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A Pragmatic Test of a Simple Calorimetric Method for Determining the Fragility of Some Amorphous Pharmaceutical Materials

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Purpose. To evaluate a simple calorimetric method for estimating the fragility of amorphous pharmaceutical materials from the width of the glass transition region.

Methods. The glass transition temperature regions of eleven amorphous pharmaceutical materials were characterized at six different heating and cooling rates by differential scanning calorimetry (DSC).

Results. Activation energies for structural relaxation (which are directly related to glass fragility) were estimated from the scan rate dependence of the glass transition temperature, and correlations between the glass transition widths and the activation energies were examined. The expected correlations were observed, and the exact nature of the relationship varied according to the type of material under consideration.

Conclusions. The proposed method of determining the fragility of amorphous materials from the results of simple DSC experiments has some utility, although "calibration" of the method for each type of materials is necessary. Further work is required to establish the nature of the relationships for a broad range of amorphous pharmaceutical materials.

KEY WORDS: amorphous; glass transition temperature; fragility; molecular mobility; activation energy.

INTRODUCTION

As a result of stresses which they experience during processing many common pharmaceutical materials exist in an amorphous or partially amorphous state (1). These materials include drugs, sugars, and polymers, and the stresses arise from processes such as spray drying, lyophilization, and milling (1). Amorphous materials can be described in terms of their "fragility" (2) which is a measure of the temperature dependence of the molecular motions in the region of their glass transition temperature (T_g). An amorphous material's fragility is very important as it can determine its chemical, physical or mechanical stability with changing temperature (1,3). Fragility (m) has been defined as (4):

$$m = \Delta H/(2.303\ R\ T_g) \qquad (1)$$

where ΔH is the activation energy for molecular motions at T_g, and R is the gas constant. A large value of m is typical of a fragile amorphous material whose rate of molecular motion changes by about one order of magnitude for every 10 K change in temperature (e.g., m = 93 for sorbitol) (5). A small value of m is representative of a non-fragile (strong) glass former whose molecular mobility changes by approximately one order of magnitude for every 25 K change in temperature (e.g., m = 30 for zinc chloride) (5).

The most common method of estimating the fragility of amorphous materials is to fit molecular mobility versus temperature data obtained above T_g to a modified Vogel-Tamman-Fulcher (VTF) equation (6):

$$\tau = \tau_0 \cdot \exp\{(D \cdot T_0)/(T - T_0)\} \qquad (2)$$

where τ is the average molecular relaxation time, T is the experimental temperature, τ_0 is the shortest possible relaxation time, T_0 is the temperature of negligible molecular mobility and D is a constant. The magnitudes of the parameters D and T_0 can be related to the fragility of the system (m) (4), and a knowledge of T_0 is potentially very useful for estimating the temperature below which the instability of amorphous systems becomes negligible (1,7). This approach has seen very little use with pharmaceutical materials because of (i) the experimental difficulties involved in determining the temperature dependence of molecular motions above T_g, and (ii) frequent material instabilities at such temperatures.

An alternative method of estimating the fragility of amorphous materials is to calculate the activation energy for molecular motions at T_g from measurements of the calorimetric T_g at different experimental scanning rates (8,9). Data from a series of differential scanning calorimeter (DSC) experiments at different scan rates are plotted according to an Arrhenius type relationship (log scan rate versus reciprocal glass transition temperature) and the activation energy (ΔH^{DSC}) is calculated from the slope of the best fit linear plot. The activation energy can then be used to estimate the fragility using equation 1. This approach requires a wide range of experimental scanning rates and very careful temperature calibration of the calorimeter at each rate in order to achieve satisfactory results.

