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Research Article

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

Bruno C. Hancock[1] and George Zografi[1,2]

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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 I). The range of T_g values typically observed for dry drugs and excipients is −100 to +250°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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[1] School of Pharmacy, University of Wisconsin-Madison, Madison, Wisconsin 53706.

[2] To whom correspondence should be addressed.

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Table I. Measured and Calculated Glass Transition Temperatures (T_g) of a Range of Amorphous Pharmaceutical Materials

Material	Measured T_g (K)	Ref. no.	Calculated T_g (K)	Method[a]	Ref. no.(s)
Poly(methylmethacrylate)	399	4	378	GAP	4
Lactose	383	4	347	MPT	3, 4
Poly(vinyl chloride)	354	4	330, 360	NFB, GAP	3, 4
Sucrose	347	5	321	MPT	5
Sulfathiazole	334	2	330	MPT	2
Quinidine	326	2	312	MPT	2
Indomethacin	313	2	305	MPT	2
Atropine	281	2	265	MPT	2
Sorbitol	270	6	268	MPT	7
Aspirin	243	2	286	MPT	2
Polyethylene oxide	218	8	200, 214	NFB, GAP	3, 4
Glycerol	180	6	205	MPT	7

[a] GAP, calculated from group additivity parameters; MPT, calculated as 0.7 of the melting point; NFB, calculated from number of flexible bonds per monomer unit.

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

$$T_{g\ mix} = \phi_1 \cdot T_{g1} + \phi_2 \cdot T_{g2} \qquad (1)$$

where ϕ 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 ρ is the true density of the material), it is possible to write Eq. (1) in terms of the weight fraction of each component:

$$T_{g\ mix} = [(w_1 \cdot T_{g1}) + (K \cdot w_2 \cdot T_{g2})]/[w_1 + (K \cdot w_2)] \qquad (2)$$

$$\text{where } K = (\rho_1 \cdot \Delta\alpha_2)/(\rho_2 \cdot \Delta\alpha_1). \qquad (3)$$

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:

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

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

$$1/T_{g\ mix} = (w_1/T_{g1}) + (w_2/T_{g2}) \qquad (5)$$

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

$$K = \Delta C_{p2}/\Delta C_{p1} \qquad (6)$$

ΔC_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 ΔC_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:

$$T_{g\,\text{mix}} = \{[(w_1 \cdot T_{g1}) + (K \cdot w_2 \cdot T_{g2})]/[w_1 + (K \cdot w_2)]\} + q \cdot w_1 \cdot w_2 \qquad (7)$$

Here q is an empirical "interaction parameter" which reflects the strength and type of interactions that occur. The value of q can be determined only by curve-fitting procedures and thus the equation cannot be tested directly against experimental results. More complex extensions of the Gordon–Taylor equation have been made and these allow a limited assessment of the molecular mechanisms responsible for deviations from ideality. In the treatment of Schneider and co-workers (11,18), a three-term virial expansion is obtained by considering the energetics of homo and hetero interaction processes. The first term of the expression that is derived is the same as the standard Gordon–Taylor expression and describes the behavior of an ideal mixture. Subsequent terms account for the effect of interaction energy differences and a changing interaction environment on the free volume of the mixture. This approach allows a linearized form of the Gordon–Taylor expression to be plotted and used to assess quantitatively the magnitude of different interaction processes. A "Schneider plot" with a horizontal line through unity on the abscissa is obtained in the ideal mixing case. Linear deviations (slope > 0.5) occur when specific interactions dominate the behavior of the mixture and curved plots result from changes in the interaction environment with changing mixture composition. The use of such an approach with large molecule–small molecule mixtures (e.g., excipient–water mixtures) is complicated by molecular size and density differences, which introduce significant entropy effects, however, minimally it should enable conformity to the ideal mixing case to be tested.

EXPERIMENTAL

The materials used experimentally were poly(vinylpyrrolidone) (PVP K90, GAF), poly(methylmethacrylate) (MW 25K, Aldrich Chemical Co. Inc.), hydroxypropylmethylcellulose (Methocel E5, Dow Chemical), freeze-dried sucrose (ACS quality, Baker Chemical Co.), and freeze-dried lactose (99.8% pure; Meggle Co.). Dry samples (5–10 mg) of these materials were equilibrated over saturated salt solutions at a range of relative humidities (5–95% RH), weighed, and transferred into hermetically sealed aluminum capsules. The T_g values were determined by heating in a differential scanning calorimeter at a rate of 20 or 40 K/min. All samples were reweighed after T_g determination to check for water loss during testing. The true densities of the dry amorphous solids were measured using a helium pycnometer (Quantachrome).

