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Research Article

Molecular Mobility of Amorphous Pharmaceutical Solids Below Their Glass Transition Temperatures

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Purpose. To measure the molecular mobility of amorphous pharmaceutical solids below their glass transition temperatures (Tg), using indomethacin, poly (vinyl pyrrolidone) (PVP) and sucrose as model compounds. ***Methods.*** Differential scanning calorimetry (DSC) was used to measure enthalpic relaxation of the amorphous samples after storage at temperatures 16-47 K below Tg for various time periods. The measured enthalpy changes were used to calculate molecular relaxation time parameters. Analogous changes in specimen dimensions were measured for PVP films using thermomechanical analysis. ***Results.*** For all the model materials it was necessary to cool to at least 50 K below the experimental Tg before the molecular motions detected by DSC could be considered to be negligible over the lifetime of a typical pharmaceutical product. In each case the temperature dependence of the molecular motions below Tg was less than that typically reported above Tg and was rapidly changing. ***Conclusions.*** In the temperature range studied the model amorphous solids were in a transition zone between regions of very high molecular mobility above Tg and very low molecular mobility much further below Tg. In general glassy pharmaceutical solids should be expected to experience significant molecular mobility at temperatures up to fifty degrees below their glass transition temperature.

KEY WORDS: amorphous; glass transition temperature; aging; molecular mobility; relaxation time.

INTRODUCTION

The use of the amorphous form of drugs and excipients to improve solubility, accelerate dissolution and promote therapeutic activity has been advocated by many workers (1). The rationale behind such a strategy is that a highly disordered amorphous material has a lower energetic barrier to overcome in order to enter solution than a regularly structured crystalline solid. In order to produce a usable amorphous system it is necessary to create a highly disordered molecular state (usually by a high energy process such as milling or lyophilisation) and then to stabilise that disordered state (usually by rapid drying or cooling or addition of stabilising agents) so that all molecular motions which might induce instability are retarded over a meaningful pharmaceutical time-scale. It is the apparent chemical and physical instability of most amorphous pharmaceutical solids which is the major factor precluding their more widespread use in solid dosage forms. These materials are often highly reactive and unstable to mechanical and thermal stresses above their glass transition temperatures (Tg) and this may result in significant variation in some of their key physicomechanical properties. Whilst many of them alone have Tg values above normal operating temperatures the plasticising effects of residual solvents, absorbed water and other additives and impurities are not easily quantified so there is still a great deal of uncertainty about their long term performance and stability in pharmaceutical dosage forms. Some uncertainty also stems from the fact that while it is often assumed that amorphous materials are inherently stable below Tg evidence does exist that destabilisation can occur in the glassy state (2). Thus the fundamental question that needs to be addressed is *"Under what conditions (e.g. temperature, humidity) do the molecular processes responsible for destabilisation of an amorphous substance become precluded or statistically improbable over the normal life-time of a pharmaceutical product?"*.

In order to address this question the importance of time scales of molecular motion in amorphous systems must be considered. If we produce an amorphous solid, say by supercooling the molten material, a system is created which is unstable and of a higher free energy than the corresponding crystalline solid (Fig. 1). At temperatures just below the crystalline melting temperature (Tm) the mean speed of the translation molecular motions (over atomic distances) in the amorphous material (a few seconds) is very rapid compared to the time scales of normal experimental measurements (several minutes or hours). By cooling the amorphous material these molecular motions can be slowed down and eventually a temperature can be attained at which the time-scale of the motions and that of our experiment coincide. This is the experimental glass transition temperature (Tg) and its exact location clearly varies with the time scale of the experimental method being used. In this context the glass

