Perspective

# Engineering Pharmaceutical Stability with Amorphous Solids

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## Introduction

One of the most important technical challenges to be overcome in developing commercial pharmaceutical products is ensuring prolonged stability during storage (shelf life). To assure product efficacy and safety over time, as well as to satisfy regulatory agency requirements, pharmaceutical products must undergo minimal chemical and physical degradation over multiyear time scales under ambient or refrigerated storage conditions. The formation of even trace amounts of degradation products can be catastrophic depending on their toxicity *in vivo.* The application of scientific and engineering principles to the stabilization of pharmaceutical products is an interesting and challenging activity to which chemical engineers can make valuable contributions. In this article one important route to the engineering of pharmaceutical stability is reviewed.

In many pharmaceutical products, amorphous solids (glasses) play an important role as vehicles for improving product stability and thereby prolonging shelf life. Pharmaceutical glasses are typically composed primarily of low molecular weight organic molecules and water, i.e., they are aqueous organic glasses (Franks, 1997). Pharmaceutical glasses constitute a relatively young field, and one that most chemical engineers have not been exposed to. During the past two decades, significant progress has been made toward a fundamental understanding of pharmaceutical aqueous organic glasses (Chopra and Dhall, 1981; Corrigan and Holohan, 1984; Mathias et al., 1991; Franks, 1993, 1997; Shalaev and Zografi, 1996; Hancock and Zografi, 1997; Zografi and Byrn, 1999; Yu, 2001). This article presents an overview of how aqueous glasses can be engineered to provide physical and chemical stability to labile molecules such as therapeutic proteins and vaccines, and highlights basic unanswered questions of interest to chemical engineers. For recent reviews and compilations of the topic, the interested reader is referred to Franks (1997), Hancock and Zografi (1997), and Yu (2001).

According to their physical state, pharmaceuticals can be classified into three categories: liquids, solids, and semi-solids (e.g., suspensions, gels). Solid dosage forms represent the majority of all commercial pharmaceutical products, including tablets, capsules, powders for reconstitution, oral suspension, or inhalation; and lyophilized (freeze-dried) products (Table 1). In many cases, the product may ultimately be administered as a solution (for example, a reconstituted lyophile), but stability in the solid state essentially determines its usable shelf life. Solid products can be crystalline, amorphous (glassy), or a physical mixture of both. Here, we will address crystalline materials only as they relate to stability in amorphous solids. Complete details regarding physical form and morphology (e.g., crystalline vs. amorphous, polymorphs, etc.) of nongeneric pharmaceutical products are not typically available, but some conclusions can be inferred from publicly-disclosed information. For example, of the approximately 60 new molecular and biological entities approved in 2000 and 2001 (Davis and Vinson, 2001, 2002), 65% are provided as solid products (Table 1). Of these, at least 20% are partially or completely amorphous, and are prepared by freeze-drying. The remainder are either crystalline or insufficient data are disclosed to make a conclusive assessment of their physical form and/or how they are processed.

**Table 1. Chemical and Biological Entities Approved by FDA in 2000 and 2001**

| Physical State of Dosage Form* | Examples | FDA-Approved Entities (2000 and 2001)** |
|---|---|---|
| Solid | Tablets; capsules; lyophiles | 65% |
| Liquid | Ready-to-use injectables; opthalmic solutions | 25% |
| Semisolid | Suspensions; gels; creams | 10% |

*As manufactured and sold
**Based on Davis and Vinson (2001, 2002).

Figure 1 illustrates a number of solid amorphous systems of pharmaceutical interest, categorized according to the path by which the glassy state is formed. There are three principal routes to pharmaceutical glass formation: cooling of a liquid in the absence of crystallization; mechanical disruption of an initially crystalline solid; and concentration of a noncrystallizing solute in solution. Figure 1 shows that in practice most systems vitrify via a combination of these routes, as exemplified by simultaneous cooling and concentration of a solute during freeze-drying.

