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 ($\Delta H_L$) 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 $T_g$ below the storage temperature (1). An alternative strategy has been investigated whereby the material of interest is combined with an antiplasti-
cizer (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 ($T_x$) chosen for this study was 61°C. This temperature represents the same degree of undercooling ($T_x - T_g \approx 20$°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 a 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-
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 (P₂O₅).

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 (P₂O₅). The water contents of the various systems were determined, using the Karl Fisher method (Aquastr 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 micron 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 #B16010, 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/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 Tg to erase the previous thermal history of the materials and then cooling to 100°C degrees below Tg. The materials were subsequently heated a second time during which the onset, midpoint and offset Tg values and the change in heat capacity at Tg (ΔCp) were determined as shown in Fig. 1a. The width of the glass transition, ΔTg,mw, was determined as the difference in the offset and onset Tg values.

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