPHISM

In light of the problems that can be caused by changes in solid form, it is imperative polymorphism be thoroughly investigated early in the drug development process. The potential for multiple polymorphs, the properties of the individual polymorphs, the desired polymorph for development, its stability, solid state reactivity, and so on must be understood. This information will be of service throughout the product lifecycle from API and product development through commercial distribution. Consider the following possible consequences if adequate information regarding polymorphs is not known and polymorph changes occur:

- Formulation development work may have problems because of changes in polymorph physical properties
- A clinical study may be affected due to solubility and bioavailability changes
- Stability problems such as precipitation from solution may occur in the commercial dosage form
- Manufacturing problems such as tablet compressing problems may occur
- Product quality changes such as grittiness in a topical cream formulation may occur
- Solidification of ointments and/or suppositories over time.

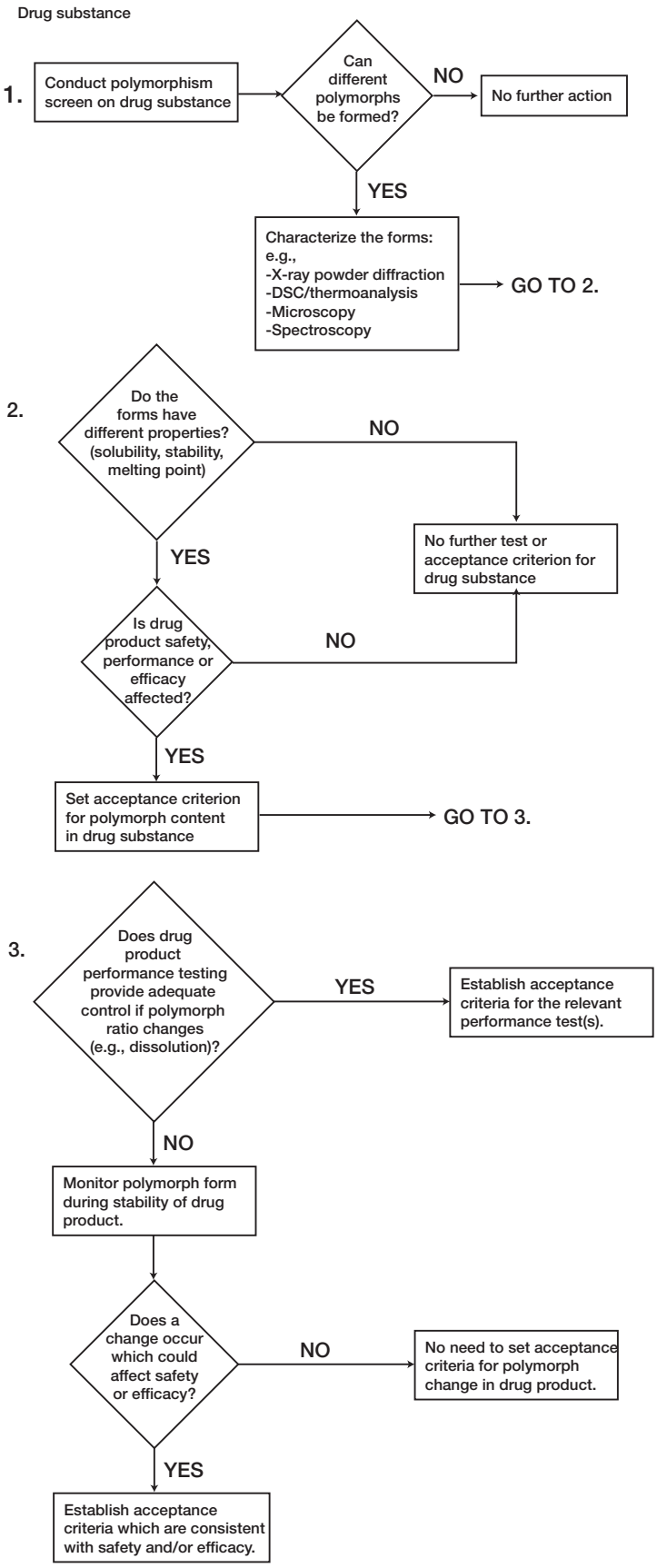
A good development process should address the solid state properties of the API. The API manufacturing process should be well controlled to yield the intended crystal polymorph. The product manufacturing process should likewise be well understood and appropriately controlled to assure that it does not cause change in the API crystal form. Product stability studies should assure there are no polymorphic changes during the product shelf life of the commercial package.

Any changes to the API manufacturing process or to the product manufacturing process should address the potential for polymorphic changes to the API crystal. The original API development work is helpful in addressing the impact of these changes. Experimental research and development studies should indicate whether there is potential for the API molecule to form multiple polymorphs, and the ease of interconversion between polymorphic forms. This information will form the basis for appropriate testing in process validation.

