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Review Article

Disordered drug delivery: destiny, dynamics and the Deborah number

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Abstract

''Disordered drug delivery'' is an innovative approach to improving the performance of new chemical entities delivered to the human body. In this technique, the molecules of the drug and/or its delivery system are kinetically trapped in a high energy non-crystalline state. The resulting disordered or ''amorphous'' material offers potential increases in solubility and biological activity of many thousand fold compared with more conventional crystalline forms of the drug. Despite having a molecular level structure akin to that of liquids, amorphous materials have macroscopic properties that are typical of solids and thus they may be presented to the patient in the form of a convenient solid dosage form. Significant advances in the fundamental understanding of amorphous pharmaceutical materials in the past ten years have permitted major steps forward in the rational design of disordered drug delivery systems. Recognition of significant levels of molecular mobility in the glassy regime and an in-depth appreciation of molecular relaxation times and their distributions have enabled rapid progress to be made in this field. Needs for the future include analytical techniques that can elucidate the complex, dynamic and heterogeneous structure of amorphous materials and reliable models to predict the physical stability and in-vivo performance of disordered drug delivery systems. There are also significant opportunities for the production of disordered drug delivery systems with tailor-made properties through the careful engineering of custom amorphous alloys.

Disordered drug delivery

The majority of drugs marketed in the past decade have been isolated and delivered to the human body in their crystalline state (Byrn et al 1999). In most instances, this state represents the lowest energy form of the drug, and the one having the greatest physical and chemical stability. The approach described herein as ''disordered drug delivery'' involves moving away from the paradigm of delivering the drug in its lowest energy crystalline form, and instead producing pharmaceutically acceptable high energy and high activity forms of the drug or the delivery system. Several potential methods for achieving such molecularly disordered materials are listed in Table 1, together with their corresponding commercial manufacturing processes. It has been shown by the author and others working in the field that disordered drug delivery provides opportunities for significantly increasing the aqueous solubility and bioavailability of the active pharmaceutical ingredient (potentially many thousand fold; Hancock & Parks 2000; Table 2), for producing new and more predictable physical properties (e.g. particle size, particle shape; Broadhead et al 1992; Walton 2000), and for combining the active moiety with other materials to

Table 1 Methods of manufacturing molecularly disordered (amorphous) pharmaceutical materials (adapted from Hancock & Zografi 1997).

From	Method	Examples
Crystal	Disruption/energy input	Grinding/milling
		Compression/decompression
		Reaction
		Dehydration
		Irradiation
Solution	Solvent removal	Freeze-drying
		Spray-drying
		Precipitation
		Polymerization
		Reaction
Liquid	Cooling/energy removal	Rapid cooling
		Nucleation suppression
		Polymerization
		Reaction
Vapour	Cooling/energy removal	Sublimation
		Reaction

Table 2 Solubility improvements for some disordered drug forms (data from Hancock & Parks 2000).

Drug	Maximum theoretical solubility enhancement	Experimentally measured solubility enhancement
Indometacin	20–100X	4.5X
Glibenclamide	110–1600X	14.0X
Iopanoic acid	12–19X	3.7X
Polythiazide	50–450X	9.8X

Table 3 Specific volume differences between the crystalline and amorphous forms of some pharmaceutical materials (data taken from Hancock & Zografi 1997).

	Crystalline (mL g^{-1})	Amorphous (mL g^{-1})	Difference (%)
Indometacin	0.72	0.76	6
Sucrose	0.63	0.70	11
Lactose	0.63	0.68	8

form an amorphous alloy with limitless combinations of physical attributes (Lu & Lai 1995). It can also be used to facilitate the delivery of biotechnology products (e.g. proteins, peptides), which often cannot be isolated in a crystalline state. Along with many improved physical properties come some genuine concerns about the long-term performance and stability of high energy drug delivery systems. As will become apparent in the later sections of this paper, recent advances in the understanding of disordered (or "amorphous") materials in other disciplines (e.g. semi-conductors, ceramics) have made it feasible for pharmaceutical scientists to confidently predict the properties, performance and stability of high energy materials so that they may be considered to be a viable option for delivering the medicines of the 21st century.

