A publication of the American Pharmaceutical Association and the American Chemical Society

JOURNAL OF Pharmaceutical Sciences

January 1997
Volume 86, Number 1

REVIEW ARTICLE

Characteristics and Significance of the Amorphous State in Pharmaceutical Systems

BRUNO C. HANCOCK*x AND GEORGE ZOGRAFI†

Received April 26, 1996, from the *Merck Frosst Canada Inc., Pointe Claire-Dorval, Quebec, H9R 4P8, Canada, and †School of Pharmacy, University of Wisconsin—Madison, Madison, WI 53706. Final revised manuscript received July 31, 1996. Accepted for publication August 1, 1996⊗.

Abstract □ The amorphous state is critical in determining the solid-state physical and chemical properties of many pharmaceutical dosage forms. This review describes the characteristics of the amorphous state and some of the most common methods that can be used to measure them. Examples of pharmaceutical situations where the presence of the amorphous state plays an important role are presented. The application of our current knowledge to pharmaceutical formulation problems is illustrated, and some strategies for working with amorphous character in pharmaceutical systems are provided.

Introduction

During the final stage of developing a synthetic procedure for a new drug entity, a great deal of emphasis is placed on obtaining material of high purity, and reproducibility in terms of its physical, chemical, and biological properties. Every effort is made to ensure a high degree of crystallinity, wherein the molecules have regular and well-defined molecular packing, and emphasis is also placed on whether or not the compound can exist in polymorphic or solvated crystal forms.[1] These forms can have different thermodynamic properties (*e.g.*, melting temperature, vapor pressure, solubility), and a knowledge of their existence is required to anticipate spontaneous changes in the properties of the solid during storage and/or handling of the material. It is also possible that upon isolation the material will be obtained in a fully or partially amorphous state.[2] The four most common means by which amorphous character is induced in a solid are shown in Figure 1. These are condensation from the vapor state, supercooling of the melt, mechanical activation of a crystalline mass (*e.g.*, during milling), and rapid precipitation from solution (*e.g.*, during freeze-drying or spray drying). Amorphous character is common with polymeric molecules used as excipients, and large peptides and proteins used as therapeutic agents, and it can also occur with small organic and inorganic molecules. When a system consists of multiple components, as with pharmaceutical formulations, it is possible that amorphous solid-state solutions can form analogous to liquid solutions. Water vapor can also be absorbed by an amorphous solid to form an amorphous solid solution.

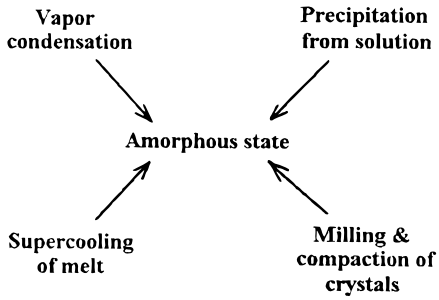

Figure 1—Schematic diagram of the most common ways in which amorphous character is induced in a pharmaceutical system.

The three-dimensional long-range order that normally exists in a crystalline material does not exist in the amorphous state, and the position of molecules relative to one another is more random as in the liquid state. Typically amorphous solids exhibit short-range order over a few molecular dimensions and have physical properties quite different from those of their corresponding crystalline states. In Figure 2 we schematically plot the enthalpy (H) or specific volume (V) of a solid substance as a function of its temperature. For a crystalline material at very low temperatures we see a small increase in enthalpy and volume with respect to temperature, indicative of a certain heat capacity (C_p) and thermal expansion coefficient (α). There is a discontinuity in both H and V at the melting temperature (T_m) representing the first-order phase transition to the liquid state. Upon rapid cooling of the melt the values of H and V may follow the equilibrium

