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Amorphous pharmaceutical solids: preparation, characterization and stabilization

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Abstract

The importance of amorphous pharmaceutical solids lies in their useful properties, common occurrence, and physico-chemical instability relative to corresponding crystals. Some pharmaceuticals and excipients have a tendency to exist as amorphous solids, while others require deliberate prevention of crystallization to enter and remain in the amorphous state. Amorphous solids can be produced by common pharmaceutical processes, including melt quenching, freeze- and spray-drying, milling, wet granulation, and drying of solvated crystals. The characterization of amorphous solids reveals their structures, thermodynamic properties, and changes (crystallization and structural relaxation) in single- and multi-component systems. Current research in the stabilization of amorphous solids focuses on: (i) the stabilization of labile substances (e.g., proteins and peptides) during processing and storage using additives, (ii) the prevention of crystallization of the excipients that must remain amorphous for their intended functions, and (iii) the selection of appropriate storage conditions under which amorphous solids are stable.

Keywords: Amorphous solid; Preparation of amorphous solid; Characterization of amorphous solid; Stabilization of amorphous solid

Contents

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1. Introduction

An amorphous solid (glass) can be defined with reference to a crystalline solid: similar to a crystalline solid, an amorphous solid may have short-range molecular order (i.e., in relationship to neighboring molecules); but unlike a crystalline solid, an amorphous solid has no long-range order of molecular packing or well-defined molecular conformation if the constituent molecules are conformationally flexible. Amorphous solids exist in many industrially important products, such as polymers, ceramics, metals, optical materials (glasses and fibers), foods, and pharmaceuticals. In the case of pharmaceutical materials, the importance of amorphous solids stems from:

1. Useful properties. Amorphous solids have higher solubility, higher dissolution rate, and sometimes better compression characteristics than corresponding crystals.
2. Instability. Amorphous solids are generally less stable physically and chemically than corresponding crystals.
3. Common occurrence. Amorphous solids can be produced by standard pharmaceutical processes and are the common form of certain materials (e.g., proteins, peptides, some sugars and polymers).

Although the amorphous solid has always been an essential part of pharmaceutical research, the current interest [1–3] has been elevated by two developments: (1) a growing attention to pharmaceutical solids in general, especially polymorphs and solvates [4–6] and (2) a revived interest in the science of glasses and the glass transition [7–9]. 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 (i.e., 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, conformations, etc.

Since the study of amorphous solids has a long and rich history, it is appropriate to ask how pharmaceutical systems differ from other systems (polymers, ceramics, semi-conductors, optical glasses, etc.). From a functional standpoint, the overriding issues for pharmaceutical systems are the physicochemical stability and bioavailability of the active ingredient, rather than such properties as mechanical strength and conductivity. From a structural standpoint, pharmaceutical systems often feature extensive hydrogen bonding, complex molecular geometry, and conformational flexibility. Such features make the problem of structural elucidation fundamentally different from, for example, that of inorganic glasses. The capacity to absorb water (hygroscopicity) and the ensuing consequences are of great concern to pharmaceutical systems. Furthermore, the stabilization of labile substances (e.g., proteins and peptides) is a distinctively pharmaceutical topic [12–14], with one objective being the prevention of structural damage during freezing and drying through the use of additives.

The topics discussed here — preparation, characterization, and stabilization of amorphous pharmaceutical solids — define a broad and active field, for which several excellent reviews have been published [1–3]. The aim of this review, therefore, is not to be comprehensive. In fact, topics well covered previously will be de-emphasized. Little will be said, for

example, about common experimental techniques, although the information derived from them is freely discussed. This should not be interpreted as a priority judgement and the reader should consult other reviews for relevant topics.

2. Preparation

For both thermodynamic and kinetic reasons, the preparation of amorphous solids is straightforward for some materials (good glass formers), but difficult for others (poor glass formers). Thermodynamically, the 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 [15]. 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, mannitol (easy) and sorbitol (difficult) [16,17]. In addition to conformational equilibria, configurational equilibria (e.g., 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 (e.g., mannitol) can be made amorphous by deliberately preventing crystallization. Familiar routes to the amorphous state include quenching of melts, rapid precipitation by antisolvent addition, freeze-drying [12], spray-drying [18,19],, and introduction of impurities [20]. The impurity effect may cause a poor glass former to exist in the amorphous state in a multi-component formulation. Amorphous solids can also result from solid-dispersion [21], a process used to enhance bioavailability, and solid-state chemical reactions (e.g., degradation) of crystalline precursors.

Process conditions can influence the amount of amorphous materials in the end product. In a freeze-drying process, rapid freezing favors the formation of an amorphous solute, whereas introducing an annealing step may promote crystallization [12]. Processes that introduce mechanical or chemical stress (e.g., 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 (say, several %), but a generally strong dependence of the physicochemical stability of a product on the presence of amorphous materials. This concern has prompted the current interest in detecting amorphous solids at low levels.

Dehydration of crystalline hydrates has been demonstrated as a feasible and ''gentle'' route to the amorphous state of organic solids. Saleki-Gerhardt et al. showed that heating the crystalline raffinose pentahydrate at 60°C in vacuum converts the material to an amorphous form identical to one produced by freeze-drying [22]. Li et al. [23] observed that the crystalline carbamazepine dihydrate becomes amorphous upon dehydration at 45°C with N_2 purge. The resulting amorphous solid undergoes a glass transition at 56°C, which is significantly above the drying temperature (45°C), and crystallizes on further heating (at 86°C). These studies indicate that apart from being a potential route to amorphous solids, the drying of crystalline hydrates may reduce their physicochemical stability through the loss of crystallinity.