Amorphous materials

Because of the traditional emphasis on the use of crystalline pharmaceutical materials to achieve maximum chemical and physical stability, very little was known about the structure and molecular behaviour of amorphous pharmaceutical materials until the early 1990s. At that time, a concerted effort was started by several members of the pharmaceutical materials science community to explore the characteristics and significance of these materials, and to identify approaches to exploit these features (Hancock & Zografi 1997). Today, it is known that amorphous materials lack long-range molecular order, and their constituent atoms are sufficiently immobile that the material will behave as a solid on a macroscopic scale. Such systems can be thought of as liquids that have been solidified by the removal of thermal energy or a solvent in a way that avoids crystallization. The individual molecules are randomly oriented relative to one another and they can exist in a variety of conformational states. Thus, each constituent molecule experiences slightly different inter- and intramolecular interactions. As the consequence of these differences in molecular level organization, the microscopic and macroscopic properties of these disordered materials are quite distinct from their crystalline counterparts, and they provide many attractive avenues for the pharmaceutical scientist to explore. For example, amorphous materials have a greater specific volume (volume per unit mass) than their corresponding crystalline forms because of the more irregular arrangement of their atoms and molecules (Nara 1979). This is illustrated for several common pharmaceutical materials in Table 3. Differences in specific volume of 10–15% are not uncommon, and this can result in drastically different performance characteristics for the crystalline and amorphous forms. In recent work with the anti-inflammatory drug indometacin, we were able to measure differences in the solubility of the amorphous and crystalline forms of up to fivefold (Figure 1; Hancock & Parks 2000).

Perhaps surprisingly, a vast range of material types can be isolated in a non-crystalline form, and examples of those that have existing pharmaceutical applications

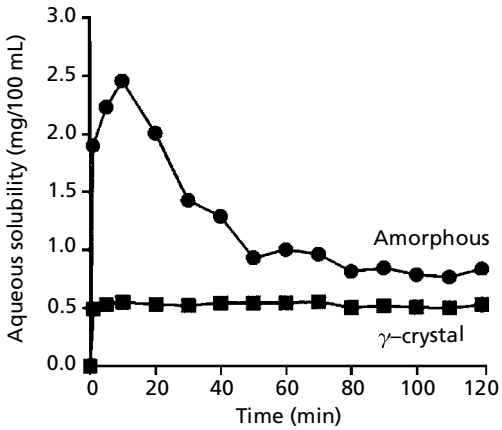

Figure 1 The aqueous solubility profiles of crystalline and amorphous forms of indometacin (data from Hancock & Parks 2000).

are presented in Table 4. Over 24 active pharmaceutical ingredients and excipients are listed in the current European Pharmacopoeia as being amorphous, and more than 25 marketed products (including tablets, capsules, injectables, suspensions and powders) are described as amorphous in the Physician's Desk Reference. These products span the entire range of therapeutic categories from hormones to anti-infectives, and from analgesics to anticoagulants. Amorphous forms of many other materials have also been produced (e.g. water, woodpulp, lipids, salts), and there are many that are in common everyday use. Window glass is perhaps the most common amorphous household item, and other examples can be found in food-stuffs (e.g. dried milk, confectionery) and common consumer items (e.g. yoghurt containers, compact discs). There is virtually no limit to the types of materials that can be made into an amorphous form, and this is one of the main reasons why this approach to drug delivery is so attractive.

Challenges for the development and commercialization of disordered drug delivery systems

After approximately ten years of intensive research into the properties and performance of amorphous pharmaceutical materials, it has become clear that there are three major challenges facing those working towards the rational development and subsequent commercialization of disordered drug delivery systems. These are: the development of meaningful characterization tools for disordered materials, performance prediction, and the engineering of custom materials. To date, the scientific instruments and theoretical approaches that

Table 4 Examples of some amorphous pharmaceutical materials (from the current European Pharmacopoeia, USP/NF, and Physician's Desk Reference).