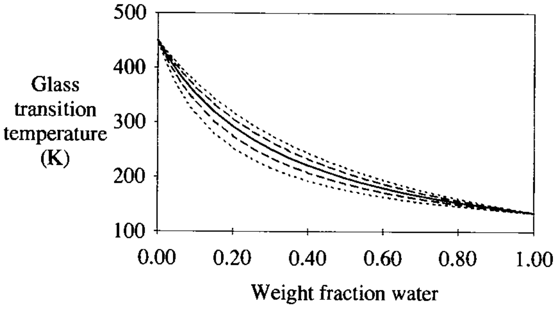

Fig. 1. Effect of solid density differences on the predicted depression of the glass transition temperature by water. From top to bottom, the densities are 0.86, 1.0, 1.2, 1.5, and 2.0 kg m^{-3} × 10^{-3}. Corresponding K values from Eq. (2) are 0.35, 0.30, 0.25, 0.20, and 0.15.

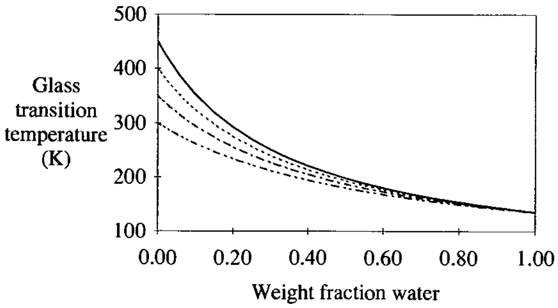

Fig. 2. Effect of solid glass transition temperature differences on the predicted depression of the glass transition temperature by water. From top to bottom, the glass transition temperatures are 450, 400, 350, and 300 K. Corresponding K values from Eq. (2) are 0.25, 0.28, 0.32, and 0.38.

RESULTS AND DISCUSSION

By systematically varying terms in the simplified Gordon–Taylor/Kelley–Bueche expression [Eq. (2)], it is possible to probe theoretically the effects of different substrate properties on the T_g of solid–water mixtures, as shown in Figs. 1 and 2. Such simulations give a smooth curve with a gradually changing slope joining the T_g values of the two pure components. In each case the gradient of the line (dT_g/dw_1) is determined by the T_g values and true densities of the solid and water. For two amorphous solids with the same T_g, the one with the higher density will be plasticized the most by any given amount of water, whereas for two materials with the same density, the one with the higher dry T_g should experience the greatest plasticization. Note that since T_g and density are closely related for both small and large pharmaceutical molecules, the value of the constant K in the simplified Gordon–Taylor/Kelley–Bueche equation is usually of the order of 0.25 ± 0.10 (Table II).

Table II. Glass Transition Temperatures (T_g), Densities, and K Values for a Range of Amorphous Pharmaceutical Materials

Material	Dry T_g (K)	True density (kg m^{-3} × 10^{-3})	K value[a]
Large molecules			
Cellulose	500	1.56	0.1731
Starch	500	1.48	0.1824
Poly(vinylpyrrolidone)	450	1.25	0.2400
Hydroxypropylmethylcellulose	428	1.19	0.2660
Poly(methylmethacrylate)	380	1.17	0.3036
Nylon 6	370	1.08	0.3378
Small molecules			
Lactose	383	1.43	0.2452
Sucrose	347	1.43	0.2721
Indomethacin	330	1.32	0.3099
Water	135	1.00	—

[a] K is the constant found in Eq. (2).

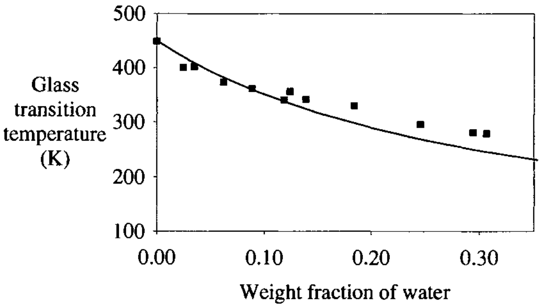

Fig. 3. Variation of the glass transition temperature of poly(vinylpyrrolidone) with water content. Line from Eq. (2).