An even simpler method of determining the activation energy from DSC experiments has been envisaged following the work of Moynihan and co-workers (10–12). For a series of more than twenty high T_g inorganic glass formers of varying fragility it was shown that:

$$\Delta H = C\ R\ /\ \{(1/T_g^{onset}) - (1/T_g^{offset})\}$$
$$= C\ R\ T_g^{onset}\ T_g^{offset}/\Delta T_g \qquad (3)$$

where T_g^{onset} and T_g^{offset} denote the onset and end of the glass transition (Figure 1), ΔT_g is the glass transition width ($T_g^{offset} - T_g^{onset}$) and C is a constant. The data generated for Moynihan's materials at heating and cooling rates of 10 and 20 K per minute resulted in a proportionality constant of about 5.0 ± 0.5 with only a few systems showing exceptional behavior. Provided equation 3 and its inherent assumptions have general applicability (and C is known for the material(s) of interest) it should be possible to use this equation to determine ΔH from simple measurements of T_g^{onset} and T_g^{offset}. If valid this approach would provide a simple method for estimating the fragility of an amorphous material from the width of the calorimetric glass transition even when significant instability exists above T_g.

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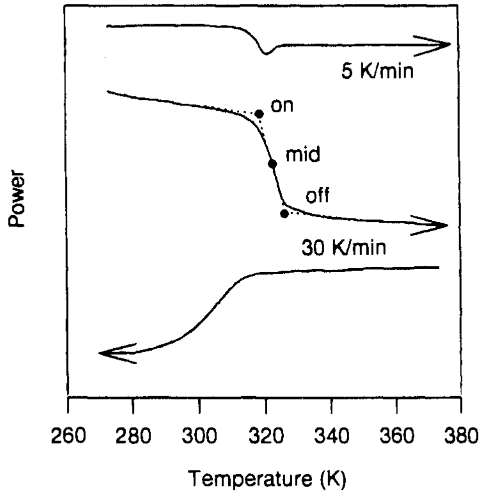

Fig. 1. Typical DSC traces obtained under different scanning conditions for amorphous indomethacin (on-T_g^{onset}, off-T_g^{offset}, and mid-$T_g^{midpoint}$).

The purpose of the work reported in this manuscript is to evaluate the applicability of equation 3 for describing the relationship between ΔH^{DSC} and the width of the calorimetric T_g for some typical amorphous pharmaceutical materials. To achieve this the T_gs of eleven amorphous drugs and excipients were measured at six different heating and cooling rates by DSC. The width of each transition was determined, and the relationship to ΔH^{DSC} values estimated from Arrhenius-type plots evaluated.

MATERIALS AND METHODS

Several pharmaceutical sugars with different glass transition temperatures were lyophilized to produce amorphous samples (13). These included sucrose (>99.5% purity, Sigma), lactose (Foremost), trehalose (Sigma), and raffinose (>99% purity, Sigma). An amorphous polymer, poly(vinylpyrrolidone) (PVP), available in several molecular weights (Kollidon 12, 17, 30, 90, BASF; Plasdone K120, GAF) with different glass transition temperatures, was used as received. Indomethacin (Sigma) and citric acid (>99.5% purity, American Chemicals) were selected as representative amorphous pharmaceutical materials with low glass transition temperatures (14,15) and were amorphized by rapidly cooling their melts in the DSC.

Samples were analyzed using a Seiko DSC (RDC-220) with a liquid nitrogen cooling system and calibrated for temperature with benzoic acid and cyclohexane (16). Calibration was performed at each experimental heating rate and frequent calibration checks were made. Precautions were taken to minimize the interfering effects of sample mass, particle size, thermal contact and heat transfer lags. A dry purge of an inert gas was employed for all runs. Samples were sealed in aluminum DSC pans with a pin-hole in the cover under low relative humidity conditions (<10% RH) and heated to at least 20 K above T_g to erase any thermal history. They were then cooled to at least 50 K below T_g and the onset, midpoint and offset of T_g on cooling recorded. The samples were reheated at the same rate to above their melting temperature and the onset, midpoint, and end of T_g on heating, and any indication of crystallization, melting or decomposition recorded. Heating/cooling rates of 5, 7, 10, 14, 20 and 30 K/minute were employed, and mean values of each parameter were determined from replicate samples. The accuracy of the determinations was about ± 0.5 K. For several of the sugars certain data could not be obtained without thermally degrading the samples. Apparent activation energies (ΔH^{DSC}) were calculated from the slope of Arrhenius-type plots of the logarithm of the DSC scan rate versus reciprocal T_g.

