

Determination of the Glass Properties of D-Mannitol Using Sorbitol as an Impurity

LIAN YU,* DINESH S. MISHRA, AND DANIEL R. RIGSBEE

Contribution from Eli Lilly and Company, Lilly Research Laboratories, Indianapolis, Indiana 46285.

Received June 6, 1997. Accepted for publication March 9, 1998.

Abstract □ Due to its strong tendency to crystallize, the glass properties of mannitol cannot be measured directly. However, because mannitol can exist in a fully or partially amorphous state in drug formulations, it is important to determine the glass properties of mannitol. We obtained the glass properties of mannitol by introducing a small amount of sorbitol, an isomer of mannitol, to delay the onset of crystallization. Extrapolation to zero sorbitol concentration yielded the following properties for the mannitol glass: $T_{g \text{ onset}} = 10.7 \text{ }^\circ\text{C}$, $T_{g \text{ midpoint}} = 12.6 \text{ }^\circ\text{C}$, $T_{g \text{ end}} = 18.4 \text{ }^\circ\text{C}$ and $\Delta C_p = 1.27 \text{ J/g/K}$. In addition, we estimated the following parameters of the mannitol glass from the width of glass transition using the results of Moynihan (*J. Am. Ceram. Soc.* **1993**, *76*, 1081) and Angell (*J. Phys. Chem.* **1994**, *98*, 13780): ΔH^* (at $T_{g \text{ onset}}$) = 103 kcal/mol, $D = 11$, and $T_0 = 222 \text{ K}$. The value of T_0 is consistent with the Kauzmann temperature T_K (236 K) obtained calorimetrically. The properties of the mannitol glass may be useful for predicting the behavior of amorphous mixtures containing mannitol.

Introduction

Pharmaceuticals are often formulated with excipients into glassy solid mixtures. Understanding the nature of these glasses (e.g., the glass transition temperature, T_g , the strength or fragility,¹ and the phase homogeneity) is important for developing formulations that are physically and chemically stable. Theoretical models have been developed for predicting the T_g of a mixture from the component properties (T_g , heat capacity change at T_g , volume expansion coefficients before and after T_g , etc.).²⁻⁴ To test and apply these models for pharmaceutical systems, it is necessary to determine the glass properties of common excipients.

D-Mannitol is a common excipient in freeze- and spray-drying. Its chief advantage is good chemical stability. For example, unlike many disaccharides, mannitol does not undergo hydrolysis at low or high pH. Despite its strong tendency to crystallize, mannitol exists in fully or partially amorphous state in certain formulations.

The glass transition of mannitol cannot be measured directly using the standard melt-quench method, because of its strong tendency to crystallize. In a typical melt-quench sequence, mannitol is melted (curve A, Figure 1), vitrified by quenching, and then reheated (curve B). Curve B shows no well-defined glass transition. Although a C_p increase is discernible (event 1, inset), which may be associated with a glass transition, the exotherm that immediately follows (event 2) makes the assignment ambiguous and the measurement of ΔC_p and the width of glass transition impossible. Events 2 and 3 are due to the crystallization of mannitol, possibly into different polymorphs.

* Corresponding author. Tel.: (317) 276 1448. Fax: (317) 277 5519. E-mail: yu_lian@lilly.com.

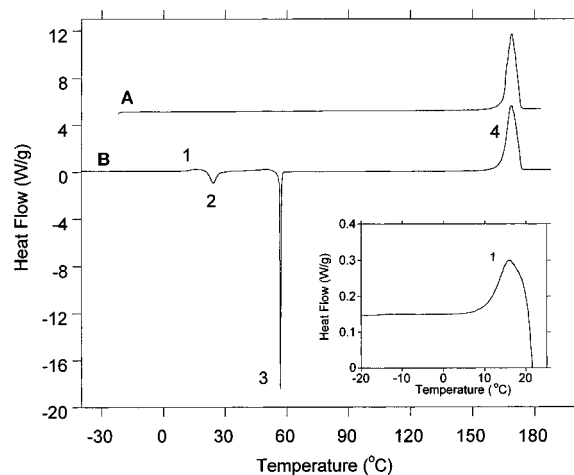


Figure 1—DSC characteristics of pure mannitol. Curve A: first heating to remove crystallinity. Curve B: second heating after quenching. The exothermic events 2 and 3 are due to the crystallization of mannitol from the supercooled melt, possibly into different polymorphs.

