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Enthalpy Relaxation in Binary Amorphous Mixtures Containing Sucrose

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Purpose. To compare the enthalpy relaxation of amorphous sucrose and co-lyophilized sucrose-additive mixtures near the calorimetric glass transition temperature, so as to measure the effects of additives on the molecular mobility of sucrose.

Methods. Amorphous sucrose and sucrose-additive mixtures, containing poly(vinylpyrrolidone) (PVP), poly(vinylpyrrolidone-*co*-vinylacetate) (PVP/VA) dextran or trehalose, were prepared by lyophilization. Differential scanning calorimetry (DSC) was used to determine the area of the enthalpy recovery endotherm following aging times of up to 750 hours for the various systems. This technique was also used to compare the enthalpy relaxation of a physical mixture of amorphous sucrose and PVP.

Results. Relative to sucrose alone, the enthalpy relaxation of co-lyophilized sucrose-additive mixtures was reduced when aged for the same length of time at a comparable degree of undercooling in the order: dextran ≈ PVP > PVP/VA > trehalose. Calculated estimates of the total enthalpy change required for sucrose and the mixtures to relax to an equilibrium supercooled liquid state (ΔH_∞) were essentially the same and were in agreement with enthalpy changes measured at longer aging times (750 hours).

Conclusions. The observed decrease in the enthalpy relaxation of the mixtures relative to sucrose alone indicates that the mobility of sucrose is reduced by the presence of additives having a T_g that is greater than that of sucrose. Comparison with a physically mixed amorphous system revealed no such effects on sucrose. The formation of a molecular dispersion of sucrose with a second component, present at a level as low as 10%, thus reduces the mobility of sucrose below T_g, most likely due to the coupling of the molecular motions of sucrose to those of the additive through molecular interactions.

KEY WORDS: enthalpy relaxation; molecular mobility; amorphous mixtures; sucrose; glass transition temperatures.

INTRODUCTION

Previous studies have shown that the presence of amorphous drugs and excipients can lead to reduced physical and chemical stability in pharmaceutical systems due to a greater degree of molecular mobility in the amorphous state relative to the crystalline state. In general, the stability of amorphous materials can be improved by storage well below the glass transition temperature (T_g) and by protection from plasticizers (e.g., water vapor) which can depress T_g to below the storage temperature (1). An alternative strategy has been investigated whereby the material of interest is combined with an antiplasticizer (i.e., a material having a higher T_g) in the form of an amorphous solid solution (2,3). The combined system is expected to have a T_g that is situated somewhere between those of the individual components, and therefore, a different degree of molecular mobility at a fixed temperature and relative humidity. Using amorphous sucrose as a model, it was demonstrated that co-lyophilization with a variety of antiplasticizing materials (e.g., trehalose, dextran, Ficoll, poly(vinylpyrrolidone) and poly(vinylpyrrolidone-co-vinyl acetate)) produced amorphous solid-solutions having a single T_g at all compositions (2,3). It was also shown that sucrose crystallization was reduced in these mixtures even when only small amounts of additive (<10%) were present, and when no significant increase in T_g over that of sucrose was exhibited. It was concluded that sucrose crystallization was inhibited due, in part, to interactions between the additive and sucrose at the molecular level which may impart subtle differences in molecular mobility in the mixture that are not reflected by T_g (3).

The purpose of this study was to compare the molecular mobility of sucrose with that of co-lyophilized sucrose mixtures having a single glass transition temperature which is similar to that of sucrose. This was achieved using differential scanning calorimetry (DSC) to measure the enthalpy changes accompanying the structural relaxation of sucrose alone and when mixed with 10% additive (trehalose, poly(vinylpyrrolidone) (PVP), poly(vinylpyrrolidone-*co*-vinylacetate) and dextran). This technique has been used previously to compare the molecular mobility of polymers (4) and single component amorphous materials of pharmaceutical importance, including sucrose, trehalose, indomethacin and PVP (5,6). It has also been used to characterize different properties of mixed polymer systems (4) and a lyophilized protein formulation (7). One study followed the enthalpy relaxation of sucrose alone and in a co-lyophilized mixture containing 10% dextran at 10°C below T_g for two hours (8).