● Organic small molecules (e.g. lactose)	● Active pharmaceutical ingredients (API) (e.g. nelfinavir mesylate)
● Polymers (natural and synthetic) (e.g. xanthan gum, povidone)	● Tablet fillers (e.g. microcrystalline cellulose)
● Sugars and carbohydrates (e.g. sucrose, dextran)	● Glidants (e.g. silicon dioxide)
● Peptides and proteins (e.g. insulin)	● Suspending agents (e.g. tragacanth, guar gum)
● Lipids and oils	
● Salts, acids and bases (e.g. zinc oxide)	
● Buffer systems	
● Frozen aqueous solutions	
● Tablets (e.g. quinapril hydrochloride)	● Anti-infectives (e.g. erythromycin ethyl succinate)
● Capsules (e.g. pancrease)	● Anticoagulants (e.g. warfarin sodium)
● Oral suspensions (e.g. cefuroxime axetil)	● Anti-asthmatics (e.g. montelukast sodium)
● Injectables (e.g. coumadin)	● Antipsychotics
● Sterile powders (e.g. cefoxitin)	● Antihypertensives
● Topicals (e.g. zinc oxide powder)	● Anti-inflammatories (e.g. indometacin)
	● Analgesics
	● Antacids (e.g. aluminium hydroxide)
	● Diuretics
	● Enzymes (e.g. pancreatin)
	● Hormones

have been used to study pharmaceutical materials (such as powder X-ray diffraction and classical thermodynamics) have largely been developed with crystalline materials in mind, and they are frequently inappropriate for use with amorphous systems because they lack specificity and sensitivity. Specific tools and analytical techniques that are more suitable for characterizing molecularly disordered pharmaceutical materials are very badly needed. This is not just for the sake of fully characterizing the raw materials, but because complete and meaningful characterization of disordered drug delivery systems is a prerequisite for addressing the important challenge of predictability. In order for any pharmaceutical product to be commercialized, it is necessary to be able to predict its performance throughout its intended lifetime (e.g. in use in the clinic, during transportation, on storage in the pharmacy). Such predictability usually comes from a combination of practical experience with the product and a fundamental scientific understanding of the molecular properties and responses of the dosage form. For amorphous pharmaceutical materials that are currently on the market, extensive empirical studies have been the main tool used to demonstrate their performance, stability and safety, and the basic scientific understanding of their properties has been minimal. As drugs become more potent and complex, and society's expectations of reliability and safety increase, the need for an improved understanding of the molecular make-up and performance of such drug delivery systems increases dramatically. If current trends continue, we are ultimately headed in the direction of requiring a complete molecular level understanding of all aspects of a medicine's in-vivo and in-vitro performance before commercialization. Fortunately, once we have achieved some basic level of understanding of disordered pharmaceutical materials, it should be possible to design custom materials with combinations of physical properties that are tailored to fit specific applications. Such "engineering" of amorphous alloys provides opportunities for drug delivery that cannot be realized with conventional crystalline drug substances. This is because disordered systems are not confined to pre-defined templates for molecular arrangements as are crystalline materials, and it is possible to solidify solutions, mixtures and multiphase systems that could never be isolated in a completely crystalline state.

Characterization of molecularly disordered pharmaceutical materials

Perhaps the most important realization in the past ten years with respect to the characterization of amorphous pharmaceutical materials has been that one needs to think in terms of such a material's molecular mobility (Oksanen 1993; Hancock et al 1995; Andronis & Zografi 1997; Yoshioka et al 1997; Aso et al 2000). At ambient conditions, all molecules have some degree of molecular mobility and, in solids, this is primarily associated with their vibrational motions. Translational (diffusive) motions of molecules are very rare in crystals, but occur more commonly in amorphous materials because of their lack of long-range molecular order and greater specific volume. At the most basic level, it is this enhanced degree of molecular mobility that gives disordered materials many of their unique and pharmaceutically desirable physical properties.

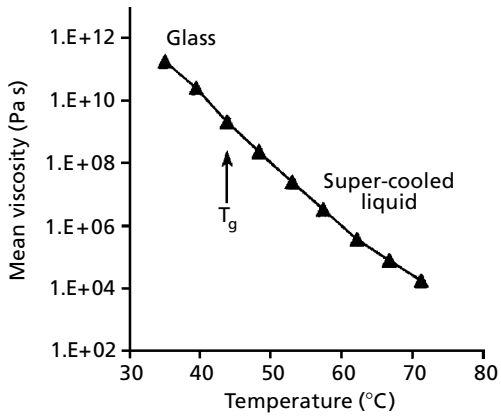

Figure 2 The apparent viscosity of amorphous indometacin at different temperatures (data from Hancock et al 1999).