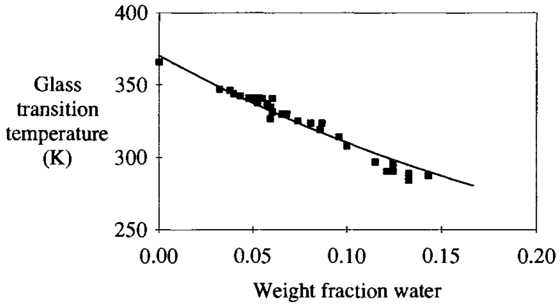

Fig. 5. Variation of the glass transition temperature of poly(2-hydroxyethylmethacrylate) with water content (21). Line from Eq. (2).

Figure 3 shows actual T_g versus water content data for poly(vinylpyrrolidone) (PVP), a water-soluble synthetic linear homopolymer used in a large number of pharmaceutical formulations. PVP has an amorphous structure, exhibits a high T_g, and spontaneously absorbs significant amounts of water from its environment even at low humidities. The fit of the simplified Gordon–Taylor/Kelley–Bueche plot to the experimental T_g data is good over the entire range of water contents normally encountered with this polymer. At low water contents the fit is particularly close, whereas at higher water contents a slightly lower T_g than measured is predicted. This may be due to phase separation of the water and the PVP at these water contents as suggested by Franks (19). It is interesting to note that this deviation occurs at a point very near to the "collapse region" of freeze-dried PVP (19).

It is well-known that when PVP and water are mixed together, heat is evolved, suggesting some sort of specific interaction between these materials (possibly hydrogen bonding). It appears that the interactions responsible for this effect either do not exert a significant influence on glass transition behavior or are balanced by entropic influences resulting in apparently ideal mixing behavior (20). This hypothesis is supported by the fact that the Flory–Huggins interaction parameter for the PVP–water system is 0.5 (19), indicating near-theta conditions overall. Data for other water-soluble and hydrophilic polymers [e.g., hydroxypropylmethylcellulose, poly(2-hydroxyethylmethacrylate) (21)] of pharmaceutical interest also fit the simplified Gordon–Taylor/Kelley–Bueche equation (Figs. 4 and 5), and these materials likewise have Flory–Huggins interaction parameters of about 0.5 (19,22).

If we consider the case of a hydrophobic non-water-soluble polymer, such as poly(methylmethacrylate) (PMMA), we observe the dT_g/dw_1 relationship shown in Fig. 6. Unlike PVP, this polymer has a very low affinity for water, taking up only a few percent of its weight in water even at extremely high relative humidities. Over the narrow range of water contents normally encountered, the simplified Gordon–Taylor/Kelley–Bueche equation predicts an almost-linear dT_g/dw_1 relationship, and as shown in Fig. 6, the experimental T_g data fit this plot quite well. It appears that the simplified Gordon–Taylor/Kelley–Bueche equation can predict with reasonable accuracy the plasticizing effect of water upon both hydrophilic and hydrophobic synthetic linear polymers of pharmaceutical interest.

In practice the pharmaceutical formulator still uses amorphous solids of natural origin so it is important to include this class of materials in our considerations. Data from the literature (23) describing the effect of water on the T_g of starch are presented in Fig. 7 (note that the dry T_g of starch was estimated from that of cellulose, which has an identical repeat unit structure). For this material of potentially complex and variable composition (due to its natural origins), the simplified Gordon–Taylor/Kelley–Bueche relationship still describes the plasticizing effect of water very well. Data for gelatin and elastin (24) have also been analyzed in this way (data not shown) and appear to fit the same theoretical relationship, giving additional confidence in the application of this type of analysis to less well-defined high molecular weight solids plasticized by water.

Another group of amorphous solids of pharmaceutical interest is the low molecular weight glass formers, such as drugs and sugars. These materials are usually made amorphous by processing (e.g., spray-drying, freeze-drying). Recent work from this laboratory (5) has shown that although

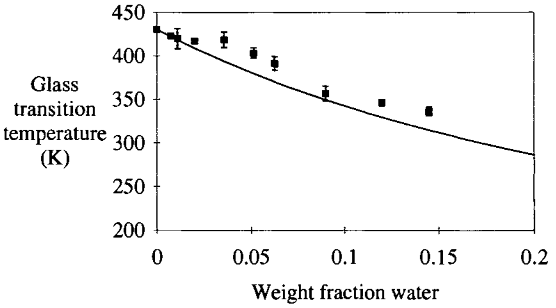

Fig. 4. Variation of the glass transition temperature of hydroxypropylmethylcellulose with water content. Line from Eq. (2).