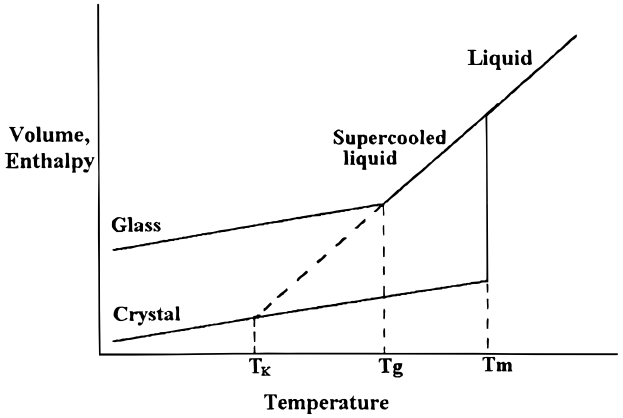

Figure 2—Schematic depiction of the variation of enthalpy (or volume) with temperature.

"supercooled liquid" region. On cooling further a change in slope is usually seen at a characteristic temperature known as the glass transition temperature (T_g). At T_g the properties of the glassy material deviate from those of the equilibrium supercooled liquid to give a nonequilibrium state having even higher H and V than the supercooled liquid. As a result of its higher internal energy (*e.g.*, ≈25 kJ·mol^{-1} for cephalosporins[3]) the amorphous state should have enhanced thermodynamic properties relative to the crystalline state (*e.g.*, solubility,[4] vapor pressure) and greater molecular motion. We would also expect amorphous systems to exhibit greater chemical reactivity[3] and to show some tendency to spontaneously crystallize, possibly at different rates below and above T_g.[5] From a pharmaceutical perspective we have an interesting situation. The high internal energy and specific volume of the amorphous state relative to the crystalline state can lead to enhanced dissolution and bioavailability,[4] but can also create the possibility that during processing or storage the amorphous state may spontaneously convert back to the crystalline state.[5]

In considering the importance of the amorphous state in pharmaceutical systems we must direct our attention to two main situations. In the first, a material may exist intrinsically in the amorphous state or it may be purposefully rendered amorphous and we would like to take advantage of its unique physical chemical properties. Under these circumstances we usually want to develop strategies to prevent physical and chemical instability of the amorphous sample. In the second case, we may be dealing with a crystalline material that has been inadvertently rendered amorphous during processing. This type of amorphous character usually exists predominately at surfaces at levels not easily detected and has the potential to produce unwanted changes in the physical and chemical properties of the system. In this situation we usually want to process the system so that the amorphous portions of the solid are converted back to the most thermodynamically stable crystalline state.

Definition and Description of the Amorphous State

The rapid cooling of a liquid below its melting point (T_m) may lead to an amorphous state with the structural characteristics of a liquid, but with a much greater viscosity (Figures 2 & 3). The enthalpy and volume changes immediately below T_m exhibit no discontinuity with those observed above T_m, so we consider this amorphous state to be an equilibrium "supercooled" liquid. This amorphous state is also called the "rubbery state" because of the macroscopic properties of this state by considering its rate and extent of molecular motions. The average time scale of molecular motions within a supercooled liquid is usually less than 100 s, the viscosity is typically between 10^{-3} and 10^{12} Pa·s (Figure 3), and both properties are strongly temperature dependent.[6–10] Cooling the supercooled liquid even further appears to reduce the molecular mobility of the material to a point at which the material is kinetically unable to attain equilibrium in the time scale of the measurement as it loses its thermal energy, resulting in a change in the temperature dependence of the enthalpy and volume. The temperature at which this occurs is the experimentally observed glass transition temperature (T_g). Below T_g the material is "kinetically frozen" into a thermodynamically unstable glassy state with respect to both the equilibrium liquid and the crystalline phase, and any further reduction in temperature has only a small effect upon its structure. Molecular motions in glasses typically occur over a period in excess of 100 s, and viscosities are usually greater than 10^{12} Pa·s.[6–10] Many of the physical properties of glassy amorphous materials (*e.g.*, thermal expansion coefficient) are different from those of the corresponding supercooled liquid above T_g.