As the environmental conditions for amorphous solids change, so does the average mobility of their molecules. The consequences of this may be seen, for example, during careful measurements of their macroscopic viscosity (data from viscosity measurements with amorphous indometacin samples stored at various temperatures are presented in Figure 2; Hancock et al 1999). At temperatures above the crystalline melting point (T_m) the molecules of a liquid are highly disordered and mobile relative to the crystal (Figure 3). On cooling, the average molecular mobility is reduced, and provided that crystallization can be prevented, it is possible to super-cool the liquid below its melting point. Supercooling of molecular liquids is very common and not as difficult as one might expect (Ediger et al 1996). The molecules in this state have a greater number of possible configurational states than in the crystalline state under identical conditions of temperature and pressure, and the overall entropy and free energy of the system is significantly greater. If one further cools the super-

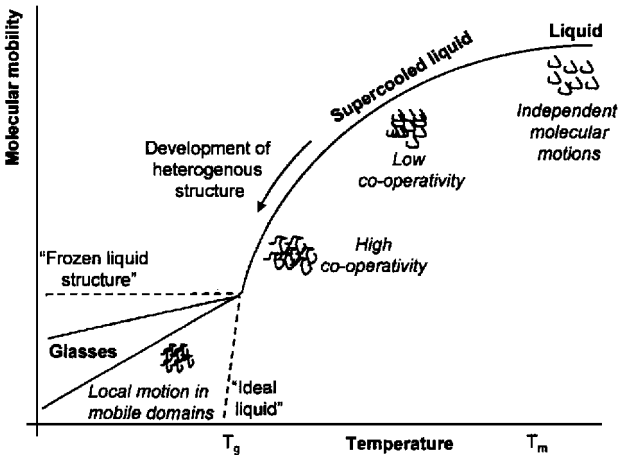

Figure 3 Schematic representation of the temperature dependence of molecular motions in molecularly disordered (amorphous) materials. T_m, melting temperature; T_g, glass transition temperature.

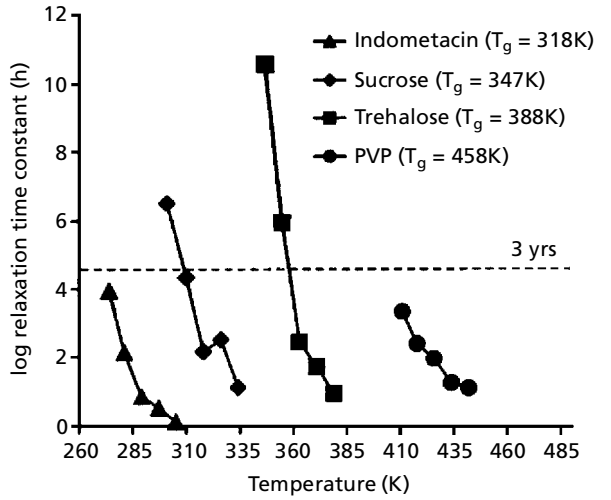

Figure 4 Variation of the average molecular relaxation time with temperature for four typical amorphous pharmaceutical materials (data from Hancock et al 1995). Note: on average, molecular motions occur more frequently than every 3 years even at temperatures that are significantly less that the glass transition temperature.

cooled liquid sample, the molecular mobility reduces almost exponentially until a region known as the glass transition is reached (Mansfield 1993; Angell 1988, 1996). At this point, the average time-scale for molecular motion approaches that of the experiment, and it becomes increasingly difficult for the material to stay in energetic equilibrium with its surroundings. Simply put, the molecules slow down to a point where they cannot dissipate energy fast enough to keep up with the changing external temperature. Cooling below the glass transition thus produces a material that is out of equilibrium with its surroundings and whose molecules are moving very slowly. Such a material is called a "glass" and it possesses some unique physical characteristics. The most important of these are that its properties reflect the conditions under which it was made (thus, there are many different possible glassy forms) and that those properties can gradually evolve over time as the material very slowly equilibrates with its new surroundings.