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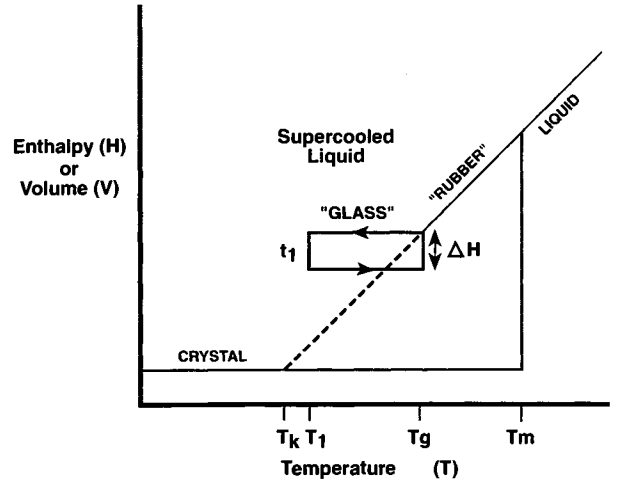

Fig. 1. Schematic representation of the enthalpy or volume-temperature relation in a typical amorphous solid (Symbols defined in the text).

transition event is usually considered to reflect co-operative type translational molecular motions, either by segments of a polymer molecule or by substituent groups of a smaller glass forming species. Below Tg translational molecular motions in the amorphous material still occur, but over longer time periods (hours and days) and thus they have to be measured using extended experimental techniques. These measurements are often referred to as "aging experiments" (3). It can be readily appreciated that whilst these molecular motions in the glassy region below Tg are relatively slow in normal experimental terms they can still have a profound influence over the life-time of a typical pharmaceutical product which is usually of the order of a few years. The failure to recognise the effects of these time-scale differences on the behaviour of amorphous systems may explain why many accelerated stability tests performed in the laboratory provide unrealistic predictions of the stability of pharmaceutical dosage forms stored under ambient conditions for much longer periods of time.

In an attempt to learn more about molecular motions in the region below Tg we have performed studies with a range of amorphous pharmaceutical materials that have been previously studied above Tg (2,4,5). In earlier studies conventional solid state nuclear magnetic resonance and thermoanalytical techniques were utilised, however, because the molecular motions that occur below Tg are relatively slow we adopted longer term "aging experiments" in this study. These techniques have been extensively described by Struik (3) and have been applied to pharmaceutical polymer coating systems by Guo (6) and Sinko (7). We utilised differential scanning calorimetry (DSC) to monitor the enthalpy relaxation that occurs with time due to the normal molecular motions below Tg within several pharmaceutical glasses. For one system (poly(vinylpyrrolidone)) we were able to cast films and could also follow the simultaneous dimensional changes using thermomechanical analysis (TMA). This paper reports the preliminary findings of those studies, with particular reference to the determination of the time scales of molecular motion below Tg, the temperature dependence of those motions and their relation to the typical processing and storage behaviour of the materials.

MATERIALS AND METHODS

Materials

Amorphous indomethacin, poly(vinylpyrrolidone) (PVP) and sucrose were selected for study as they represent the range of amorphous materials encountered pharmaceutically (i.e., drugs, polymers & sugars) and because data for their behaviour above Tg was already available (2,4,5). Each of these materials is chemically and physically stable for 24 hours or more at Tg, yet each has a different physical and chemical stability when stored for longer times at ambient temperatures (2,5). PVP also could be formed into amorphous films which allowed it to be studied using thermomechanical testing techniques. Crystalline sucrose (ACS grade, > 99.5% pure) and crystalline indomethacin were purchased from Sigma Chemicals. The sucrose was made amorphous by freeze drying an aqueous solution (5) and amorphous indomethacin was produced by rapid cooling of the melt (2). A high molecular weight grade ($\approx 10^6$ Da) of amorphous poly(vinylpyrrolidone) (PVP K90) was obtained from GAF Corporation and was used as received.