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## Stability in Amorphous States

Glassy matrices confer stability to labile products through the kinetic arrest of chemical and physical processes, such as diffusion and reaction, that contribute to product degradation. Attaining a vitreous state, however, is not sufficient to guarantee stability, as the preponderance of evidence for biomolecules suggests that specific interactions between the matrix material and the labile molecule must also occur (Carpenter et al., 1999; Pikal, 1999). Cases where the glassy state is detrimental to stability will be briefly addressed before concentrating on the deliberate use of vitrification as a means for improving product stability.

In many pharmaceutical applications, amorphous states are to be avoided if possible due to reasons including: decreased chemical and physical stability relative to the stable crystalline form; increased variability in product quality (due to the processing history-dependent properties of glasses); and difficulties with analytical characterization of product properties. Solid-state organic reactions often occur more rapidly for molecules in amorphous states, compared to the same reaction in a crystalline state (Zografi and Byrn, 1999; Yu, 2001; Byrn et al., 2001). This picture can be further complicated when the product of a crystalline solid-state reaction is incommensurate with the existing crystal lattice. Its formation then leads to "amorphization" of the surrounding environment that effectively auto-catalyzes the reaction (Byrn et al., 2001; Shalaev et al., 1997; Skwierczynski, 1999). Thus, even a small amount of amorphous material in an otherwise crystalline product can lead to dramatically reduced shelf life. The production of local amorphous solid-state regions in an originally crystalline material may also occur via dehydration/hydration of hydrate/anhydrous crystals (Byrn et al., 2001) or through application of mechanical energy during milling or compression (Byrn et al., 2001). In these situations, it is critical to understand how an initially crystalline material is "amorphized" and to characterize the extent of amorphization and its impact on both physical and chemical stability. These are areas of active investigation.

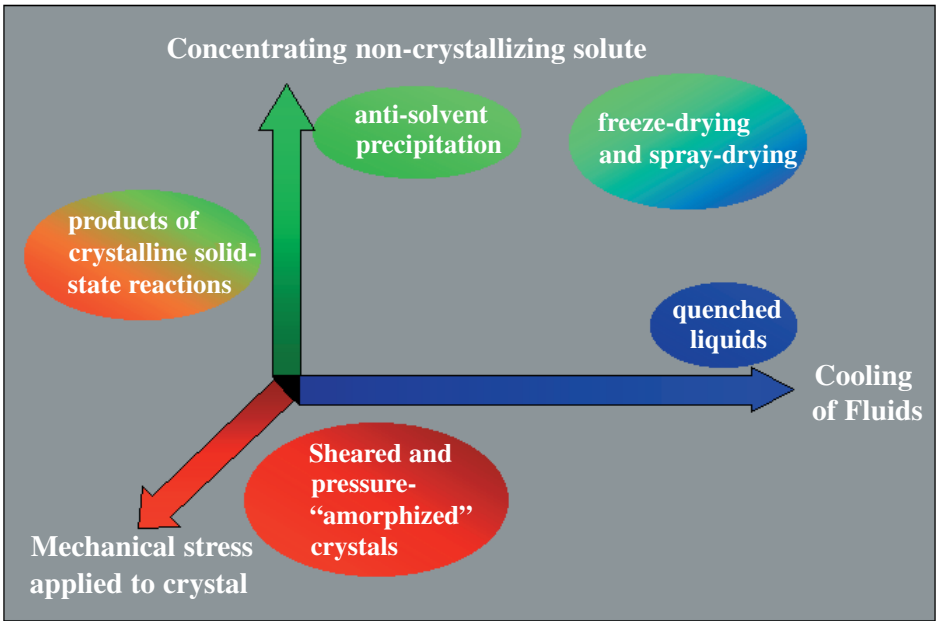


**Figure 1. Principal routes to the formation of pharmaceutical glasses.**

In many practical situations, glassy states are in fact crucial to the development of a successful product. Examples include spray- and freeze-dried products where labile organic pharmaceuticals or biomolecules are encapsulated in an inert organic matrix to impart chemical and physical stability (Franks, 1997; Pikal, 1999; Carpenter et al., 1999). Often a crystalline product is not viable due to the system's inherent propensity to vitrify rather than crystallize under practical conditions, e.g., low-moisture systems of small organic molecules such as carbohydrates and organic acids/bases. Crystalline lyophiles are not uncommon for low-molecular-weight organic synthetic pharmaceutical molecules, but solid biopharmaceuticals are almost inevitably formulated in glassy matrices.

