The Relationship Between the Glass Transition Temperature and the Water Content of Amorphous Pharmaceutical Solids

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The glass transition temperature of an amorphous pharmaceutical solid is a critical physical property which can dramatically influence its chemical stability, physical stability, and viscoelastic properties. Water frequently acts as a potent plasticizer for such materials, and since many amorphous solids spontaneously absorb water from their surroundings the relationship between the glass transition temperature and the water content of these materials is important. For a wide range of amorphous and partially amorphous pharmaceutical solids, it was found that there is a rapid initial reduction in the glass transition temperature from the dry state as water is absorbed, followed by a gradual leveling off of the response at higher water contents. This plasticization effect could generally be described using a simplified form of the Gordon–Taylor/Kelley–Bueche relationships derived from polymer free volume theory. Most of the systems considered showed a nearly ideal volume additivity and negligible tendency to interact. This is consistent with the hypothesis that such mixtures behave as concentrated polymer solutions and indicates that water acts as a plasticizer in a way similar to that of other small molecules and not through any specific or stoichiometric interaction process(es).

KEY WORDS: glass transition temperature; water content; water vapor sorption; amorphous solid.

INTRODUCTION

Many pharmaceutical solids possess a significant amorphous character, either as a result of high-energy processing (e.g., micronizing, freeze-drying) or because of their large molecular size (e.g., polymers, proteins). Although thought of as being highly disorganized in molecular terms, such amorphous solids can exhibit a great deal of consistency (1), and this allows their properties and behavior to be anticipated with accuracy. The glass transition temperature, \( T_g \), of an amorphous solid determines its chemical stability, physical stability, and viscoelastic properties. The \( T_g \) usually becomes a critical parameter when it is approached or exceeded by the temperature encountered by the product during processing (e.g., drying temperature, storage temperature). This may occur intentionally (e.g., during curing) or, as is more common, unintentionally, due to an inadequate understanding of the processing conditions and material performance characteristics. The \( T_g \) of amorphous solids is usually determined by calorimetric, thermomechanical, and volumetric methods. In addition, it can be determined using several spectroscopic techniques. Despite the wide range of approaches available for measuring the \( T_g \), it is often difficult to determine for pharmaceutical solids. In this instance an estimate of the \( T_g \) of the dry material can be made from its crystalline melting point, from other physicochemical properties, or by using group additive approaches (2–4) (Table 1). The range of \( T_g \) values typically observed for dry drugs and excipients is \(-100\) to \(+250^\circ\text{C}\).

It is well-known that compatible blends of amorphous materials exhibit a single \( T_g \) that is intermediate to the \( T_g \) values of the component materials and shows some relationship to the mixture composition (3). When an additive lowers the \( T_g \) of a substance we speak of its plasticizing effect, whereas when it raises the \( T_g \) it has an antiplasticizing effect. It has been well established that water, with a reported \( T_g \) of \(135\) K (9), acts as a potent plasticizer for amorphous and partially amorphous solids. Since most amorphous solids spontaneously absorb significant amounts of water vapor from their surroundings, it would be useful to establish a general predictive relationship between \( T_g \) and water content, with the ultimate aim of being able to predict the \( T_g \) of a system of a given water content a priori from the \( T_g \) values of its individual components. Such a relationship would allow the pharmaceutical formulator to anticipate the extent to which a given water content would reduce the \( T_g \) of a material and thus cause it to assume any particular physicochemical properties.

The purpose of this paper is to explore the quantitative relationship between \( T_g \) and water content in the context of the theoretical approaches that have been developed to describe the \( T_g \) of compatible blends of amorphous polymers and copolymers. In particular, we wish to explore whether the plasticizing effect of water on amorphous solids having a range of hydrophobic/hydrophilic properties and molecular sizes (i.e., small molecules vs macromolecules) can be predicted using a single quantitative relationship derived from

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such an approach. We would also like to know whether water has any unexpected or specific effects because of its extremely low $T_g$, small molecular size, and high hydrogen bonding capability.