Methods

When a glassy amorphous material is stored at a temperature (T_1) for a certain time (t_1) it experiences gradual spontaneous losses in enthalpy (ΔH) and volume (ΔV) due to the coupling of the normal molecular motions occurring under those conditions with the thermodynamic driving force towards a more stable crystalline state (Fig. 1) (3). Provided the glassy material is prepared in a consistent manner the rate of enthalpy/volume loss can be considered to reflect the level of molecular mobility in the non-equilibrium glassy amorphous sample (3). Upon reheating the "aged" glassy material the enthalpy (ΔH) and volume losses are fully recovered at or near Tg (Fig. 1) and can be very easily quantified using standard thermoanalytical techniques (e.g., differential scanning calorimetry (DSC) and thermomechanical analysis (TMA)).

Differential Scanning Calorimetry (DSC)

Samples of the amorphous materials were subjected to several different DSC experiments to assess the effects of various test procedures (heating and cooling rates) and storage conditions (time and temperature) on the enthalpy changes occurring in each system. Approximately 2-10 mg samples of each amorphous solid were sealed in aluminum DSC pans with a pin hole in the lids. The samples were analysed under a dry nitrogen purge in a Seiko SSC5200 DSC fitted with an automated liquid nitrogen cooling accessory. This fitting enabled heating and cooling rates of 1-40K/minute (±1%) to be achieved over the entire experimental temperature range. Initially samples were heated at 20K/minute to 10-25K above their glass transition temperature and then cooled at the same rate to 200K below Tg to minimise and standardise the effects of sample history. The samples were then heated to a storage temperature in the range 16-47K below Tg and were held at that temperature for 1, 2, 4, 8, or 16 hours. The samples were subsequently cooled at 20K/minute and then reheated through their Tg to measure

the enthalpy recovery (ΔH). A schematic depiction of this procedure is shown in Fig. 2. In all of the systems studied a pronounced enthalpy recovery was observed at Tg following storage for different periods at several temperatures (*e.g.*, Figure 3) and this was quantified for each set of conditions by calculating the area between the DSC curve of the aged sample and that of the extrapolated supercooled-liquid baseline (3). The DSC was calibrated for temperature and heat flow using pure samples of tin, indium and gallium, and the results of replicate experiments varied by less than 1%. Selected samples were reweighed and inspected after analysis to look for signs of decomposition and/or recrystallisation and the sucrose and indomethacin samples were heated to above their melting points in the DSC after measurement to verify that there had been no recrystallisation during storage or testing. Prolonged aging experiments of up to 1060 hours were also performed on amorphous indomethacin samples at one temperature.

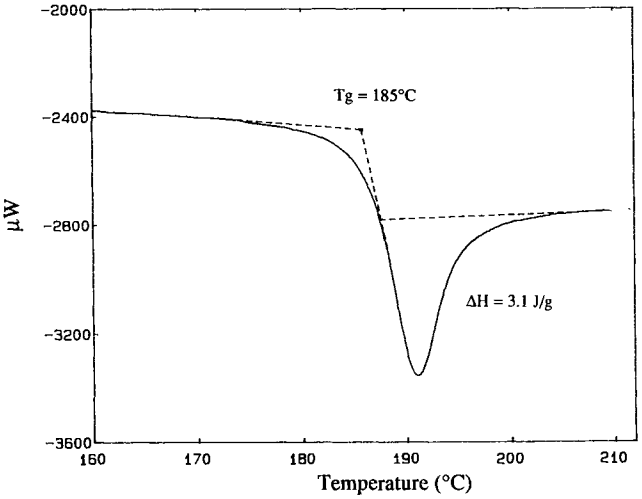

Fig. 3. Typical DSC trace (for poly(vinylpyrrolidone)) showing the enthalpy relaxation endotherm at the glass transition temperature.

