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THE EFFECTS OF CO-LYOPHILIZED POLYMERIC ADDITIVES ON THE GLASS TRANSITION TEMPERATURE AND CRYSTALLIZATION OF AMORPHOUS SUCROSE

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Abstract

The purpose of this study was to measure the effect of co-lyophilized polymers on the crystallization of amorphous sucrose, and to test for a possible relationship between the ability of an additive to raise the T_g of a sucrose-additive mixture, relative to the T_g of pure sucrose, and its ability to inhibit crystallization. Differential scanning calorimetry was used to measure the glass transition temperature, T_g, the non-isothermal crystallization temperature, T_c, and the induction time for crystallization, Q, of sucrose in the presence of co-lyophilized Ficoll or poly(vinylpyrrolidone) (PVP). The effect of these polymers on the crystallization of sucrose was significant as demonstrated by a marked increase in T_c, and in the induction time (Q) in the presence of relatively small amounts (1–10%) of additive. Surprisingly, small amounts of polymeric additive had no effect on the T_g of sucrose, although at higher concentrations, the T_g increased proportionally. Thus, it appears that the inhibition of sucrose crystallization by the additition of small amounts of a higher-T_g component cannot be attributed solely to changes in molecular mobility associated with an increase in T_g.

Keywords: amorphous, crystallization, glass transition temperature, sucrose

Introduction

The properties and applications of sucrose are of widespread interest in the food science and pharmaceutical science fields, and they have been the subject of much research over the past several decades [1]. Under certain processing conditions, crystalline sucrose can undergo partial or complete transformation to a disordered, higher energy, amorphous solid state. Such transformations may occur unintentionally during normal drying and milling operations, or they may be intentionally caused to occur by processes such as lyophilization, spray-drying or coating, to take advantage of certain properties that are characteristic

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of the amorphous state. Once in this higher energy state, however, sucrose exhibits a strong tendency to crystallize, particularly at higher temperatures and relative humidities. Therefore, it would be important to be able to predict such behavior and to inhibit it if so desired.

The earliest comprehensive studies of sucrose crystallization from the amorphous state were carried out by Makower and Dye [2] and Palmer *et al.* [3], who exposed amorphous sucrose to various relative humidities in the range of 4.6 to 33.6% at 25°C, and then followed the time required for the first appearance of crystallization, as reflected in an initial loss of sample weight due to the expulsion of absorbed water, i.e. an induction period. It was found that the induction period was reduced from years or months to days or hours, as the relative humidity (RH) was increased above 20%. Similar experiments using amorphous lactose and sucrose have also been reported [4, 5]. Using the same technique with sucrose at 30°C, Saleki-Gerhardt and Zografi [6] showed that the induction time at 32.4% RH was about 18 h, and that this period was shortened to 8 and 3 h by adding 10% and 88% by weight, respectively, of crystalline sucrose. Presumably, the addition of crystalline sucrose increased nucleation rates by seeding the process. Differential scanning calorimetry (DSC) was also used to induce non-isothermal crystallization of sucrose containing 1 to 3% absorbed water. Saleki-Gerhardt and Zografi were also able to measure the effects of absorbed water on T_g, the glass transition temperature, T_c, the crystallization temperature, and T_m, the melting temperature. It was shown that increasing water content reduced all three temperatures, and that T_c always fell roughly mid-way between T_g and T_m, supporting a direct correlation between the effect of water as a plasticizer in reducing T_g and its effect on T_c [7]. Since T_g reflects the mechanical or dynamic relaxation behavior of a solid in the amorphous state at a particular temperature T, it was concluded that crystallization rates were directly linked to the temperature difference between T and $T_g(T-T_g)$, where greater differences were associated with greater relaxation rates, and a greater degree of molecular mobility, and hence a greater tendency for crystallization to occur. Direct support for this concept has been provided by the work of Roos and Karel [5], in which they measured isothermal induction times, Q, for the crystallization of sucrose and lactose in the dry state, using DSC to follow the heat of crystallization. Using values of Q as a measure of crystallization rate at various values of $T-T_g$, they attempted to fit the data to a form of the WLF (Williams-Landel-Ferry) equation [8], expressed as:

$$\log Q = \log Q_g - \frac{C_1(T - T_g)}{C_2 + T - T_g} \tag{1}$$

where Q_g is the induction time at T_g, and C_1 and C_2 are the WLF constants.