From a pharmaceutical perspective, it used to be thought that below the glass transition temperature (T_g) the molecular mobility was so low as to be negligible, and that one could ensure long-term product stability by storing amorphous pharmaceuticals at sub-T_g temperatures. In our early work in this area, we studied a range of disordered pharmaceutical materials (polymers, drugs and sugars) at temperatures below T_g and made measurements of their molecular relaxation rates using scanning calorimetry and thermo-mechanical methods (Hancock et al 1995). It was our hypothesis that determining molecular relaxation times for amorphous pharmaceutical materials would provide a means of characterizing their "reactivity" and thus give an indication of their likely pharmaceutical performance. The energetic and dimensional changes of a series of carefully prepared pharmaceutical glasses were monitored over a range of temperatures for several days, and relaxation time constants were estimated using the empirical Kohlrausch–Williams–Watts equation:

$$\phi(t,T) = \exp((-t/\tau)^{\beta}) \quad (1)$$

where $1-\phi$ represents the relative change in energy or volume at experimental time t and temperature T, τ is the average molecular relaxation time during the experiment, and β describes the non-exponentiality of the relaxation behaviour. From the results of this work, we were able to demonstrate that in order for the average relaxation time constants to significantly exceed the projected shelf-life for a pharmaceutical product (approx. 3 years), it was often necessary to store the amorphous materials as much as 50°C below the glass transition region. A sample data set is shown for four typical pharmaceutical materials in Figure 4. This was a much greater degree of super-cooling than had previously been thought necessary to ensure long-term stability, and it indicated that pharmaceutical glasses still retain a significant degree of molecular mobility and potential reactivity below the glass transition region. Over the past five years, this observation has been confirmed by several groups and has led to the gradual realization of an important, but perplexing, choice for those working with molecularly disordered drug delivery

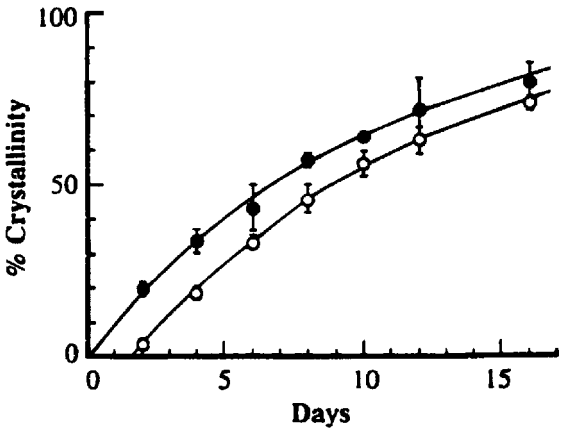

Figure 5 Differences in the crystallization performance of samples of amorphous indometacin prepared by different techniques: ●, slowly cooled; ○, rapidly cooled (adapted from Yoshioka et al 1994).

systems. That is, whether to choose to work with super-cooled liquids that are in effective equilibrium with their surroundings and are generally well understood, but whose physical and chemical stability is often adversely affected by the high temperatures associated with this regime, or to work with less well understood glasses that often have improved chemical and physical stability, but whose structure and properties can slowly change as the system equilibrates with its surroundings. In many instances, the elevated temperatures needed to work in the super-cooled liquid state are prohibitive, particularly for thermally labile biomolecules, and thus it has been necessary for those working in this field to study glassy materials and to develop suitable approaches and methods for dealing with these systems on a practical laboratory time-scale (Hancock & Zografi 1997; Hancock et al 1999; Shamblin et al 1999). For example, the author and co-workers have proposed several approaches for estimating the relaxation behaviour of pharmaceutical glasses using simple calorimetric measurements of T_g, the width of the glass transition, the temperature and enthalpy of fusion, and the heat capacity of the crystalline and amorphous materials (Hancock et al 1998a, b; Hancock & Shamblin 2001). In the future, such methods will need to further evolve so that they can be used to characterize the dynamic molecular heterogeneity that has recently been shown to exist in many amorphous materials near the glass transition (Reinsberg et al 2001), and so that apparently different amorphous forms of drugs and excipients (such as those of amorphous indometacin shown in Figure 5) can be readily distinguished from one another (Angell 1997).

Performance prediction

As with all pharmaceutical products, it is important to be able to predict the long-term performance and stability of disordered drug delivery systems. Fortunately, if we look around us we can be encouraged by the many common examples of amorphous materials whose performance far exceeds that demanded of a normal pharmaceutical product. For instance, mediaeval stained glass windows in churches throughout Europe have stood the test of time without cracking, crystallizing or sagging. This use of an amorphous material is very demanding, requiring structural integrity, versatility (many colours), and extreme longevity under adverse environmental conditions. Turning such everyday observations of the long-term performance of amorphous materials into confident predictions of the attributes of disordered drug delivery systems turns out to be a significant challenge. It is, however, a research area in which marked progress has been made in recent years, largely by leveraging the learning of allied scientific disciplines.