There has been a previous report on the glass-transition properties of mannitol ($T_g = 9 \text{ }^\circ\text{C}$, $\Delta C_p = 1.14 \text{ J/g/K}$).⁵ Unfortunately, no experimental details are given in this report on the technique used and how the problem of crystallization was solved. The T_g of mannitol can be estimated from the melting point (T_m) using a variety of scaling rules.⁶ However, the crudeness of these rules, along with the problem of polymorphism (mannitol polymorphs melt at 158, 166.0, and 166.5 $^\circ\text{C}$),⁷ makes such predictions inadequate for precise work. It is also possible to back-calculate the T_g of mannitol from the T_g of an amorphous mixture containing mannitol. To do so, however, one must assume that one of the several T_g -composition models²⁻⁴ correctly applies to the mixtures because they cannot all apply at the same time.⁸

A well-known technique for measuring the glass properties of "poor glass formers" (materials with strong tendency to crystallize) is by introducing a small amount of melt-miscible impurity to delay the onset of crystallization.⁹ If the glass transition is successfully observed, one then extrapolates to the zero impurity concentration to obtain the glass properties of the pure material.

This technique was adopted in this study to measure the glass properties of mannitol. For several reasons we selected sorbitol, a stereoisomer of mannitol, as the impurity. Because of their structural similarity, sorbitol and mannitol were expected to be melt-miscible and form a nearly ideal solution. In addition, the properties of the sorbitol glass are known^{5,10-12} and can serve as a reference point.

We report here a set of parameters characterizing the mannitol glass (T_g , the width of glass transition, ΔC_p , D , T_0 , and ΔH^*). The first three parameters were obtained by extrapolation. The last three parameters were esti-

Table 1—Glass Transition Characteristics of Mannitol–Sorbitol Mixtures

x_m^a	$T_{g\ onset}, ^\circ\text{C}$	$T_{g\ midpoint}, ^\circ\text{C}$	$T_{g\ midpoint} - T_{g\ onset}, ^\circ\text{C}$	$T_{g\ end}, ^\circ\text{C}$	$T_{g\ end} - T_{g\ onset}, ^\circ\text{C}$	$\Delta C_p, \text{J/g/K}$
0	-3.4 ± 0.2^b	-1.6 ± 0.2^b	1.81 ± 0.05^b	4.2 ± 0.2^b	7.6 ± 0.2^b	1.17 ± 0.02^b
0.743	6.36	8.36	2.00	14.08	7.72	1.29
	6.36	8.33	1.97	13.88	7.52	1.27
0.821	7.62	9.58	1.96	15.17	7.55	1.29
	7.82	9.87	2.05	15.88	8.06	1.28
0.869	8.60	10.48	1.88	16.14	7.54	1.24^c
	8.50	10.34	1.84	16.30	7.80	1.23^c
0.949	9.97	11.86 ^c	1.89 ^c	17.69 ^c	7.72 ^c	—
	9.72	11.60 ^c	1.88 ^c	17.24 ^c	7.52 ^c	—
1.000	10.7 ± 0.1^d	12.6 ± 0.1^d	1.84 ± 0.04^d	18.4 ± 0.2^d	7.7 ± 0.2^d	1.27 ± 0.03^e

^a Mole fraction of mannitol. ^b Average \pm standard deviation from four measurements. ^c Estimated from data in which the glass transition and mannitol crystallization are not completely separated (see the text). ^d Extrapolated (average \pm standard deviation). ^e Estimated by averaging the ΔC_p values of mannitol–sorbitol mixtures.

mated from the width of glass transition using the results of several previous studies.^{1,5,13–15}

Experimental Section

Materials—D-Mannitol (99+%, mp 167–170 °C) and D-sorbitol (99+%, mp 98–100 °C) were obtained from Aldrich Chemical Co. and used without further purification. In preparing the mannitol–sorbitol mixtures, we took precautions to ensure low moisture (because of the strong plasticizing effect of water) and thorough mixing (because of the high viscosity of molten mannitol and sorbitol). The mannitol–sorbitol mixtures were prepared as follows: (1) mix the two components, each accurately weighed, by grinding; (2) melt the physical mixtures and mix by swirling; (3) cool the mixtures to room temperature under dry nitrogen; (4) grind the solidified mixtures; (5) vacuum-dry the mixtures at 40 °C for 2 days; and (6) store the mixtures in freeze-drying vials sealed with Teflon-coated stoppers until use. Karl Fischer titration showed that the mixtures thus produced contain 0.1–0.2% moisture. The melt-miscibility of mannitol and sorbitol was confirmed both visually and with the aid of hot-stage microscopy.