It was concluded that for dry sucrose and lactose, as well as some samples containing water [9], Equation 1, using the universal constants of 17.4 and 51.6 for C_1 and C_2, respectively, adequately fit the data, and therefore, that the crystallization behavior of these sugars could be scaled to T_g. Recently, Nelson and Labuza [10] have argued that this conclusion may be inappropriate, since an adequate fit was also possible using other values of C_1 and C_2. Futhermore, the relatively narrow range of temperatures over which such data can be obtained may allow fit of the Arrhenius equation to these data. Putting aside the question of exact fit, based on all work done to date with both dry and moist sucrose, it would appear that some relationship exists between T_g and the tendency for sucrose to crystallize at some temperature, T, above T_g. Previous work also suggests that using additives that raise the overall T_g above that of pure sucrose should reduce molecular mobility and inhibit crystallization.

To date, few studies have systematically examined the crystallization of sucrose in the presence of co-amorphous additives, where the additive had a higher T_g than that of sucrose. Van Scoik and Carstensen [11] demonstrated an inhibiting effect on induction times associated with crystallization at 30°C and 33.6% RH in the presence of gelatin, raffinose, invert sugar or fructose, but developed no relationships in the context of T_g. Saleki-Gerhardt and Zografi [6] used co-lyophilized mixtures of sucrose with raffinose, trehalose or lactose, and measured isothermal crystallization at 30°C and 33.6% RH, as well as T_g and T_c from non-isothermal measurements. The three sugar additives all had values of T_g around 100°C and did not crystallize at 30°C and 33.6% RH under the conditions of these experiments. In all cases, significant inhibition of sucrose crystallization occurred at levels as low as 1–10% w/w additive. The effects of the two disaccharides were almost identical; however, raffinose, a trisaccharide, despite having the same T_g, seemed to be slightly more effective as an inhibitor of crystallization. This suggested that more specific effects, in addition to changes in T_g, might have occurred in this case, but the differences in T_g between sucrose and the other sugars were quite small, and it was difficult to test these ideas further with these systems. The purpose of the present study was to use co-lyophilized mixtures of sucrose and selected polymers, the latter having much higher T_g values than sucrose, and to test the hypothesis that the crystallization inhibition observed in the previous study is directly scaled to changes in T_g. The polymers chosen for this study were poly(vinylpyrrolidone) (PVP) and Ficoll, a crosslinked poly(sucrose).

Experimental

Materials

Crystalline sucrose was obtained from J. T. Baker Chemical Co. (99.8% purity), Ficoll 400, a polymer of sucrose molecules crosslinked with epichlorohydrin, was obtained from Sigma Chemical Co. PVP K90 was obtained from GAF Chemical Co. The Ficoll and PVP samples had stated weight-average molecular weights of 400.000 and 1.000.000, respectively. The polydispersity values of both samples were unreported by the suppliers.

Sample preparation

Amorphous sucrose was prepared by lyophilizing a 10% w/v aqueous solution of sucrose, using an FTS Systems (Stone Ridge, NY) tray-dryer coupled with a Dura-Dry MP condenser module. The sucrose solution was cooled to –45°C, and the pressure was reduced to 50 mTorr or less and then held for 72 h. The temperature was then raised successively as follows: –35°C for 24 h; –30°C for 24 h; –20°C for 24 h; –10°C for 12 h; and 0°C for 12 h. Secondary drying of amorphous sucrose was performed at 25°C for 24 h and then at 60°C for 48 h. Following secondary drying, the moisture content of amorphous sucrose was less than 0.1%, as determined by Karl Fisher titration (Aquastar® C2000, EM Science, Cherry Hill NJ).

Amorphous mixtures were prepared by lyophilizing solutions of components that had been combined at proper proportions in the dry state to give a final concentration of 10% w/v. Prior to preparation of the mixtures, sucrose was dried at a pressure of 100 mTorr and a temperature of 95°C (2 h), and Ficoll and PVP were dried under vacuum at 105°C (12 h).