A theoretical basis for predicting the behaviour of molecularly disordered pharmaceuticals, built around understanding the importance of time-scales for molecular motions, has been proposed by the author and co-workers (Hancock et al 1995; Shamblin et al 1999, 2000). It was first noted that the majority of physical and chemical processes that occur in disordered drug delivery systems (e.g. diffusion of drug) are linked to the molecular mobility of the system, and the rate of those processes is dependent on the rate or time-scale of those molecular motions. It was then realized that an assessment of whether the time-scale for a particular physical or chemical process should be of concern requires an appropriate reference time-scale to compare against. By considering the time-scales for molecular motions and choosing appropriate reference time-scales, it has been demonstrated that it is possible to use statistical arguments to provide a solid assurance of amorphous product performance (Shamblin et al 1999, 2000). The approaches developed consider the probabilities of various molecular processes occurring, and are very similar to those used to ensure that sterility is achieved during an autoclaving process. The most easily understood example of this approach involves the prediction of the stability of disordered drug delivery systems. In this instance, the objective is to reduce the probability of the molecular motions that result in product degradation to an insignificant level over the desired lifetime of the product. The key features here are the choice of an appropriate reference time-scale (the product shelf-life), the selection of a meaningful signifi-

cance level (how much degradation is permissible over the product lifetime), and a focus on the most relevant molecular motions (those that result in product instability).

An approach that we have recently used to assess the likely performance of amorphous pharmaceutical samples is to calculate the so-called ''Deborah number'' (D), which is most commonly used in the field of rheology to rank the viscosity of fluids and semi-solids (Van Krevelen 1990):

$$D = \text{average molecular relaxation time } (\tau)/\text{reference time } (t_{ref}) \quad (2)$$

This is simply the ratio of the time-scale for molecular motion to the desired reference time-scale, and it can be considered to be an index of relative molecular mobility. In the context of pharmaceutical product stability, D values of significantly greater than unity indicate a stable system over the reference time-frame. Typically, a laboratory experiment takes less than 24 h, whereas a typical pharmaceutical stability requirement is 3 years (26000 h). If an amorphous drug sample is determined to have a molecular relaxation time of, for example, 300 h at ambient conditions, it would have a Deborah number of 12.5 for the laboratory experiment and just 0.01 for the stability study. One can see that, using this approach, such a sample would be judged to be stable for the purposes of the laboratory experiment, but that it would not be sufficiently inert to survive long-term storage as a pharmaceutical product.

Superimposed on the considerations of relative time-scales for molecular motion are more complex issues relating to distributions of molecular relaxation times in amorphous materials and changes in these distributions over time and with molecular positioning. These occur as a consequence of the multitude of possible molecular orientations that are possible in disordered materials, and the energetic inequivalence of these configurational states owing to differences in the individual inter- and intramolecular interactions. In the pharmaceutical sciences, these issues have only been considered for the first time quite recently (Shamblin et al 1999, 2000); however, it is clear that the impact of seemingly subtle differences, for example in the underlying distribution(s) of relaxation times (e.g. Gaussian vs log-normal), can be quite profound and may have a marked effect on the expected performance of amorphous pharmaceutical materials. This is illustrated by the data in Table 5, where the time required for several different amorphous samples to reach an equivalent degree of molecular relaxation (a surrogate for the product shelf-life) is estimated from parameters that describe their average relaxation time and distribution of relaxation times. In the upper part of the table the data show that the predicted shelf-life could be as long as 5.1 years or as short as 0.6 years depending on the exponentiality of the relaxation behaviour and the underlying distribution of relaxation times (Shamblin et al 2000).

Table 5 Predicted shelf-life for amorphous pharmaceutical products based on their average relaxation time constants (τ) and relaxation time distribution parameters (β) calculated from equation 1 (adapted from Shamblin et al 2000).

Average relaxation time constant (τ)	Non-exponentiality parameter (β)	Maximum theoretical product shelf-life[a] (years)
10	0.9	5.1
10	0.7	2.8
10	0.4	0.6
10	0.4	0.6
20	0.4	1.2
30	0.4	1.8
50	0.4	3.0

[a]For this comparative example, the maximum shelf-life is taken to be the theoretical time for 10% of the product to have reached a fully relaxed state.