In this study the enthalpy relaxation of co-lyophilized sucrose mixtures containing 10% additive was measured at a single temperature for different aging times up to 750 hours. The aging temperature (T_a) chosen for this study was 61°C. This temperature represents the same degree of undercooling (T_g-T_a ≈ 20°C) for sucrose and the mixtures since they all have similar T_g values. This particular degree of undercooling was selected, based on the results of previous studies (5), to maximize the enthalpy relaxation that would occur over practical aging times. In addition to the changes in enthalpy with time, the structural relaxation of sucrose and the mixtures was assessed by comparison of the enthalpy change required for the different systems to approach an equilibrium supercooled liquid from the glassy state and the rate at which the glasses approach a relaxed state.

MATERIALS

Sucrose, α-D-glucopyranosyl-β-D-fructofuranoside, was obtained from J. T. Baker Chemical Co. with of purity of greater than 99.5%. α,α-trehalose (α-D-glucopyranosyl-α-D-glucopyranoside) dihydrate, was obtained from Sigma Chemical Co. with a purity of 99.9%. Poly(vinylpyrrolidone) (PVP) K90 was obtained from ISP with a weight-average molecular weight of 1,000,000 (9). Poly(vinylpyrrolidone-*co*-vinylace-

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tate) (PVP/VA) (BASF) is a random copolymer containing vinyl pyrrolidone and vinyl acetate at a molar ratio of 60:40. This copolymer has a weight-average molecular weight ranging from 45,000–70,000 as reported by the supplier. Dextran T500 (Pharmacia) has an average molecular weight of 500,000 with Mn/Mw = 1.5 and is reported by the supplier to be primarily linear. All materials were used without further purification and were stored at room temperature over a desiccant (P_2O_5).

METHODS

Preparation of Amorphous Mixtures by Lyophilization

Prior to mixing, the powdered materials were dried in a vacuum oven at a pressure less than 50 mTorr until a constant weight was obtained. The drying temperatures that were used for the different materials were as follows: crystalline sucrose, 95°C; crystalline trehalose, 130°C; PVP/VA, 60°C; PVP, 105°C; dextran, 105°C. In a dry atmosphere glovebox (<10% RH), materials were combined in the appropriate proportions according to their dry weight, and then dissolved in purified water at a concentration of 10% w/v. The resulting solutions were stirred at room temperature for approximately two hours to ensure complete dissolution and mixing. Solutions containing dextran were warmed to approximately 60°C while stirring to completely dissolve the solid material. These solutions were cooled to room temperature without evidence of phase separation. The solutions were freeze-dried using a commercial tray dryer (Dura-Stop, FTS Systems, Stone Ridge, NY) in combination with a condenser module (Dura-Dry-MP, FTS Systems, Stone Ridge, NY). The solutions were freeze-dried using the method previously described for sucrose (2). Secondary drying was performed at 60°C in a vacuum oven following which the samples were cooled to ambient temperature and stored over a desiccant (P_2O_5). The water contents of the various systems were determined, using the Karl Fisher method (Aquastar C200, EM Science, Cherry Hill, NJ), and found to be less than 0.1% using a minimum of three individual samples. The mixtures were determined to be amorphous using X-ray powder diffraction (XRPD) (see later for details) and by the absence of birefringence under polarized light in an optical microscope.

Preparation of Physical Mixtures of Sucrose and PVP

Amorphous sucrose, prepared by lyophilization of a 10% w/v aqueous solution by the method of Saleki-Gerhardt (2), was lightly ground and passed through a 600 micrometer sieve to remove large particles. PVP K90 was also ground with a mortar and pestle and passed through a 600 micrometer sieve. The components were combined in a dry atmosphere glovebox (RH < 10%) and *very lightly* ground with a mortar and pestle for approximately 5 minutes. Physical mixtures were analyzed by XRPD and optical microscopy to ensure that crystallization of amorphous sucrose did not occur during processing.

X-Ray Powder Diffraction

The scanning x-ray powder diffractometer was a PadV, Scintag (Scintag Inc., Santa Clara, CA) controlled by a computer (Model #B10610, Tektronix, Tektronix Inc., Wilsonville, OR). The radiation used was generated with the aid of a copper Kα filter, with a wavelength of 1.5418Å at 45 kV and 40 mA. Samples were scanned over a range of 2θ values from 10 to 50 at a scan rate of 5 degrees 2θ/minute.