Measurements of the T_g and T_c of sucrose in the presence of co-lyophilized additives

The T_g and non-isothermal T_c of sucrose alone and in the presence of co-lyophilized additives were measured using a Seiko SSC 220/5200 DSC (Seiko Instruments, Horsham PA). DSC experiments were performed using a dry nitrogen purge through the instrument. The instrument was calibrated using tin, indium and gallium as standard materials.

Sucrose and sucrose-additive mixtures were analyzed by DSC using heating and cooling rates of 20°C min^{-1}, unless otherwise stated. Samples were first heated to a temperature 20°C above T_g, cooled to 100°C below T_g using a liquid nitrogen cooling accessory, and then heated a second time to 200°C. This procedure was used to give all samples a similar thermal history. The T_g was recorded during the second scan as the onset of the change in heat capacity at the glass transition, and the non-isothermal T_c of sucrose was recorded as the temperature corresponding to the maximum of the exothermic peak associated with crystallization. To measure the effect of heating rate, the T_g and T_c of sucrose alone and in the presence of 5% additive were measured as a function of heating rate during the second scan, using the procedure described above.

Isothermal crystallization of sucrose

The isothermal crystallization of sucrose alone and in the presence of co-lyophilized additives was measured as a function of temperature, using DSC, as originally described by Roos and Karel [5]. Samples were first heated to 20°C above T_g, cooled to 100°C below T_g, and then heated a second time to a predetermined temperature 20–80°C above T_g, using heating and cooling rates of 20°C min^{-1}. Samples were held at each temperature for 3 hours or until crystallization was observed while monitoring the thermal activity. The induction time for crystallization was defined as the time elapsed from when the appropriate temperature was attained to the onset of the exothermic peak associated with crystallization.

Density measurements

The densities of amorphous sucrose, Ficoll and PVP were determined using a Quantachrome Multipycnometer (Quantachrome, Boyton Beach, FL). Measurements were made using helium as the purge gas and were performed at 25°C. The densities of amorphous sucrose, Ficoll and PVP, using this technique, were determined to be 1.43, 1.38 and 1.25 g cm^{-3}, respectively.

Results

T_g

The T_g values for various sucrose-additive mixtures, measured by DSC at a heating rate of 20°C min^{-1}, are reported in Table 1 as the average of 2–3 replicate scans. The uncertainty associated with these numbers is 1–2°C. Previous studies over a range of scanning rates had revealed changes in T_g of 2–10°C for various systems [12, 13]; thus, a heating rate of 20°C min^{-1} was chosen as a representative and convenient rate for measurement of T_g. At low additive concentrations (1–10%), the T_g values were nearly equal to that for pure sucrose, while at higher concentrations, the T_g increased with increasing additive concentration, as expected. In addition, we observed that PVP consistently produced higher T_g values in a mixture of the same % composition, as might be expected, since PVP has a higher T_g than that of Ficoll.

Table 1 Glass transition temperatures of co-lyophilized sucrose-polymer mixtures

Additive, % (w/w)	PVP K90 T_g/°C	Ficoll 400 T_g/°C
0	74	74
1	74	73
5	75	73
10	76	74
20	80	76
25	86	76
50	99	80
80	152	103
100	178	132

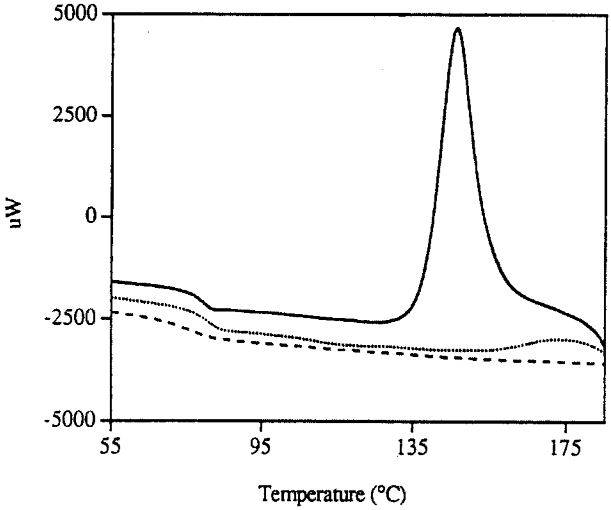

Fig. 1 T_g and T_c of amorphous sucrose alone and co-lyophilized with 5% and 10% PVP, measured by DSC at a heating rate of 20°C min^{-1}: — pure sucrose; ..... 5% PVP; ----- 10% PVP

