ARTICLE

Screening for Amorphous Drug Substance

The term *amorphous* is used loosely in the pharmaceutical industry. A strict definition would limit amorphous to those materials which truly have no long range order, only the short range order characteristic of liquids. However, the term is popularly used to encompass other materials, such as disordered crystalline and microcrystalline solids. In this application note, *amorphous* is used in the popular way. A thoughtful analysis of terminology will be the subject of a future application note.

In recent years several amorphous active pharmaceutical ingredients (APIs) have been marketed as drug products. Examples include Accolate® (zafirlukast), Ceftin® (cefuroxime axetil), and Accupril® (quinapril hydrochloride). Lilly's Humulin L® contains both amorphous and crystalline insulin to provide immediate and long-term effects. An amorphous material can be substantially more soluble than the corresponding crystalline material, as much as 1600 times more soluble, according to a recent publication.[1] In some cases, this increased solubility leads to bioavailability advantages. Because of these potential benefits, solid form screening should encompass a search for both crystalline and amorphous forms.

This application note suggests a strategy for finding the best amorphous form early in drug development, using small amounts of material, with the overall goal of reducing time to market. There are three main steps involved in the strategy. The first step is assessment of the API solubility. If there is a possibility of improved solubility, the second step is screening for amorphous forms. The third step is determination of the stability of amorphous forms. A flow chart to guide development of amorphous API was published in 1995.[2]

Multiple Non-Crystalline Phases

The ability of materials to exist in more than one non-crystalline form is well known.[3] Non-crystalline forms do not exhibit the typical x-ray powder diffraction (XRPD) produced by crystalline materials with long-range three-dimensional order. Exceptions to this are the so-called microcrystalline or nanocrystalline solids, which have crystalline domains too small to produce characteristic x-ray diffraction and which exhibit physical properties different from the crystalline phase. The term amorphous generally refers to non-crystalline solids that have the thermodynamic properties of liquids in the form of either super-cooled liquids or glasses.[2] These are by far the most common non-crystalline solid forms found for organic solids. It is important to recognize that, depending on the method of preparation and the subsequent history of the sample, it is possible to obtain amorphous materials with different thermodynamic and/or kinetic properties.[4] It is also possible to prepare non-crystalline solids which fall into the category of crystal mesophases, such as liquid crystals, having structural and dynamic properties that are distinct from crystalline and amorphous phases.[4] Since these are intermediate in behavior to crystalline and amorphous forms, they can exhibit unique and unexpected properties.[4]

For any API, multiple metastable, non-crystalline forms also are possible. One compound under study at Curia exists in many non-crystalline forms, all of which are producible at will under ambient conditions and exhibit no sharp reflections in their XRPD patterns. These forms differ in their XRPD patterns, glass transition temperatures, and vibrational spectroscopic behavior. It is likely, therefore, that such materials will exhibit different solubility and stability properties as well.

Clearly the term amorphous is insufficient to describe the various molecular arrangements possible in materials that do not exhibit sharp XRPD reflections. It is important in screening studies to be aware of the possibility that different non-crystalline forms may be found, and, if that happens, to consider evaluation of each in the search for an API with the most desirable properties.

The Amorphous Solubility Advantage

Whether an amorphous API will offer a practical advantage based on solubility is dependent on the aqueous solubility of the compound and the relative free energies of the solid forms. If the aqueous solubility of a crystalline form is less than about 1 mg/mL, there is a chance that an amorphous form will afford increased bioavailability; if the crystalline form is soluble at less than 1 µg/mL, the amorphous form has a high probability of providing an advantage. On the other hand, an amorphous form has little likelihood of improving bioavailability if the crystalline form exists in a stable high free energy or poorly ordered crystalline state.

There are advantages to using an amorphous API for toxicological studies, even if the final form used in the product turns out to be crystalline. Higher blood levels are expected from an amorphous compound. Therefore, toxicological data obtained using an amorphous compound represent the “worst-case” scenario and should be predictive of clinical toxicity independent of the solid form selected for the drug product.