Differential Scanning Calorimetry

Samples (2–5 mg in weight) were sealed in aluminum pans (TA Instruments, New Castle) and analyzed under a dry nitrogen purge in a Seiko SSC5200 DSC fitted with an automated liquid nitrogen cooling accessory. Unless otherwise noted, heating and cooling rates of 20°C/minute were used. The DSC was calibrated for temperature and enthalpy using tin, indium and gallium standards. Glass transition temperatures were determined by first heating the materials and their mixtures to 20°C above T_g to erase the previous thermal history of the materials and then cooling to 100°C degrees below T_g. The materials were subsequently heated a second time during which the onset, midpoint and offset T_g values and the change in heat capacity at $T_g(\Delta C_p)$ were determined as shown in Fig. 1a. The width of the glass transition, ΔT_{gw}, was determined as the difference in the offset and onset T_g values.

Prior to aging, the single components and the mixtures were heated to 20°C above T_g (approximately 110°C), then cooled to 100°C below T_g to form a glass with a standardized thermal history. The glasses were then heated to 61°C which was the aging temperature (T_a). The samples were held isothermally for 0–16 hours, cooled to 100°C below T_g, and subsequently heated through T_g to 200°C. During the final heating scan the pronounced endothermic recovery peak located at the

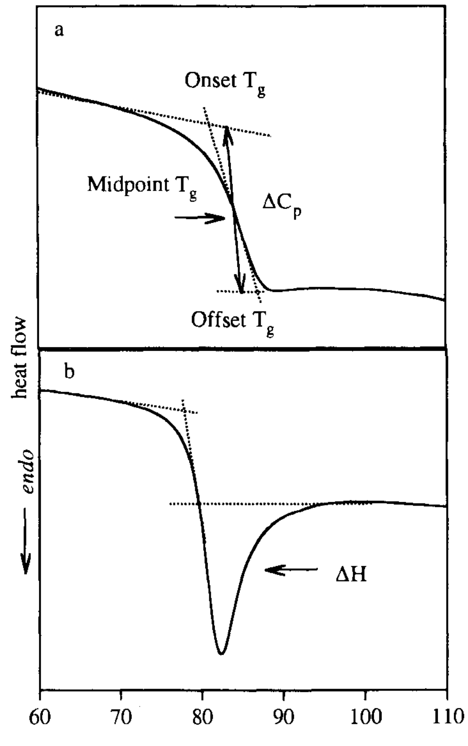

Fig. 1. A schematic representation of the glass transition measured using DSC for: an unaged sample showing the location of the onset, midpoint, and offset T_g values and the change in heat capacity, ΔCp, at T_g (a); an aged sample where the area under the endotherm associated with T_g is defined as enthalpy recovery, ΔH, (b).

end of the glass transition region, reflecting enthalpy relaxation, was analyzed. The area of the endotherm (ΔH) was determined following different aging times by constructing a tangent to the heat curve in the region above T_g and extrapolating to lower temperatures as shown in Fig. 1b. Samples were aged at even longer times (200–750 hours) by storing in an oven at 61°C ± 1°C. At the end of the aging period, samples were removed from the oven and then heated through T_g to determine ΔH.

RESULTS

Characterization of the Glass Transition for Single Components and Sucrose Mixtures

The midpoint glass transition temperatures of sucrose, the additives and the sucrose mixtures measured by DSC are listed in Table I. The T_g values of sucrose and mixtures with 10% trehalose and 10% PVP/VA are not significantly different from that of sucrose, while mixtures with 10% PVP and 10% dextran are three degrees greater than that of sucrose. These results are consistent with previous studies that reported no or very small differences in the T_g for sucrose and mixtures containing small amounts of additive (2,10). The ΔC_p values at T_g for the different systems are also listed in Table I. Although the different additives have different ΔC_p values at T_g, when they are mixed with sucrose at a level of 10%, the resulting mixtures have ΔC_p values that are not significantly different from that of sucrose. The widths of the glass transition region (ΔT_{gw}) for the single components range from 6–12°C and are listed in Table I. The ΔT_{gw} values for the mixtures of sucrose and trehalose and PVP/VA are not significantly greater than that of sucrose while mixtures with PVP and dextran are 2–3°C greater than sucrose alone.