The next section focuses on simple water-carbohydrate glasses, using freeze-dried glasses as primary examples (Yu, 2001; Hancock and Zografi, 1997; Franks, 1990). Alternative preparation routes for pharmaceutical glasses such as spray drying (Broadhead et al., 1992) or less conventional methods such as near-ambient dehydration, foaming plus drying, and mechanical disruption of the crystal are also important (Mathias et al., 1991). Indeed, spray drying has been used to great advantage for preparing bulk excipients such as lactose and malto-dextrin (Broadhead et al., 1992). Lyophilization, however, is the most common route for the formation of glassy commercial pharmaceutical products, and henceforth we focus on this process. Detailed reviews and discussions of freeze-drying and spray-drying, as well as other potentially viable commercial techniques for preparation of glassy pharmaceuticals, are available elsewhere (Franks, 1990; Mathias et al., 1991; Knutson et al., 1996; Broadhead et al., 1992; Maa and Prestrelski, 2000).

## Freeze-Dried Systems

Freeze-dried or lyophilized pharmaceutical products are almost exclusively intended for eventual reconstitution before administration to a patient. In most instances, a freeze-dried formulation is required due to the poor storage stability of the drug molecule in an aqueous solution, along with the need for rapid dissolution of the product upon reconstitution. For conventional lyophiles, a major stabilizing aspect of freeze-dried states is their low moisture content, leading to a significant reduction of hydrolysis rates and reduced molecular mobility, and consequently to decreased drug degradation rates. In addition to residual water and the active ingredient, the formulation usually consists mainly of a glassy matrix composed of, for example, carbohydrate molecules or "inert" water-soluble polymers (Franks, 1997; Carpenter et al., 1999; Pikal, 1999). In many cases, the nature of this matrix is critical as it provides not only structural arrest but may also interact strongly with the active ingredient or other excipients.

Figure 2 shows a so-called "supplemented" phase diagram (MacKenzie, 1977) for a water (*w*)-carbohydrate (solute, *s*) binary system. Although real lyophilized formulations include additional substances (excipients), which serve purposes such as buffering, physical or chemical stabilization, and antimicrobial preservation, their concentration is usually low and the basic principles can be illustrated by considering the water-carbohydrate diagram.

A typical freeze-drying process begins with a water-rich solution (**a**), which is cooled relatively slowly (~10°C/min) and supercools significantly relative to the equilibrium freezing line for ice (ice liquidus, **b-e**). At some temperature during supercooling, ice nucleates and grows (**c**), resulting in freeze-concentration of the nonfrozen solution due to water removal as ice. This causes the solution composition to change until it reaches the metastable extension of the ice liquidus (**e-f**) at the current product temperature (**d**). Note that this type of freezing behavior relies on the ability of the nonwater component(s) to supersaturate essentially indefinitely on the time scale of the freeze-drying process. Upon further cooling, the composition of the nonfrozen solution continues to follow **e-f** until the viscosity increases via concentration and cooling to such a point that the solution effectively vitrifies (**f**). At this point, no further water can be removed from the solution by freezing, and the existing ice is removed via sublimation under reduced pressure at a temperature approximately equal to that of **f** (usually denoted $T_g'$). Once this primary drying stage is completed, a secondary drying stage is used to further reduce the water content. This involves continually drying as $T$ is raised to maintain the product close to its glass transition temperature, which increases dramatically as the water content decreases (Figure 2). That is, the composition in the nonfrozen phase loosely follows the glass transition curve $T_g(w)$ in Figure 2 (**f-g**) until the final drying temperature is reached (**g**). Drying continues isothermally for some additional period (**g-h**) so as to achieve a finally dried glassy system with a glass transition temperature $T_g$ significantly above the desired storage temperature $T_s$ (typically near room temperature).

