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General Commentary

Interrelationships Between Structure and the Properties of Amorphous Solids of Pharmaceutical Interest

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ABSTRACT

This commentary explores fundamental issues associated with the structure of amorphous solids of pharmaceutical interest in terms of the effects of such structure on: various thermodynamic properties; the glass transition temperature, T_g , physical aging of glasses, polyamorphism; molecular mobility by primary diffusive and secondary Johari-Goldstein relaxations; solid-state crystallization; water vapor absorption; and the formation of active pharmaceutical ingredients—polymer dispersions. Recognizing that small organic molecules, as well as polymers used pharmaceutically, tend to exhibit highly “fragile” behavior in the supercooled liquid state, that is, significant increases in relaxation time or viscosity with decreasing temperature as T_g is approached, particular emphasis has been placed on local and global structural factors, that appear to give rise to the nonexponential dependence of the structural relaxation time and viscosity associated with spatial and temporal heterogeneity, at temperatures below the “crossover temperature,” T_x , (1.2 – $1.4 T_g$), using theoretical random close packing and “jamming” models. Utilizing a “2-region” structural model of the glassy state, wherein glasses consist of clustered domains surrounded by a higher energy and less dense “microstructure,” it has been possible to better understand the underlying structural factors that give rise to a number of important phenomena which occur in the glassy state.

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Introduction

In recent years, there has been a significant interest in the amorphous solid-state properties of active pharmaceutical ingredients (API) and excipients. Reasons for this interest include: (1) some APIs and excipients cannot be crystallized or maintained in a stable and useful crystalline form under practical conditions of handling, storage, and use¹; (2) inadvertent formation of amorphous regions in crystalline solids often occurs during pharmaceutical processing, for example, milling and drying²; (3) intentional formation of amorphous solids as miscible API-polymer dispersions can be used to overcome poor crystalline API dissolution and oral bioavailability in solid dosage forms by providing high levels of supersaturation in solution after oral administration³; and (4) formulations of lyophilized and spray-dried proteins are prepared and stabilized as reconstitutable injectable or powder inhalation products by forming protein-disaccharide amorphous dispersions.⁴ Key to the use of amorphous forms of API and

excipients, or for dealing with inadvertent process-induced formation of amorphous structure in crystals, is the need to understand the underlying principles that give rise to differences in the thermodynamic and kinetic properties of amorphous solids and their corresponding crystalline state. Such understanding is critical for determining and controlling the therapeutic functionality and stability of amorphous systems. Although much research with pharmaceutical systems has been directed at determining various thermodynamic and kinetic properties of molecules in the amorphous state, little, if any analysis has dealt with their unique structural characteristics and how a knowledge of such structural features can be used to better understand the various physical chemical phenomena that impact these properties at the molecular level.

This article, therefore, seeks to explore certain issues associated with the structure of amorphous solids in the context of some important thermodynamic and kinetic properties that are generally measured in any assessment of a particular pharmaceutical amorphous system. We will first present a few well-known examples of some thermodynamic properties of amorphous systems and then discuss in more detail the nature of molecular mobility. This will be followed with an assessment of what is known about the local and

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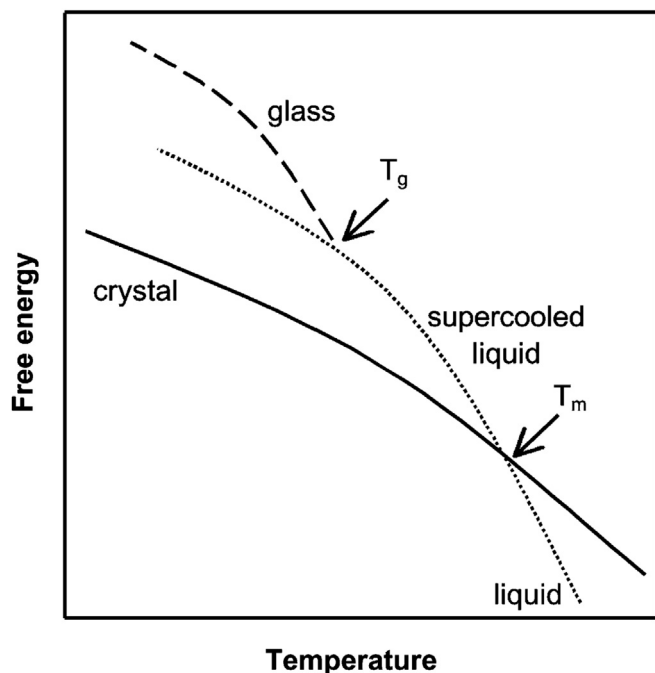


Figure 1. Free energy-temperature diagram for a single-component system. Reproduced with permission from Hancock and Shamblin.⁵

global structure of amorphous systems relative to that of the corresponding crystalline forms, with particular emphasis on highly viscous supercooled liquids and glasses. Finally, we will attempt to illustrate how knowledge of the local and global structure of amorphous solids can be used to help explain a number of phenomena of pharmaceutical interest, which often are observed and measured but, to date, often lack a definitive molecular explanation in terms of amorphous structure.