Enthalpy Changes for Co-lyophilized Sucrose Mixtures Following Aging

The DSC traces for sucrose after storage at an aging temperature of 61°C for different times are shown in Fig. 2. The size of the recovery endotherm accompanying the glass transition increases with storage time reflecting greater structural relaxation of the glass towards the equilibrium supercooled liquid state. The DSC traces for the various mixtures following aging below T_g are qualitatively similar to the scans in Fig. 2. The enthalpy changes that were measured for sucrose and the mixtures following aging for up to 16 hours are shown in Fig. 3. Comparison of the enthalpy changes for sucrose and these mixtures at the short aging times indicates that all of the mixtures exhibited smaller enthalpy changes than did sucrose alone following any given aging time. The results with dextran are consistent with those from a previous study that also examined

Table I. The Midpoint T_g, ΔC_p, and Width of the Glass Transition (ΔT_{gw}) for Sucrose, the Additives, and the Mixtures

	Midpoint T_g (°C)	ΔC_p[a] (J/g°C)	ΔT_{gw} (°C)
Sucrose	78	0.64	6.0 ± 0.3
Trehalose	123	0.53	5.0 ± 0.7
PVP/VA	112	0.33	12.3 ± 0.5
PVP	185	0.26	10.8 ± 0.1
Dextran	229	0.40	9.0 ± 1.0
10% trehalose	79	0.66	6.6 ± 0.1
10% PVP/VA	79	0.60	6.4 ± 0.6
10% PVP	81	0.62	7.4 ± 0.4
10% dextran	81	0.63	8.6 ± 0.6
20% PVP co-lyophilized mixture	85	0.40	9.6 ± 0.4
20% PVP[b] physical mixture	76	0.60	6.2 ± 0.4

[a] The reported ΔC_p values are accurate to within ±0.02 J/gK.

[b] The reported values correspond to the lower transition corresponding to the sucrose phase. Data for the higher transition are not reported due to the interference of the sucrose crystallization exotherm with the glass transition for PVP.

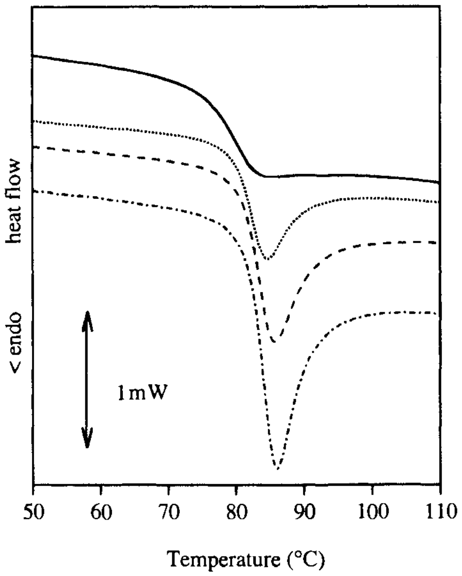

Fig. 2. DSC traces for amorphous sucrose after aging at 61°C; 0 hrs (solid line), 4 hours (dotted line), 8 hours (dashed line), 16 hours (dot-dashed line). Curves have been shifted along the y-axis for presentation purposes.

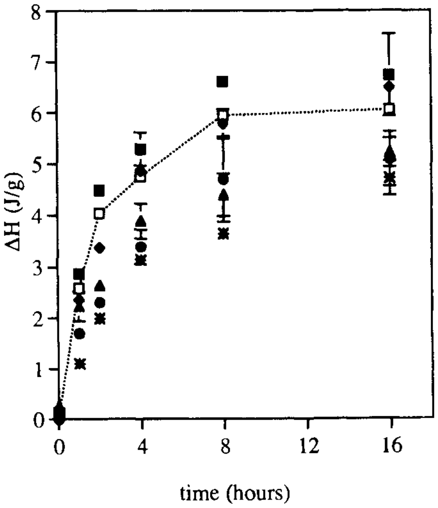

Fig. 3. ΔH values for sucrose and mixtures measured after aging at 61°C for up to 16 hours. sucrose (■); 10% trehalose (◆); 10% PVP (●); 10% PVP/VA (▲); 10% dextran (✱). Prediction of a 10% dilution in the ΔH values for amorphous sucrose (line connected by symbols).

Table II. The Degree of Undercooling (T_g-T_a), ΔH_{750}, ΔH_∞, and $t_{\phi(t)=0.5}$ for Sucrose and the Mixtures Aged at 61°C

	T_g-T_a (C°)	ΔH_{750} (J/g)	ΔH_∞ (J/g)	$t_{(\phi=0.5)}$ (hours)
Sucrose	17	9.7 ± 0.4	10.9 ± 0.6	3
10% trehalose	18	10.6 ± 0.1	11.9 ± 0.5	6
10% PVP/VA	18	9.4 ± 0.7	10.8 ± 0.4	10
10% PVP	20	12.1 ± 0.6	12.4 ± 0.4	30
10% dextran	20	11.2 ± 0.1	12.6 ± 0.6	30

a sucrose-dextran mixture (8). Following the longest aging time, 750 hours, the total enthalpy change measured for all of the mixtures was on the order of 10–14 J/g (see Table II).