There is clearly some way to go before precise and reliable predictions of product stability can be made on a routine basis because of the shear number and complexity of the molecular processes that can contribute to product failure. However, the theoretical foundations of this work have been laid and refinement of the basic principles is ongoing. In our recent work, we have attempted to consider the distribution of relaxation times in amorphous materials, and have developed methods for making ''worst-case'' predictions of sample performance by considering the most mobile and potentially most reactive molecules in the system (Shamblin et al 1999, 2000). Such conservative predictions should provide a useful margin of safety so that samples can withstand temporary excursions beyond normal conditions without fear of unexpected changes in their performance. These kinds of developments will ultimately enable the prediction of amorphous pharmaceutical product performance to become routine and robust, and will undoubtedly advance the development of disordered drug delivery systems to a point that such products can be confidently and rapidly commercialized.

Engineering amorphous alloys

A highly advantageous and attractive feature of amorphous materials is their ability to form molecular level

multi-component mixtures that can be solidified without phase separation. Historically, this fact has been exploited for the formation of many so-called "drug–polymer dispersions" (Ford 1986). To date, the preparation of such dispersions has mostly been empirical and any enhancements in the drug's biopharmaceutical performance have been largely fortuitous (Craig 2002). Given the enhanced level of understanding that pharmaceutical scientists now have regarding the molecular properties of amorphous materials, a case can be made for a more systematic and rational engineering of "amorphous alloys", whose components are selected on the basis of their molecular level properties and their ability to interact with the drug substance to form a homogenous amorphous state. This should permit the creation of custom pharmaceutical materials with unique combinations of properties, much in the same way that metals are co-processed to create custom alloys for critical engineering applications.

In order to be able to understand the best way to produce customized amorphous pharmaceutical materials, we must first consider all the different ways in which molecular disorder can be created. Some of the more common methods are summarized and categorized in Table 1. A disordered drug delivery system may be processed using one or many of these different unit operations and may be formed from crystalline, liquid (pure, emulsion, solution), or gaseous starting materials. For liquids and gases, the most critical feature of the manufacturing process is the rapidity at which the mobility of the molecules is reduced, with rapid reductions in mobility being most likely to result in the formation of a molecularly disordered product (Sakaguchi 1995). For solids, the disruptive driving force must outweigh the driving force for molecular organization (crystallization) and this is usually achieved by maintaining low temperatures and using high energy processing steps such as jet-milling (Ahlneck & Zografi 1990; Elamin et al 1994; Lu & Lai 1995). Currently, the most commonly exploited methods for manufacturing amorphous pharmaceutical materials are freeze-drying, spray-drying and melt extrusion. This is because it is possible to control the product temperature and energy input most precisely by using these particular unit operations.

Several years ago, in collaboration with colleagues at the University of Wisconsin, evaluations of the properties of some model two-component amorphous drug delivery systems were initiated with the aim of understanding how modifying the molecularity of the drug substance using carefully selected additives could alter its physical properties and pharmaceutical performance. Initially, water vapour was introduced as a probe that greatly enhanced the molecular mobility of a variety of amorphous pharmaceutical materials (e.g. drugs, excipients, polymers). It was found that amorphous solids are particularly susceptible to water vapour sorption ('hygroscopic') because of their molecularly disordered state. Several mathematical models based on simple lattice theories and changes in the specific volume of the system on mixing the two components were found to describe the interactions between the amorphous materials and water vapour very well, and significant advances in the understanding of the plasticizing effects of water vapour and the hygroscopicity of amorphous materials were made (Hancock & Zografi 1993, 1994).

Early on in this work, we also studied the drug indometacin, which has a T_g of about 40°C, and discovered that crystallization can take place from the glassy state at ambient temperatures ($\sim$ 20°C) in just a few days (Yoshioka et al 1994). Based on the hypothesis that the molecular mobility of the indometacin glass was still quite significant at $\sim$ 20°C below its T_g, we set out to circumvent the physical instability of the amorphous drug by making an amorphous alloy with the potent antiplasticizing polymer poly(vinylpyrrolidone) (Yoshioka et al 1995). This polymer was selected because of its miscibility with the drug, its tendency to lower the molecular mobility of many materials at ambient conditions, and its ability to interact at a molecular level almost exclusively as a hydrogen-bond donor. Several amorphous alloys were manufactured by the rapid removal of solvent from alcoholic solutions of the drug and polymer in different proportions. Co-processing the polymer, which has a T_g of about 185°C, in this way with the drug in varying amounts resulted in the formation of a series of single-phase alloys with glass transition temperatures between those of the two starting materials (Figure 6). Interestingly, the glass transition data for these samples, which can be thought of as indicating their relative molecular mobility at ambient conditions, could be predicted quite closely at low and high polymer contents using a simple theoretical model of mixed amorphous materials (Gordon & Taylor 1952; Gordon et al 1977; Yoshioka et al 1995):