Non-isothermal T_c

Figure 1 shows typical DSC traces for pure sucrose and sucrose in the presence of 5 and 10% PVP, measured at a heating rate of 20°C min^{-1}. The progressive loss of the peak area associated with crystallization indicated that the inhibition of crystallization at low additive concentration had occurred. Figure 2 shows plots of T_c *vs.* heating rate, over a range of 2–40°C min^{-1}, for pure sucrose and for mixtures containing 5% polymer. Clearly, the value of T_c depended on the rate, of heating; however, it appeared to be leveling off in the vicinity of 20°C min^{-1}, and perhaps more importantly, the relative effects of heating rate shown in Table 2, were very similar for all three systems. From the T_c values measured at a heating rate of 20°C min^{-1}, we see that as little as 5% additive had a very significant effect in both cases, and that no crystallization was observed for mixtures containing 10% and greater PVP and 25% and greater Ficoll.

Isothermal crystallization

The induction times, Q, for the crystallization of sucrose and sucrose-additive mixtures are presented as a function of temperature in Table 3. The values reported represent an average of 2–3 replicate scans, and the uncertainty associated with each of these values is roughly 1–2 min. The largest error in this measurement occurs at the higher $T–T_g$ values where the time for crystallization is short relative to the time of the experiment. Data for the various systems revealed little differences in Q values between those for pure sucrose and 1%

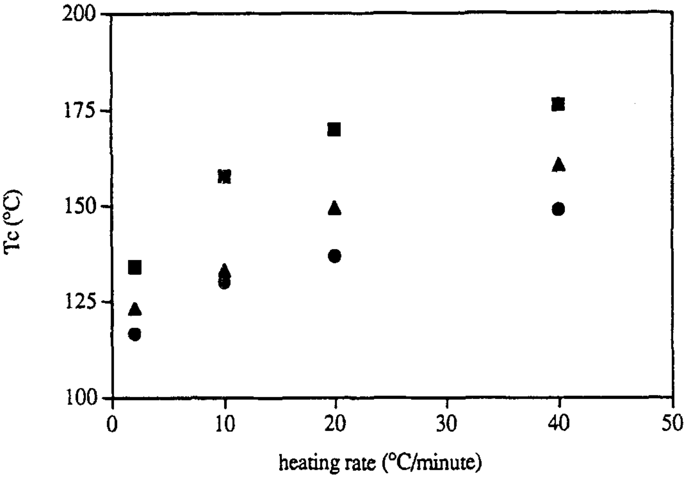

Fig. 2 The effect of heating rate on the T_c of amorphous sucrose alone and in the presence of 5% Ficoll and 5% PVP: ● pure sucrose; ▲ sucrose with 5% Ficoll; ■ sucrose with 5% PVP

Table 2 The effect of co-lyophilized polymers on the non-isothermal crystallization temperature, T_c, of amorphous sucrose

Additive, % (w/w)	PVP K90 T_c/°C	Ficoll 400 T_c/°C
0	140	140
1	147	141
5	169	151
10	173	160
20	nc	170
25	nc	171

nc = no crystallization observed

mixtures with either Ficoll or PVP. However, very significant effects occurred at 5–10% additive, as reflected by great increases in the induction times.