One explanation for the reduced enthalpy changes that were observed for the mixtures relative to sucrose alone (Fig. 3) is a dilution effect due to the presence of the additive. This assumes that the additives do not contribute significantly to the total relaxation of the mixture at 61°C. To test for such a possible effect, a 10% dilution of the enthalpy changes for sucrose alone are shown in comparison to the data obtained for the mixtures at the shorter aging times in Fig. 3. All of the mixtures exhibited enthalpy changes that were reduced beyond what can be predicted from simple dilution, with the exception of trehalose. The apparent correlation of the enthalpy relaxation of the trehalose mixture with a dilution effect is most likely coincidental since it is difficult to rationalize why an additive, which is also a disaccharide having a T_g only 35°C greater than sucrose, would not contribute significantly to the relaxation of the mixture. In view of these results in general, we would conclude that molecular interaction of sucrose with each of the components most likely leads to some coupling of molecular motion. Thus, the mobility of the mixture is the net result of the effect of each component on the mobility of the other. Support for this hypothesis is provided by the results of a previous study which showed that significant interaction occurs through hydrogen bonding of the components of two of the mixtures used in this study, sucrose and PVP and sucrose and PVP/VA (10). It appears from this study, therefore, that such interactions may be important to the observed difference in the enthalpy relaxation for all of the sucrose systems in comparison to sucrose alone.

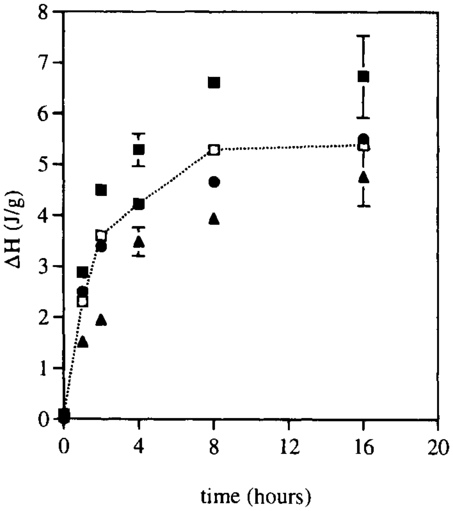

Fig. 4. ΔH values for sucrose mixtures containing 20% PVP; sucrose (■), a physical mixture with 20% PVP (●) and co-lyophilized mixture with 20% PVP (▲). Prediction of a 20% dilution in the ΔH values changes for amorphous sucrose (line connected by symbols).

Enthalpy Relaxation of Physical Mixtures of Sucrose and PVP

To further test the importance of the molecular interaction to the enthalpy relaxation of a miscible amorphous solution, it was of interest to compare the enthalpy relaxation of a co-lyophilized mixture with one that was prepared by physically mixing the individual amorphous components. For this purpose mixtures containing 20% PVP were chosen. The larger amount of additive relative to 10% w/w used in the other studies was selected to insure optimal physical mixing and sample homogeneity.

The T_g, ΔC_p and ΔT_{gw} for the sucrose mixtures containing 20% PVP are listed in Table I. Note that the values of T_g, ΔC_p and ΔT_{gw} for the physical mixture are very close to those for sucrose alone, whereas for the co-lyophilized sample these values are quite different. The enthalpy changes for sucrose (T_a = 61°C), the physical mixture at 61°C (T_g-T_a = 15°C) and the co-lyophilized mixture at 69°C (T_g-T_a = 16°C) are compared in Fig. 4, where it can be seen that ΔH values for the physical mixture are smaller than for sucrose alone, even though the aging temperature is 8°C higher. It is likely in the case of the physical mixture that the observed enthalpy changes are associated only with the relaxation of the sucrose since this represents a T_g-T_a of 117°C for PVP where minimal enthalpy changes are expected (5). Assuming this to be the case, the ΔH values for the physical mixture were compared to a value represented by a 20% dilution of the enthalpy relaxation of the sucrose shown as the dotted line in Fig. 4. The coincidence of these two curves in Fig. 4 strongly suggests that a dilution effect is indeed responsible for the smaller enthalpy changes for the physical mixture relative to those for sucrose. The enthalpy changes for the co-lyophilized mixture containing the same proportion of PVP measured at the same T_g-T_a were significantly less than not only those for sucrose but also the physical mixture (Fig. 4). As was the case for the co-lyophilized mixtures containing 10% additive, the decrease in the enthalpy relaxation of the co-lyophilized mixture containing 20% PVP is in excess of what could be explained by a simple dilution effect. This result confirms that the enthalpy relaxation of sucrose is affected by the presence of PVP only when sucrose and PVP are mixed at the molecular level.