The molecular processes which contribute to the glass transition are currently the subject of intensive research and debate. Whether the changes in thermodynamic properties (*e.g.*, specific heat, volume) that are seen during cooling (or reheating) are due to a real thermodynamic phase transition or are of purely kinetic origin is a controversial issue, and no theory has yet been proposed which accounts for all the observed experimental features. Several excellent reviews which describe the current thinking in this field have been published.[6–8,10,11] Models based on statistical mechanical or free volume theories are the simplest and most widely invoked. Polymer scientists, metallurgists, ceramists, *etc.* each have their preferred approaches with specific advantages for the materials and processes with which they are working. From Figure 2 it can be seen that the glass transition can be considered to be a thermodynamic requirement for a supercooled liquid since without such a transition the amorphous material would attain a lower enthalpy than the crystalline state at some critical temperature and would eventually attain a negative enthalpy. This critical temperature is known as the Kauzmann temperature (T_K) and is thought to mark the lower limit of the experimental glass transition (T_g) and to be the point at which the configurational entropy of the system reaches zero.[9,10] Experimental studies of the glass transition are complicated by the existence of many different modes of molecular motion in most systems (*e.g.*, rotational or translational), changes in the scale and type of motions with temperature, and cooperativity or coupling of molecular motions. One can only say for certain that at T_g the mean molecular relaxation time (τ) associated with the predominant molecular motions is about 100 s and that T_g can be expected to vary with experimental heating and cooling rates, sample molecular mass,[12,13] sample history, sample geometry,[14,15] and sample purity.[16] The experimental glass transition temperature is also influenced by the choice of technique used to measure it because of the varying sensitivities of available techniques to different types and speeds of molecular motions.

The temperature dependence of molecular motions directly determines many important physical properties of amorphous materials, including the location of the glass transition temperature and the ease of glass formation. This temperature dependence is most frequently described using the empirical Vogel-Tammann-Fulcher (VTF) equation:[7,8,10]

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

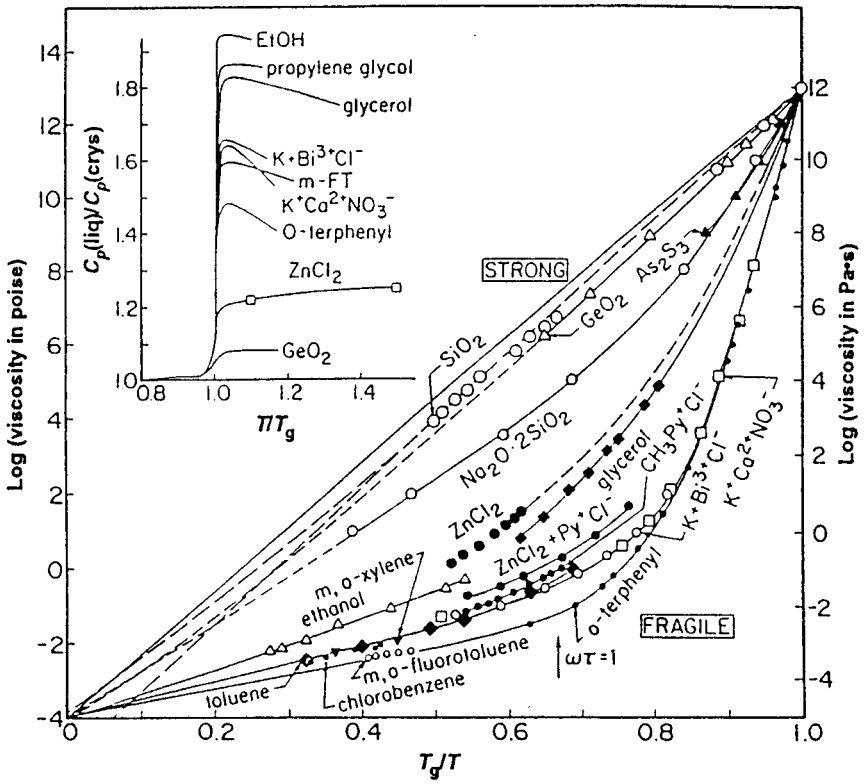

Figure 3—Molecular mobility (or viscosity) of amorphous materials as a function of normalized temperature above T_g.[7,8] Reprinted with permission from ref 8. Copyright 1995 American Association for the Advancement of Science.

