Solid State Characterization

Introduction
Characterization of solid active pharmaceutical ingredients (APIs) continues to be an area of great interest. This is particularly true when a solid drug is delivered in tablets or capsules, but also relevant to other dosage forms such as suspensions and powders.

Solubility and Permeability
These characteristics dictate bioavailability and thus dosage form efficacy. The Biopharmaceutical Classification System (BCS) classifies compounds on the basis of solubility and membrane permeability, and guides formulation development.

A first step in any strategy is to obtain a pH solubility profile. For compounds that are weakly acidic or weakly basic, these results establish the relationship between charge state and pH; the ionization constant (pKₐ) gives a basis for understanding solubility and membrane permeability.

Stability
Besides solubility, physical and chemical stability of solid drug forms must be adequately characterized. To accomplish this, solids are subjected to stresses (heat, humidity, light) and analyzed. Chemical stability evaluates susceptibility to oxidation, reduction, hydrolysis, decomposition, photochemical reactions, and thermal rearrangements, and is investigated in solution as well as in solid-state. With respect to the latter, physical stability knowledge is equally important. Some common physical forms of solid drugs are summarized below.

Polymorphs
Many compounds can exist in multiple crystal forms, i.e., chemically identical but physically distinct. The existence of drug polymorphs has important implications for patent claims; it can also impact formulation strategies and bioavailability.

Early polymorph screening involves recrystallization of the drug from a variety of solvents under different conditions. It is generally desirable to identify and develop the most stable polymorph, bypassing forms that may be more soluble but metastable. This goal is not always possible, resulting in eventual complications. An extreme example is the drug ritonavir, where late stage appearance of a new, more stable polymorph compromised product performance.

Hydrates/Solvates
In addition to polymorphs, solvated or hydrated drug crystal forms can exist, sometimes referred to as pseudopolymorphs. In “channel” hydrates such as the antibiotic cephalaxin, solvent or water molecules can comprise an integral part of the crystal structure, which is prone to collapse when the stabilizing solvent molecules are removed.

While API solvates and hydrates are generally prepared by recrystallization, they may also occur during formulation, e.g., a stable hydrate can result from wet granulation of an anhydrous drug.

Stability
Understanding and preventing crystallization of amorphous solid formulations (e.g., through use of crystallization inhibitors) is key to their successful development. Detection and quantification of crystalline content in an amorphous matrix requires appropriate methods; XRD is a common technique, along with spectroscopic methods (FTIR, NIR, Raman, solid-state NMR), isothermal microcalorimetry, and dynamic vapor sorption.

The glass transition temperature (Tg) which can be measured by DSC, signifies conversion of amorphous or semi-crystalline material to a glassy state and is often used to predict amorphous form stability. In general, the Tg value of amorphous material should be as high as possible to maintain adequate physical stability. Tg decreases significantly in the presence of moisture, leading to crystallization.

Formulation Considerations
During manufacture, a solid drug is exposed to multiple processes on its way to a finished product. In the case of a tablet, the drug is in combination with a variety of excipients; drug-excipient incompatibility can com-
promise physical and chemical stability of the API. Rational choice of excipients for solid dosage formulation is critical, and is supported through compatibility experiments conducted during preformulation. Other characteristics of the solid drug (such as moisture content) may influence formulation behavior, particularly in tabletting processes such as compression or granulation. These can lead to physical defects and dissolution problems, culminating in product failure.

There is considerable interest in combination tablets as a way to overcome the incompatibility between certain drugs. As an example, atorvastatin is acid labile while aspirin undergoes alkaline hydrolysis. A bilayer tablet limits contact between the two actives, preventing degradation and allowing treatment of multiple therapeutic indications with one dosage form. Coating of one or both actives affords additional protection from degradation. Granulation and compression steps may also require adjustment to preserve stability of both APIs, e.g., reducing mechanical shear during the latter process.

Finally, properties of the solid drug can influence how it is packaged and stored (i.e., desiccant to prevent moisture uptake or amber glass containers to minimize light exposure). Sensitivity of the API to high temperature, high humidity, light, and other potentially harmful conditions must be controlled to maintain product integrity, particularly during transport.

Case Studies

Selected case studies are presented as examples of solid drug characterization. These studies also highlight a few of the techniques available for sample analysis.

1) Solubility Enhancement (Amorphous)

Drug substance: a poorly soluble crystalline drug was converted to the amorphous form by spray drying. Conversion was confirmed by polarized light optical microscopy and XRD; Figure 1 illustrates the visual difference between crystalline starting material and amorphous product where the crystalline material (a) shows typical birefringence, or double refraction, which is not present in the amorphous material (b). As measured by DSC, the T of the dry product was above 200 °C, indicating this amorphous material was very stable in the absence of moisture. The amorphous form also demonstrated significant enhancement of solubility and intrinsic dissolution rate compared to the crystalline form.

Drug product: An amorphous drug product was deliberately produced by injection molding, resulting in a solid dispersion. In these systems, an excipient carrier stabilizes the amorphous drug within the formulation matrix, helping to retard crystallization. Such interactions frequently involve hydrogen bonding between the drug and excipient, which were readily confirmed by characteristic spectral shifts in the Raman spectrum.

2) Solubility Enhancement (Conversion to Salt)

Insoluble material isolated from API salt solution: API salt screening led to selection of a phosphate salt. This salt demonstrated good water solubility, but on occasion haziness was observed when the drug substance powder was reconstituted in aqueous solution. Isolation of the precipitate revealed that it was the much less soluble base form of the drug; this was evident from comparing the respective FTIR spectra (Figure 2). DSC also provided evidence that the precipitate corresponded to the base form. Clearly the amount of base in the API salt batches required strict control to avoid solution precipitation. Fortunately, techniques such as FTIR, Raman, DSC, and XRD were available to monitor the presence of the undesirable solid form.

Conclusion

Properties of solid drugs impact on all stages of drug development, from synthesis to production of clinical supplies. Appropriate analytical methods are needed not only to generate information during form screening, but also for troubleshooting unexpected problems with solid drug substance and product.

References

1. Particle Sciences Technical Brief 2011 Volume 9, Biopharmaceutical Classification System and Formulation Development.
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