DISCUSSON

Relaxation to the Supercooled Liquid State

The results of this study show that only when an antiplasticizing component is combined with sucrose in the form of a molecular dispersion does that component have an effect on the enthalpy relaxation, and hence molecular mobility, of sucrose. To gain a better quantitative understanding of the relative effects that the different additives have on the mobility of the co-lyophilized sucrose mixtures containing 10% additive, the extent of relaxation of the different mixtures was first compared with respect to the total enthalpy change that was required for the mixtures to relax from the glassy state to an equilibrium supercooled liquid. For this discussion the supercooled liquid is regarded as an equilibrium state in relation to the glassy state while recognizing that it is actually a pseudo-equilibrium state since the crystal is actually the lowest energy state in this temperature regime. The enthalpy change that is necessary for a glass to relax to a supercooled liquid state depends upon the degree of supercooling (temperature) and the thermal history of the glass (time). Since these glasses were subjected to the same thermal treatment prior to aging, the enthalpy change needed to reach a pseudo-equilibrium state depends only on the degree of supercooling. In theory the enthalpy change necessary for a glass to relax to a supercooled liquid (ΔH_∞) increases linearly as the degree of supercooling increases as described by the equation (11),

$$\Delta H_\infty = \Delta C_p(T_g - T_a) \tag{1}$$

where ΔC_p, the difference in the heat capacity of the supercooled liquid and glassy states at T_g, is assumed to be constant from T_a to T_g. The ∞ symbol is invoked because in theory an equilibrium state cannot be achieved due to the self-limiting character of structural relaxation in glasses (12). Structural relaxation of glasses is self-limiting because of the decrease in volume and in the degree of molecular mobility accompanying the loss in enthalpy. As a consequence, there is an asymptotic approach to the equilibrium state and a corresponding enthalpy change associated with an equilibrium state (ΔH_∞). The degree of undercooling (T_g-T_a) for sucrose and each of the mixtures at an aging temperature of 61°C is listed in Table II. The values range from 17–20°C and are not significantly different for sucrose and the mixtures containing 10% trehalose and 10% PVP/VA. However, for mixtures with 10% PVP and 10% dextran there is a small but significant increase in the degree of undercooling (i.e., 3°C) relative to the other systems. The T_g-T_a values were used in conjunction with the ΔC_p values (Table I) to estimate ΔH_∞ using Eq. 1. The ΔH_∞ values for sucrose and the mixtures listed in Table II range from 12–14 J/g and are not significantly different from one another. Thus, Eq. 1 predicts that when mixed with sucrose the additives do not significantly alter the enthalpy change required for the glasses to relax to a pseudo-equilibrium state.

Having shown that sucrose and the mixtures will undergo similar changes in enthalpy in the approach to equilibrium supercooled liquid states, it was of interest to compare the ΔH values measured at the longer aging times in relation to the estimated ΔH_∞. As shown in Table II, the enthalpy changes measured after aging for 750 hours appear to be approaching values that are similar magnitude to the ΔH_∞ values predicted using Eq. 1. Within the limits that they could be measured or predicted the values of ΔH_{750} and ΔH_∞ are comparable to one another. The close approach of the experimental ΔH values to those predicted from Eq. 1 also has been observed for glassy polymers that were aged for several hundred hours at a similar degree of undercooling to that used in this study (13). This establishes that ΔH_∞ values predicted using Eq. 1 do indeed represent the enthalpy change that is required for sucrose and sugar-mixtures to approach a pseudo-equilibrium state for this particular aging temperature.