temperature, and τ_0, D, and T_0 are constants. The value of T_0 in the VTF equation is believed to correspond to the theoretical Kauzmann temperature (T_K), and τ_0 can be related to the relaxation time constant of the unrestricted material.[7,8] When T_0 is 0, the familiar Arrhenius equation is obtained, and D is directly proportional to the activation energy for molecular motion. When T_0 is greater than 0, there is a temperature dependent apparent activation energy. The Williams−Landel−Ferry (WLF) equation[17] describing the temperature dependence of viscosity (η) in polymers above T_g is a special case of the VTF equation:

$$\eta = \eta_g \exp\{C_1(T - T_g)/(C_2 + (T - T_g))\} \qquad (2)$$

where η_g is the mean viscosity at T_g and C_1 and C_2 are constants. This equation can be derived from first principles based on polymer free volume theories. The constants C_1 and C_2 are found to be quite universal for a range of polymers[17] and are equivalent to $DT_0/(T_g - T_0)$ and $(T_g - T_0)$, respectively, in the VTF equation. The WLF equation has been shown to fit viscosity data for several small organic molecules using the universal constants,[18−20] making it useful for predicting the relaxation behavior or molecular mobility of amorphous pharmaceutical solids. However, it is important to recognize that this is not always the case and such predictions cannot always be assumed to be accurate.

Depending upon the magnitude and temperature dependence of the apparent activation energy for molecular motions near and above T_g in supercooled liquids, it is possible to classify them as either "strong" or "fragile" amorphous systems (Figure 3).[7,8] A strong liquid typically exhibits Arrhenius-like changes in its molecular mobility with temperature and a relatively small change in heat capacity at T_g. Proteins are good examples of strong glass formers, with their changes in heat capacity at T_g often being so small that they cannot be supercooled liquid has a much stronger temperature dependence of molecular mobility near T_g and a relatively large change in heat capacity at T_g and will typically consist of nondirectionally, noncovalently bonded molecules (*e.g.*, ethanol). The constant D in the VTF equation is an indicator of fragility, with low values (<10) corresponding to very fragile glass formers and high values (>100) indicating strong glass-forming tendencies. The value of T_0 in the VTF equation is also linked to the fragility of the system with $(T_g - T_0) > 50$ typical of strong glass formers and $(T_g - T_0) < 50$ usual for fragile materials. A simple graphical means of ranking materials in terms of their strength/fragility is to plot the molecular mobility (or viscosity) as a function of the temperature normalized to the experimental glass transition temperature (*e.g.*, Figure 3).[7,8] A "rule of thumb" for determining fragility without relaxation time data has also been proposed based on the relative magnitudes of the melting and glass transition temperatures: strong, T_m/T_g (in K) >1.5; fragile, T_m/T_g (in K) < 1.5)[7, 8] (Table 1). (See Note Added in Proof.)

The extent of departure of a *glass's* properties from equilibrium is determined by its formation conditions, so we can presume the existence of multiple metastable glasses *below* T_g (Figure 2),[2,3] and even polyamorphic glasses that convert via first-order transitions.[22−24] As a result of this, the temperature dependence of molecular motions *below* the glass transition temperature is highly dependent upon the conditions under which the glass was formed.[12] This temperature dependence is generally less extreme than above T_g and more linear, with some authors proposing an Arrhenius-like relationship. That molecular motions do occur below T_g is unquestionable, and the consequences of the relaxation or "aging" of glassy materials have been widely reported. For example, Guo *et al.*[25] described effects upon the film-coat water permeability and dissolution rate of film coated tablets, and Byron and Dalby[26] studied the effects of aging on the perme-

Table 1—Measured Physical Properties of Some Amorphous Pharmaceutical Materials[a]