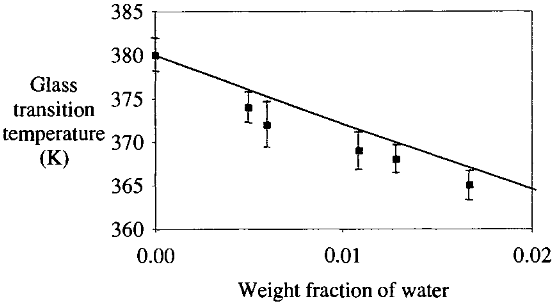

Fig. 6. Variation of the glass transition temperature of poly(methylmethacrylate) with water content. Line from Eq. (2).

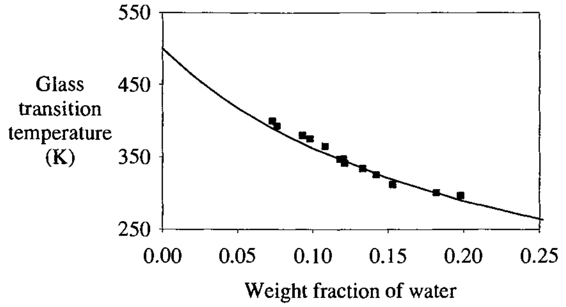

Fig. 7. Variation of the glass transition temperature of starch with water content (23). Line from Eq. (2).

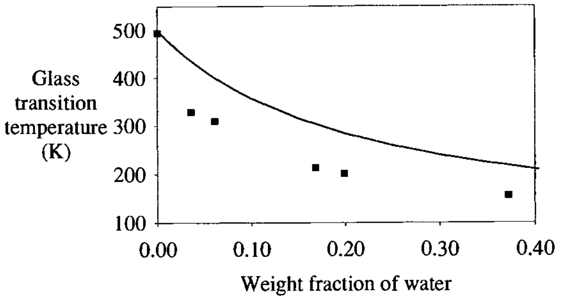

Fig. 9. Variation of the glass transition temperature of cellulose with water content (25). Line from Eq. (2).

materials of this type often recrystallize at moderate moisture contents, the T_g of the amorphous form is still significantly affected by the presence of low levels of moisture. Indeed it is the molecular mobility conferred by the presence of small amounts of absorbed water in these systems which induces many of them to recrystallize. In this situation for the range of moisture contents where the solid remains in the amorphous form, an approximately linear dT_g/dw_1 relationship is predicted by the simplified Gordon–Taylor/Kelley–Bueche equation (as with PMMA), and again we find that the experimentally determined T_g data are very close to the predicted plots (e.g., lactose in Fig. 8).

We could find only a few examples of T_g versus water content data which did not fit the simplified Gordon–Taylor/Kelley–Bueche relationship very well. One example taken from the literature is that of cellulose (25) (Fig. 9). In this instance the depression of T_g is far greater than predicted by the theoretical relationship. One possible reason for this behavior is the presence of crystalline regions in the cellulose, which may directly influence the measured T_g or true density (26). Perhaps more importantly, as it is known that any water present in a partially crystalline sample will be preferentially absorbed into the amorphous regions, the water content of the sample should be calculated based only on the volume fraction of amorphous material present. If this procedure is followed [assuming a crystallinity of 60% (27)], the agreement with the simplified Gordon–Taylor/Kelley–Bueche expression is greatly improved (28). Note also that water may disrupt hydrogen bonding in cellulose, and at water contents which depress T_g to near room temperature this may allow changes in the crystallinity of the sample to take place during the course of the experiment.

Another set of T_g versus water content data which do not appear to fit the simplified Gordon–Taylor/Kelley–Bueche relationship is that of the sucrose–water system. The measured T_g is consistently lower than that predicted by the theoretical model, and in this instance the presence of partially crystalline regions has been discounted using X-ray diffraction measurements (5). To test the significance of this deviation these data and those measured for lactose were replotted in a linear form using the approach of Schneider and co-workers (11,18) (Fig. 10). For the ideal mixing case a linear plot with a gradient of between +0.5 and −0.5 passing through unity on the abscissa should be attained. For lactose such a plot is actually obtained, indicating no significant deviation from "ideal" mixing behavior. In contrast, the data for sucrose show a negative deviation from ideality, suggesting that specific interactions between the sucrose and the water molecules are significantly affecting the overall free volume of the system and hence the T_g of the mixture.

