AMORPHOUS PHARMACEUTICAL SOLIDS

Edina Vrani}*
Department of Pharmaceutical Technology, University of Sarajevo, Faculty of Pharmacy, Bosnia and Herzegovina
*Corresponding author

Abstract

Amorphous forms are, by definition, non-crystalline materials which possess no long-range order. Their structure can be thought of as being similar to that of a frozen liquid with the thermal fluctuations present in a liquid frozen out, leaving only "static" structural disorder.
The amorphous solids have always been an essential part of pharmaceutical research, but the current interest has been raised by two developments: a growing attention to pharmaceutical solids in general, especially polymorphs and solvates and a revived interest in the science of glasses and the glass transition.
Amorphous substances may be formed both intentionally and unintentionally during normal pharmaceutical manufacturing operations. The properties of amorphous materials can be exploited to improve the performance of pharmaceutical dosage forms, but these properties can also give rise to unwanted effects that need to be understood and managed in order for the systems to perform as required.

Key words: amorphous solids, preparation, characterization, stabilization

Introduction

Amorphous forms are, by definition, non-crystalline materials which possess no long-range order. Their structure can be thought of as being similar to that of a frozen liquid with the thermal fluctuations present in a liquid frozen out, leaving only "static" structural disorder (1). The degree of crystallinity, according to the USP, depends on the fraction of crystalline material in the mixture, which is termed the two-state model. Another way of viewing this situation is that the crystallinity has a range from 100 percent for perfect crystals (zero entropy) to 0 percent (non-crystalline or amorphous); this is known as the onestate model (2). Amorphous solids exist in many industrially important products, such as polymers, ceramics, metals, optical materials (glasses and fibers), foods, and pharmaceuticals. The amorphous solids have always been an essential part of pharmaceutical research, but the current interest (3,4,5) has been raised by two developments:

- a growing attention to pharmaceutical solids in general, especially polymorphs and solvates (6,7) and
- a revived interest in the science of glasses and the glass transition (8,9)

Studies of crystalline and amorphous solids are often so intertwined that it is natural to treat the two solids as "polymorphs" of each other. This view is harmonious with one definition of polymorphism (any solids that share the same liquid state) (10), and with the "energy landscape"' model of solids (11), which regards crystalline and amorphous states as connected minima on a multi-dimensional potential energy surface corresponding to different molecular packing and conformations.

Preparation of amorphous solids

The preparation of amorphous solids, for thermodynamic and kinetic reasons, is easy for some materials (good glass formers), but difficult for others (poor glass formers). Thermodynamically, glass forming ability originates from a crystalline state that is not substantially more stable than the amorphous state, which may be the case for molecules that pack poorly or contain many internal degrees of freedom. Kinetically, a slow crystallization rate allows a material to become a "frozen liquid" or vitrify without crystallization.
One general cause for reduced crystallization tendency among organics is conformational flexibility (12). Since conformationally flexible molecules can exist in a crystallizing medium as multiple conformers, the process of crystallization must select the "right"' ones from among the "wrong" ones, a difficulty not encountered by rigid molecules. The effect is amplified if the conformers in crystals correspond to high-energy and low-concentration conformers in solution, which implies that the act of crystallization requires the average molecule to undergo a significant conformational change. The effect is believed to underlie the different crystallization tendencies of two stereoisomers, for example, mannitol (easy) and sorbitol (difficult) (13,14).
In addition to conformational equilibria, configurational equilibria (that between carbohydrate anomers) should have similar effect on the tendency of crystallization. The effects of these equilibria on the glass-forming ability have not been well studied.
Poor glass formers can be made amorphous by deliberately preventing crystallization. The routes to the amorphous state include molecular quenching of melts, rapid precipitation by antisolvent addition, freeze-drying (15), spray-drying (16,17) and introduction of impurities (18). The impurity effect may cause a poor glass former to exist in the amorphous state in a multi-component formulation. Also, amorphous solids can result from solid-dispersion, a process used to enhance bioavailability, and solid-state

chemical reactions (degradation) of crystalline precursors. Process conditions can influence the amount of amorphous materials in the end product. In a freeze drying process, rapid freezing favours the formation of an amorphous solute, whereas introducing an annealing step may promote crystallization (15).
Processes that introduce mechanical or chemical stress (grinding, milling, and wet granulation) can render crystalline materials fully or partially amorphous. The concern over crystalline-to-amorphous conversion and the ensuing effects is amplified by the relative insensitivity of common techniques to small crystallinity changes (several %), but a generally strong dependence of the physicochemical stability of a product on the presence of amorphous materials.