DSC Measurement—DSC measurement was conducted using a Perkin-Elmer DSC 7. Temperature was calibrated using indium and water (ice melting) and checked against the NaCl–water eutectic point. Heat-flow was calibrated using indium. The sample (8–12 mg) was pressed into a pellet using a custom-made stainless steel tool and sealed in an Al pan. The sample preparation was carried out in a glovebox purged with dry nitrogen (RH < 1%). DSC conditions were as follows: (1) heat the sample to just above the melting point, (2) quench the sample by contact with a –80 to –85 °C metal block (the DSC 7 heat-sink) for approximately 30 s, and (3) scan for T_g from –30 °C at 7 °C/min.

Results and Discussion

Figure 2 shows the effect of adding sorbitol on the DSC characteristics of mannitol. As the sorbitol concentration increased, the crystallization exotherm (event 2) was increasingly delayed from event 1. With enough separation, event 1 was recognized as a glass transition. The glass transition of sorbitol was recorded under the same conditions for comparison (curve 6).

From a well-defined glass transition (curves 4–6 in Figure 2), we measured three temperatures (defined on curve 6): $T_{g\ onset}$ (point a), $T_{g\ midpoint}$ (point b), and $T_{g\ end}$ (point c). The heat capacity change upon glass transition (ΔC_p) was also measured. If the post- T_g baseline was not well-defined but the end of the glass transition was discernible (curves 3 and 4), we measured only $T_{g\ onset}$ and $T_{g\ midpoint}$ and estimated $T_{g\ end}$ and ΔC_p by drawing a post- T_g baseline, starting from the maximum of the endothermic “overshoot” (due to enthalpy relaxation, see later discussion), that matched the post- T_g baseline of a well-defined glass transition (e.g., curve 5). We made no attempt to measure curve 1 (pure mannitol). The glass transition data are summarized in Table 1.

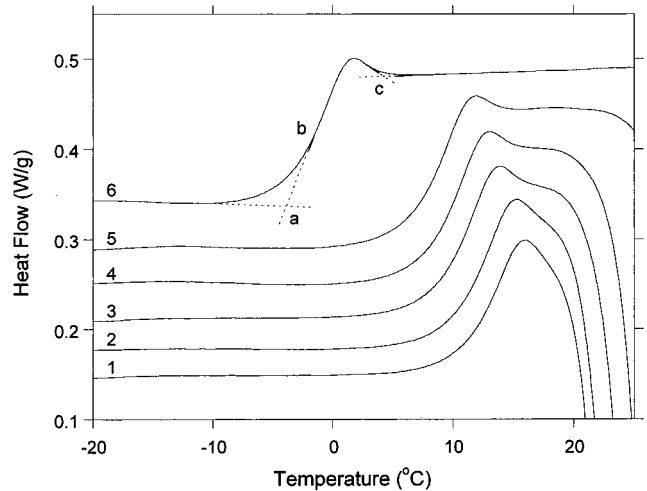


Figure 2—DSC characteristics of mannitol–sorbitol mixtures as a function of the mannitol mole fraction (x_m): $x_m = (1)$ 1, (2) 0.949, (3) 0.869, (4) 0.821, (5) 0.743, (6) 0. On curve 6, the different temperatures characterizing a glass transition are defined: (a) $T_{g\ onset}$, (b) $T_{g\ midpoint}$, (c) $T_{g\ end}$.