Thermomechanical Analysis (TMA)

The dimensional changes occurring in amorphous PVP samples at temperatures below Tg analogous to the enthalpy changes described above were measured using a standard thermomechanical analyser. Films of PVP were spin-cast from 5%w/v ethanolic solutions as described previously (4) and the average thickness of the films was determined to be 45 μm using a calibrated micrometer. Rectangular specimens (20 × 3mm) were carefully cut from the middle of the films using a scalpel and a template and were mounted in the chucks of a Seiko TMA/SS thermomechanical analyser (TMA). The temperature of the sample in the TMA was calibrated with respect to the melting points of pure indium and a high molecular weight polyethylene oxide. The film samples were placed under a tension of 100 mg, which supported the sample and held it flat, but caused negligible elongation at any of the temperatures encountered during testing. Each sample was then heated at 5K/minute to 5K above Tg under a dry nitrogen purge and subsequently cooled, by immersion in an atmosphere of evaporating liquid nitrogen ("rapid cooling") or by blowing air over the outside of the furnace using a hand held laboratory fan ("slow cooling"), to standardise the sample history. After cooling the sample was reheated at 5K/minute to a storage temperature in the range 32-120K below Tg and held for up to 32 hours. Any changes in the length of the sample after attainment of the storage temperature were monitored with time as a measure of the volume relaxation occurring below Tg (see Fig. 1). The results reported are the mean (± standard deviation) of triplicate measurements.

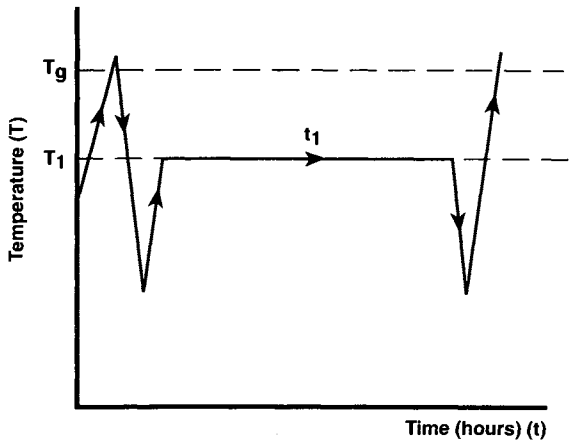

Fig. 2. Schematic representation of the conditions used to measure the enthalpy recovery at the glass transition temperature (Symbols defined in the text).

RESULTS

Differential Scanning Calorimetry (DSC)

The experimental glass transition temperature of the materials varied according to how the glassy material was formed (cooling conditions) and how the Tg measurements were made (heating conditions). Identical behaviour has been noted for many other glass forming materials (8) and has been attributed to the different coincident points of the rate of molecular motion in the sample and the frequency associated with a particular set of test experimental conditions. The relaxation enthalpy at the glass transition also varied with the experimental conditions in all three materials. As the heating and cooling rates decreased (and the experimental time increased) enthalpy relaxation started to occur over the duration of the preparation and test procedures. To minimise these phenomena and to standardise the thermal history of the samples the heating and cooling rates for all subsequent DSC experiments were optimised and fixed at 20K/minute.

As seen in Figures 4, 5, and 6, all three materials studied showed marked signs of relaxation or aging upon storage below Tg confirming that molecular motions below Tg could be measured quite easily using the method described. The enthalpy recovery of each material at Tg was found to be very reproducible (typically less than 5% variation) and in each case the recovery increased with storage time in an approximately exponential manner as has been described for many other glassy materials (3). Changes in the enthalpy of the three glassy pharmaceutical materials over the course of the experiments were very similar when expressed on a "per

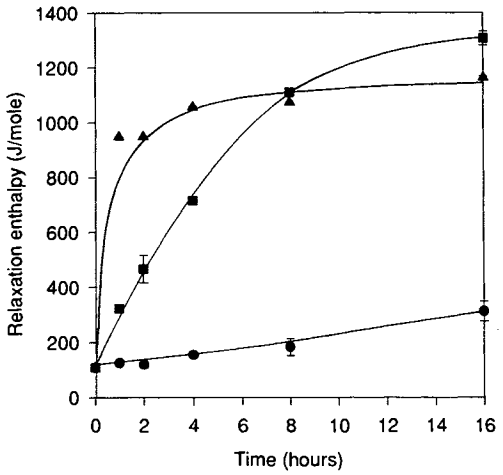

Fig. 4. Variation of the relaxation enthalpy with storage time for indomethacin (● Tg-47, ■ Tg-32, ▲ Tg-16).