Properties of amorphous solids

Amorphous solids exhibit properties unique to their disordered state relative to their crystalline counterparts such as:

- the apparent aqueous solubility of amorphous materials is much higher than that of their crystalline counterparts. This is a kinetic phenomenon and, eventually, the solute in the supersaturated solution that is formed will begin to crystallize and the equilibrium solubility of the crystalline phase will be attained. The transient increase in solubility is often significant (>10x) and can be exploited to give markedly improved biopharmaceutical performance (19).

- the mechanical properties of amorphous materials are noticeably different from their crystalline counterparts because of the different number and type of intermolecular interactions (20). It is found (21) that at temperatures more than 50 K below Tg, an amorphous drug powder formed compacts that were significantly more brittle than those formed from the crystalline form of the drug; the tensile strengths of the compacts were similar.

- amorphous materials have enhanced water uptake, so they will absorb significant amounts of water vapor from their surroundings relative to their crystalline counterparts (22).

Characterization of amorphous solids

The strategy for characterizing amorphous solids differs from that for crystalline solids. Molecular level structural elucidation, as is feasible for crystalline solis by diffraction and spectroscopic methods, is less applicable to amorphous solids, and greater emphasis is placed on structural mobility and changes. It is customary to characterize an amorphous material both below and above the glass transition temperature (both as the frozen solid and as the supercooled viscous liquid). The physical characterization of amorphous solids utilizes a wide range of techniques and offers several types of information:

a) Structure Amorphous solids are not random at the molecular level, but may possess short-range order, residual crystallinity, polymorphic states, and regions of different density. The structure of an amorphous solid is usually described as possessing crystal-like short-range molecular arrangement, but lacking long-range order. Also, the immediate environment of a molecule in an amorphous solid may not be significantly different from that in a crystal (similar number of and distance to the nearest neighbors), but an amorphous solid lacks any long-range translational-orientational symmetry that characterizes a crystal.
b) Thermodynamics. Amorphous solids have higher energy, entropy and free energy than the corresponding crystals. The excess properties are parameters in some theoretical models of crystallzation and structural relaxation.
c) Changes. Amorphous solids can crystallize or undergo structural relaxation owing to the instability with respect to the corresponding crystals and "equilibrium" glasses.

Structure

Amorphous solids may co-exist with and have the potential to convert to crystalline solids. Techniques for determining the degree of crystallinity include XRD, DSC (23), solution calorimetry (24), water sorption (4), isothermal calorimetry (25), and thermally stimulated current (TSC) (26). Amorphous materials will not diffract X-rays in a coherent manner; thus powder X-ray diffraction patterns are broad halos with no or very few characteristic peaks for these materials. (27).
Dielectric studies of secondary relaxation in amorphous solids advanced the view that a glass may have different regions: the glass transition (primary relaxation) involves cooperative motions in high-density regions, whereas secondary relaxation involves low-density regions lying between high- density regions.
Data from a TSC study have been interpreted as indicating the existence two amorphous regions (true and "rigid") in a drug sample (28).

Thermodynamics

Thermodynamic properties of an amorphous solid are often presented as excess properties relative to the crystalline state. Excess enthalpy, entropy and free energy can be obtained from heat capacities of the crystalline and amorphous phases as a function of temperature. Excess enthalpy also can be obtained from heats of solution (by solution calorimetry) or crystallization (by scanning or isothermal calorimetry). In principle, excess free energy

can be calculated from the solubility of crystalline and amorphous phases, provided that the equilibrium solubility of the amorphous solid can be measured without crystallization.