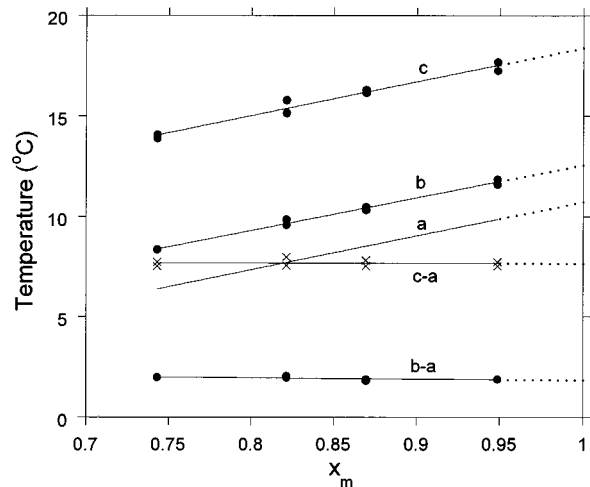


Figure 3—Determination of the T_g of mannitol by extrapolation: (a) $T_{g\ onset}$, (b) $T_{g\ midpoint}$, (c) $T_{g\ end}$, (b – a) $T_{g\ midpoint} - T_{g\ onset}$, (c – a) $T_{g\ end} - T_{g\ onset}$.

In the concentration range studied ($x_m = 0.743$ –1, where x_m is the mole fraction of mannitol), the T_g – x_m data were well-fitted by straight lines (Figure 3). Extrapolating these lines to $x_m = 1$ yielded $T_{g\ onset} = 10.7 \pm 0.1$ °C ($r = 0.998$), and $T_{g\ midpoint} = 12.6 \pm 0.1$ °C ($r = 0.996$), and $T_{g\ end} = 18.4 \pm 0.2$ °C ($r = 0.985$). These temperatures were assigned to the glass transition of mannitol. The extrapolated $T_{g\ onset}$ matched the start of event 1 in Figure 1, indicating that event 1 is indeed the onset of glass transition.

The quantities $(T_{g \text{ midpoint}} - T_{g \text{ onset}})$ and $(T_{g \text{ end}} - T_{g \text{ onset}})$, the “half and full widths” of the glass transition, were essentially independent of concentration (Table 1). Extrapolating the lines that best fit the $\Delta T_g - x_m$ data to $x_m = 1$ yielded $(T_{g \text{ midpoint}} - T_{g \text{ onset}}) = 1.84 \pm 0.04$ °C and $(T_{g \text{ end}} - T_{g \text{ onset}}) = 7.7 \pm 0.2$ °C (Figure 3). These values were, within experimental error, identical with those of sorbitol (Table 1).

Because a good post- T_g baseline is necessary for a reliable measurement of ΔC_p , we had less data for extrapolation. However, Table 1 shows that ΔC_p does not change significantly with concentration in the x_m range studied (Table 1). Therefore we estimated the ΔC_p of mannitol by averaging over the ΔC_p 's of the mixtures, which gave $\Delta C_p = 1.27 \pm 0.03$ J/g/K.

From the measured $T_{g \text{ onset}}$ and $T_{g \text{ end}}$, we were able to calculate additional properties of the mannitol glass using the results of Moynihan¹³ and Angell.¹⁴ Moynihan finds that for structurally similar glasses the following function is approximately constant:¹³

$$\Delta H^*/R(1/T_{g \text{ onset}} - 1/T_{g \text{ end}}) = C \quad (1)$$

where ΔH^* is the activation energy for enthalpy relaxation, a parameter describing the temperature dependence of the structural relaxation time (τ).¹ For a group of high- T_g inorganic glasses, Moynihan finds $C = 4.8$. For sorbitol, we calculated C from $T_{g \text{ onset}}$ and $T_{g \text{ end}}$ (Table 1) and $\Delta H^* = 93$ kcal/mol.¹¹ This gave $C = 4.75$, which is in surprisingly good agreement with Moynihan's value. Assuming $C(\text{mannitol}) = C(\text{sorbitol})$, which seemed reasonable for the two structurally similar glasses, we obtained $\Delta H^* = 103$ kcal/mol for mannitol.

Next, we estimated the strength parameter (D) and the temperature of “zero mobility” (T_0). These parameters describe the temperature dependence of structural relaxation time (τ) through the VTF equation:¹

$$\tau = \tau_0 \exp[DT_0/(T - T_0)] \quad (2)$$

One can estimate D and T_0 from $T_{g \text{ onset}}$ and $T_{g \text{ end}}$ using eq 1 and the assumption¹⁴ that there exists a 17 order of magnitude difference between τ at T_g and τ_0 (the high-temperature limit of τ). Pikal has given a procedure (unpublished) on how to carry out the estimation.¹⁵ Pikal and co-workers recently investigated the general applicability of this estimation procedure and concluded that the Moynihan constant C is not a “universal” constant for the pharmaceutical materials studied, but can be regarded as such within a “subclass” of materials.¹⁶ Hatley has used Pikal's procedure to estimate D and T_0 for sucrose and trehalose.¹⁷