Material	M_w	T_m (K)	T_g (K)	T_m/T_g	ΔC_p (J·g^{-1}·K^{-1})	$\rho_{crystal}$ (kg·m^{-3})	ρ_{amorph} (kg·m^{-3})
Indomethacin	358	438	320	1.37	0.466	1.38	1.32
Sucrose	342	453	348	1.30	0.544	1.59	1.43
Lactose (anhydrous)	342	486	383	1.27	0.472	1.60	1.48
Trehalose (anhydrous)	342	476	385	1.24	0.534	1.58	1.49
Dextran	$\approx 5 \times 10^5$	—	498	—	0.400	—	0.92
Poly(vinylpyrrolidone)	$\approx 1 \times 10^6$	—	458	—	0.260	—	1.25
Water[b]	18	273	136	2.01	0.100	<0.95	≈0.95

[a] M_w = molecular mass; T_g = glass transition temperature; T_m = melting temperature; ΔC_p = heat capacity change at T_g; ρ = density. [b] Reference 134.

drug. The effects of aging are often detrimental, but they can also be used to improve a product's performance with a deliberate "annealing" process. This strategy is particularly useful when small amounts of amorphous character have been unintentionally introduced into a system by high-energy processing (see later).[27,28] The time scale of molecular motions in a glass is much longer than above T_g ($\tau \gg 100$ s) and requires different experimental techniques for its study. In almost all cases the molecular relaxation processes that occur in glasses follow a nonexponential function. This nonexponentiality has been widely studied and modeled[29] and appears to be the result of a heterogeneous microstructure within glasses which leads to a distribution of types and rates of molecular motion under any given time and temperature conditions. The reader is referred to some excellent reviews for detailed information on the application of these models to glassy systems.[12,29] The empirical Kohlrausch–Williams–Watts (KWW) stretched exponential function is most often used to describe the distribution of molecular motions:[10]

$$\phi(t) = \exp\{-(t/\tau)^{\beta}\} \tag{3}$$

where $\phi(t)$ is the extent of relaxation at time t, τ is the mean molecular relaxation time, and β is a constant. A β value of unity corresponds to a single relaxation time with exponential behavior. The smaller the value of β, the more the distribution of molecular motions deviates from a single exponential. β has been shown to correspond to the strength/fragility of the material above T_g, but no similar relationship has yet been established below T_g. By fitting data to the KWW function it is possible to determine the mean molecular relaxation time (τ) and β for any well-defined glass.[30] A general means of ranking glasses in terms of the temperature dependence of molecular motions, similar to Angell's strong/fragile classification system above T_g, would be of great use to pharmaceutical materials scientists but has not yet been developed because of the greater complexities of the glassy state.

Perhaps the most important question relating to amorphous pharmaceutical systems is, *At what temperature do the molecular motions responsible for physical and chemical instabilities cease to become likely over the lifetime of that particular system*?[30] It has been suggested that this lower temperature limit might correspond to the Kauzmann temperature (T_K). Although this appears to be the case for some systems, there also appears to be an influence from the strength/fragility of the system, and also from whether or not the molecular motions that are responsible for the glass transition and any instabilities are identical.[30] Mean molecular relaxation times have been reported for several pharmaceutical glass formers as a function of temperature following enthalpy relaxation and thermomechanical relaxation experiments, and the temperature of negligible molecular mobility during a 3-year shelf life varied according to (i) the method used to assess the molecular motions and (ii) the identity of the glass former.[30] As yet there is no reliable means of predicting the temperature of negligible molecular mobility required when defining storage and processing conditions for amorphous pharmaceutical systems (see later).