Changes

When analyzed using common thermal analytical methods (differential scanning calorimetry-DSC), amorphous materials will exhibit an apparent second-order phase transition (the so-called "glass transition temperature", or Tg) in a temperature range that is significantly below the melting point of the crystalline material. The Tg of an amorphous material is one of its characteristic properties and can be used to assess its likely stability and suitability for use in pharmaceutical dosage forms (4).
If crystallization is avoided, many liquids of pharmaceutical relevance vitrify at the glass temperature, Tg, approximately 2/3 to 4/5 of the crystalline melting point Tm. So, Tg is a useful material descriptor owing to its correlation with structural and thermodynamic properties. If a more stable crystalline state exists, an amorphous material can crystallize when sufficient molecular mobility exists. Pharmaceutically important examples include crystallization in freeze- and spray- drying, from supercooled melts, and from amorphous materials during storage, especially on exposure to heat and humidity. Of interest in this context are factors affecting the rate of crystallization (, temperature and plasticizers), means to promote or prevent crystallization, and the characteristics of crystals produced under conditions unfavorable for growing "high quality" crystals (the high-concentration and high-viscosity media encountered in freeze-or spray-drying).

Stabilization of amorphous solids

The aim of stabilization of amorphous solids is multifaceted, including:

- the stabilization of labile biomolecules (proteins and peptides) through additives,
- the prevention of crystallization of excipients that must remain amorphous for their intended functions,
- the specification of appropriate storage temperatures to achieve acceptable shelf life, and
- the prevention of chemical degradation and microbial growth through anti-oxidant, pH buffer, preservatives (29).

The chemical and physical stability of amorphous pharmaceutical materials is controlled by the same basic factors as for crystalline materials (molecular structure, purity, molecular orientation and molecular mobility). For any sample of a given molecular structure and purity, there will be more possible molecular orientations that occur in an amorphous sample than in, crystalline sample. Thus many more different types of chemical and physical transformations could potentially take place. At a given temperature, the molecular mobility in an amorphous material will also be significantly higher than in any of the corresponding crystalline forms, and this can give rise to a greater chemical and physical reactivity in the amorphous sample.
However it is important to realize that a very close interdependence (or "coupling") between the mechanism of the chemical or physical instability of interest (, charge transfer free radical attack) and the molecular orientation and/or mobility of the sample is necessary for an amorphous sample to be significantly less stable than its crystalline counterpart (30).
In many instances (free radical initiated oxidation reactions), the stability of a drug compound is not significantly affected by either its molecular mobility or the orientation of the molecules; thus the amorphous form has comparable stability to the crystalline material. In some cases (insulin), the more ordered structure of the crystalline material can actually increase the likelihood of certain intermolecular contacts and cause the crystalline form to have a lower level of stability.
So, the main factors, which are necessary to keep in mind during the earliest stages of drug development are:

- physical transformations (solid-state crystallization) are more often directly linked to molecular mobility and orientation than the most common chemical reactions (oxidation and hydrolysis); thus the major stability concern for amorphous materials is with their tendency to revert to the crystalline state. As with all crystallization processes, there are the normal nucleation and propagation (crystal growth) stages to consider, and procedures that increase the barrier to nucleation or slow the rate of crystal growth can be used to physically stabilize many amorphous materials.
- the greater purity of most crystalline materials, which can contribute significantly to their enhanced stability.

- the tendency for amorphous materials to sorb significant amounts of water vapor from their surroundings can give rise to a markedly reduced chemical and physical stability relative to the crystalline form of the material. The sorbed water may participate in a chemical reaction (hydrolysis), or may simply act as a catalyst for a chemical reaction.

- sorbed solvents such as water will also plasticize most amorphous pharmaceutical materials (31), and this can have a negative impact on both physical and chemical stability by increasing the molecular mobility of the sample at any given temperature.

Conclusion

Amorphous substances are an important class of pharmaceutical materials that exhibit distinct physical and chemical properties. They are ubiquitous, and may be formed both intentionally and unintentionally during normal pharmaceutical manufacturing operations. The properties of amorphous materials can be exploited to improve the performance (bioavailability and dissolution rate) of pharmaceutical dosage forms, but these properties can also give rise to unwanted effects (physical instability) that need to be understood and managed in order for the systems to perform as required.

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