To carry out this estimation, one first obtains the relationship between ΔH^* and the VTF parameters in eq 2 using the definition $\Delta H^* = d(\ln \tau)/d(1/T)$. This yields eq 3:

$$\Delta H^*/(RT) = D(T/T_0)/(T/T_0 - 1)^2 \quad (3)$$

The “17-order of magnitude” assumption¹⁴ and eq 2 lead to

$$T_{g \text{ onset}}/T_0 = 1 + D/39.1 \quad (4)$$

Substituting eqs 1 and 4 into eq 3 yields

$$1/D = 0.000653C(1 - T_{g \text{ onset}}/T_{g \text{ end}}) - 0.0255 \quad (5)$$

Equations 4 and 5 allow the calculation of D and T_0 from

$T_{g \text{ onset}}$ and $T_{g \text{ end}}$, provided that the Moynihan constant is known (e.g., from structurally similar compounds).

Applying eqs 4 and 5 to sorbitol and using $C = 4.75$ (see above), we obtained $D = 11$ and $T_0 = 209$ K. These values agree with those obtained from the combined fit of viscosity and DSC data ($D = 8$ and $T_0 = 215$ K)¹¹ and from the constrained fit of the dielectric relaxation data ($D = 12.7$ (constraint) and $T_0 = 208$ K).⁵ This agreement provided some confidence in the calculation procedure.

Next, we applied the procedure to mannitol (assuming $C = 4.75$) and obtained $D = 11$ and $T_0 = 222$ K. Angell and Smith have reported the Kauzmann temperature T_K of mannitol to be 236 ± 10 K,⁵ which is considered identical with T_0 .¹ Therefore, the agreement between T_0 and T_K also indicates some internal consistency.

A potential error in the above calculations may originate from the thermal gradients in DSC samples (“thermal lag”).¹⁸ To assess the effect of this error, let us retrace the steps of the calculation. The thermal lag should not significantly affect $T_{g \text{ onset}}$ nor therefore the ΔH^* of sorbitol derived from $T_{g \text{ onset}}$ vs heating rate q .¹¹ However, this effect can affect $T_{g \text{ end}}$ and, in turn, $C(\text{sorbitol})$ calculated by eq 1. If we assume that the observed width of glass transition $\Delta T_g = (T_{g \text{ end}} - T_{g \text{ onset}})$ differs from the true width by a factor f , i.e., $\Delta T_{g \text{ obs}} = f\Delta T_g$, then eq 1 gives an *apparent* C that differs from its true value by approximately the same factor: $C_{\text{app}} \approx fC$. Now it is likely that mannitol will experience the same thermal lag as sorbitol (same f). Therefore if we use C_{app} and the observed T_g to calculate the ΔH^* of mannitol (eq 1), the errors in the two parameters approximately cancel out. As a result, the ΔH^* of mannitol is essentially free of the error from thermal lag. Similarly, the calculation of D (eq 5) is also essentially unaffected by thermal lag. The subsequent calculation of T_0 (eq 4) does not involve $T_{g \text{ end}}$ and therefore is not influenced either.

The validity of these arguments is supported by the agreement between the calculated and independently measured parameters (see above). In the case of sorbitol, the ΔH^* s obtained from both the $T_{g \text{ onset}}-q$ data and the $T_{g \text{ end}}-q$ data can be combined smoothly with the high-temperature viscosity data.¹¹ This may suggest that the thermal lag does not cause a significant error in the $T_{g \text{ end}}$ for sorbitol and the structurally similar mannitol.

On the basis of the D parameters, the sorbitol and mannitol glasses can be classified as “fragile to intermediate” in the fragility/strength spectrum.¹ On the other hand, one would expect high fragility on the basis of the large ΔC_p upon glass transition in these glasses ($C_{p \text{ liquid}}/C_{p \text{ glass}} \approx 2$).¹² These implications are reconciled if one recognizes the H-bonded nature of polyol glasses.¹ The need to rupture intermolecular H bonds for molecules to undergo rearrangement perhaps makes the liquid to appear less fragile than the large ΔC_p would indicate.