Thermodynamic Properties of Amorphous Solids

To begin to address the thermodynamic properties of amorphous solids, we can examine a schematic representation of the molar free energy of a molecule as a function of temperature, as illustrated in Figure 1.⁵ Here, as expected, we observe the lower free energy of the crystalline state at temperatures below the melting temperature, T_m , the reduction in free energy of the crystal with increasing temperature, and the lower free energy of the liquid state relative to that of the crystal above T_m . Slowly cooling the liquid at or below T_m , to allow time for nucleation and growth to occur, restores the crystalline state, whereas, rapid cooling below T_m most often prevents crystallization and leads to a supercooled liquid. As seen by the lack of a discontinuity at the melting temperature, the supercooled liquid appears to retain the equilibrium properties of the liquid until the system is cooled to T_g , the glass transition temperature, a point at which it becomes sufficiently viscous, to slow down molecular diffusion relative to the rate of cooling, causing the system to fall out of equilibrium into a glassy state. An important aspect of the change in thermodynamic properties and corresponding molecular mobility, as the temperature is decreased, is the marked loss in entropy that occurs with cooling, presumably because of an increasing domain size of a cooperatively clustered region of molecules, which rapidly reduce the number of possible conformations and, hence, the entropy that the material can assume, particularly as the temperature approaches and goes below T_g .⁶

Since the glass, below T_g , is in a nonergodic unstable state, it is very likely that the manner in which the glass is formed from the

supercooled liquid, for example, rate of cooling or when another method is used to form the glass, for example, rapid precipitation from solution, vapor deposition, or milling, can lead to different glassy structures with different thermodynamic properties, for example, molar volume, density, enthalpy, and entropy. In such situations, different values of T_g will occur, typically a 3-5 K difference for a one-order of magnitude change in cooling rate.⁷ It is often convenient to express the thermodynamic energy levels of the various possible glassy states in terms of a potential energy landscape, as illustrated in Figure 2, whereby the molecule in the glassy state has a number of relatively shallow local energy minima into which it can settle with the potential over time, or under certain processing conditions, to overcome the energy barriers and move from higher to lower energy levels, thus explaining the different properties that can be exhibited due to the manner of forming the glass.⁸ It is also important to recognize that molecules in the glassy state are thermodynamically unstable relative to the supercooled liquid with the potential, when held not too far below T_g , to transform into increasingly more highly dense and lower energy glassy states as a function of time, approaching the properties that the corresponding supercooled state would have at that temperature.

The process whereby molecules in the glassy state spontaneously undergo such transformations is generally referred to as “physical aging” or some form of “annealing” that produces glasses with more negative enthalpy and entropy and greater density (less free volume).⁹ Such behavior can be experimentally observed using differential scanning calorimetry (DSC) to heat the system above T_g , rapidly cooling it below T_g to a particular temperature, T , and then holding the temperature constant over various periods. The decrease in enthalpy that occurs during the aging process is then recovered as the sample is reheated to above T_g to produce a distinct DSC endotherm just below T_g . As shown in Figure 3, the area of this endotherm reflects the extent to which recovery has occurred at a particular temperature and time after the initial formation of the glass; the greater the extent of recovery reflects a greater extent of annealing and higher density in the initial sample.¹⁰ Importantly, a number of studies have shown distinct differences in such enthalpy relaxation profiles for glasses produced by, for example, a slow melt quench at room temperature as opposed to a rapid quench in liquid nitrogen¹¹ and for glasses made by slow vapor deposition as opposed to those prepared by a melt quench.¹² In both cases, the slower process of glass formation produced distinctly greater enthalpy recovery, reflecting greater initial density in those samples. The slower condensation of the

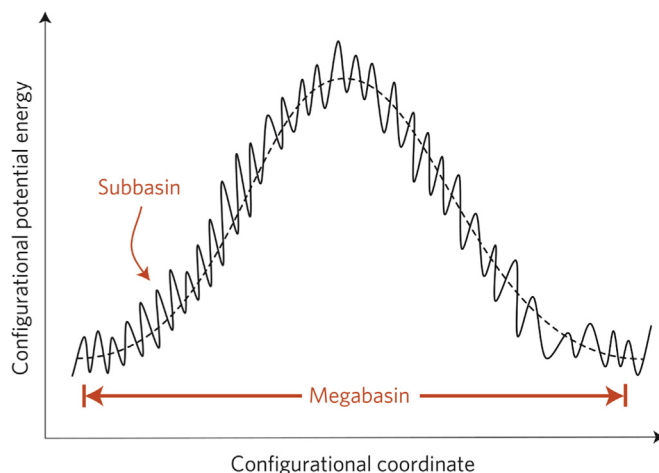


Figure 2. Schematic illustration of a typical potential energy landscape indicating various possible energy states in a glass. Reproduced with permission from Ye et al.⁸

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