It is somewhat surprising that any of the water–solid mixtures considered obey an ideal mixing rule, if only because molecular size differences would lead us to expect a significant entropy of mixing discrepancy in such systems (20). The results of our analyses at first suggest that molecular size effects do not have a large effect on free volume behavior and subsequent glass transition behavior. There is literature evidence both for and against this hypothesis. Variation of T_g with molecular weight in polymers has been reported (29), suggesting that size effects can be important, however, other sources indicate that the free volume of glassy materials of differing molecular sizes is approximately constant (1). For many of the systems considered it is also known that mixing with water is an exothermic process so the enthalpy of mixing is not zero either (19). These systems

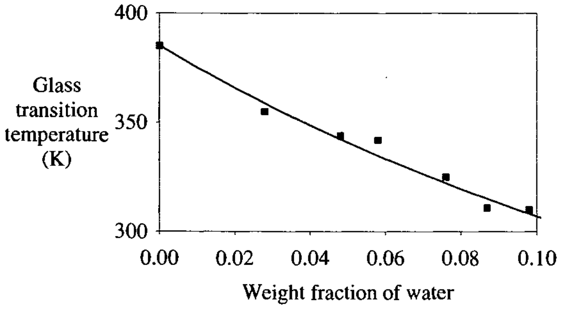

Fig. 8. Variation of the glass transition temperature of lactose with water content. Line from Eq. (2).

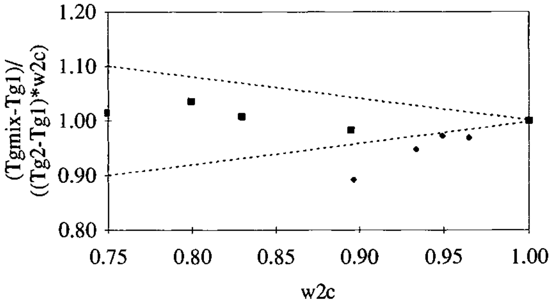

Fig. 10. Schneider plots for lactose–water and sucrose–water mixtures. Lines have gradients of +0.5 and −0.5. (■) Lactose; (◆) sucrose.

may appear to obey the ideal mixing case because entropic and enthalpic effects balance each other out (11). Alternatively any specific interactions which occur giving rise to entropic or enthalpic nonidealities may not have a direct influence on the free volume of the glassy amorphous mixtures. Note that the overall free energy of mixing must be zero or less; otherwise phase separation will take place upon heating above T_g. This means that the enthalpy of mixing (ΔH_{mix}) must be less than or equal to the entropy of mixing at T_g ($T_g \cdot \Delta S_{mix}$) in all the cases considered.

The simplified Gordon–Taylor/Kelley–Bueche equation is based on the assumption of perfect volume additivity in the glassy state. The PVP–, PMMA–, cellulose–, and elastin–water systems considered earlier are all known not to show perfect volume additivity in the glassy state. These materials exhibit excess volumes on mixing with water of the order of a few percent (30), and it appears that the effect of these small volume changes on the glass transition behavior is negligible or directly counteracted by some other nonideality. It should be noted that such small changes can significantly effect other properties of amorphous pharmaceutical solids which are dependent upon their free volume [e.g., water vapor sorption (30)].

Overall given the uncertainty involved in using T_g values from several sources, the agreement between the experimental data and the behavior predicted from theory is very good. Since the simplified Gordon–Taylor plot is easy to calculate, requires a knowledge of only a minimum number of easily measurable parameters, and provides a good estimate of the experimental data in most cases, it is suggested that this equation would be suitable for predicting the behavior of any unknown material.

CONCLUSIONS

It is concluded that water is a potent plasticizer for a wide range of amorphous and partially amorphous pharmaceutical solids. It appears to act in the same way as other low molecular weight plasticizers and its effect can generally be described by a simple mixing equation based on polymer free volume theory, assuming perfect volume additivity at T_g and no interactions between the water and the amorphous solid. While general adherence to such a mixing equation does not prove ideality of mixing, it does allow the behavior of new drugs and excipients to be anticipated with reasonable confidence and it also enables any significant deviations from "normal behavior" to be identified. Fortunately a minimum number of data is required for this procedure, and as there are no adjustable parameters the approach can be used in a truly predictive fashion. The theoretical origins of this approach indicate that the effect of water on the physicochemical properties of amorphous pharmaceutical solids can be linked to three easily determined parameters/properties—the T_g of the dry solid relative to the operating temperature, the density of the amorphous solid, and the tendency for the solid to take up and interact with water from its surroundings. This paper and a previous one (30) have shown that these parameters are important because each is directly linked to the structure, free energy, and free volume of the glassy amorphous solid.

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