3. Characterization

The strategy for characterizing amorphous solids differs from that for crystalline solids. Molecular-level structural elucidation, as is feasible for crystalline solids 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 amor-

phous material both below and above the glass transition temperature, i.e., both as the frozen solid and as the supercooled viscous liquid. The physical characterization of amorphous solids utilizes a wide range of techniques (Table 1) and offers several types of information:

1. 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.
2. Thermodynamics. Amorphous solids have higher energy, entropy and free energy than the corresponding crystals. The excess properties are parameters in some theoretical models of crystallization and structural relaxation.
3. Changes. Amorphous solids can crystallize or undergo structural relaxation owing to the instability with respect to the corresponding crystals and ''equilibrium'' glasses.
4. Multi-component systems. Many pharmaceutical formulations are multi-component, with water being a ubiquitous ingredient. It is desirable to predict properties of multi-component systems from those of individual components.

3.1. Structure

The structure of an amorphous solid is usually described as possessing crystal-like short-range molecular arrangement, but lacking long-range order. As illustrated by Fig. 1, the immediate environment of a molecule (m) in an amorphous solid may not be significantly different from that in a crystal (e.g., similar number of and distance to the nearest neighbors), but an amorphous solid lacks any long-range translational-orientational symmetry that characterizes a crystal.

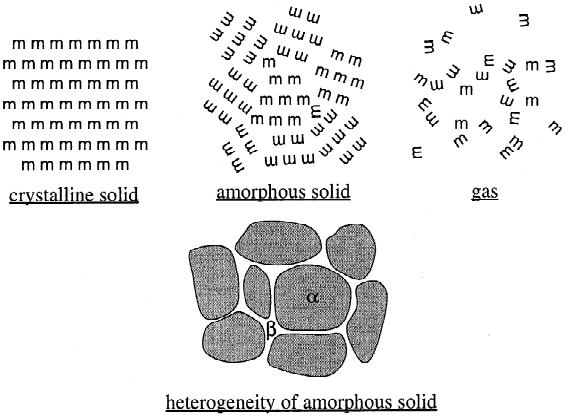

Fig. 1. Schematic representation of the structure of an amorphous solid. The molecular arrangement in an amorphous solid is not totally random, as in the gas phase, but features short-range molecular order similar to that in a crystalline solid. However, unlike crystals, an amorphous solid lacks the long-range order of molecular packing. According to some models, an amorphous solid has distinct regions (e.g., α and β) which have different densities and relaxation behaviors.

Table 1
Physical techniques for characterizing amorphous solids.[a]

Technique	Information
X-ray Diffraction (XRD)	DOC, CK
Molecular Spectroscopy	SR (e.g., Raman and NMR), microheterogeneity
Diff. Scan. Cal. (DSC)	DOC, microcrystalline or truly amorphous, CK, SR
Isothermal Calorimetry	SR, CK, DOC
Modulated DSC (MDSC)	Reversing vs. non-reversing heat flow, C_p, SR (0.1–0.01 Hz)
Solution Calorimetry	Excess enthalpy, DOC
Adiabatic Calorimetry	Excess enthalpy, entropy and free energy
Dielectric Analysis (DEA)	SR, primary vs. secondary processes
Dyn. Mech. Anal. (DMA)	SR
Viscometry	SR
Dilatometry	T_g, liquid/glass expansion coefficients
Solubility	Excess free energy
Density	Density difference from crystalline solids
Therm. Stimul. Cur. (TSC)	SR, DOC, microheterogeneity
Water Absorp. (gravimetric)	Hygroscopicity, DOC, CK

[a] Key: SR = structural relaxation (T_g, τ vs. T, fragility, etc.); DOC = degree of crystallinity; CK = crystallization kinetics.

3.1.1. Truly amorphous or microcrystalline

Grinding or milling of crystals can remove all traces of crystallinity according to XRD. Is the resulting material amorphous? Although successive micronization should eventually lead to an amorphous structure, a possibility exists that the material has achieved a *microcrystalline* state, containing crystals so small that they pass the detection of XRD. Johari et al. [24] used DSC to distinguish between amorphous and microcrystalline states based on the presence or absence of glass transition when XRD failed to do so.

3.1.2. Degree of crystallinity

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 [25], solution calorimetry [26], water sorption [2], isothermal calorimetry [27], and thermally stimulated current (TSC) [28] (Table 1). Among these, water sorption [2] and TSC [29] are reported to provide greater sensitivity to low level amorphous solids. Isothermal calorimetry carried out in a vial-in-vial configuration is a popular technique for detecting crystallization in an amorphous sample. In this configuration, a sample is sealed in a vial along with a smaller vial containing a saturated salt solution, which provides an elevated humidity to accelerate crystallization.

3.1.3. Microheterogeneity

Dielectric studies of secondary relaxation in amorphous solids [30,31] 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 (Fig. 1). Data from a recent TSC study have been interpreted as indicating the existence two amorphous regions (true and ''rigid'') in a drug sample [32].

Similarly, Tanaka [33] describes a supercooled liquid as having two competing tendencies of ordering: density ordering that leads to global crystallization and bond ordering that leads to locally favored structures whose packing and symmetry may differ from macroscopic crystals. In this model, locally favored structures are analogous to chemical impurities in that they can frustrate crystallization and influence the glass-forming ability.