Discussion

From earlier studies dealing with crystallization of sucrose from the amorphous state, dry or in the presence of residual water, there appears to be a direct relationship between the rate and extent of crystallization and the T_g of the system. If we assume that crystallization is dominated in these cases by the molecular mobility of sucrose in such systems, then a correlation is reasonable. Recognizing the uncertainty in using the WLF equation over a limited temperature range, as opposed to the Arrhenius equation, in Fig. 3 we show, in agree-

Table 3 Isothermal induction times (in minutes) for crystallization of sucrose alone and in the presence of co-lyophilized additives at various temperatures

T/°C	Pure sucrose	1% Ficoll	5% Ficoll	10% Ficoll	1% PVP	5% PVP	10% PVP
95	136.4	156.7					
100	63.1	56.6	97.8	133.9	89.2		
105	28.1	19.9	37.5	64.5	29.0		
110	9.0	5.5	13.8	31.5	18.0	75.6	
115	2.7		4.3	13.7	3.6	52.6	
120				4.4	1.8	30.0	108.7
125						17.4	59.6
135						5.8	24.0
145						2.9	15.7
155							3.5

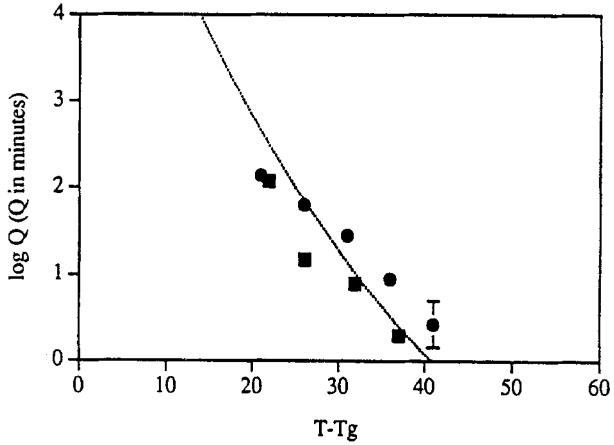

Fig. 3 Induction time for crystallization of pure sucrose as a function of temperature relative to T_g: • this study; ■ Roos and Karel [5]; ----- fit of the WLF eq., using universal constants

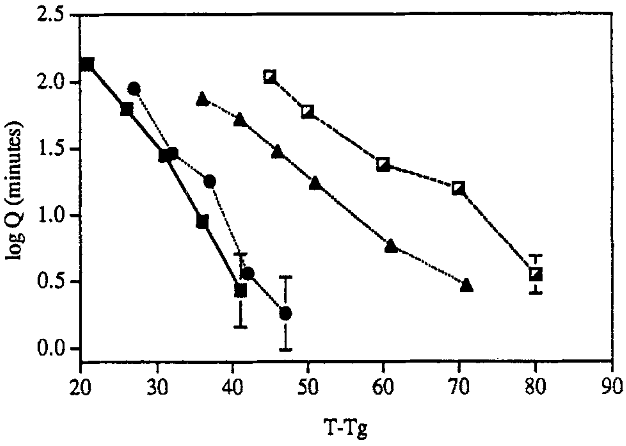

Fig. 4 Log$Q$ for sucrose alone and in the presence of 1%, 5%, and 10% PVP, as a function of temperature scaled to T_g: ■ pure sucrose; • 1%PVP; ▲ 5% PVP; □ 10% PVP

ment with Roos and Karel [5], that Eq. [1], using the universal WLF constants, does fit the data for dry sucrose reasonably well. If, indeed, molecular mobility were the sole factor controlling the inhibition of sucrose crystallization by PVP and Ficoll, illustrated in Table 3, we would expect the plot of log Q *vs.* T–T_g for these data to superimpose on the same line for all samples containing sucrose. Clearly, as seen in Figs 4 and 5, this was not the case, particularly for the 5 and 10% PVP and Ficoll samples. What is also important to note is that significant inhibiting effects on crystallization occurred in all cases at compositions where the T_g of sucrose was hardly changed by the additive, despite its much higher

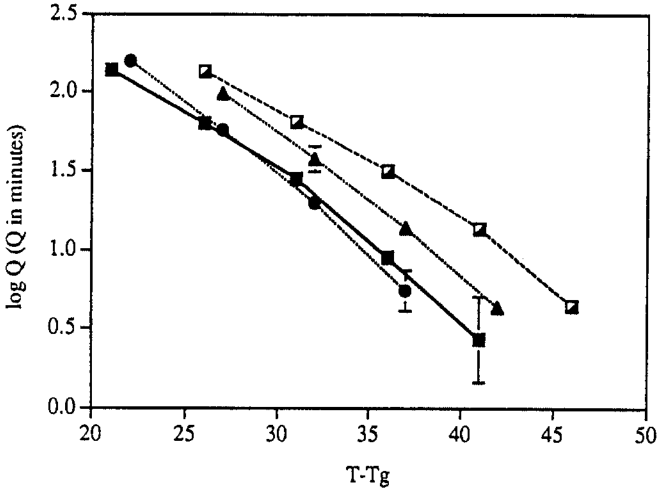

Fig. 5 Log$Q$ for sucrose alone and in the presence of 1%, 5%, and 10% Ficoll, as a function of temperature scaled to T_g: ■ pure sucrose; • 1% Ficoll; ▲ 5% Ficoll; □ 10% Ficoll

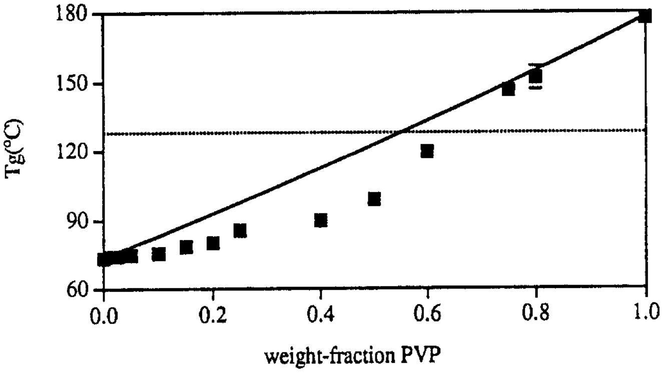

Fig. 6 T_g of sucrose-PVP mixtures *vs.* weight-fraction PVP: ■ experimental values; — Eq. (2) in text; ..... T^* from Eq. (5) in text

T_g. Thus, to understand why these additives act as crystallization inhibitors of sucrose in the amorphous state, it appears that we must look for other factors more associated with the molecular environment in these mixtures and the thermodynamic and geometric factors that control nucleation.

In the context of the T_g measurements presented in this paper, however, we may gain some perspective, if we can better understand why the values of T_g for the various mixtures remained equal or very close to that of pure sucrose, over the range where significant crystal inhibition was observed (Table 3). To put this observation into better perspective, we show, in Figs 6 and 7, plots of T_g *vs.* weight-fraction of polymer, along with predictions based on the Gordon-Taylor

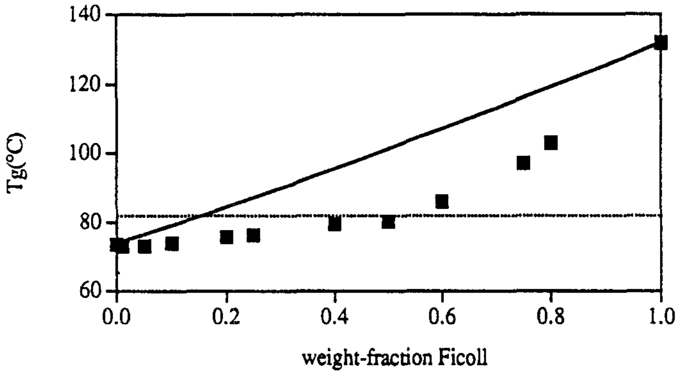

Fig. 7 T_g of sucrose-Ficoll mixtures *vs.* weight-fraction Ficoll: ■ experimental values; — Eq. (2) in text; ..... T^* from Eq. (5) in text

equation, which assumes ideal mixing of free volumes from each component [14]. Here,

$$T_g = \frac{w_1 T_{g1} + K w_2 T_{g2}}{w_1 + K w_2} \tag{2}$$

where w_1 and w_2 are weight-fractions of each component, and T_{g1} and T_{g2} are the corresponding T_g values of each component. The value of K can be conveniently estimated with knowledge of the densities (ρ_1, ρ_2) of both components, using the Simha-Boyer [15] rule, to give:

$$K \approx \frac{T_{g1}\rho_1}{T_{g2}\rho_2} \tag{3}$$

Equation 2 has been shown to be applicable for small- and large-molecule systems [6, 16]; however, as seen in Figs 6 and 7, there are significant negative deviations from expected ideality for both systems, with some indication that PVP assumes more ideal behavior around weight-fractions at and above 0.8. What is particularly interesting, as mentioned earlier, is the apparent lack of antiplasticizing (i.e. T_g-elevating) [7] effects of these materials over a very wide range of composition, despite their complete miscibility with sucrose.

In the context of polymer blends, a number of approaches have been used to correct the Gordon-Taylor equation for such non-idealities. In one approach, Kovacs proposed that the T_g of a mixture of components with large differences in their T_g values cannot be predicted at certain intermediate compositions, because of the limited temperature range over which free-volume additivity is valid [17].

The free volume of a component in a mixture is defined as [17]:

$$f_i = f_{gi} + \Delta\alpha_i(T^* - T_{gi}) \tag{4}$$

where f_{gi} is the free volume at T_g, $\Delta\alpha_i$ is the thermal expansion coefficient for free volume above T_{gi}, and T^* is the T_g of the mixture that corresponds to the critical concentration of the *i*th component. When the difference between T^* (T_g of a mixture) and the T_g of the higher-T_g component becomes negative, f_i becomes zero. Below this critical temperature and corresponding critical composition, this equation predicts a contribution to free volume, from the higher-T_g component, which is negative and thus physically meaningless. The critical temperature for a higher-T_g component in a binary mixture can be calculated by setting Eq. (4) to zero and solving for T^*. Rearrangement of Eq. (4), to give T^* for the higher-T_g component, is shown as Eq. (5), where the subscript 2 represents values corresponding to the higher-T_g component.

$$T^* = T_g - \frac{f_{g2}}{\Delta\alpha_2} \tag{5}$$

The T^* values for Ficoll and PVP, calculated assuming the universal values for f_{g2} (0.025) and $\Delta\alpha$ (0.000484) [8], are approximately 50°C below T_g, i.e. 82°C and 125°C for Ficoll and PVP, respectively. Interestingly, as seen in Fig. 6 , the T^* (represented by the dotted line) corresponds closely to the temperature below which the T_g values for sucrose-PVP mixtures show significant deviation. In the case of Ficoll (Fig. 7), however, deviation of the T_g values extends well above and below the critical temperature, and suggests that use of the universal constants to predict T^* (dotted line) for Ficoll may not be valid, possibly due to its crosslinked nature. The Kovacs theory, however, does offer some insight to the limits in the ability of a higher-T_g component (polymer) to reduce the free volume of a small molecule (sucrose), in that it shows that the ability of an additive to raise T_g may be expected to be non-ideal, when the difference in the T_g values of the two components becomes significant.

A number of other models have been proposed, which attempt to correlate empirically obtained fitting parameters to factors that contribute to non-ideal behavior in polymer blends [18–20]. Collectively, these models use the concepts of non-ideal volume additivity, specific interactions between components, and the tendency for demixing to explain observed deviations. Based on a thermodynamic interpretation of the meaning of these models, it appears that strong interactions between two components should lead to T_g values that are greater than values predicted from Eq. (4), whereas negative deviations would be expected in systems with a tendency towards demixing (greater interactions between like components). However, to date, our attempt to fit such models to sucrose-polymer systems has not offered any additional insight to the sources of the observed non-ideal behavior. We believe that this may be intrinsic to the combination of a small molecule with a polymer, bringing into play geometric factors not taken into account by these models, such as the effects associated with the accumulation of polymer at the surface of individual sucrose particles. Consequently, in future work, we plan to take into account chemical similarities and dissimilarities, as well as relative molecular size, and will extend the range of materials to be mixed with sucrose.

Conclusion

Using DSC, we have studied non-isothermal and isothermal crystallization of sucrose from amorphous co-lyophilized mixtures with the polymers, PVP and Ficoll. We found significant inhibition of sucrose crystallization at weight concentrations of additive as low as 1–10%. Analyses of the isothermal data, in the context of the effects of additives on T_g, revealed that these additives produced very little change in T_g in the concentration range where significant inhibition of crystallization occurred. It was concluded, therefore, that the effects of these additives are not linked directly to the glass transition, and that other factors involved in the crystallization process should be examined in the context of such mixture effects.

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