The behavior of amorphous systems as defined in Figure 2 is dependent upon the assumption of constant pressure and composition. Pressure effects upon amorphous materials have not been widely studied but are likely to be significant with effects on molecular packing potentially modifying the glass transition temperature, the thermal expansion behavior, and the strength/fragility of a supercooled liquid.[10,31,32] From a practical perspective the glass transition temperature of a system containing volatile components may only be experimentally accessible at elevated pressures. For example, the widespread and significant plasticizing effects of sorbed water vapor in high-T_g amorphous polymers have only recently been fully realized because of advances in sample-handling methods which allow samples of varying water content to be sealed at ambient temperature and then heated through T_g without loss of their sorbed water vapor.[33] The properties of a glassy amorphous solution prepared by lyophilization are also likely to be significantly different from those of the same system prepared at ambient pressure since the reduced pressure within a lyophilization chamber will affect the structure of the amorphous cake that is formed and also the composition of the solution through the primary and secondary drying processes. Angell *et al.*[34] have noted that for aqueous solutions the fragility of the supercooled solution is dependent upon the solute concentration in the solution. From the limited data available it can be concluded that some supercooled aqueous solutions become stronger as they become more dilute (*e.g.*, sugars), whereas others become more fragile (*e.g.*, electrolytes, salts). The type of behavior observed appears to be linked to the extent of hydrogen bonding in the aqueous solution. The fragility of such mixed systems may also be related to the ideality of their mixing behavior. Simple mixing rules have been used by many authors[35,36] to describe the variation of the glass transition temperature with blend composition; however, the effects of nonidealities (*e.g.*, immiscibility, molecular size differences, specific interactions, *etc.*) are often significant. The simplest and most reliable approach for use with amorphous pharmaceutical materials appears to be a modified Gordon–Taylor equation[35,36] which is based on free volume theories with some simplifying assumptions. For simple two-component mixtures,

$$T_{gmix} = (w_1 T_{g1} + K w_2 T_{g2})/(w_1 + K w_2) \tag{4}$$

where T_g is the glass transition temperature, w_1 and w_2 are the weight fractions of components 1 and 2, and K can be calculated from the densities (ρ) and glass transition temperatures (T_g) of the components:

$$K = (T_{g1}\rho_1)/(T_{g2}\rho_2) \tag{5}$$

Similar equations can be readily derived for mixtures of more than two components. A perfecty miscible system will display a single sharp glass transition event. Immiscibility, incom-

theoretical equation, the appearance of more than one T_g, or "broadening" of the glass transition event. Deviations from ideal behavior can also be identified and their most likely causes assessed using the graphical approach of Schneider and co-workers.[36,37] Deviations usually occur over discrete composition ranges and often can be explained in terms of molecular size effects and the disappearing free volume of the high-T_g component at lower temperatures and compositions.[38,39] Such an approach is analogous to percolation theories and has considerable potential for describing mixed amorphous systems. Simple solution theories also can be used to describe such systems and to provide a qualitative understanding of the important factors regulating the glass transition in pharmaceutical systems. For example, it is likely that, when a macromolecule is mixed in small amounts with an amorphous small molecule, it will introduce a considerable excess free volume to the system because of its much larger molecular size. In this situation the glass transition temperature of the mixture probably will not be elevated as much as predicted by theory. The addition of low levels of a small molecule to an amorphous macromolecular system probably will be much less disruptive. Both materials will make near ideal contributions to the overall free volume of the mixture, and in this instance the predictions of the mixing equations are likely to be quite accurate for at least the first 50 K change in T_g. This is very important since the presence of very low levels of low molecular weight contaminants or additives (including water vapor) is predicted and observed to have significant plasticizing effects on pharmaceutical glasses,[36] whereas the addition of low levels of high molecular mass additives often has minimal antiplasticizing effect.[39] It should be noted that the concept of a critical additive composition (W_g) at which a glassy macromolecular material is sufficiently plasticized by a low molecular weight penetrant that it transforms to a rubbery amorphous solid under ambient conditions has been described by several authors.[33,40]