3.1.4. Polyamorphism

The idea that there exist distinct amorphous phases separated by first-order phase transitions is a provocative one [34,35] It is unclear whether this phenomenon has any pharmaceutical relevance. However, the term polyamorphism has been used in a different way to describe amorphous states produced by different annealing times or preparative routes. An example is glasses that have been aged below T_g for different times and hence developed various degrees of ''relaxation enthalpy''. This should be considered an incorrect usage of the term, since these structures are related by structural relaxation (see later), not first-order transitions.

3.2. Thermodynamics

Thermodynamic properties of an amorphous solid often are presented as *excess properties* relative to the crystalline state (Fig. 2). Excess enthalpy, entropy and free energy can be obtained from heat capacities of the crystalline and amorphous phases as a function of temperature [36]. 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.

Excess thermodynamic properties are parameters in several theoretical models of structural changes in amorphous materials. The excess free energy is a parameter in the classical theory of nucleation, which along with surface tension gives the work necessary to form a nucleus of critical size [37]. The excess entropy enters the Adam-Gibbs model of structural relaxation [38], giving the dynamic behavior a thermodynamic underpinning.

3.3. Changes

3.3.1. The glass transition temperature

If crystallization is avoided, many liquids of pharmaceutically relevance vitrify at a temperature (the glass temperature, T_g) approximately 2/3 to 4/5

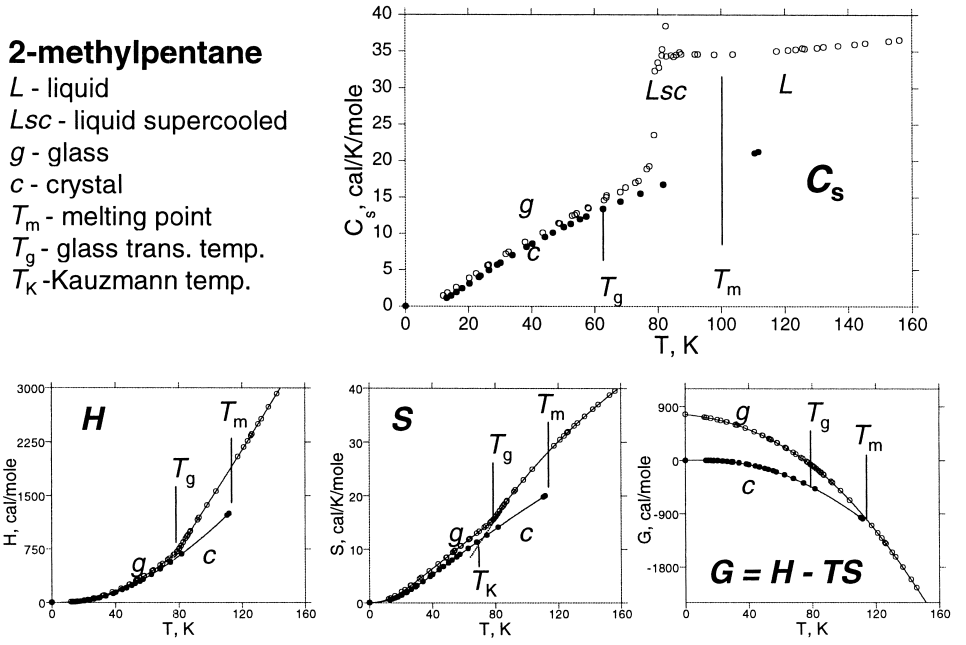

Fig. 2. Thermodynamic properties of the crystalline and amorphous phases of 2-methylpentane. The heat capacity (C_s) data (Douslin, D. R.; Huffman, H. M. *J. Am. Chem. Soc.***1946**, *68*, 173) have been integrated to give the enthalpy (H), entropy (S), and free energy (G). Excess properties correspond to the difference between the crystalline and amorphous lines. The ''entropy crisis'' of Kauzmann (Kauzmann, W. *Chem. Rev.***1948**, *43*, 219–256) is seen in the S panel as the impending crossing of the liquid line with the crystal line as the temperature decreases below the crystal melting point T_m. If not for the intervention of the glass transition at T_g, the liquid line would have crossed the crystal line at T_K. This would be an absurdity, since the liquid entropy would be lower than crystal entropy below T_K.

of the crystalline melting point T_m measured in Kelvin [3,39]. Unlike T_m, T_g is a kinetic parameter, depending on temperature scanning rate and thermal history. Nonetheless, T_g is a useful material descriptor owing to its correlation with structural and thermodynamic properties.

Although numerous material properties (heat capacity, volume, dielectric relaxation, etc.) can be used for T_g measurement, DSC has recently become a principal source of T_g data for many types of materials, including pharmaceuticals [3]. Quantitative measurement of T_g takes into account the effect of impurities (often water), scanning rate, and annealing, and distinguishes between onset, midpoint, and endpoint temperatures (Fig. 3). In more sophisticated analyses, the limiting fictive temperature T_f' is calculated [40], which gives the ''true'' liquid-glass crossing point of the enthalpy-temperature curves that is independent of scanning rate. Thus, T_f' obtained upon cooling from well above the glass transition region depends solely on the material. However, the measurement of cooling T_f' may be confounded by thermal degradation and lower definition of the glass transition as compared to the measurement of T_g by heating.