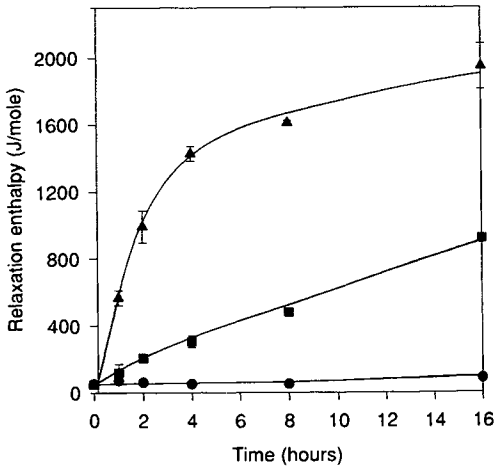

Fig. 6. Variation of the relaxation enthalpy with storage time for sucrose (● Tg-47, ■ Tg-32, ▲ Tg-16).

gram" basis (data not shown) but were quite different when expressed "per mole or repeat unit." The results of experiments 8K apart were significantly different and for each material the relaxation at Tg-47K (the lowest storage temperature) was small but detectable over the longest (16 hour) storage time. Enthalpy changes were measured for indomethacin at one temperature (303K) for up to 1060 hours (44 days) and identical trends were seen even over this extended time period (data not shown). This represents four orders of magnitude in time and suggests that extrapolation of laboratory data to predict relaxation behaviour for up to several years may be feasible.

Thermomechanical Analysis (TMA)

Measurement of the contraction of rapidly cooled PVP films stored at different temperatures below Tg confirmed that dimensional changes occur in this glassy material as it relaxes (Fig. 7). As with the enthalpy relaxation the dimensional changes exhibited an approximately exponential relationship with storage time. The temperature range over which the dimensional changes were seen was much greater than for the enthalpy changes (compare Figs. 5 & 7) suggesting that the different modes of measurement used either have different sensitivities to the relaxation processes below Tg, or that they detect slightly different molecular motions in this material. Earlier workers have usually attributed such phenomenon to the latter case because of the different time scales of the different measuring techniques. This situation is practically very useful since it allows data to be collected using the most appropriate method for the type of material being considered. Experiments in which the effects of different cooling rates ("rapid" & "slow") on the contraction of glassy PVP films were studied (results not shown) were consistent with earlier DSC experiments.

The fact that dimensional changes can occur in non-film forming pharmaceutical glasses is evidenced by data for indomethacin presented by Fukuoka *et al* (9). These authors measured the mechanical properties of glassy indomethacin as it was heated through its glass transition temperature after storage under various conditions. Close examination of these data reveals that pronounced volumetric recoveries occurred in the indomethacin samples at Tg, analogous to

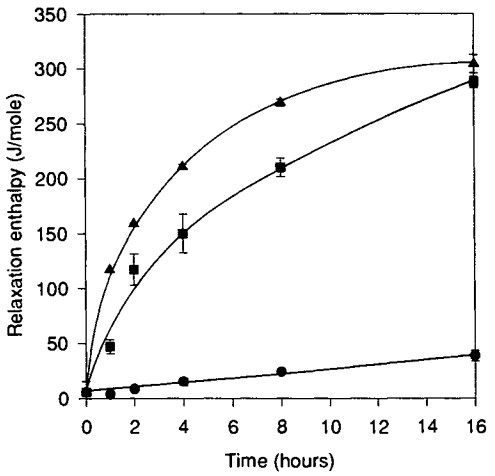

Fig. 5. Variation of the relaxation enthalpy with storage time for PVP (● Tg-47, ■ Tg-32, ▲ Tg-16).