Pharmaceutical solids rarely exist as 100% crystalline or 100% amorphous phases so it is necessary at this point to consider how partially crystalline or amorphous systems are likely to behave. The coexistence of two thermodynamically different states of a material will probably result in (i) significant and measurable structural heterogeneities and (ii) batch to batch variations in physical properties. The presence of one phase in another can act as a focal point for spontaneous phase transitions such as crystallization.[28,41,42] In addition, as each phase is intimately dispersed in the other, there may not be complete independence of their behavior. For example, the dispersion of crystalline drug in an amorphous carrier has been reported to alter the observed glass transition temperature of the amorphous phase.[43] For macromolecules there may even be molecules which are part of both crystalline and amorphous domains physically linking the two regions together. Partially ordered systems have traditionally been described using either "one-state" or "two-state" models.[4,28,41,42] In the two-state model, domains of material are assumed to be either 100% amorphous or 100% crystalline and they coexist side by side in a molecular mixture. This type of system can be simulated to some extent by making physical mixtures of reference samples of crystalline and amorphous materials.[3] The one-state model consists of domains which are truly partially crystalline and in which the molecules have formed a semiordered structure as a result of being restricted in their motion during crystallization, or following the disruption of a more perfect crystalline state. The one-state model seems intuitively more likely than the two-state model but raises many questions which cannot be readily answered by studying mixtures of the reference crystalline and amorphous materials. In metallic systems there is also a state known as

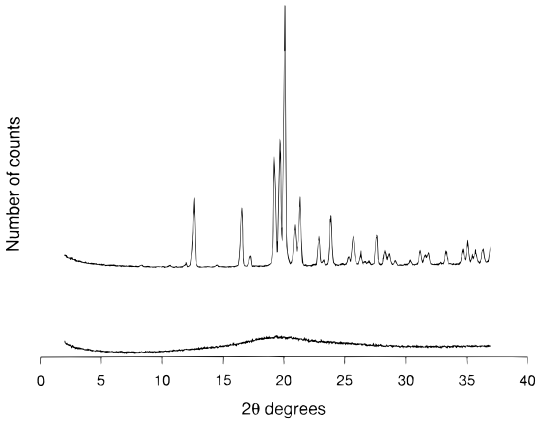

Figure 4—X-ray powder diffraction patterns for amorphous (bottom) and crystalline (top) lactose.

to those of the amorphous and crystalline states,[44] and the concept of "glassy" or "plastic" crystals has recently been described.[45] Clearly the ability to distinguish between crystalline and amorphous states of a material and to be able to quantify one phase in the presence of the other is critical to the successful design and production of amorphous pharmaceutical systems.

Characterization of the Amorphous State

Upon passing into the supercooled liquid state or through the glass to rubber transition it is possible to observe changes in a multitude of material physical properties including density, viscosity, heat capacity, X-ray diffraction, and diffusion behavior. Techniques which measure these properties (directly or indirectly) can be used to detect the presence of an amorphous material (glass or rubber), and some of these methods are sensitive enough to allow quantification of the amount of molecular order or disorder (amorphous content) in a partially crystalline system.

As there is no long-range three-dimensional molecular order associated with the amorphous state, the diffraction of electromagnetic radiation (*e.g.*, X-rays) is irregular compared to that in the crystalline state (Figure 4). Diffraction techniques are perhaps the most definitive method of detecting and quantifying molecular order in any system, and conventional, wide-angle and small-angle diffraction techniques have all been used to study order in systems of pharmaceutical relevance.[3,5,41] The specificity and accurate quantitative nature of these nondestructive techniques make them first line choices for studying partially crystalline pharmaceutical materials. Conventional X-ray powder diffraction measurements can be used to quantify non-crystalline material down to levels of about 5%[41] and with temperature and environmental control can also be used to follow the kinetics of phase transformations, or to quantify the presence of a crystalline drug in an amorphous excipient matrix.[46] Small-angle X-ray measurements have been used to study subtle structural (density) changes in polymers in the glassy state upon annealing,[47] and neutron scattering is gaining wider use in the characterization of short-range two-dimensional order in amorphous materials.[48] It should be remembered that diffraction techniques only "see" molecular order, and thus disorder is only implied.

The irregular arrangement of molecules in the amorphous state usually causes them to be spaced further than in a crystal so that the specific volume is greater and the density lower than that of the crystal, and we say that there is a

DOCKET ALARM

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts

Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research

With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips

Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS
Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS
Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS
Sync your system to PACER to automate legal marketing.