Modulated DSC [41] can be used to separate the reversing and non-reversing components of a glass transition (e.g., in spray-dried lactose [42]), a beneficial utility in the assignment of glass transitions that are weak or overlap with other thermal events (Fig. 3). It is of interest to obtain T_g of poor glass formers (e.g., mannitol and glycine), because of its use in estimating T_g of mixtures in which the poor glass former remains amorphous. Apart from quench cooling, a melt-miscible impurity may be introduced to inhibit crystallization [43].

3.3.2. Crystallization

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-

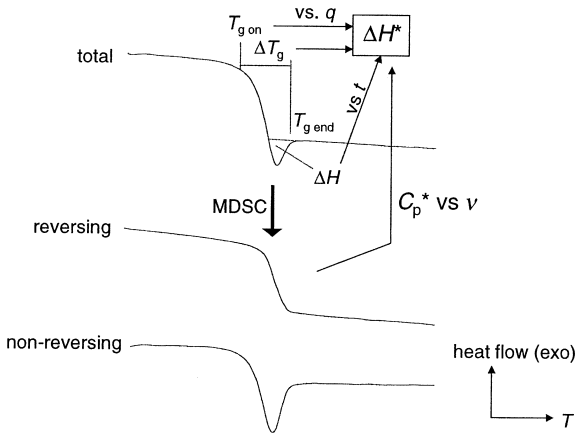

Fig. 3. Illustration of the uses of DSC data for measuring T_g and ΔH^* (the activation energy for enthalpy relaxation). $T_{g\,on}$, $T_{g\,end}$, and ΔT_g indicate the onset, end, and width of the glass transition. Modulated DSC (MDSC) allows the separation of the total heat flow into reversing and non-reversing components. ΔH^* can be evaluated from (*i*) the dependence of $T_{g\,on}$ on scanning rate q, (*ii*) ΔT_g, (*iii*) the dependence of the ''relaxation enthalpy'' ΔH (area of the ''overshoot'') on annealing time, and (*iv*) the dependence of the complex heat capacity C_p^* (obtainable by MDSC) on modulation frequency ν. See text for details.

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 (e.g., temperature and plasticizers), means to promote or prevent crystallization, and the characteristics of crystals produced under conditions unfavorable for growing ''high quality'' crystals (e.g., the high-concentration and high-viscosity media encountered in freeze- or spray-drying).

Crystallization of carbohydrates and derivatives, which are common pharmaceutical excipients, presents special challenges. Elusive crystallization behaviors of such compounds are familiar to carbohydrate researchers. Xylitol, discovered as a syrup, crystallized initially as a metastable polymorph, then as a more stable polymorph, with the metastable form being impossible to make again [44]. The crystallization of D-glucose is influenced by the presence of α (36%) and β (64%) anomers in solution in so-called mutarotational equilibrium [45]. Although the β-anomer is more stable in solution, the commercial crystal form contains the α-anomer only. A similar situation exists for lactose [46], which in solution takes on two anomeric forms, α (38%) and β (62%), but crystallizes normally as an α-anomer monohydrate from water. A β-anhydrate precipitates from concentrated solutions above 93.5°C. Crystallization of amorphous lactose produced by spray-drying (24% α and 76% β) produces a crystalline mixture of α-monohydrate and β-anhydrate containing 29% α [47]. Mannitol and sorbitol, two isomers with different stereochemistry on only one carbon, have significantly different tendencies to crystallize, which have been attributed to whether or not a major conformational change is required on crystallization [16,17].

The existence of multiple crystal forms, as shown by spray-dried lactose [47], further complicates the crystallization of amorphous solids. Mannitol [20,48–59], sorbitol [60], dulcitol [61], lactose [46], and trehalose [62] all show polymorphism and/or hydrate formation. Crystallization of mannitol from freeze-concentrated solutions can yield pure polymorphs a hydrate [59] polymorphic mixtures, or crystalline-amorphous mixtures, depending on concentration, processing conditions, and the presence of other ingredients [63–66]. It is unclear whether different anhydrous polymorphs of mannitol can significantly impact the properties of a freeze-dried product. However, the difference between anhydrous and hydrated crystals or between crystalline and amorphous solids is likely to cause pronounced differences in product performance. For example, the formation of a mannitol hydrate during freeze-drying may retain more water in the product, which may be subsequently released (e.g., at a high storage temperature), causing accelerated degradation of the active component [59].

The nucleation-growth model recognizes two distinct steps in crystallization that have different temperature dependence: lower temperature favors nucleation and higher temperature favors growth [67]. As a result, maximum crystallization rate occurs between preferred temperatures of nucleation and growth. In the case of indomethacin crystallizing from the amorphous state, the α polymorph has a maximum nucleation rate at 60°C and a maximum growth rate at 90°C [68]. The nucleation-growth model also provides a practical guide for controlling crystallization. For example, it is a familiar DSC observation that many supercooled liquids do not

crystallize during cooling, but do so upon reheating, often soon after passing T_g. Cooling a 10% w/v mannitol solution in water can cause partial solute crystallization (after ice crystallization). However, even at a slow cooling rate (say, 0.5°C/min), crystallization of mannitol is incomplete in the cooling step and additional crystallization occurs during reheating (near −25°C). This crystallization can be so violent as to break freeze-drying vials [69,70]. These phenomena are explained by the efficient nucleation at low temperature and the subsequent growth of these nuclei to mature crystals at higher temperatures.