CONCLUSIONS

Although the chemical and physiological properties of a pharmaceutical compound determine the potential of the compound as a commercially viable drug product, the solid state properties of the compound are extremely important in determining whether it can be reproducibly manufactured. Laboratory studies are key to determining the potential of a compound to form multiple

Figure 4: Example decision tree from FDA and ICH guidelines.



polymorphs, under what conditions the polymorphs are formed, the physical properties of each polymorph, and the stability of each polymorph. Awareness, knowledge, and understanding of polymorphism is important throughout the product lifecycle. Polymorphism may impact product development, clinical studies, product manufacturing, product quality, and product stability. The large majority of manufacturing problems encountered in commercial scale manufacturing are related to the physical properties of the API and/or excipients. These problems may be caused by polymorphic changes. Change management and validation in API manufacturing and product manufacturing should address the potential impact of formulation and process changes on API polymorphism.

FUTURE INSTALLMENTS OF "PHARMACEUTICAL SOLIDS"

The properties of pharmaceutical solids are generally categorized at three levels: Molecular level properties, particulate level properties, and bulk level properties. Molecular level properties are those properties that could be measured for a small group of individual molecules. These properties are spectroscopic in nature, such as those determined by ultraviolet spectroscopy, vibrational spectroscopy such as infrared spectroscopy and nuclear magnetic resonance spectroscopy. Particulate level properties are those characteristics which can be determined on a small number of particles or crystals. These properties are determined by microscopic methods, particle size methods, x-ray, and thermal methods such as differential scanning calorimetry and thermogravimetric analysis. Bulk level properties are those determined on a relatively large sample of material. These include surface area determination, porosity, powder flowability, angle of repose, solubility, water sorption, and powder bulk density.

Several of the above methods and their relevant applications will be discussed in future installments of "Pharmaceutical Solids." Solid polymorphic form is only one of several physical properties of the drug substance that can be critical to manufacturing and control. Future discussions in this column will address other properties of pharmaceutical solids such as particle size and surface area. Pharmaceutical solids include the active drug as well as the inactive excipients in the dosage form. Manufacturers often forget that excipients are also pharmaceutical solids and that the solid form of major excipients can also have an impact on stability, compressibility, wetability, and other properties that are important to a reproducible manufacturing process. The solid properties of active drugs and excipients must be considered for good understanding of a manufacturing process. Good understanding of manufacturing processes is consistent with recent quality by design principles.

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GLOSSARY

Amorphous solid: A solid in which there is no long-range order of the positions of the atoms.

Crystal: A solid formed by the solidification of a chemical and having a highly regular atomic structure, has regularly repeating internal structure.

Dehydrated hydrate: The activated species that exists when the water molecules are removed from the crystalline structure of a hydrate without destroying the crystal structure.

Desolvated solvate: The activated species that exists when the solvent molecules are removed from the

crystalline structure of a solvate without destroying the crystal structure.

Enantiotropic system: A set of polymorphic forms in which the different forms are most stable depending on temperature and humidity.

Hydrate: A crystalline solid with molecules of water incorporated in the solid state structure, which can often be removed partly or completely by relatively gentle heating.

Hygroscopic material: A material that readily absorbs moisture from the atmosphere.

Metastable polymorph: Polymorph that can exist but does not have the lowest energy under a defined set of temperature and humidity conditions. A polymorph that is considered metastable under one set of conditions can also be the stable polymorph under a different set of conditions.

Monotropic system: A set of polymorphic forms in which the same form is most stable regardless of temperature and humidity.

Polymorph: One of several distinct crystal packing arrangements, potentially having a different energy of formation and melting point than other polymorphic forms of the same molecule.

Polymorph, kinetic form: The polymorphic form that requires the least energy to form and therefore is usually the first and fastest form to crystallize. It is not always the most stable form and can convert to a different polymorph over time.

Polymorph, thermodynamic form: The polymorphic form that is of lowest energy under a particular set of temperature/humidity conditions and therefore is the most stable form and will not convert to other forms.

Seeding: A process that uses a small crystal to start and direct a crystallization process.

Solvate: A crystalline solid with molecules of a solvent incorporated in the solid state structure, which can often be removed partly or completely by relatively gentle heating.

Stable polymorph: Polymorph with the lowest energy under a defined set of conditions.

Unit cell: The smallest building block of a crystal, whose geometric arrangement defines a crystal's characteristic symmetry and whose repetition in space produces a crystal lattice.

X-Ray powder diffraction: An analytical test method X-Ray diffraction on powder or microcrystalline samples for structural characterization of the materials. Can often supply a fingerprint for each individual polymorph of a compound.

ARTICLE ACRONYM LISTING

API	Active Pharmaceutical Ingredient
FDA	US Food and Drug Administration
ICH	International Conference on Harmonisation
NIR	Near-Infrared Spectroscopy
PAT	Process Analytical Technology
ssNMR	Solid State Nuclear Magnetic Resonance