RESULTS AND DISCUSSION

Representative DSC traces obtained in the glass transition region for indomethacin at the most extreme heating and cooling rates are shown in Figure 1. Significant differences were observed in such traces for this and the other materials. The midpoint glass transition temperatures ($T_g^{midpoint}$) of all the materials at the different heating and cooling rates are compared in Figure 2. For any given experimental conditions the high molecular weight PVP samples had the greatest T_g value, and the smaller molecular weight PVP samples, the sugars, the indomethacin and the citric acid exhibited successively lower glass transition temperatures. The T_g values for sucrose were

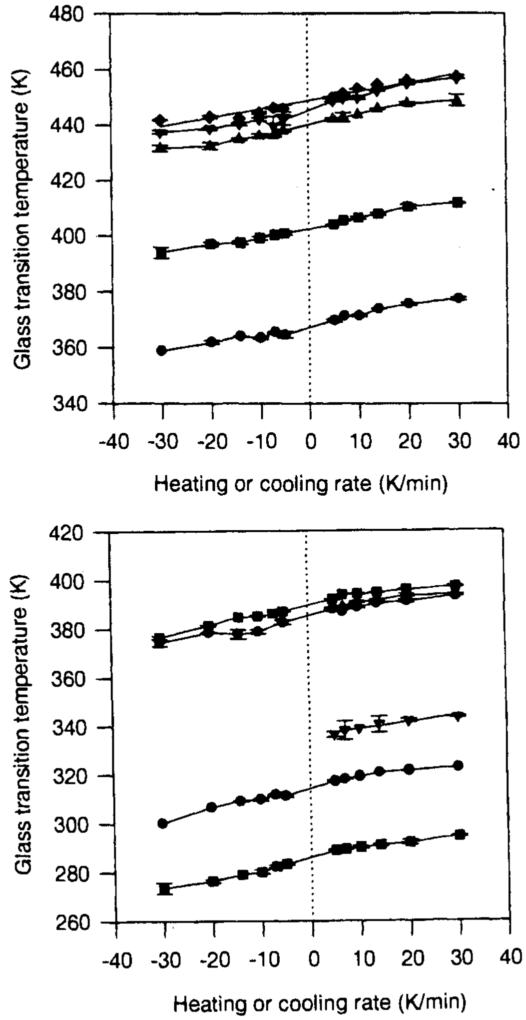

Fig. 2. Variation of glass transition temperature with heating (+) and cooling (−) rate. From top to bottom: a) PVP K120, 90, 30,17,12; b) Trehalose, lactose, raffinose, sucrose, indomethacin, citric acid.

slightly lower than reported elsewhere (13) because approximately 0.1% water remained in the lyophilized material. The continuity of the results from the heating and cooling experiments indicated that the temperature calibration was valid for both the heating and cooling experiments (16). For all the materials the T_g changed by about 7 K for a ten fold change in scanning rate. This sensitivity to scan rate is less than reported by Moynihan for high T_g inorganic glass formers but similar to that reported for other amorphous pharmaceutical materials (8,17,18).

Table I lists the transition widths under the different experimental conditions and it is possible to observe changes in this parameter with both the direction and rate of the experimental temperature change. In almost all cases the transition width increased with increasing scanning rate and was greater during cooling than heating (see also Figure 1). According to equation 3 these changes should be accompanied by changes in the activation energy (ΔH) at T_g, including a greater ΔH on heating than on cooling.