Cooling rate also affects the rate of nucleation [71]. Slow cooling allows the maintenance of a steady-state nucleation rate, whereas rapid cooling prevents a full development of viable nuclei. As a result, rapid cooling not only facilitates glass formation but also enhances glass stability against crystallization. However, a rapid entry into the glassy state may give rise to another instability, that with respect of structural relaxation (see later). The balance between these two types of stability illustrates the dimensions to be explored in the optimization of material properties.

A method for studying the nucleation effect on crystallization is two-step DSC [72]. As Fig. 4 shows, the temperature dependence of the crystallization rate is evaluated first by cooling the system from an equilibrated liquid state to different crystallization temperatures, T_c (so-called one-step experiment). For a system following a nucleation-growth mechanism, the one-step experiment will produce the temperature of maximum crystallization rate, $T_{c\ max}$. In the two-step experiment, the system is cooled from the same initial liquid state to a temperature $T_n < T_{c\ max}$ and then returned to $T_{c\ max}$. If there is a nucleation effect, the two-step crystallization rate will be significantly faster than the one-step crystallization rate. In the example shown, the crystallization of sorbitol spherulites from a supercooled melt was measured. The maximum one-step crystallization rate occurs at approximately 40°C. By briefly exposing the sample to $T_n = 20$°C, where the sample has negligible crystallization, the crystallization rate at 40°C becomes significantly faster.

3.3.3. Structural relaxation

When a material is isolated in a metastable crystalline state, it may behave as if it is independent from the stable crystal form, until a ''catastrophic'' first-order polymorphic transition takes place. An amorphous solid, on the other hand, may behave as if it always ''recognizes'' the presence of the more

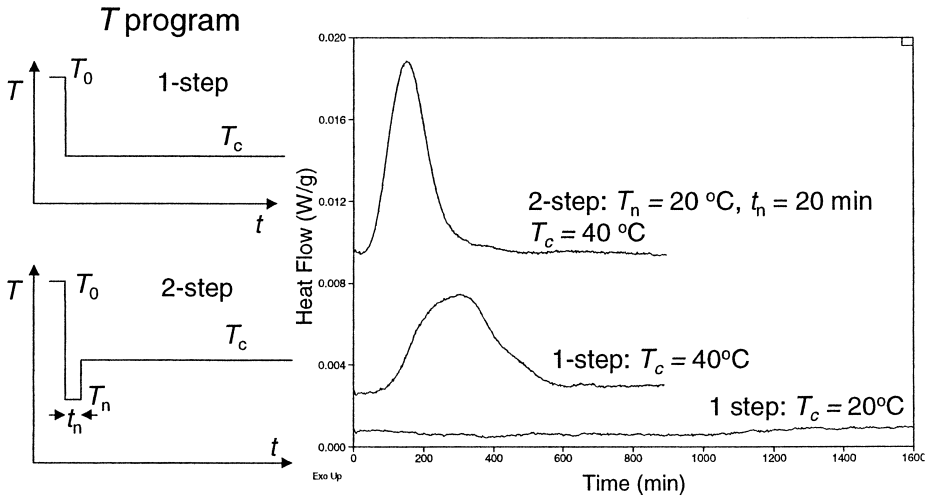

Fig. 4. An illustration of the two-step DSC experiment for investigating the effect of nucleation on crystallization. If lower temperature causes faster nucleation, results similar to what is shown here may be observed: the total crystallization rate observed in the two-step experiment (T_c followed by T_n) may be significantly faster than that observed in one-step experiments conducted at either T_c or T_n.

stable equilibrium glassy state and continuously evolves towards it in a manner predictable from its thermal history and the degree of non-equilibrium. This process is known as structural relaxation, physical aging, or annealing.

If structural relaxation occurs exponentially, a characteristic time, τ, can be defined, which is a measure of the ''mobility'' in the material. Structural relaxation can be studied on different time scales by following the time evolution or frequency dependence of many material properties: enthalpy, volume, viscosity, shear modulus [73], dipole relaxation, depolarization current [74], and nuclear spin relaxation [75] (Table 1). The τ vs. T (temperature) data thus obtained are usually plotted as ln τ vs. $1/T$, the slope of which gives the activation enthalpy of structural relaxation ΔH^* [$= -Rd \ln \tau/\mathrm{d}(1/T)$].

When the property measured is enthalpy, DSC can be used to characterize structural relaxation, now called enthalpy relaxation (Fig. 3). T_g vs. scanning rate (q) data can be used to determine ΔH^* [76]. ΔH^* obtained in this way is found indistinguishable from ΔH^* of viscous flow [77]. T_g used for this analysis can be obtained in two ways: (1) $T_{g\ onset}$ measured at different heating rates q_h after cooling at the same rates ($q_h = q_c$) without annealing; (2) limiting fictive temperature T_f' recorded (at any fixed heating rate, say 10°C/min) after cooling at different rates q_c without annealing. An advantage of Method (2) over Method (1) is that Method (2) does not require absolute temperature calibration at each scanning rate [40]. In principle, the cooling T_g can also be used in this analysis. However, it is necessary to perform absolute temperature calibration during cooling, a non-trivial task since most first-order transitions used for DSC calibration (e.g., indium melting) show significant supercooling. For temperature calibration in the cooling mode, low-energy transitions in liquid crystals are useful [78,79].