Relationship Between Aging Time and the Proportion of Glass that Has Relaxed

In addition to the total enthalpy changes that may accompany the approach to a equilibrium supercooled liquid, it is important to consider the rate at which these different systems relax. The enthalpy changes measured at different aging times can be normalized with respect to the change in enthalpy that is required for the glass to relax to an equilibrium supercooled-liquid state using the equation (4),

$$\phi(t) = 1 - \frac{\Delta H}{\Delta H_\infty} \tag{2}$$

where $\phi(t)$ is the proportion of the glass that has relaxed at time t. The ΔH values measured for sucrose and the mixtures were normalized to the values of ΔH_∞ (Table II) obtained from Eq. 1 and the extent of relaxation for sucrose and the mixtures versus aging time is shown in Fig. 5. For each of the mixtures a smaller proportion of the mixtures has relaxed in comparison to sucrose alone at any given aging time. The rate that the mixtures approach a pseudo-equilibrium state differs in the order: trehalose > PVP/VA > PVP ≈ dextran.

One way to describe the rate of relaxation by amorphous materials is to use the Kohlrausch-Williams-Watts equation (KWW) (5,11,13). The KWW equation (Eq. 3) is a stretched exponential function that describes the approach to a fully relaxed state (14),

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

where τ and β are relaxation time constants. The constant, τ, is a characteristic or average relaxation time and β describes the extent to which the relaxation process is non-exponential. Typically relaxation processes in amorphous systems are non-exponential, in which case β takes on a values less than one and both τ and β are necessary to describe the relaxation process, particularly as $\beta \rightarrow 0$.

While the relaxation of sucrose has been described by the KWW expression with reasonable values of τ and β, i.e.,

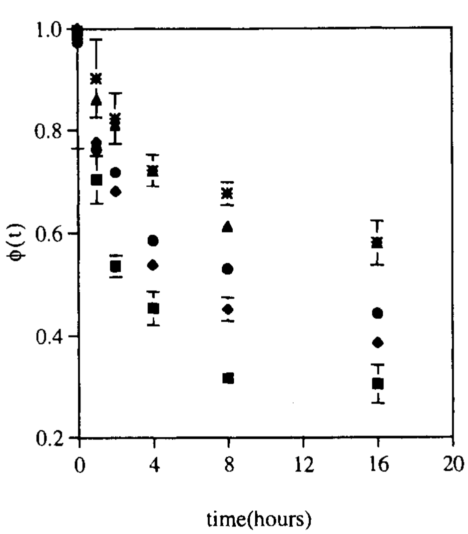

Fig. 5. Proportion of glass that has relaxed with aging time. sucrose (■); 10% trehalose (◆); 10% PVP (●); 10% PVP/VA (▲); 10% dextran (✱).

τ = 12 hours, β = 0.51 at 61°C (5), this was not the case for the sucrose mixtures in this study. Generally there was significant error associated with the estimation of τ and β using a non-linear regression algorithm to describe experimental data with Eq. 3, preventing any meaningful comparisons from being made. The inability of the KWW expression to describe the relaxation of the mixtures most likely indicates that there are significant differences in the distribution of relaxation times for the mixtures in comparison to single component amorphous materials. The relaxation processes of amorphous materials are very complex to begin with, and as indicated by Eq. 3, an accurate description of such processes usually requires two parameters (τ and β) even for a single component. It is likely that in multi-component systems there is a more complex distribution of relaxation times, and consequently, a simple expression like the KWW equation cannot accurately describe the relaxation. It is also possible that the observed differences in relaxation process of the mixtures, in comparison to sucrose alone, are a consequence of a different distribution of relaxation processes. Evidence for this has been demonstrated with dielectric and dynamic mechanical techniques which have shown that relaxation processes in mixtures occur over a broader range of temperatures or frequencies than single component amorphous materials (15,16). For the sucrose mixtures in this study the width of the glass transition was shown to be slightly larger than for sucrose alone again suggesting that there may be heterogeneities in the molecular dynamics that are in excess of those in the single components (17–19). In this context the midpoint T_g may represent an "average" T_g. At this temperature some molecular clusters may have become fluid-like while others still have a local viscosity that is characteristic of a glass. Due to this variation in viscosity at the molecular level, there is very likely a different proportion of the glass that can undergo structural relaxation in comparison to a single component at comparable degrees of undercooling. This means that at any aging temperature below the midpoint T_g, which represents an average T_g, there may be a smaller contribution to the relaxation from regions with the highest local viscosity. It follows then that as the width of the T_g region increases, a smaller proportion of the glass contributes to the relaxation. This could also be one explanation for the inability of the KWW expression to describe the relaxation of these mixtures.