Apparent activation energies for molecular motions at T_g were calculated from plots of the logarithm of the DSC scanning rate versus reciprocal T_g (e.g., Figure 3). Typically the linear fit of the data was very good, with 95% confidence limits for the slope in the range ± 4–17%. The activation energies obtained in this way were of a similar magnitude to those reported for other pharmaceutical materials (8,17–19) and were material specific (Table II) (20). Notably the value of ΔH^{DSC} was significantly greater when calculated from heating data rather than cooling data as demanded by equation 3 (see above). There was also a difference depending on whether ΔH^{DSC} was calculated from T_g^{onset}, $T_g^{midpoint}$ or T^{offset}_g (Table II). That is, ΔH^{DSC} decreased as the temperature at which T_g was determined increased. Such behavior has previously been attributed to a strong temperature dependence of ΔH near T_g, or "fragile behavior" (8,9). Significant fragility is in apparent conflict with the linearity of the Arrhenius-type plots (e.g., Figure 3), however the relatively narrow range of scanning rates available combined with enthalpy-entropy compensation effects and/or structural heterogenieties at the glass transition probably account for this discrepancy (21–23).

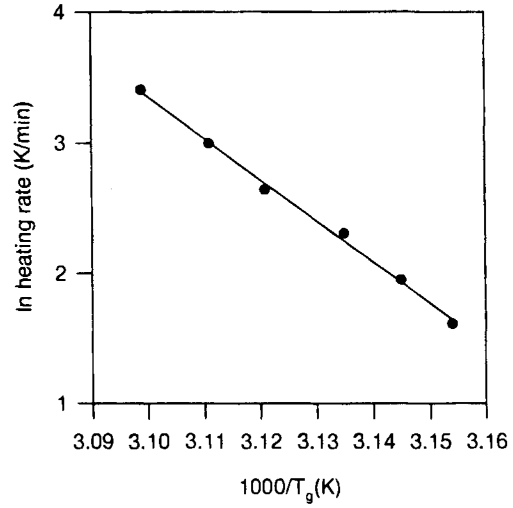

Fig. 3. Plot of DSC heating rate versus reciprocal glass transition temperature for amorphous indomethacin.

The ΔH^{DSC} and T_g values in Tables I and II result in m values of between 36 and 60 (using equation 1) and therefore

Table I. Width of the Glass Transition Region at Various Heating and Cooling Rates

Material	Rate	$T_g^{midpoint}$ 10 K/min	5 K/min	7 K/min	10 K/min	14 K/min	20 K/min	30 K/min
			Width					
Sucrose	HEAT	338.6	7.0	9.2	8.3	14.8	12.9	14.3
	COOL	—	—	—	—	—	—	—
Raffinose	HEAT	388.5	3.8	4.0	5.3	3.9	5.1	8.9
	COOL	378.8	17.4	—	20.7	21.8	22.1	25.8
Trehalose	HEAT	394.0	3.0	5.8	4.4	5.4	6.1	9.8
	COOL	385.1	11.2	18.8	15.3	19.2	20.7	20.9
Lactose	HEAT	390.8	4.6	4.9	5.4	6.1	9.0	7.8
	COOL	—	—	—	—	—	—	—
Indomethacin	HEAT	319.0	3.2	3.6	4.4	4.6	6.3	7.4
	COOL	309.8	15.7	16.7	21.7	18.8	21.3	24.9
Citric acid	HEAT	289.9	5.5	5.7	7.3	7.8	9.0	10.2
	COOL	280.1	14.5	15.4	18.6	18.4	19.6	21.5
PVP K12	HEAT	371.3	13.8	14.7	16.4	15.1	16.1	16.6
	COOL	363.4	26.0	25.0	29.6	29.0	28.4	38.4
PVP K17	HEAT	406.5	11.0	13.2	14.4	12.9	14.3	16.1
	COOL	399.2	21.7	14.5	24.9	26.0	28.3	33.5
PVP K30	HEAT	443.6	8.3	7.8	10.3	9.2	10.3	13.4
	COOL	436.0	23.1	14.4	24.2	22.2	25.8	24.4
PVP K90	HEAT	449.5	6.4	6.3	9.1	8.2	9.0	10.9
	COOL	441.9	23.7	14.8	23.5	26.0	23.9	37.1
PVP K120	HEAT	453.0	6.2	4.9	6.1	6.2	7.3	9.4
	COOL	444.3	21.2	26.5	22.1	21.8	22.4	20.9