Screening for Amorphous Materials

The goal of a micro amorphous screen is to prepare amorphous forms on the micro scale using a variety of methods. Methods used at Curia include flash evaporation, lyophilization, and quench cooling of the melt. Such procedures are performed at scales that provide about 0.1 to 5 mg of each sample. If larger amounts of material are available, grinding experiments at ambient or liquid nitrogen temperatures are carried out. Samples are analyzed by x-ray powder diffraction (XRPD), followed by other techniques as needed. Estimation of the solubility and stability of amorphous material prepared in the screen can also be accomplished using the small, initially formed samples.

Curia uses several technologies for carrying out microscale reactions. One is Curia’s patented capillary crystallization technology, which provides very high supersaturation levels through simple evaporation experiments, establishing conditions conducive to the formation of solid forms ranging from the most stable to higher free energy solids to very unstable forms.[5] Amorphous materials are not as thermodynamically stable as their crystalline counterparts, and thus are commonly found using the capillary method. Samples generated in capillaries can be analyzed in situ by XRPD, optical microscopy, Raman spectroscopy, and differential scanning calorimetry. The small amount of sample necessary for generation and analysis of a solid in a capillary (0.05 to 1 mg) makes this technology ideal for micro screening.

Solid Form Stability

Because of the lower thermodynamic stability of an amorphous compound relative to its crystalline counterpart, there is always impetus for the amorphous material to crystallize. Whether this is a practical problem or not depends on the rate of crystallization. Sometimes transformations in the solid occur very slowly or not at all, an example being conversion of diamond to graphite. While graphite is more thermodynamically stable under ambient conditions, the transformation from diamond to graphite does not occur even over geologic time periods. On the other hand, such transformations can be very fast. An example is conversion of nabumetone form II to form I, which occurs in seconds after mechanical disturbance of a form II sample.[5] If an amorphous solid is formulated in contact with something in which it is soluble, such as in a transdermal patch or other suspension, a low energy pathway (dissolution/recrystallization) is available for crystallization.

The physical stability of an amorphous API must be investigated during development. Properties of the material such as the glass transition temperature and the effect of absorbed water on molecular mobility need to be determined.[6] Simple measurements can be used to predict the stability of an amorphous compound. If crystallization is expected under processing, storage, or use conditions, then stabilization is indicated.

Molecular dispersions of amorphous APIs and excipients are frequently used to stabilize the APIs. For example, co-precipitation of indomethacin and polyvinylpyrrolidone (PVP) not only is an effective method of generating amorphous indomethacin, but provides a dispersion in which the rate of indomethacin crystallization is greatly reduced.[7] Curia can apply microscale techniques to screen for stable molecular dispersions.

Scale-Up

Preparation of amorphous forms or amorphous mixtures at large scale can be complex and difficult. Our scientists use techniques including precipitation from solution, lyophilization, spray drying, and melt extrusion. Significant reduction in development time can be achieved by an early understanding of the fundamental nature of the materials involved and knowledge of the preferred analytical methodologies for monitoring the process. Early, small-scale preparations using methods amenable to scale-up are an important part of the solid form selection process.

Reducing Time to Market

The strategy outlined above can be timed to coincide with toxicological and clinical trials. Micro screening for amorphous forms and determination of stability should be performed as soon as a solubility problem is recognized. In this way, information needed for the next step in the development process can be gathered during toxicological and clinical trials. The extent and type of information gathered can be tailored to fit the development processes of different companies. This strategy keeps development studies off the critical path and helps reduce time to market.

Importance of cGMP

Observance of cGMP has always been a major issue in pharmaceutical development and its importance continues to increase. Development reports, which are now required in New Drug Applications, must document how the development process was carried out and the basis for the decisions that were made. Decisions based on data from calibrated equipment and properly documented research will be likely to have desirable regulatory consequences. The importance of conducting studies bearing on specifications under cGMP conditions is clear.

References

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