In spite of these uncertainties the time required for each glass to reach a semi-relaxed state (50% of ΔH_∞) was evaluated in an attempt to learn more about the relaxation of the mixtures in quantitative terms. This time ($t_{\phi(t)=0.5}$) can be determined from plots of ΔH versus log time shown in Fig. 6. The exact value of $t_{\phi(t)=0.5}$ was determined by fitting a straight line through the data and solving for $\phi(t)$ = 0.5. The $t_{(\phi(t)=0.5)}$ values for sucrose and the mixtures are listed in Table II. Generally, this time increases relative to that for sucrose indicating the extent to which the mixtures relax more slowly than sucrose alone.

Although mixing sucrose with antiplasticizing components results in a decrease in the rate of relaxation that is somewhat related to the order of the T_g of each individual additive, this cannot be explained by a significant shift in the T_g of the mixtures relative to T_a since such shifts were negligible or at best small; there was at most a three degree increase in T_g for mixtures containing either PVP or dextran relative to sucrose and this in turn resulted in only a slightly larger T_g-T_a for these mixtures. Such a small shift in T_g relative to T_a may not seem sufficient to yield differences in the relaxation of the mixtures with dextran and PVP from that of sucrose alone and the mixtures with trehalose and PVP/VA. However, the significance of a three degree shift in temperature with respect the rate at which a material relaxes is governed by the dependence of these processes on temperature. Relaxation processes for most amorphous materials are non-Arrhenius in their temperature dependence and the apparent activation energies vary with temperature. Typically the temperature regime where the apparent activation energy changes the most is in the region of the T_g. For very fragile materials, changes in temperature of 3–5°C can lead to changes in the rate of relaxation on the order of one decade (14). It has been shown in previous studies that the temperature dependence for the enthalpy relaxation values of sucrose, trehalose, and PVP alone are non-Arrhenius (5,6) indicating that to some extent they are fragile. It is reasonable to assume that these sucrose mixtures are also fragile and that it is this sensitivity to small changes in temperature that may in fact contribute to differences in the rate of relaxation due to even a very small and apparently insignificant shift in T_g relative to T_a. However, it is important to stress that even trehalose and PVP/VA, which did not increase the T_g of sucrose at a level of 10%, had a significant retarding effect on enthalpy relaxation.

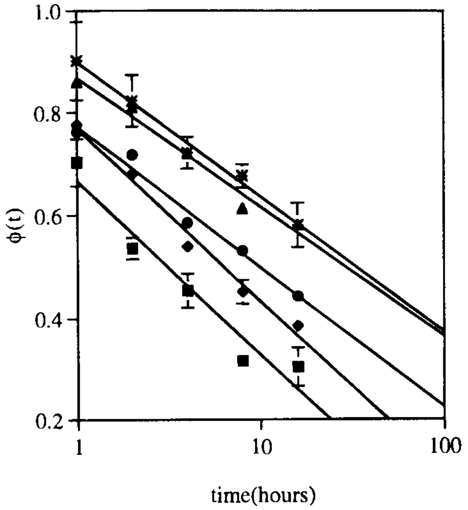

Fig. 6. Proportion of glass that has relaxed with aging time plotted on a logarithmic scale; sucrose (■); 10% trehalose (◆); 10% PVP (●); 10% PVP/VA (▲); 10% dextran (✻). The straight lines through the symbols represent linear fits to the data using least squares regression. The time at $\phi(t)$ = 0.5, $t_{(\phi(t)=0.5)}$, obtained from these fits are listed in Table II.

SUMMARY

The enthalpy changes associated with the approach of amorphous sucrose alone and co-lyophilized with different additives to an equilibrium supercooled-liquid state were measured at a single temperature below T_g using DSC. The enthalpy changes for the different mixtures were significantly less than for sucrose alone and dependent on the additive that was mixed with sucrose. The enthalpy change required to reach a pseudo-equilibrium state is approximately the same for sucrose and the mixtures. However, the rate that sucrose and the mixtures approach a relaxed state is reduced for the mixtures, with those containing high molecular weight polymers being the slowest. Thus, although these mixtures have T_g values that are similar to sucrose, the molecular mobility of such mixtures near the glass transition temperature is reduced relative to sucrose. The decrease in mobility is attributed to interactions between the components that lead to coupling of the molecular motions of sucrose to the additive, and in part to heterogeneities in the molecular dynamics that are not present in single component amorphous materials.

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