The overall change in water content ($\Delta w_s$, weight fraction) from **a** to **h** is typically 0.9. Thus, all noncrystallizing species are expected to increase their bulk concentration by 1 to 2 orders of magnitude (on a mol fraction basis). Therefore, although moisture levels (and, presumably, the driving force for hydrolysis) are extremely low, the potential for interactions and reactions of otherwise labile drug molecules with each other, as well as with the other components of the glassy mixture, is greatly enhanced (Franks, 1990). It can then be appreciated why control over the local molecular environment can be critical for assuring stability in such systems (Franks, 1990, 1997; Pikal, 1999; Carpenter et al., 1999). In addition, since many formulations include buffers, salts, and other pharmaceutical additives, it is not surprising that such factors as solid-state "pH" (Shalaev et al., 2000; Song et al., 2001), the presence of reactive impurities or buffer species, and specific noncovalent drug excipient interactions (e.g., hydrogen bonding) can be critical parameters for stability (Pikal, 1999; Carpenter et al., 1999).

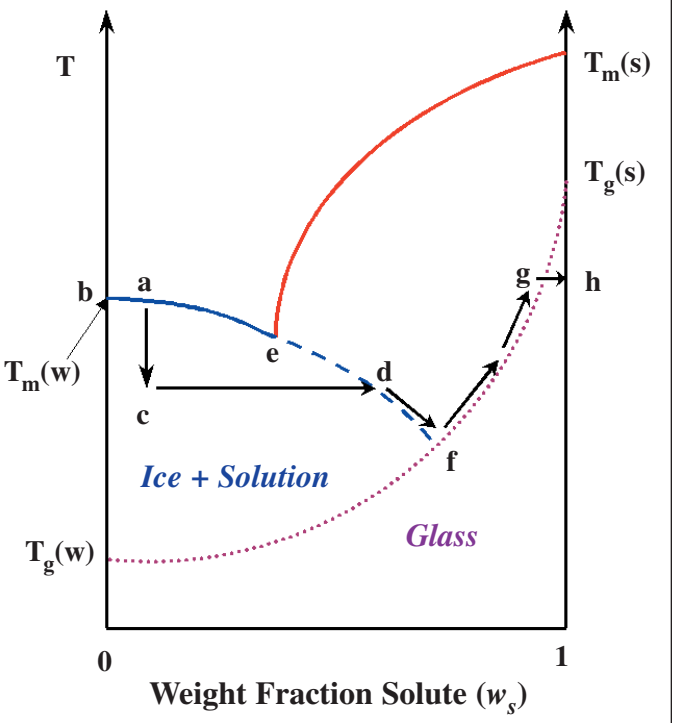


**Figure 2. Supplemented phase diagram for a glass-forming binary system composed of water (*w*) and carbohydrate (solute, *s*).**
$T_m$ and $T_g$ denote the melting and glass transition temperatures, respectively. The dotted line joining the pure-component glass transition temperatures is the mixture glass transition curve.

The preceding concerns notwithstanding, there are some general principles for the design of stable glassy pharmaceuticals (Franks 1990, 1997; Pikal, 1999). It is necessary to assure $T_s<T_g$ in the final product (Franks, 1990, 1997; Pikal, 1999; Hancock et al., 1998), as this restricts molecular mobility which then typically slows degradation. In some instances, there is evidence that $T_s$ should be maintained below a lower temperature $T_0$ ($T_0<<T_g$) to suppress all relevant molecular mobility on multiyear time scales (Hancock et al., 1998; Tanaka et al., 2000). It is also important to provide an inert or even favorable local molecular environment surrounding each drug molecule, within the constraints of available toxicologically and medicinally benign excipients (Franks, 1997; Carpenter et al., 1999; Pikal, 1999; Shalaev et al., 2000).