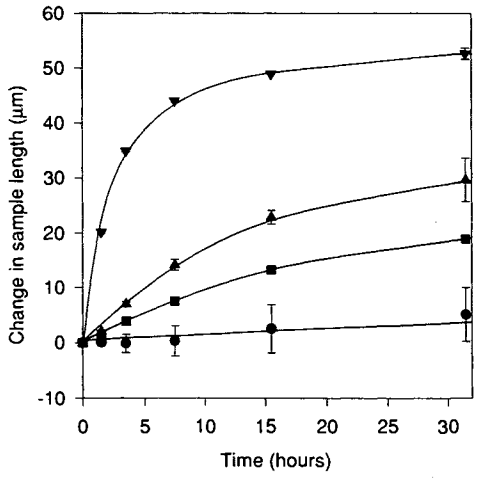

Fig. 7. Change in the length of the glassy PVP film samples with aging time (● Tg-119, ■ Tg-99, ▲ Tg-79, ▼ Tg-32).

the enthalpy recoveries which we have measured for this material and have described above.

DISCUSSION

From the results of our experiments we can say that many glassy pharmaceutical materials will exhibit significant molecular mobility and subsequently experience enthalpic and/or volumetric relaxation at temperatures significantly below their Tg. In addition, it appears that these aging phenomena occur under similar time and temperature conditions for both large (polymeric) and small glass forming species. In order to be able to make a direct and meaningful comparison of the molecular mobilities of different materials it is necessary to calculate their molecular relaxation time constants (τ). These time constants represent the average time taken for a single molecular motion of a particular type to occur and can be readily calculated from enthalpy relaxation data (10). First the maximum enthalpy recovery at any given temperature (ΔH_∞) is calculated from the following equation:

$$\Delta H_\infty = (Tg\text{-}T).\Delta C_p \quad (1)$$

where Tg is the glass transition temperature, T is the experimental temperature and ΔC_p is the change in heat capacity at Tg. From this maximum enthalpy recovery it is possible to calculate the extent to which a material relaxes (ϕ_t) under any given time (t) and temperature (T) conditions:

$$\phi_t = 1\text{-}(\Delta H_t/\Delta H_\infty) \quad (2)$$

where ΔH_t is the measured enthalpy recovery under those conditions. This information is then used to calculate the molecular relaxation time constants, τ. The most widely used approach is based on the empirical Williams-Watts equation which was originally developed for describing dielectric relaxation data (11). Typically it is assumed that there are multiple relaxation processes with a distribution of relaxation times, and the data is fitted to a stretched exponential function using non-linear regression. This provides a mean τ value for all the molecular motions occurring under a given set of conditions (t,T):

$$\phi_t = \exp(-t/\tau)^\beta \quad (3)$$

where τ is the mean relaxation time constant and β is a relaxation time distribution parameter with a value of between 0 and 1. If β is equal to unity there is a single relaxation time and the data can be described using a simple single relaxation time model. It is also possible to evaluate ΔH_∞, τ and β simultaneously by combining equations 2 and 3 and fitting the experimental enthalpy recovery data to the resulting expression using non-linear regression. This procedure usually results in slightly lower estimates of ΔH_∞, and τ and slightly higher estimates of β (13). This method could not be used for the data collected in this study because of the relatively wide range of experimental temperatures used.

Molecular relaxation time constants were calculated from our enthalpy recovery data using equations 1, 2, and 3 and the Curve Fit feature of Sigma Plot for Windows (Version 1.0, Jandel Scientific, California, U.S.A.). An iterative non-linear regression procedure based on the Marquardt-Levenberg algorithm was used to find the best fit to the data. The initial parameters provided were τ = 100 and β = 0.5 for all three materials. The range of τ values calculated for indomethacin, PVP and sucrose is shown in Fig. 8. For ease of comparison the data are presented with the temperature scale normalised by subtracting the storage temperature from the Tg. For each material the mean relaxation time constant varied from experimental time scales to geological time scales over the temperature range studied (16-47K below Tg). The corresponding β values were between 0.3 and 0.8 for all three materials (Indomethacin: 0.3-0.6; PVP: 0.5-0.8; sucrose: 0.4-0.8) indicating that a distribution of time scales was required to accurately describe each set of data. Similar β values have previously been reported (12), with smaller molecules generally having higher β values than polymers, and this was also seen for our systems. Only small variations in β with temperature were expected (12) and this was observed. Both PVP and indomethacin appeared to show slight reductions in β with increasing temperature indicating that their aging processes are not thermorheologically simple (13).

