ARTICLE

Amorphous Solids: Implications for Solubility and Stability

Amorphous Solids in Pharmaceutical Development

Typically, new drug candidates enter the pharmaceutical development process in a crystalline state. This tends to ensure a high level of purity and stability, particularly if the crystal is in its most thermodynamically stable form. By introducing thermal and mechanical energy, processing can lead to full or partial loss of crystallinity and the formation of amorphous or disordered crystalline material. Whereas crystals exhibit long-range molecular order, molecules in the amorphous state have no long-range order but retain the short-range order typical of liquids.

In pharmaceutical development, we encounter amorphous and disordered crystalline materials in a number of ways. Many polymers and other excipients intrinsically exist in these forms, e.g., PVP, microcrystalline cellulose, and magnesium stearate. Lyophilized or spray-dried mixtures of proteins with various cryoprotectants and lyoprotectants are purposefully prepared in amorphous forms to physically stabilize biopharmaceutical products, while many hydrophobic drugs are made amorphous by co-precipitation or co-melting from mixtures with polymeric excipients to enhance their aqueous dissolution rates and, hence, oral bioavailability. Very often, upon crystallization a material is not completely crystalline. Moreover, crystalline drugs may be inadvertently rendered disordered or partially amorphous through processing such as milling, compaction, drying, granulation, and polymer film coating.

From a pharmaceutical perspective, whenever amorphous material is present there must be significant concern since, relative to the crystalline state, the amorphous state is less thermodynamically stable. Consequently, molecules in the amorphous state generally exhibit greater chemical instability, enhanced dissolution rates, altered mechanical properties, and greater hygroscopicity. When these properties are not anticipated, prevented, or controlled, they can lead to great difficulty on processing, storage, and use of of pharmaceutical products. Also, since the amorphous state is metastable relative to the crystalline state, there is always the potential for unexpected crystallization during storage, leading to macroscopic changes in specific surface area, flow, and concretion. Such observations led to the hypothesis that most solid-state instabilities of pharmaceutical interest preferentially occur in the disordered noncrystalline regions of the solid. (C. Ahlneck and G. Zografi “The Molecular Basis for Moisture Effects on the Physical and Chemical Stability of Drugs in the Solid-State,” Int. J. Pharm. 1990, 62, 87-95.) A basic understanding of the principles underlying molecular properties in the amorphous state is essential for those involved in stability studies, any type of bulk drug manufacturing, suspension characterization, or solid dosage design, evaluation, and manufacture.

Amorphous Characteristics

The key to understanding the properties of the amorphous state is recognition that molecules in this state can exhibit significant molecular motion over timescales of pharmaceutical interest both above and below the glass transition temperature (Tg). The glass transition temperature is where an amorphous substance changes from a super-cooled liquid with relatively low viscosity to an unstable glass with much greater viscosity. Motion in the form of translational and rotational diffusion, which is essential for any physical or chemical process, can generally be described in terms of temperature, viscosity, and molecular size. It can occur in seconds at and above Tg to months or years below Tg.

In some cases amorphous materials can be produced by mixing solids so that molecular dispersions result. The dispersions will have properties distinct from those of the individual components. Molecular dispersions are important in pharmaceutical situations such as: stability in sugar-protein lyophilized and spray-dried products; dissolution of orally administered drug-polymer dispersions; crystallization in transdermal patches; mechanical characteristics of plasticizer-polymer film

coating systems; and process-induced drug-excipient interactions.

In dealing with the properties of amorphous pharmaceutical solids, the presence of residual water must be considered. Water can exist in an amorphous state with a Tg of about -138 ºC (135K). A molecular dispersion made from water and an amorphous solid would be expected to exhibit a Tg which is greatly reduced relative to that of the pure dry solid. The effect on Tg can be critically important for a solid that has been rendered only partially amorphous. In such cases most of the water will be located in the disordered region, the actual percent of water in the disordered region will be considerably higher, and the Tg in that region will be considerably lower.

Evaluation of the Amorphous State

It is important to have both a clear, science-based understanding of how the amorphous active drug is formed and also a comprehensive characterization of its fundamental properties, such as Tg, water vapor sorption, and relaxation time as a function of temperature and relative humidity. These properties must be specifically assessed with respect to pertinent excipient systems in amorphous molecular dispersions containing a drug. To use the amorphous state to enhance dissolution rates or otherwise improve dosage form characteristics, methodologies must be developed to stabilize the system against physical and chemical transformations. Alternatively, if it is suspected that amorphous structure can be inadvertently introduced into a solid system, approaches must be developed to prevent such introduction or to anneal the sample to its original crystalline form without altering product performance. Such investigations are also helpful in assessing whether or not one can use polymer-drug molecular dispersions to enhance dissolution of poorly soluble drugs.

If a physical or chemical transformation is diffusion-rate limited and hence dependent on molecular mobility of the involved molecules, there should be some quantitative correlation of the overall rate constant, k, and the viscosity or relaxation time, t. Thus the dependence of t on temperature (fragility) can be used to indicate how the reaction rate might also change with temperature, if the rate is molecular mobility-dependent. Measurement of molecular mobility directly below Tg through techniques such as enthalpy relaxation, NMR, or DEA will determine what storage conditions will be required to maintain shelf-life stability below Tg.

Specifically, using only DSC, it is possible to estimate molecular mobility by measuring heat capacity or the scanning rate dependence of Tg. Solid-state NMR can be used to obtain a more complete understanding of mobility.

It is very likely that most solid-state instabilities of pharmaceutical interest and timescale occur in the process-induced disordered regions of a solid, because of the enhanced molecular mobility in these regions relative to that in the crystalline state. Therefore, attempts to characterize the amorphous state of a particular solid through measurement of relaxation times, fragility, and other amorphous characteristics can provide a basis for predicting the timescale for unacceptable solid-state degradation or crystallization as a function of temperature and relative humidity.

A good approach to understanding the amorphous state and predicting its stability involves:

- Complete characterization of the crystalline drug substance
- Complete characterization of the amorphous drug substance
- Preparation of stabilized amorphous systems and verification that they do not crystallize

If instabilities are introduced by processing, it should be determined if these instabilities are caused by amorphous or disordered crystalline material. Once this is determined, processing steps that introduce disorder can be eliminated or modified to achieve a more stable product. New approaches to avoid processing altogether are also considered; for example, avoiding milling by crystallizing the correct particle size.

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