$$T_g^{1,2} = (w^1 T_g^1 + w^2 T_g^2 K)/(w^1 + w^2 K) \quad (3)$$

where T_g represents the glass transition temperature of components 1 and 2 and their mixture (1,2), and K is a constant derived either from the densities (ρ) and glass transition temperatures of the individual components or their specific heat capacity changes at T_g (ΔC_p):

$$K = \Delta C_p^2/\Delta C_p^1 = (T_g^1 \rho^2)/(T_g^2 \rho^1) \quad (4)$$

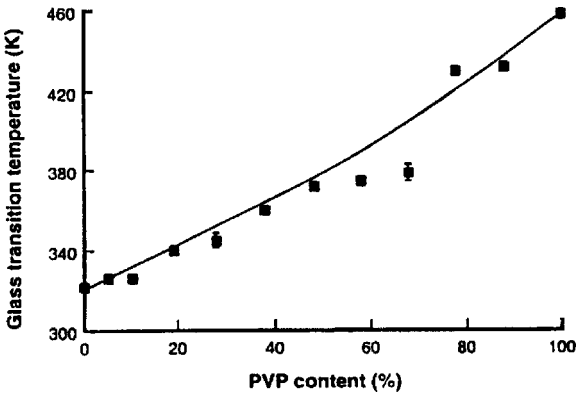

Figure 6 Variation of the glass transition temperature of non-crystalline indometacin–poly(vinylpyrrolidone) alloys with polymer content (data from Yoshioka et al 1995). The line represents predicted behaviour according to the Gordon–Taylor mathematical model.

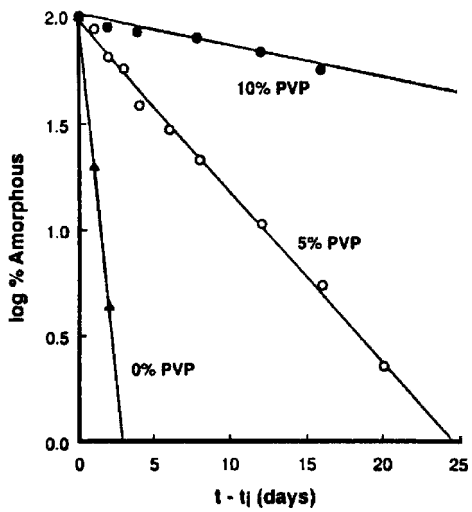

Figure 7 Crystallization rate plots for indometacin–poly(vinylpyrrolidone) (PVP) co-precipitates at 70°C (data from Yoshioka et al 1995).

By carefully controlling the proportion of drug and polymer in the custom amorphous alloys of indometacin, it was also possible to achieve varying degrees of stability against crystal growth following a simple heterogeneous nucleation event (Figure 7). Later studies in this laboratory and elsewhere showed that the manipulation of compositions for other mixed amorphous alloys could be used to direct their properties and performance in a similar way (Taylor & Zografi 1997, 1998; Lu & Zografi 1998; Shamblin et al 1998). The results of these studies provide the most compelling evidence to date that engineering amorphous alloys by using targeted additives with different abilities to modify the molecular mobility of the drug substance (e.g. citric acid, sucrose, trehalose) can permit the properties of molecularly disordered drug delivery systems to be carefully controlled. In the long-term, this type of work will allow the attributes of amorphous pharmaceutical materials to be customized and their performance in pharmaceutical dosage forms to be optimized to a very high degree.

Conclusions

Significant advances have been made in the past decade towards the understanding of the molecular properties and subsequent macroscopic performance of amorphous pharmaceutical materials. An enhanced understanding of the role and importance of molecular relaxation phenomena has been critical to this advancement, and pharmaceutical scientists are now able to begin to predict the attributes of such systems. Significant opportunities still exist for the development of better characterization tools, more accurate physical models, as well as for practical approaches that permit the rational engineering of custom pharmaceutical materials for use in disordered drug delivery systems.

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