## Manufacturing and Marketing Considerations

The prevalence of freeze-drying in the production of glassy pharmaceutical products is derived not only from scientific considerations, but also from manufacturing and marketing constraints, and from a historical precedent. The majority of commercial pharmaceuticals that have been engineered as amorphous solids are based on biomolecules targeted for administration parenterally (that is, as a sterile injection) or on synthetic molecules that resist all efforts to induce them to crystallize. In such cases, freeze-dried products have been traditionally preferred over alternative manufacturing techniques, such as spray-drying, supercritical fluid processing, and near-ambient drying (without freezing).

Major practical advantages of freeze drying include: (1) rapid reconstitution due to high surface area to volume ratios; (2) a minimal number of manufacturing steps, each with tight controls, leading to simpler or less expensive production of sterile products than alternative methods; (3) low product temperatures, which can suppress impurity formation; (4) high yields; (5) established commercial facilities, obviating the need for additional expenditure to create and validate new unit operations; (6) a long track record of commercial successes on file with regulatory agencies such as the FDA.

Although the alternative manufacturing processes may each be comparable to freeze-drying in some of the above elements, it must be emphasized that all of the above items are important considerations that together make freeze-drying an industry standard. This is not to imply that freeze-drying is without its shortcomings. Some of the most obvious ones include the energy requirements and resulting costs for evaporation and subsequent condensation of water removed from each product vial, limitations on product volumes (per vial), incompatibility of some common excipients and buffers with lyophilization, and constraints on initial and/or final product concentrations.

Finally, the fact that the pharmaceutical industry is highly regulated results in a strong preference for the (perceived) lower risk and investment involved in commercializing a product based on established pharmaceutical manufacturing processes. Until the alternative processes are shown to be as broadly applicable as freeze drying, and perhaps more importantly, until a significant number of products produced by such processes are registered, it is likely that freeze drying will remain the predominant route for producing commercial pharmaceutical glasses.

## Outlook and Future Research Directions

Amorphous solids are not new to pharmaceuticals. In the past, however, they have been generally avoided due to their inherently metastable nature: unlike crystalline solids, glasses are not true equilibrium systems and therefore their properties depend on their processing history. Additionally, these properties can change during storage, as glasses age irreversibly toward lower free energy states (Debendetti, 1996; Angell et al., 2000). On the other hand, as our understanding of aqueous glasses has improved, the appeal of amorphous solid states as an alternative to crystalline materials has grown. Amorphous solids dissolve faster than their crystalline counterparts, offering improved bioavailability profiles (Corrigan and Holohan, 1984; Nerurkar et al., 2000; Hancock and Parks, 2000); they provide alternative physical forms for drug molecules (Byrn et al., 2001); and offer attractive stabilization or even delivery options for both labile biomolecules (Franks, 1997, 1999; Carpenter et al., 1999) and alternative drug delivery systems such as liposomes (Crowe et al., 1987). In the latter case, this is done by providing stable solid forms of these labile aqueous systems that might be incorporated into more traditional controlled-release media.

The long-term usefulness of aqueous organic glasses for these and other applications will benefit from our ability to answer a number of fundamental questions. The molecular mechanisms underlying the glass-mediated stabilization of biological molecules remain poorly understood. The quantitative prediction of storage stability is thus not possible at present. Understanding the dynamics of structural relaxation of the glassy matrix on the time scale of years is also a challenging problem, and one in which progress must be made before storage stability can be reliably estimated and engineered. The precise, quantitative characterization of structure in amorphous systems is an interesting scientific question (Truskett et al., 2000) that carries important process control and product design implications. The development of improved methods for structural characterization should allow tighter control over product specifications. Relaxation in the glassy state can often lead to the formation of apparently distinct amorphous states. The nature of such transitions (that is, continuous vs. discontinuous), as well as their intrinsic kinetics, are not well understood at present. Chemical reaction kinetics in aqueous organic glasses are also poorly understood.

To sum up, the glassy state offers intriguing possibilities for the formulation of pharmaceutical products with improved storage stability. Chemical engineers can contribute to this interesting and relatively new field provided they broaden their knowledge and interests to include the physical chemistry of the amorphous solid state.

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