The mean relaxation time constants decreased with increasing temperature in all three systems studied. In each case the temperature dependence was non-linear and significantly greater than that predicted by a simple logarithmic

Table I. Physicochemical Properties of the Dry Pharmaceutical Materials

	PVP	Indomethacin	Sucrose
Molecular wt. of repeat unit	111	358	342
True density (g/ml)	1.25	1.32	1.43
Glass transition temp. (Tg) (K) (Heat & cool rate 20K/min)	458	320	350
Melting point (T_m) (K)	None	438	453
T_m/T_g	—	1.37	1.29
Change in heat capacity at Tg (ΔCp) (J/K.mole)/(J/K.g)	28.86/ 0.260	166.90/ 0.466	186.05/ 0.544

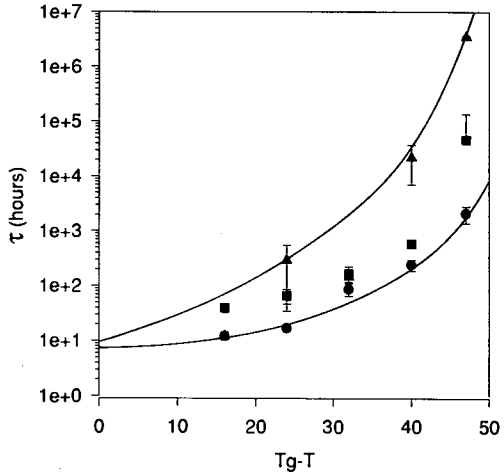

Fig. 8. Variation of the relaxation time parameter, τ, with scaled temperature Tg-T. ▲ Sucrose, ■ Indomethacin, ● PVP. Lines indicate the range of values observed.

relationship (Fig. 8). Relaxation time data collected below Tg for other polymers and small molecules show similar variations with temperature (14,15). The slopes of the lines of best fit through each set of data were all slightly different indicating different structural responses to temperature variation for these materials in the glassy state. To obtain a rough estimate of the magnitude of this temperature dependence of the molecular mobility in our pharmaceutical glasses we used the mean slopes of the lines of best fit through the data to estimate approximate and apparent Arrhenius activation energies (E_A). These E_A values are summarised in Table II and their magnitude confirms that co-operative translational molecular motions are most likely occurring over the temperature range studied for all three materials (13). That is, the molecular motions 16-47K below Tg in these systems involve multiple atoms and bonds and are not isolated vibrational or rotational motions of individual atomic species.

Since identical experimental conditions were used in all the DSC studies the value of τ at Tg should be similar for all three materials and the data in Fig. 8 should approach each other at Tg. This appears to be the case even though the modes of molecular motion and the distribution of those motions are probably unique to each material. By extrapolation of lines of best fit through the three data sets we have estimated mean relaxation time constants at Tg in the range of 1-10 hours for these materials. This range is significantly higher than that reported by Slade and Levine (16) but similar to that reported by Barlow *et al* (17). Since it is very difficult to accurately measure enthalpy recovery at storage temperatures near to Tg this level of agreement between our data and the literature is considered reasonable.