Moynihan [80] observed that the width of glass transitions correlates with the activation energy ΔH^* in the form $(\Delta H^*/R)(1/T_{g\ on} - 1/T_{g\ end}) = \mathrm{C} = 4.85$ for a group of high-T_g inorganic glasses. Bruning and Sutton [81] reached a similar conclusion by comparing two dimensionless parameters: $T_g(\mathrm{d}^2T_f/\mathrm{d}T^2)|_{T=Tg}$ for width and $-T_g(\mathrm{d} \ln \eta/\mathrm{d}T)|_{T=Tg}$ for activation energy.

Other DSC-based techniques have been applied to study the structural relaxation in amorphous systems. The use of modulated DSC (MDSC) can determine the frequency dependence of the complex heat capacity and probe structural relaxation at a relatively low frequency (0.1–0.01 Hz) [82]. Isothermal DSC has been used to study sub-T_g enthalpy recovery in ethylene–water solution [83] and in glycerol and propylene glycol [84]. The effect of isothermal annealing was measured relative to non-annealed control to determine the temperature and time dependence of enthalpy relaxation. The time-evolution of the excess enthalpy has been measured by tracking the size of the DSC enthalpy relaxation peak as a function of sub-T_g annealing time for sucrose, PVP and indomethacin [85], as well as for binary systems containing sucrose [86]. These data reveal a non-Arrhenius character of enthalpy relaxation in these systems.

Fragility. The idea of fragility [87] originates from plotting the structural relaxation time τ in the Arrhenius form with the temperature scaled by T_g, i.e., log τ vs. T_g/T. In this plot (the ''Angell plot''), materials of many types intersect at $T_g/T = 1$ with $\tau = 10^2$ s. Furthermore, some materials, called strong, show quasi-Arrhenius behavior (log τ linear in T_g/T), whereas others, called fragile, deviate significantly from the Arrhenius behavior. The strong–fragile pattern observed in this plot is well reproduced by Eq. (1):

$$\tau = \tau_0 \exp[DT_0/(T - T_0)] \quad (1)$$

In Eq. (1), the ''strength parameter'' D describes the deviation from the Arrhenius behavior, with strong systems featuring $D > 25$ and fragile systems $D < 10$ (Fig. 5). The parameter T_0 is sometimes called the temperature of ''zero'' mobility and is found to correlate with D in the approximate form $T_g/T_0 = 1 + D/39.1$.

As the temperature scale of Fig. 5 indicates, the idea of fragility applies to supercooled liquids near and above T_g. Even so, the fragility classification is meaningful to amorphous solids because it is near the T_g when rate processes become more important in real time. In other words, fragility indicates how fast structural relaxation accelerates as a glass approaches and traverses the glass transition region.

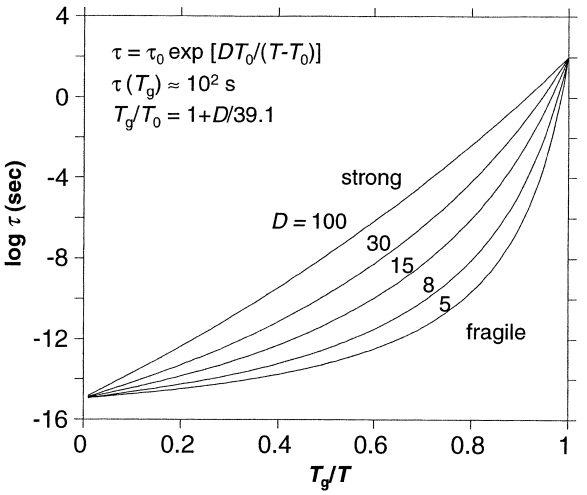

Fig. 5. The strong–fragile pattern that characterizes the temperature dependence of structural relaxation times of supercooled liquids. The series of curves are generated by Eq. (1) using different D values and give a good reproduction of the pattern that emerges from the ''Angell plots'' (log τ vs. T_g/T) of many liquids. Strong liquids (e.g., SiO_2) are characterized by large D and quasi-Arrhenius behavior and fragile liquids (e.g., many small-molecule organics) by small D and non-Arrhenius behavior.

This characteristic is not captured by T_g, which, in fact, is independent of fragility [81].

The empirical fragile–strong pattern has been given a thermodynamic basis [87] through the Adam–Gibbs model [38], in which the rate of structural relaxation is linked to the excess entropy in the amorphous state. A key feature of the linkage is the identity between T_0 in Eq. (1) (from kinetic measurements) and the Kauzmann temperature T_K (from thermodynamic measurements). Fragility has also been correlated with features of the energy ''landscape'' [87] and the non-exponential character of structural relaxation [88].

The success of the fragility concept has prompted searches for the structural basis of fragile and strong behaviors [87,81]. Examples of strong glasses are given by materials with self-reinforcing network structures (e.g., SiO_2) and certain proteins [89,90]. Systems containing non-directional intermolecular/interatomic bonds and internal flexibility tend to be fragile. Small-molecule organics often are found in the fragile category.