One utility of the parameter ΔH^* is to estimate the effect of heating rate (q) on the observed T_g through eq 6:¹⁹

$$d(\ln q)/d(1/T_g) = -\Delta H^*/R \quad (6)$$

Using eq 6, we estimated that increasing q from 7 to 10 °C/min would increase the $T_{g \text{ onset}}$ by 0.6 °C and decreasing q from 7 to 2.5 °C/min would decrease the $T_{g \text{ onset}}$ by 1.6 °C. This dependence is the same as that for sorbitol,¹¹ which is expected because of their structural similarity.

The T_g of sorbitol obtained by this work (Table 1) is consistent with a previous report ($T_g = -2.0$ °C), which is obtained under similar conditions (quenching by liquid N₂ vapor to -60 °C, heating at 10 °C/min).¹⁰ Our result, however, is considerably higher than those of another group ($T_{g \text{ onset}} = -7$ °C⁵ and -8 °C¹²). Several factors may explain

this difference. First, the sorbitol sample in the previous work has slightly more moisture (0.61%)⁵ than ours (0.1–0.2%). Second, the difference may result from the different heating rate, q . The previous value $T_{g\text{ onset}} = -8\text{ }^{\circ}\text{C}$ is obtained at $q = 2.5\text{ }^{\circ}\text{C}/\text{min}$.¹² Changing q from 7 to 2.5 $^{\circ}\text{C}/\text{min}$ will lower the T_g by approximately 1.6 $^{\circ}\text{C}$.¹¹ Finally, the cooling rate of the vitrification step may play a role. The previous work uses the same cooling rates as the heating rates, whereas we employed a much faster cooling rate to prevent mannitol crystallization. In principle, different cooling rates lead to glasses that are “relaxed” to different extents,⁶ which, on reheating, yield different T_g 's. However, as long as the heating rate is constant and the cooling rate/heating rate ratio is within a reasonable range (0.2–5), the T_g is not significantly affected by the initial cooling rate.¹³ For sorbitol, the endothermic “overshoot”, which is due to enthalpy relaxation, does not change significantly with cooling rates; for example, the “overshoot” observed in this study (fast cooling) was not significantly different from that observed after much slower cooling.^{11,12} Therefore, the sorbitol glass seems to relax so rapidly that the cooling rate has little influence on T_g .

The $T_{g\text{ onset}}$ and ΔC_p for mannitol (Table 1) are in reasonable agreement with the previous values (9 $^{\circ}\text{C}$ and 1.14 J/g/K, respectively).⁵ The difference in T_g may result from similar causes as enumerated above for sorbitol. However, the lack of experimental details in ref 5 precludes more detailed comparisons.

The $T_{g\text{ onset}}/T_m$ ratio was 0.64 for mannitol and 0.73 for sorbitol. (In both cases, the T_m of the highest melting polymorph was used in the calculation: 167.5 $^{\circ}\text{C}$ for mannitol⁷ and 98 $^{\circ}\text{C}$ for sorbitol.²⁰) Although both values are reasonable according to the $T_g - T_m$ scaling rules,⁶ the significant difference between the two structurally similar molecules warrants some attention.

The use of linear extrapolation, instead of extrapolations based on well-known T_g -composition models,^{2–4} may require some discussion. First we note that linear extrapolation was *sufficient* for our purpose because there was no indication of nonlinearity in the x_m region considered. Second, it was impossible to decide a priori which model best describes the mannitol–sorbitol system, for the different models cannot be correct for the same system simultaneously.⁸ The linear extrapolation, on the other hand, does not depend on the validity of any theoretical model, for all models are reduced to a linear $T_g - x_m$ relationship as x_m approaches unity. We intend to investigate the question as to which model best fits the mannitol–sorbitol system in a future study.

Conclusions

We have obtained the glass-transition properties of mannitol using sorbitol as an impurity, including $T_{g\text{ onset}}$, $T_{g\text{ midpoint}}$, $T_{g\text{ end}}$, and ΔC_p . We have estimated additional parameters (ΔH^* , D , and T_0) from the width of glass transition using the results of Moynihan¹³ and Angell.¹⁴ These properties should be useful for predicting the properties of mannitol-containing glassy mixtures.³ The question as to how the fragility changes when mannitol is mixed with “strong” glasses (e.g., proteins¹⁴) seems particularly interesting. We are currently investigating the

T_g -composition behavior over the full concentration range for the mannitol–sorbitol system and other binary polyol mixtures.

Acknowledgments

We thank Professor M. Pikal of University of Connecticut for helpful discussions and one of the reviewers for pointing out a previous report on the T_g of mannitol.

References and Notes

1. Angell, C. A. Relaxation in Liquids, Polymers and Plastic Crystals – Strong/Fragile Patterns and Problems. *J. Non-Crystalline Solids*. **1991**, 131–133, 13.
2. Fox, T. G. Influence of Diluent and of Copolymer Composition on the Glass Transition Temperature of a Polymer System. *Bulletin of Am. Phys. Soc.* **1956**, Series II, Vol. 1 (3), 123.
3. Couchman, P. R. The Composition-Dependent Glass Transition: Relations between Temperature, Pressure, and Composition. *Polymer Eng. and Sci.* **1984**, 24(2), 135.
4. Gordon, M.; Taylor, J. S. Ideal Copolymers and the Second-Order Transitions of Synthetic Rubbers. I. Non-Crystalline Copolymers. *J. Appl. Chem.* **1952**, 2, 493.
5. Angell, C. A.; Smith, D. L. Test of the Entropy Basis of the Vogel–Tamman–Fulcher Equation. Dielectric Relaxation of Polyalcohols near T_g . *J. Phys. Chem.* **1982**, 86, 3845.
6. Roe, R.-J. Glass Transition, in Encyclopedia of Polymer Science and Engineering, John Wiley and Sons: New York 1985.
7. Burger, A.; Hetz, S.; Weissnicht, A. On the Polymorphism of Mannitol. *Eur. J. Pharm. Biopharm.* **1994**, 40(S), 21S.
8. Goldstein, M. Glass Temperature Mixing Relations and Thermodynamics. *Macromolecules* **1985**, 18, 277.
9. Angell, C. A.; Sare, J. M.; Sare, E. J. Glass Transition Temperatures for Simple Molecular Liquids and Their Binary Solutions. *J. Phys. Chem.* **1978**, 82, 2622.
10. Timko, R. J.; Lordi, N. G. Thermal Analysis Studies of Glass Dispersion Systems. *Drug Development and Industrial Pharmacy* **1984**, 10(3), 425.
11. Angell, C. A.; Stell, R. C.; Sichina, W. Viscosity–Temperature Function for Sorbitol from Combined Viscosity and Differential Scanning Calorimetry Studies. *J. Phys. Chem.* **1982**, 86, 1540.
12. Barkatt, A.; Angell, C. A. Optical Probe Studies of Relaxation Processes in Viscous Liquids. *J. Chem. Phys.* **1979**, 70, 901.
13. Moynihan, C. T. Correlation between the Width of the Glass Transition Region and the Temperature Dependence of the Viscosity of High-Tg Glasses. *J. Am. Ceram. Soc.* **1993**, 76, 1081.
14. Green, J. L.; Fan, J.; Angell, C. A. The Protein-Glass Analogy: Some Insights from Homopeptide Comparisons. *J. Phys. Chem.* **1994**, 98, 13780.
15. Pikal, M. J.; Rigsbee, D. R.; Roy, M. L. The Relationship between Glass Transition Temperature, T_g , and Stability of Freeze-Dried Human Growth Hormone (hGH). *Symposia Abstract for AAPS Annual Meeting*, 1995, Miami Beach, FL.
16. Hancock, B. C.; Dalton, C. R.; Pikal, M. J.; Shamblin, S. L. Is There a Simple Calorimetric Method for Determining the Fragility of Amorphous Pharmaceutical Materials? *Symposia Abstract for AAPS Annual Meeting*, 1997, Boston, MA.
17. Hatley, R. H. M. Glass Fragility and the Stability of Pharmaceutical Preparations – Excipients Selection. *Pharm. Dev. & Technol.* **1997**, 2, 257–264.
18. Hutchinson, J. M.; Ruddy, M.; Wilson, M. R. Differential Scanning Calorimetry of Polymer Glasses: Correction for Thermal Lag. *Polymer*, **1988**, 29, 152–159.
19. Moynihan, C. T.; Easteal, A. J.; Wilder, J. Dependence of the Glass Transition Temperature on Heating and Cooling Rate. *J. Phys. Chem.* **1974**, 78, 2673.
20. Sztatisz, J.; Gal, S.; Fodor, L.; Pungor, E. Thermal Investigation on the Crystallization of Sorbitol. *J. Thermal Anal.* **1977**, 12, 351.

JS9702240