Table II. Activation Energies (ΔH^{DSC}) Determined from Heating and Cooling Data

	Heating			Cooling		
Material	Δ^{onset} (kJ/mole)	$\Delta H^{midpoint}$ (kJ/mole)	ΔH^{offset} (kJ/ mole)	ΔH^{onset} (kJ/mole)	$\Delta H^{midpoint}$ (kJ/mole)	ΔH^{offset} (kJ/mole)
Sucrose	407	239	153	–	–	–
Raffinose	352	346	256	460	153	154
Trehalose	732	460	265	277	192	124
Lactose	532	363	265	–	–	–
Indomethacin	385	263	190	218	109	85
Citric acid	351	213	162	169	115	78
PVP K12	301	268	235	405	273	96
PVP K17	359	306	244	1060	334	156
PVP K30	439	398	292	373	420	220
PVP K90	478	356	278	483	483	117
PVP K120	536	407	345	420	551	415

the materials studied appear to be of an intermediate fragility according to the classification criteria given earlier. It should be noted that the m values calculated using this approach vary considerably with the experimental conditions used. In order to test the relationship between ΔH and the T_g^{onset} and T_g^{offset} values (according to equation 3) we restrict our subsequent analyses to the ΔH values calculated from $T_g^{midpoint}$ values recorded at a standard scan rate of 10 K per minute (2).

An analysis of the heating and cooling data at 10 K per minute according to equation 3 for the non-polymeric materials ('small molecules') is shown in Figure 4. A similar analysis is presented for the different molecular weight grades of PVP in Figure 5. It is clear that the small molecules and polymeric materials fall into distinct 'families' for the purpose of these analyses. According to equation 3 such plots should be linear with a slope of C and pass through the origin. The data for the low molecular weight materials (citric acid, indomethacin and sugars) fall on a single straight line but with a positive 'best fit' intercept. The correlation suggests that an estimate of the fragility of a low molecular weight pharmaceutical glass might be obtained by combining equation 1 with the relationship:

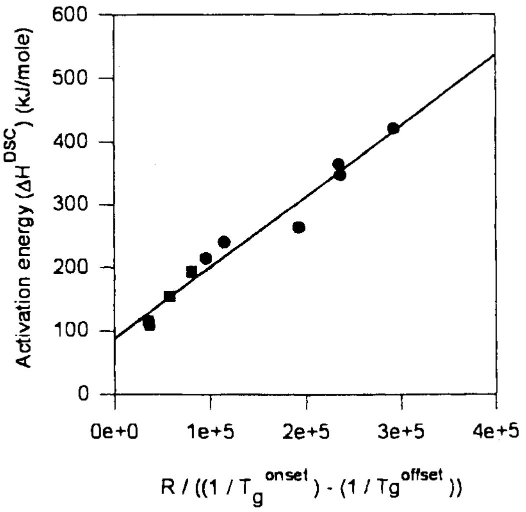

Fig. 4. Plot of the glass transition temperature data according to equation 3 for the non-polymeric samples (■ - cooling data, ● - heating data).

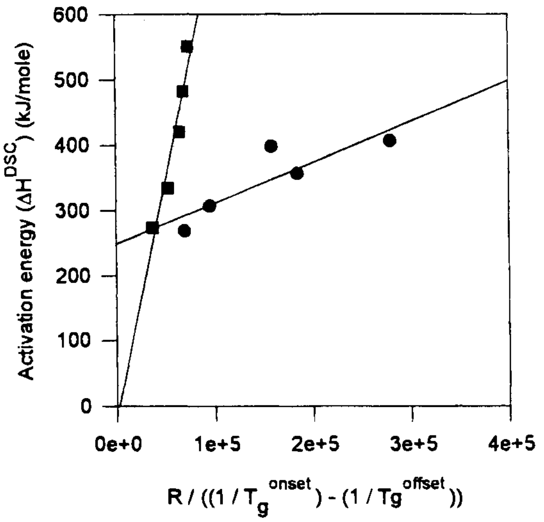

Fig. 5. Plot of the glass transition temperature data according to equation 3 for the poly(vinylpyrrolidone) samples (■ - cooling data, ● - heating data).

$$\Delta H^{DSC}\,(\text{kJ/mol}) = 87 + 1.12R/((1/T_g^{onset}) - (1/T_g^{offset})) \quad (4)$$

The cooling data for the PVP fall on another straight line with a zero intercept (as predicted by equation 3), and the heating data fit a different straight line with a positive intercept (Figure 5). That is, cooling and heating data give quite different correlation functions for this polymeric material.