Although the qualitative meaning of the strong/fragile behavior is well accepted, how fragility should be quantified is still being defined. The strength parameter D is obtained by fitting viscosity or dielectric relaxation data to Eq. (1) [87].. The disadvantages of the D metric are that the Eq. (1) behavior is not always followed and that D approaches infinity as T_0 approaches 0 K, resulting in a mathematical inconvenience [91]. The steepness parameter m, defined by $m=(T_g)^{-1}\mathrm{d}\ \ln\tau/\mathrm{d}(1/T)|_{T=Tg}$, eliminates model dependence and can be determined from the activation energy for structural relaxation ΔH^* (see above). With this metric, strong systems feature $m<40$ and fragile systems $m>75$. The $F_{1/2}$ metric is defined in terms of T_g and the temperature $T_{1/2}$ at which structural relaxation time equals 10^{-6} s: $F_{1/2}=2[T_g/T_{1/2}-0.5]$ [92]. The value of $F_{1/2}$ lies between 0 (strong) and 1 (fragile). $F_{1/2}$ is also model independent and compared to m, a more robust quantity, since material properties change rapidly near T_g, where m is measured, causing larger experimental errors. Angell proposed a procedure for measuring $F_{1/2}$ based on a DTA measurement in the presence of a $10^{5.2}$ Hz oscillating electric field, which provides T_g and $T_{1/2}$ from a single scan [93]. The width of glass transition has also been used to assess fragility [20,80,81]. This correlation was recently substantiated by comparing to the $F_{1/2}$ metric and used to justify the strong behavior of water in the glass transition region (ca. 136 K) and a fragile-to-strong transition in water [94]. Hancock et al., however, report that the width method requires careful ''calibration'' for general applications [95].

Primary (α) vs. secondary (β) processes. In addition to the glass transition, the so-called primary or α process, many glasses (polymeric and small-molecule) exhibit a secondary or β process [24,30]. Although secondary relaxations are generally weak, and can weaken with annealing, some pharmaceutical materials, e.g., sorbitol [96,97], exhibit surprisingly strong secondary relaxation. The α-process is usually described as general, cooperative, non-Arrhenius, linked to viscous flow, and synonymous with the glass transition, whereas the β-process as specific, local, Arrhenius, and of molecular origin. Hikima et al. proposed that the crystal growth rate in triphenylethylene near T_g is controlled by the β process, rather than the α process [98].

3.4. Multi-component systems

A central question concerning multi-component systems, to which most pharmaceutical formulations belong, is whether the structures, thermodynamics, and changes can be predicted from the properties of its components. For example, how do additives affect the rates of crystallization and structural relaxation? What is the effect of water absorption on amorphous solids? Since sugars and sugar alcohols are commonly used to stabilize proteins and peptides (Section 4), what are the behaviors of these solid systems of small- and large-molecule components?

In the case of T_g, several equations have been introduced to link the T_g of a mixture to the T_g's of its components, including Fox [99], Couchman [100], and Gordon-Taylor [101]. Which equation performs better has not been firmly established and in certain circumstances, the difference in performance is marginal. Since the nature of interactions between pharmaceutical components varies greatly, depending on molecular size and ionic state, it is unlikely that any equation applies universally. The plasticizing effect of water has been modeled successfully using a simplified Gordon-Taylor equation [102].

The crystallization of amorphous indomethacin can be inhibited using low-level polymeric additives [poly(vinylpyrrolidone) and poly(vinylpyrrolidone-co-vinylacetate)] [103]. The effect of additives on the structural relaxation in sucrose has been examined using the ΔH (overshoot) technique (Fig. 3). This type of study may be beneficial to the understanding of protein–carbohydrate formulations.

The special importance of water has prompted studies of its effect on amorphous pharmaceutical solids. Apart from plasticization, water can accelerate chemical degradation and crystallization. Shalaev and Zografi [104] considered scenarios in which water can affect chemical degradation in amorphous materials: as reactant, product, medium, or plasticizer. Water can affect the crystallization of amorphous solids both as a plasticizer to enhance structural mobility and as a building unit of hydrated crystals. The latter scenario is relevant to excipients that can crystallize as hydrates: lactose (monohydrate), trehalose (dihydrate), glucose (monohydrate), and mannitol (stoichiometry unknown).

4. Stabilization

Research aimed at stabilizing amorphous solids is multi-faceted, including: (i) the stabilization of labile biomolecules (e.g., proteins and peptides) through additives, (ii) the prevention of crystallization of excipients that must remain amorphous for their intended functions, (iii) the specification of appropriate storage temperatures to achieve acceptable shelf life, and (iv) the prevention of chemical degradation and microbial growth through anti-oxidant, pH buffer, preservatives, etc. Our discussion focuses on the ''physical'' aspects of stabilization (i–iii). Lai and Topp have reviewed chemical degradation pathways common to proteins and peptides in the solid state [105].

4.1. Stabilization of labile biomolecules

Freezing and drying are essential steps in the preparation of protein and peptide formulations [12] and in the preservation of organisms [14]. Such treatments can be detrimental to these naturally hydrated species. It has been observed that the proteins, peptides and organisms can be effectively protected against freezing and drying damages when they are co-processed with certain excipients, typically carbohydrates and derivatives (sucrose, trehalose, mannitol, sorbitol, etc.) [12–14,106]. Although the mechanism of stabilization is not firmly established, it is thought to involve both vitrification and direct interactions.

4.2. Vitrification

Vitrification-based stabilization relies on the immobilization and isolation of labile substances in rigid glasses of inert stabilizer molecules. Vitrification is expected to reduce the potential for protein aggregation and diffusion of small molecules required to initiate hydrolysis, oxidation, etc. [105] The general assessment of the vitrification hypothesis seems to be that vitrification is necessary but insufficient for stabilizing labile substances and that direct (specific) interactions also are required [14].

