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What Everyone Needs to Know about Polymorphs

If you're involved in late drug discovery, API manufacture, drug product formulation, clinical material production, or manufacture of final dosage form, a basic understanding and awareness of solid form issues could save you a great deal of difficulty, time, and money during drug development.

What is polymorphism?

Polymorphs are crystalline materials that have the same chemical composition but different molecular packing. The concept is well demonstrated by the different crystalline forms of carbon. Diamond, graphite, and fullerenes are all made of pure carbon, but their physical and chemical properties vary drastically. Polymorphs are one type of solid form. Other solid form types include solvates, hydrates, and amorphous forms. Solvates are crystalline materials made of the same chemical substance, but with molecules of solvent regularly incorporated into a unique molecular packing. When water is the solvent, these are called hydrates. An amorphous form of a substance has the same chemical composition, but lacks the long-range molecular order of a crystalline form of the same substance. Many organic and inorganic compounds, including APIs, can exist in multiple solid forms. Some APIs may have only one or two known solid forms. Others may exist in twenty different forms, each having different physical and chemical properties.

Does solid form matter?

Sometimes the properties of two solid forms of a drug are quite similar. In other cases, the physical and chemical properties can vary dramatically and have great impact on pharmacokinetics, ease of manufacturing, and dosage form stability. Properties that can differ among solid forms of a substance include color, solubility, crystal shape, water sorption and desorption properties, particle size, hardness, drying characteristics, flow and filterability, compressibility, and density. Different solid forms can have different melting points, spectral properties, and thermodynamic stability. In a drug substance, these variations in properties can lead to differences in dissolution rate, oral absorption, bioavailability, levels of gastric irritation, toxicology results, and clinical trial results. Ultimately both safety and efficacy are impacted by properties that vary among different solid forms.

Stability presents a special concern, since it's easy to inadvertently generate the wrong form at any point in the development process. Because energy differences between forms are usually relatively small, form interconversion is common and can occur during routine API manufacturing operations and during drug product formulation, storage, and use. The stakes are high. Encountering a new solid form during late stages of development can delay filing. A new form appearing in drug product can cause product withdrawal.

When should a search for solid forms begin?

The key to speed in the drug development process is to do it right the first time. For solid pharmaceuticals, that means:

- identify the optimum solid form early in drug development
- make the same form for clinical material and commercial API
- develop a crystallization process that assures control of solid form
- produce a drug product with solid form stability through expiration

Our scientists strongly recommend that investigation of possible solid forms of a new chemical entity be carried out as early in the development process as drug supply will allow. The best approach has three stages. The first stage, more relevant to some development processes than to others, is a milligram-scale abbreviated screen on efficacious compounds prior to final IND candidate selection. This early information can be used to guide selection of salts and solid forms for scale-up and toxicology studies. The second stage is full polymorph screening and selection of optimum solid form. This stage is important to all development processes and should certainly occur before the first GMP material is produced. In the case of ionic drugs, various salts should be prepared and screened for polymorphs and hydrates. The third stage, an exhaustive screen carried out before drug launch, is an effort to find and patent all of the forms of a high-potential drug. Staging the screening in this way optimizes the balance among the factors of early knowledge of options, probability of commercial success, and judicious investment of R&D money.

Delay in understanding solid form issues results in problems like different batches of clinical material having different solid forms. Another common and preventable dilemma arises when clinical trials are carried out with one form while commercial production generates another. In this case, bridging studies are required to demonstrate to regulatory agencies that the clinicals are relevant. ICH guidelines require a search for solid forms, comparison of properties that might affect product efficacy, and, if appropriate, setting of solid form specifications.

How is solid form controlled in API manufacture?

It is important to control solid form during API synthesis in order to demonstrate complete process control to regulatory agencies. Different solid forms can have different solubilities and can affect recovery of API. Purification efficiencies can vary due to differential exclusion of impurities. Filtration and transfer characteristics often differ between forms. Ease of drying can vary due to different abilities to bind solvent and water in the crystal lattice.

A prevalent but incorrect belief is that solid form is determined primarily by choice of crystallization solvent. In fact, it is well established that parameters like temperature, supersaturation level, rate of concentration or cooling, seeding, and ripening can have an overriding effect. These variables must be controlled to ensure consistency of solid form in API.

Can solid form problems arise in drug products, too?

The potential for solid form variation does not end at API production. Solid form issues remain through formulation, manufacture, storage, and use of drug product. It is common to observe form transformation during standard manufacturing operations like wet granulation and milling. Excipient interactions and compaction can induce form changes. Changes can occur in the final dosage form over time. Suspensions, including those in transdermal patches, are particularly vulnerable because they provide a low-energy pathway (dissolution/recrystallization) for form interconversion. Lyophile cakes are normally amorphous, but can crystallize on storage leading to difficulty in reconstitution. Even products containing drug in solution, such as filled gel caps, can be affected if the solution is or becomes supersaturated with respect to one of the possible solid forms of the drug.

How can you tell when you have a solid form problem?

Whenever there is a specification failure in drug product or drug substance, solid form changes should be considered in the search for causes. Particularly symptomatic is failure to meet melting point or dissolution specifications. Changes in humidity, crystallization conditions, or crystallization solvent can produce unwanted forms. Solvents known to readily produce solvates include water, alcohols, chlorinated hydrocarbons, cyclic ethers, ketones, nitriles, and amides. Changes in the appearance of gel caps or cracking of tablet coatings can indicate solid form problems. Various solid-state analytical techniques can be used to identify solid form in API. Some techniques can even determine solid form of API in intact final dosage form. Among the most useful techniques for solid-state characterization are melting point, DSC, TGA, hot stage and optical microscopy, solid-state NMR, IR and Raman spectroscopy, and X-ray powder diffraction.

Is there any good news about polymorphism?

Polymorphism presents opportunities as well as challenges. Investigation of the properties of different forms of a commercial drug can lead to new products with improved onset time, greater bioavailability, sustained release properties, or other therapeutic enhancements. New forms can bring improvements in manufacturing costs or API purity. These improvements are patentable and can provide a competitive advantage. An underutilized potential of polymorphism is to solve formulation problems that cause the abandonment of potentially useful drugs in which much investment has already been made.

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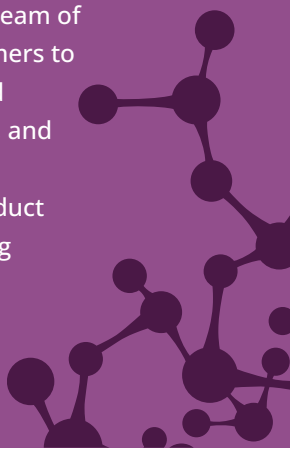

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