Analogous plots to Figures 4 and 5 using data obtained at the other scanning rates (5, 7, 14, 20 & 30 K/minute) were qualitatively similar to these figures, and the slopes of straight line plots forced through their origins (equivalent to the proportionality constant (C) of equation 3) were between 1.1 and 7.3. This range of slope values is wider than that reported for the high T_g inorganic glass formers (11,12) and the individual values differed significantly from the mean value of 5.0 previously obtained. For all the materials there was a small but significant increase in slope with increasing scanning rate as predicted by Moynihan (11), and the slope of the best fit line for PVP was considerably greater on cooling than on heating (Figure 5). One can speculate that these differences may be due to complex intermolecular interactions, or even different multiple configurational entropic states within the particular amorphous systems chosen for study which allow different energetic levels to exist (24).

While the scatter in the glass transition width and ΔH^{DSC} values (Tables I & II) is significant it does not seem likely that differences in their relationship from that reported by Moynihan reflect only random error. Rather, it appears that the precise correlation depends upon type of material and direction of temperature change (i.e., heating or cooling) (see above) and/or the data carry a systematic bias (25). The existence of different proportionality constants (C values) for different classes of materials should not really be surprising given that the size of their cooperatively rearranging regions and the extent of their structural heterogenieties would be expected to be quite different, and these properties are known to strongly influence the width of the measured glass transition (21–23,25,26). Such effects would not have been apparent in Moynihan's analysis because his work was restricted to one class of materials whose members would be expected to have similarly sized and distributed domains for molecular motions. For the polymeric PVP samples there will be a range of molecular weights and sizes within each sample (polydispersity). This is analogous to having a blend of different molecular weight materials and would also be expected to broaden T_g considerably. Such broadening is a reflection of an increased distribution of molecular relaxation times within the sample and could easily introduce a systematic bias in the slopes of the plots shown in Figures 4 & 5 (11). A positive intercept for the line of best fit (e.g., PVP heating data in Figure 5) may be indicative of sample relaxation during heating. Such relaxation, which usually decreases the measured glass transition width, could have occurred despite having taken precautions against it (e.g., matching heating and cooling rates), and having observed no significant signs of enthalpic relaxation in the DSC traces (1,7). Underlying equation 3 is an assumption of similar distributions of relaxation times between materials, an equivalency of ΔH from viscosity and DSC measurements, and equivalently sized cooperatively moving regions at T_g (10–12). The diverse glass forming properties of amorphous pharmaceutical materials mean that it is quite likely that one or more of these assumptions will be contravened. Thus, it is not really surprising that equation 3 is a somewhat crude approximation. From a practical perspective we can conclude that it will be necessary to measure the proportionality constant for each class of amorphous pharmaceutical material before equation 3 can be used to estimate fragility. Classes of amorphous materials will probably need to be defined according to the nature of their inter and intra molecular interactions (e.g., hydrogen bonding interactions) and, whilst this research has established the correlation functions for some single component low molecular weight pharmaceutical materials and PVP, the impact of structural chemistry, thermal history, and the behavior of more complex mixed amorphous pharmaceutical systems (e.g., formulations) still needs to be determined.

CONCLUSIONS

A simple calorimetric method for estimating the fragility of amorphous pharmaceutical materials has been tested. With modification this approach appears to be valid for some subclasses of these materials under well defined and carefully controlled conditions. There is evidence that the conditions required for general applicability of the approach with a "universal" constant cannot be met, and further work is required to determine the influences of chemical structure, thermal history, and multicomponent mixtures on the observed relationships.

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