In vitrification-based stabilization strategies, T_g provides a concrete guide to the selection of stabilizers and storage temperatures. By eliminating plas-

ticizers (e.g., water) and introducting antiplasticizers, one increases T_g and reduces structural mobility. Shamblin and Zografi [85] showed that antiplasticizers effectively reduce structural mobility in amorphous sucrose. A more sophisticated analysis takes into account of both T_g and fragility, using the ''zero-mobility'' temperature T_0 as the parameter for ranking the relative stability of potential formulations [107].

4.3. Direct or specific interactions

Besides vitrification, direct drug-excipient interactions are important for stabilization [14]. An example of such interactions is the selective hydrogen bonding between stabilizing excipients and the drug molecules. These interactions may resemble the way in which water molecules are integrated into the structures of proteins and peptides (the water-replacement hypothesis).

A well developed concept is that conformational change of proteins during freeze-drying is generally detrimental and should be avoided [13]. This is a sound strategy so long as the conformational change is irreversible. In the crystallization of carbohydrates and other small-molecule organics [108], conformational changes upon solidification are common, but often reversible upon dissolution. If such cases, conformational changes on freezing and drying would not be indicative of structural damage.

4.4. Protection against crystallization of stabilizing excipients

It is generally accepted that in order to act as stabilizers, an excipient must mix homogeneously with the drug to be stabilized [12]. However, certain excipients (e.g., mannitol) have strong tendency to crystallize, leading to phase separation and loss of stabilizing power. Crystallization can also lead to the formation of slow dissolving particles, causing slow reconstitution of parenteral products.

Despite potential crystallization problems, excipients with strong tendency to crystallize can sometimes make suitable stabilizers. In the case of mannitol, its crystallization tendency is compensated by a superior chemical stability against oxidation and hydrolysis in comparison to disaccharides. For example, mannitol is stable at low or high pH where disaccarides undergo hydrolysis. Amorphous sucrose can undergo acid-catalyzed inversion even at very low levels of residual water [109]. In some cases [63,66], the ''flaw'' of mannitol as a poor glass former can be remedied by proteins and peptides themselves, which effectively inhibit crystallization.

4.5. The T_0 or T_g −50 K rule

Molecular mobility that allows physical aging and crystallization [110] of glasses below T_g implies that T_g is unsatisfactory as an indicator for the temperature below which molecular motions ''cease'' for practical purposes. If structural relaxation follows Eq. (1), then the parameter T_0 represents the temperature at which the relaxation time τ goes to infinity (''zero'' mobility). It has been proposed [2,111] that T_0, rather than T_g, be used as a practical guide for selecting storage temperatures. For many fragile glasses, T_0 is approximately 50 K below T_g.

The $T_g - 50$ K rule is an important reminder of the finite structural mobility below T_g. This rule, of course, is dependent on several conditions: fragile systems, Eq. (1) behavior, and α-relaxation process. With strong materials, T_0 will lie significantly below $T_g - 50$ K. For materials that deviate from Eq. (1), the T_0 parameter becomes irrelevant. Finally, even though it is plausible that structural changes required for crystallization and chemical degradation correlate with the cooperative α-process, it has been suggested that the β-process also may regulate the crystallization process [98].

4.6. Trehalose

Trehalose has achieved a special status among stabilizing excipients, even though its superiority is unproven [112]. Comparison has been made between trehalose and sucrose, for example, to understand their potential difference in stabilizing ability. Trehalose exists commonly as a dihydrate and has anhydrous polymorphs [62], whereas sucrose exists as anhydrate (with some hygroscopicity) and is not known to be polymorphic. Trehalose has higher T_g [112] and is more fragile [111,113], both in the dry state and in aqueous solutions, than sucrose. Trehalose is believed to have a greater ''destructuring''

effect on the water structure, thus preventing ice formation, than sucrose and maltose [114]. Such differences have been used to argue for the effectiveness of trehalose as a stabilizer: higher T_g lends rigidity to the matrix, fragility and polymorphism make the matrix more ''adaptable'' to guest molecules, high T_g and high fragility lead to high T_0 (temperature of ''zero'' mobility), the ''destructuring'' effect makes trehalose a better anti-freezing agent, and the ability of forming a hydrate ''sequesters'' moisture otherwise available for chemical degradation.

Although these arguments are persuasive for this pair of sugars, the question about the uniqueness of trehalose has not been satisfactorily answered. In every respect that trehalose is ''superior'' to sucrose, other compounds exist that match or surpass trehalose. It is also unclear whether the chemical stability of trehalose (a non-reducing sugar) is important to its stabilizing function.

5. Concluding remarks

Amorphous solids exist widely in and impart special properties to pharmaceutical products. This review has examined concepts and approaches that are relevant to the preparation, characterization and stabilization of amorphous pharmaceutical solids. What can we extrapolate from the present state of affairs? The recognition of broad patterns of structural relaxation dynamics justifies searches for similar patterns shown by rate processes of greater complexity and importance: crystallization and chemical degradation. Given their instability, general strategies for stabilizing amorphous solids against crystallization and structural relaxation would be desirable. Continuing studies on the stabilization of labile biomolecules should benefit from a better knowledge of the relative importance of vitrification and direct interaction. General behaviors of multi-component systems deserve attention. Amorphous solids prepared by unconventional routes (e.g., drying of crystalline hydrates) are of interest for understanding the structural and relaxational aspects of the glassy state. The nature of crystallization in amorphous solids, as it differs from that in dilute solutions, warrants attention, as do the effects of annealing and conformational and configurational complexity of organic molecules.

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