THEORETICAL BACKGROUND

A large number of relationships between the $T_g$ and the phase composition of mixed amorphous systems have been proposed (10,11). Initially these were derived for mixtures of glass formers of similar molecular weights (e.g., polymer blends), and they were then improved and expanded upon for use with mixtures of low and high molecular weight materials. Early workers proposed some empirical relationships based on the behavior of a limited number of systems. More theoretically meaningful relationships can be derived if we consider the glass transition behavior of amorphous solids in terms of polymer free volume theory. By assuming perfect volume additivity at $T_g$ and no specific interaction between the two components, we can write

$$T_g^{\text{mix}} = \phi_1 \cdot T_{g1} + \phi_2 \cdot T_{g2}$$  \hspace{1cm} (1)

where $\phi$ is the volume fraction of each component. This relationship is based on a simple mixing rule similar to that used to describe ideal solution behavior. Since $\phi = [(\Delta \alpha \cdot w)/\rho]$ (where $\Delta \alpha$ is the change in thermal expansivity of $T_g$, $w$ is the weight fraction, and $\rho$ is the true density of the material), it is possible to write Eq. (1) in terms of the weight fraction of each component:

$$T_g^{\text{mix}} = [(w_1 \cdot T_{g1}) + (K \cdot w_2 \cdot T_{g2})]/[w_1 + (K \cdot w_2)]$$  \hspace{1cm} (2)

where $K = (\rho_1 \cdot \Delta \alpha)/(\rho_2 \cdot \Delta \alpha_1)$.  \hspace{1cm} (3)

This is the well-known Gordon–Taylor equation (12), which has been used to describe the glass transition behavior of many compatible polymer blends. An equation identical to this has also been derived for polymer–plasticizer blends by Kelley and Bueche (13), based on viscosity and free volume effects. The constant $K$ in both these equations can be considered to be a ratio of the free volumes of the two components under any given conditions.

By applying the Simha–Boyer rule (12) ($\Delta \alpha \cdot T_g \approx$ constant), we can simplify the Gordon–Taylor/Kelley–Bueche equations and calculate the constant $K$ from the densities of the two components:

$$K = (\rho_1 \cdot T_{g1})/(\rho_2 \cdot T_{g2})$$  \hspace{1cm} (4)

This is useful if $\Delta \alpha$ is not known, as is the case with water, where the $T_g$ is very low and $\Delta \alpha$ is subsequently very difficult to measure. If the densities of the two components are equal, then the Gordon–Taylor/Kelley–Bueche equations simplify to

$$1/T_g^{\text{mix}} = (w_1/T_{g1}) + (w_2/T_{g2})$$  \hspace{1cm} (5)

which is commonly referred to as the Fox equation (15). For synthetic and semisynthetic polymers plasticized with water, the ratio of densities will be approximately unity, and Eq. (5) provides a convenient simplification of the Gordon–Taylor-type equation. However, for most low molecular weight glass formers (e.g., drugs, sugars), the difference in densities will be significant and thus the Fox equation will not be satisfactory.

Based on thermodynamic considerations, Couchman and Karasz (16) have derived an equation for describing the $T_g$ behavior of polymer–plasticizer blends which is identical to the Gordon–Taylor/Kelley–Bueche equations except that

$$K = \Delta C_p^{\text{mix}}/\Delta C_p$$  \hspace{1cm} (6)

$\Delta C_p$ being the change in specific heat capacity at the $T_g$. Several authors have found this equation to be useful for describing the plasticizing effect of low molecular weight additives in film forming materials. Unfortunately a value for $\Delta C_p$ of water is not easy to obtain, so the Couchman–Karasz equation is of limited use in the present work.

In some situations there are likely to be significant specific interactions between the materials in a two-component mix. Several authors (e.g., Ref. 17) have suggested that in this case an additional quadratic parameter should be added to the standard Gordon–Taylor-type equation: