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The Effects of Absorbed Water on the Properties of Amorphous Mixtures Containing Sucrose

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Purpose. To measure the water vapor absorption behavior of sucrose-poly(vinyl pyrrolidone) (PVP) and sucrose-poly(vinyl pyrrolidone co-vinyl acetate) (PVP/VA) mixtures, prepared as amorphous solid solutions and as physical mixtures, and the effect of absorbed water on the amorphous properties, *i.e.*, crystallization and glass transition temperature, T_g, of these systems.

Methods. Mixtures of sucrose and polymer were prepared by co-lyophilization of aqueous sucrose-polymer solutions and by physically mixing amorphous sucrose and polymer. Absorption isotherms for the individual components and their mixtures were determined gravimetrically at 30°C as a function of relative humidity. Following the absorption experiments, mixtures were analyzed for evidence of crystallization using X-ray powder diffraction. For co-lyophilized mixtures showing no evidence of crystalline sucrose, T_g was determined as a function of water content using differential scanning calorimetry.

Results. The absorption of water vapor was the same for co-lyophilized and physically mixed samples under the same conditions and equal to the weighted sums of the individual isotherms where no sucrose crystallization was observed. The crystallization of sucrose in the mixtures was reduced relative to sucrose alone only when sucrose was molecularly dispersed (co-lyophilized) with the polymers. In particular, when co-lyophilized with sucrose at a concentration of 50%, PVP was able to maintain sucrose in the amorphous state for up to three months, even when the T_g was reduced well below the storage temperature by the absorbed water.

Conclusions. The water vapor absorption isotherms for co-lyophilized and physically mixed amorphous sucrose-PVP and sucrose-PVP/VA mixtures at 30°C are similar despite interactions between sugar and polymer which are formed when the components are molecularly dispersed with one another. In the presence of absorbed water the crystallization of sucrose was reduced only by the formation of a solid-solution, with PVP having a much more pronounced effect than PVP/VA. The effectiveness of PVP in preventing sucrose crystallization when significant levels of absorbed water are present was attributed to the molecular interactions between sucrose, PVP and water.

KEY WORDS: water vapor absorption; crystallization; antiplatsticizer; polymer; sucrose.

INTRODUCTION

The formation of molecular dispersions of two or more components in the amorphous state has increasingly attracted the attention of pharmaceutical scientists involved in the formulation of drug products. Interest exists, particularly, in two types of systems: amorphous mixtures of poorly water-soluble drugs with water-soluble polymers which raise the metastable drug solubility of the drug in water, and hence increase the initial dissolution rates and bioavailability (1,2); and freeze-dried or spray-dried protein-sugar mixtures, where the sugars impart physical and chemical stability to the protein during processing and storage (3–5). Since the amorphous state is metastable relative to the crystalline state, it is important to ensure that low molecular weight crystallizable components (e.g., drugs or sugars) remain in the amorphous state during processing and storage.

Previous studies from this laboratory, using sugar-polymer systems, have been concerned with tendencies in such systems for miscibility or immiscibility of amorphous components, and the potential for non-idealities in miscible systems (6), the role of hydrogen bond interactions between components (6,7), and the effects of additives on the rates of structural relaxation below the glass transition temperature, T_g (8). To examine the ability of additives to affect the physical stability of small molecular weight compounds we have also studied the extent and rates of crystallization of sucrose at various temperatures above the T_g of the mixture (9).

All studies to date with such systems have been carried out under extremely dry conditions to avoid the plasticizing effects of absorbed water vapor (10,11), and hence to simplify initial interpretations. However, under most practical situations some level of residual water cannot be avoided (12). Hence it was of interest to study the behavior of some model sucrose-polymer systems containing various amounts of absorbed water. In this study three types of experiments were carried out with physically mixed and co-lyophilized mixtures of sucrose-poly(-vinyl pyrrolidone) (PVP) and sucrose-poly(vinyl pyrrolidone-*co*-vinyl acetate) (PVP/VA). We first measured water vapor absorption at 30°C, as a function of relative humidity (RH) for physical and co-lyophilized mixtures and the individual components, to see whether or not water absorption by the mixtures could be predicted from the individual absorption isotherms. This would test the hypothesis that molecular interactions between components in the co-lyophilized miscible systems might influence accessibility of water to individual components in such mixtures. Correspondingly, the T_g values of sucrose alone and in co-lyophilized mixtures were measured as a function of RH to assess whether the plasticizing effects of water would be offset by the presence of the polymer acting as an antiplasticizer. Finally, the relative tendencies for the polymers to inhibit crystallization of sucrose over a 3-month period at 30°C were monitored as a function of water content, and in relation to the T_g of the system.

Materials

Sucrose, α-D-glucopyranosyl-β-D-fructofuranoside, was obtained from J.T. Baker Chemical Co. with a purity of greater than 99.5%. Poly (vinylpyrrolidone) (PVP) K90 was obtained with a weight-average molecular weight of 1,000,000 as determined by the supplier from light scattering experiments (13). Poly(vinylpyrrolidone-co-vinylacetate) (PVP/VA) is a random copolymer containing vinyl pyrrolidone and vinyl acetate at a molar ratio of 60:40. The weight-average molecular weight was reported by the supplier to range from 45,000–70,000 (13). All

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materials were used without further purification and were stored at ambient temperature over a desiccant (P_2O_5).

Salts were used as received to prepare saturated solutions for control of relative humidity. Cesium fluoride, lithium chloride, potassium acetate, magnesium chloride, potassium carbonate, potassium iodide, potassium bromide, potassium iodide and ammonium chloride were obtained from Sigma Chemical Co. Sodium hydroxide, potassium chloride, potassium nitrate and potassium dichromate were obtained from J.T. Baker Chemical Co. All salts were ACS grade (i.e., 99.99% purity). Phosphorous pentoxide was obtained from Fisher.

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 m torr until a constant weight was obtained. The drying temperatures that were used for the different materials were as follows: crystalline sucrose, 95°C; PVP/VA, 60°C; PVP 105°C. In a dry atmosphere (<10% RH) glovebox materials were combined in the appropriate proportions according to their dry weights, 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. 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), using the method previously described for sucrose (10). Final 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), to be less than 0.1% using a minimum of three different 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(Olympus BH2).

Preparation of Physical Mixtures

Amorphous sucrose, prepared by lyophilization of a 10% w/v aqueous solution by a method reported previously (10), was lightly ground and passed through a 600 micrometer sieve to remove large particles. PVP and PVP/VA were also ground with a mortar and pestle and passed through a 600 micrometer sieve. The components were combined in a dry atmosphere (RH < 10%) glovebox with gentle mixing for approximately 5 minutes using a mortar and pestle. Physical mixtures were analyzed by XRPD to ensure that crystallization of amorphous sucrose did not occur during processing (see later).

X-Ray Powder Diffraction

A scanning X-ray powder diffractometer (PadV, Scintag, Scintag Inc., Santa Clara, CA) controlled by a computer (Model #B10610, Tektronix, Tektronix Inc., Wilsonville, OR) was utilized to confirm the absence or presence of crystalline sucrose in various samples. 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.

Water Vapor Absorption

Water vapor absorption isotherms for sucrose, PVP, PVP/VA, and various binary mixtures were determined gravimetrically at 30°C. Dry samples (<0.1% water) of approximately 5 g were placed in glass vials and stored for up to three months in desiccators containing saturated salt solutions to control the relative vapor pressure. Sample weights were recorded periodically and were found to reach a constant weight within 2–6 weeks depending on the relative humidity. Water contents obtained at constant weight are reported as weight-fraction on a dry basis and represent the average of three independent samples.

Differential Scanning Calorimetry

Samples (2–5 mg in weight) were placed into hermetically sealed aluminum pans (Mettler, Toledo) 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. Glass transition temperatures were determined by first heating the materials and their mixtures to 20°C above T_g to erase previous thermal histories, and then cooling to 100°C degrees below T_g. These materials were subsequently heated a second time during which the glass transition temperature was determined as the temperature corresponding to the onset of the step-wise change in heat capacity. Sample weights monitored before and after measurement indicated that the water content was constant throughout the measurement of T_g. This was confirmed for selected samples by cycling the temperature between 20°C above T_g and 50°C below T_g three times and observing that the T_g of the second and third scans were equal.

RESULTS

Absorption Isotherms for Single Components

The absorption isotherms for amorphous sucrose, PVP and PVP/VA at 30°C are shown in Fig. 1. The absorption isotherms for sucrose and PVP were consistent with those reported previously (11,14,15), while the absorption isotherm for PVP/VA was in good agreement with data provided by the supplier (13). Water vapor absorption for amorphous sucrose could only be measured up to 21% RH due to rapid crystallization at higher relative humidities (10,14). Since crystalline sucrose does not absorb significant quantities of water below its deliquescence point (75% RH), any decrease in water content below this point can be used as an indication of sucrose crystallization (10,14). Qualitatively the isotherms for PVP and PVP/VA were similar, however at lower relative humidities the amount of water absorbed by PVP/VA was approximately one-third of that absorbed by PVP. The fact that PVP/VA absorbs less water than PVP is most likely due to the presence of the vinyl acetate moiety which contains a carbonyl group that is less basic than that in the pyrrolidone ring, and hence less prone to hydrogen bonding (6). At higher relative humidities the amount of water absorbed by the two polymers converge to nearly the same

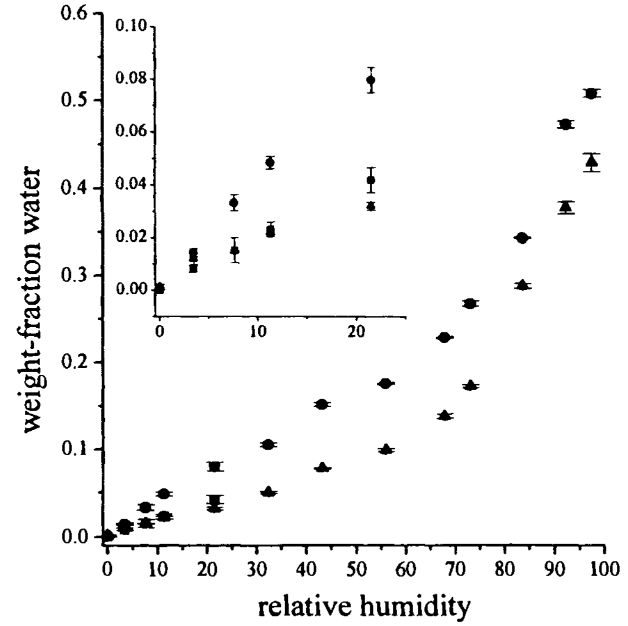

Fig. 1. Absorption isotherms for sucrose (■), PVP (●), and PVP/VA (▲) at 30°C.

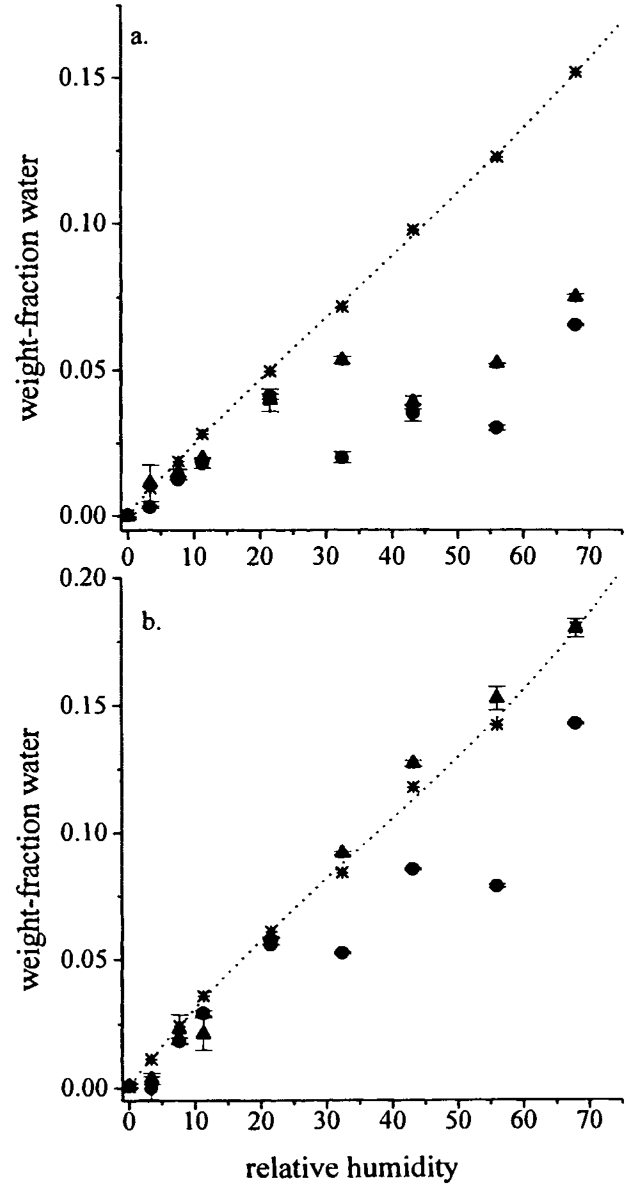

Fig. 2. Absorption isotherms for physical (●) and co-lyophilized (▲) sucrose-PVP mixtures at 30°C: (a) 20% PVP, (b) 50% PVP. Isotherms predicted assuming a weighted sum of the individual component isotherms are also shown (✱) with lines drawn to guide the eye.

value, indicating that the selective interactions of water with specific groups on the PVP/VA molecule are less important at higher RH values.

Water Vapor Absorption by Mixtures

The absorption isotherms for the various sucrose-polymer mixtures at 30°C are shown in Fig. 2 and 3. These values are taken after 3 months storage to allow some time for possible crystallization. The amount of water absorbed into the physical and co-lyophilized mixtures before any crystallization occurs corresponds in all cases to the weighted average of the water absorbed by each component under the same conditions. Thus, it appears that the amount of water absorbed by sucrose or polymer is unaffected by the presence of the other component, regardless of whether physically mixed (where no effect is expected) or molecularly dispersed (where such an effect might occur). This suggests that even in the co-lyophilized mixtures where hydrogen bonding between the polymer and sucrose is present, water has full access to both components.

Note, for the physical mixtures that the amount of water absorbed increases continuously up to 21% RH, but that above this RH there is a sharp decrease in water uptake. This decrease occurs at the same RH as pure sucrose, indicating that in the physically mixed systems the polymers offer no protection against crystallization of sucrose. Note, however, that above 21% RH water continues to be absorbed as sucrose crystallizes, presumably due to the continual increase in the absorption of water vapor by the polymer with increasing RH. This inability of physically mixed polymers to inhibit sucrose crystallization upon exposure to water vapor is consistent with earlier observations for sucrose physically mixed with PVP in the absence of water, wherein non-isothermal crystallization of sucrose was not affected by the presence of PVP (9).

For the co-lyophilized systems a very different picture evolves. For example, the amount of water absorbed by the 20% PVP mixture increased continually to about 32% RH, rather than 21% RH, before showing a discontinuity (Fig. 2a), while for the 50% PVP sample there was no discontinuity at all up to 67% RH (Fig. 2b). Thus the formation of a molecular dispersion of sucrose and PVP appears to inhibit water-induced sucrose crystallization with much greater effect as the concentration is increased from 20% to 50% PVP, even though the amount of water associated with sucrose is apparently the same as in the physical mixture and sucrose alone.

As shown in Fig. 3a, the absorption of water vapor into the 20% PVP/VA co-lyophilized mixture was continuous up to 32% RH, as with 20% PVP. However, for the mixtures containing 50% PVP/VA, the isotherm in Fig. 3b reveals crystallization between 32% and 40% RH. Thus, although PVP/VA has

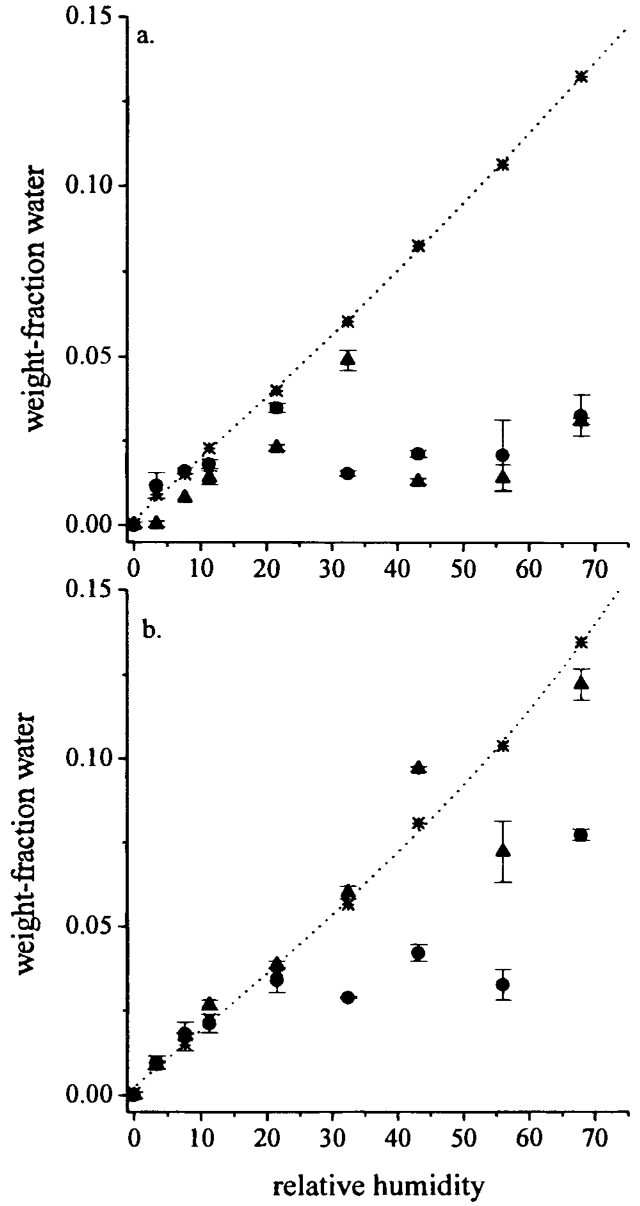

Fig. 3. Absorption isotherms for physical (●) and co-lyophilized (▲) sucrose-PVP/VA mixtures at 30°C: (a) 20% PVP/VA, (b) 50% PVP/VA. Isotherms predicted assuming a weighted sum of the individual component isotherms are also shown (✱) with lines drawn to guide the eye.

some inhibiting effects at comparable compositions to PVP, it is not as effective as PVP in inhibiting sucrose crystallization induced by the presence of water. It is interesting to note in Figs. 2 and 3 that this is the case even though the mixtures containing PVP absorb significantly more water than those containing PVP/VA at comparable RH values where the isotherms are continuous or below the sharp loss in absorbed water. Thus, the larger amounts of absorbed water by PVP are still not able to offset the crystal inhibiting effects of PVP.

To more directly assess the appearance of crystals during the storage of various samples, and to confirm the conclusions drawn from the water absorption isotherms presented in Figs. 2 and 3, X-ray powder diffraction measurements were carried out at fixed intervals up to a period of 3 months. As previously reported for sucrose, the formation of crystals was followed by monitoring the appearance of diffraction peaks at 2θ angles of 18° and 25° (17). A summary of results for the various systems is given in Table 1. For samples retaining the characteristic amorphous halo after 3 months, the symbol "NC" is used, whereas for samples showing detectable peaks at 2θ of 18° and 25°, the symbol "C" is used. In general, the samples which showed evidence of sucrose crystallization from X-ray diffraction studies were those for which loss of water content was observed in the absorption isotherms. A noted exception is the co-lyophilized mixture containing 50% PVP for which the isotherm appeared to be continuous up to 67% RH, while the X-ray technique detected very small peaks above 57% RH after 3 months. This apparent discrepancy may be due to the fact that at higher RH values the amount of water taken up by the mixture is due primarily to PVP. Furthermore, it is possible that PVP takes up any of the water released by the low levels of crystallized sucrose. This indicates the danger of only relying on the loss of water as an indicator of crystallization in mixtures.

With regard to the appearance of crystals as a function of RH following three months' storage, it also is interesting to note that while physical mixtures containing PVP/VA exhibited the same behavior as sucrose alone, sucrose crystals were detected in the physical mixtures containing PVP at RH values where sucrose alone did not. This effect seems to be dependent on the PVP composition. It is not clear why this happens. It is possible that the process of physically mixing materials introduces additional nucleation sites for crystallization, but the similarly processed PVP/VA systems do not show this. It seems more likely that this effect somehow is tied to the significant amount of water brought into these PVP systems, perhaps producing a greater plasticizing effect on sucrose at the interface between PVP and sucrose particles. In any case, it is clear that molecular dispersions made by co-lyophilization are consistently more effective in offsetting the plasticizing effects of water while not significantly reducing the amounts of water taken up by sucrose.

Glass Transition Temperature of Co-lyophilized Mixtures in the Presence of Absorbed Water

The results so far indicate that when co-lyophilized with sucrose, PVP and PVP/VA, particularly PVP at a level of 50%,

Table 1. Assessment of Various Systems for Crystalline Sucrose as a Function of Relative Humidity

mixture	type[a]	0% RH	11% RH	21% RH	32% RH	43% RH	56% RH	67% RH
sucrose	—	NC[b]	NC	NC	C	C	C	C
20% PVP	pm	NC	C[b]	C	C	C	C	C
50% PVP	pm	NC	NC	C	C	C	C	C
20% PVP/VA	pm	NC	NC	NC	C	C	C	C
50% PVP/VA	pm	NC	NC	NC	C	C	C	C
20% PVP	co	NC	NC	NC	NC	C	C	C
50% PVA	co	NC	NC	NC	NC	NC	NC	C
20% PVP/VA	co	NC	NC	NC	NC	C	C	C
50% PVP/VA	co	NC	NC	NC	NC	NC	C	C

[a] pm = physical mixture, co = co-lyophilized mixture.
[b] NC = no sucrose crystals, C = sucrose crystals.

have an inhibiting effect on the crystallization of sucrose, even though water vapor appears to have full access to sucrose in these systems. This is in contrast to physically mixed systems where no inhibition is observed. To further probe the underlying factors involved in the inhibition by the co-lyophilized systems, the effect of water on the glass transition temperature, T_g of the various systems was examined. Tg as a function of RH for PVP and PVP/VA is shown in Figs. 4a and 4b, respectively, with a comparison to that of sucrose alone, and for samples showing no crystallization over a 3-month period. Note that for the mixtures containing 20% and 50% PVP/VA and 20% PVP, T_g is nearly the same as that for sucrose alone. This result is consistent with earlier studies where it was shown that the T_g of sucrose mixtures did not change in these concentration ranges because of significant non-idealities of mixing (6). With increasing RH the T_g values of these mixtures are comparable to those for sucrose alone, despite the fact that the total water content of the polymer systems is greater than for sucrose alone at the same RH. In contrast, the 50% PVP mixture (Fig. 4a) has a T_g that is about 20°C higher than sucrose alone at 0%RH, as observed earlier (6). This 20°C increase in T_g relative to sucrose alone is maintained at higher RH values with increasing relative humidity as the mixture becomes hydrated.

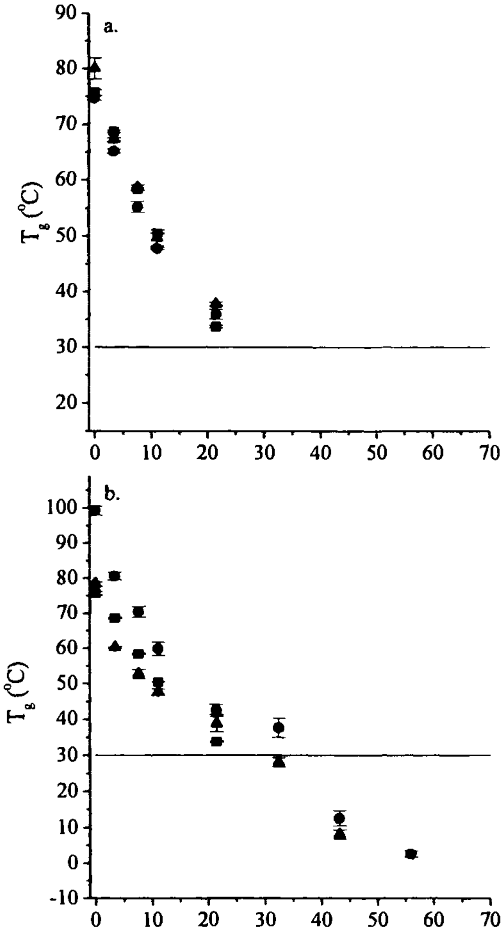

Fig. 4. Glass transition temperature as a function of relative humidity for co-lyophilized sucrose-PVP mixtures: pure sucrose (■), 20% polymer (▲), 50% polymer (●): (a) PVP/VA, (b) PVP. Horizontal line drawn at 30°C is the temperature at which the absorption isotherms were measured.

In Figs. 4a and 4b the line at T_g equal to 30°C corresponds to the point where T_g is reduced to the temperature at which absorption isotherms were measured. Note that for sucrose and the mixtures containing PVP/VA (20% and 50%) no points exist below 30°C since all sucrose crystallization occurs at water contents that reduce T_g below 30°C. However, despite the significant amount of water present in the PVP systems, PVP, particularly at a 50% level, inhibits crystallization over 3 months even when T_g is reduced to about 0–10°C yielding a $T - T_g$ of 20–30°C. This clearly shows that co-lyophilized PVP is able to inhibit sucrose crystallization at RH values where crystallization occurs quite readily, even though the amount of water apparently associated with sucrose has not been reduced.

DISCUSSION

Previous studies have shown that when sucrose is co-lyophilized with PVP and PVP/VA, miscible amorphous mixtures are formed in all proportions, that hydrogen bonding occurs between components, and that a greater degree of hydrogen bonding of sucrose occurs with PVP than with PVP/VA (6,7). In the absence of water the inhibition of sucrose crystallization only occurs when sucrose and polymer are both present in a single amorphous phase (9). Correspondingly, it has been shown that significant nonidealities in mixing sucrose with these polymers produces T_g values that are essentially the same as that of sucrose alone up to polymer compositions of about 30% w/w of PVP and 50% PVP/VA (6). Thus, the expected antiplasticizing effects of these polymers with higher T_g values are offset for polymer concentrations at or below these compositions due to non-ideal mixing (6,9). Furthermore, we have shown that the crystallization of sucrose is inhibited even though the T_g of the co-lyophilized mixtures remains the same as that of pure sucrose. Some hint of why inhibition of crystallization occurs may be obtained from studies of enthalpy relaxation below T_g which showed that, after accounting for dilution effects, the rate of structural relaxation (degree of molecular mobility) was reduced in miscible sucrose-PVP and sucrose-PVP/VA mixtures relative to sucrose alone, despite the fact that the T_g values of the mixtures were unchanged relative to that of sucrose (8). This would suggest that it is a reduction of local molecular mobility of sucrose, not linked directly to the glass transition temperature of the mixture, that plays an important role in inhibiting crystallization. This reduced mobility most likely comes about from a coupling of sucrose and polymer through hydrogen bonding, linking the local motions of sucrose to that of the polymer. This effect is greater with PVP than PVP/VA because of increased hydrogen bonding with PVP (6), and because PVP has a much higher T_g (178°C) than PVP/VA (104°C) and hence is a more effective antiplasticizer.

The results of this study, wherein a third component, water, is added, appear to lend further support to the importance of the molecular interactions formed through hydrogen bonding to the resulting properties of the system, e.g., tendency for crystallization. An important observation is that the absorption of water vapor by sucrose in the co-lyophilized molecular dispersions is not disproportionally affected by the presence of the polymer, giving water full access to sucrose at any RH. Yet, the polymers continue to show some tendency to inhibit crystallization at the 20% and 50% levels. This same accessibility of water to sucrose is apparently present in the physical mixtures, yet no such inhibition of crystallization was observed. Thus we can conceptualize a ternary "amorphous solution" of water-sucrose-polymer, where the polymer, presumably due to its coupling to sucrose and water, is still able to slow down the local motions needed for nucleation and growth of sucrose crystals. Thus although the amount of water taken up by the mixture at a particular RH clearly influences T_g, the degree to which sucrose is associated with polymer must offset such plasticizing effects at the local level. This is so even when the 50% PVP-sucrose system is plasticized so that it exists in the amorphous state 20°–30° above its T_g, *i.e.*, well into a range where significant "softening" or viscoelasticity is introduced into an amorphous system (16). In other words sufficient sucrose-PVP hydrogen bonding remains intact, despite the presence of absorbed water, so as to maintain adequate local immobilization. Of course, going from 20% to 50% PVP also dilutes the sucrose molecules and lessens tendencies for nucleation. However, the same degree of dilution of sucrose by 50% PVP/VA does not produce the same level of crystal inhibition.

CONCLUSIONS

1. Water vapor absorption behavior of physical and co-lyophilized amorphous mixtures of sucrose-PVP and sucrose-PVP/VA at 30°C can be described by a weighted contribution of each individual absorption isotherm of the various components. Hence in these sucrose-polymer systems, despite evidence for hydrogen bonding between sucrose and polymer in the co-lyophilized molecular dispersions, no disproportionate effects of water absorption of sucrose are caused by the presence of the polymer.

2. Measurement of the glass transition temperatures of various co-lyophilized sucrose-polymer mixtures as a function of relative humidity reveal that the reduction in T_g, because of the plasticizing effects of water, occurs in a manner indicating no unusual antiplasticizing effects due to the presence of the polymer that works against the plasticizing effects of water. This is consistent with observations made with the water absorption studies.

3. Estimation of tendencies for sucrose crystallization in various mixtures reveals no protective effects of physical mixtures, but some protective effects for co-lyophilized systems, despite no apparent change in the water content of sucrose in the presence of co-lyophilized polymer and no unusual antiplasticizing effects by the polymers. Only the 50% PVP-sucrose system, however, was able to maintain a completely amorphous system for 3 months storage at 30°C, when the Tg had been reduced below 30°C, the point at which significant increases in molecular mobility, based on the relationship between glass transition temperature and the storage temperature, might have been expected.

4. It is concluded that any inhibitory crystallization in co-lyophilized sucrose-polymer mixtures due to absorbed water, most likely arises from reduced local motions of sucrose caused by a coupling of sucrose mobility to the motions of the polymer.

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