For all our materials the data indicate that for the molecular motions detected by DSC to be slowed to a point where they are insignificant over the normal lifetime of a pharmaceutical product it is necessary to cool to temperatures at least 50K below the glass transition temperature (Fig. 8). This region corresponds to that at which the configurational entropy of the supercooled liquid tends to zero (the Kauzmann temperature, T_K) (Fig. 1) (18) and where the true thermodynamic glass transition of Gibbs and DiMarzio is located (19). It also coincides with the point at which the experimental Tg would be expected to occur at infinitely slow heating and cooling rates and where the free volume of the amorphous material should become zero and its viscosity become infinite (17). Thus, the molecular motions detected by DSC appear to require a complete "freezing out" of all the entropy and free volume in the system before they can be considered to be totally inhibited over normal pharmaceutical time-scales. This observation clearly has major implications for those wishing to define storage conditions and shelf-lives for pharmaceutical dosage forms containing amorphous drugs or excipients. From Fig. 8 we can estimate a "shelf life" (based on the time for one relaxation) at room temperature (298K) of many years for dry PVP and sucrose, but only about 3 days for dry indomethacin. Such storage lives are very similar to those determined in our laboratory by trial and error (2,5) and this suggests that enthalpy relaxation studies may have some practical use in the prediction of pharmaceutical product stabilities.

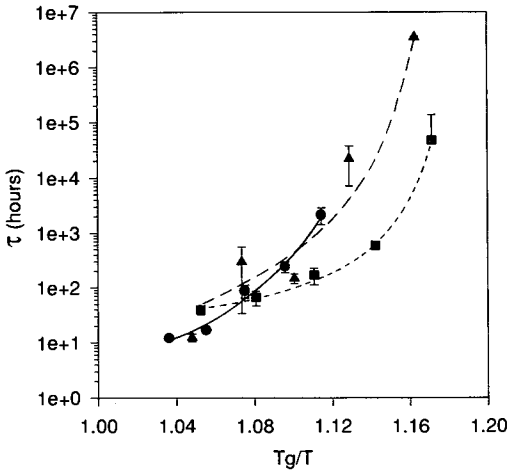

Fig. 9. Variation of the relaxation time parameter, τ, with scaled temperature Tg/T. ▲ Sucrose, ■ Indomethacin, ● PVP. Lines indicate the best fits to the VFT equation.

Table II. Arrhenius and VFT Constants Derived from the Mean Relaxation Times

	PVP	Indomethacin	Sucrose
Activation energy (E_A) (from Fig 8) (kJ/mole)	300	180	360
A (from VFT eqn) (hours)	7.1×10^{-9}	0.95	1.9×10^{-8}
B (from VFT eqn) (K)	54.8	26.1	75.7
C (from VFT eqn) (K)	395	267	290

Amorphous materials have been classified by Angell (20) as either "strong glass formers" or "fragile glass formers" based on a number of physical properties. Strong glass formers typically exhibit relatively small changes in heat capacity (ΔCp) at their Tg (21), have melting point to glass transition temperature ratios (Tm/Tg; in K) of 1.5 or greater (20) and have β (relaxation time distribution parameter) values of near to unity (22). Conversely, fragile glass formers typically exhibit relatively large ΔCp values, having Tm/Tg ratios of between 1 and 1.5, and β values significantly less than 1. The reason for the different types of amorphous behaviour lies in the way in which the molecular structures of different systems respond to changes in temperature. Strong glass formers (exemplified by silicon dioxide) show a near linear dependence of the log of their relaxation rate (or viscosity) on the inverse of temperature, whereas fragile glass formers (exemplified by the small molecule 0-terphenyl) show marked negative deviations from such linear behaviour (20).

As an aid to identifying and ranking amorphous materials in terms of their strength/fragility Angell and other workers have utilised plots of log relaxation time (or viscosity) versus T/Tg. Such plots correspond to the empirical Volgel-Fulcher-Tamman (VFT) function (20):

$$\tau = A.\ \exp\ (B/(T-C)) \qquad (4)$$

where A, B, and C are constants. This equation simplifies to the well known linear Arrhenius equation when C = O (assuming a temperature independent activation energy for molecular motions) (22), and is equivalent to the popular Williams-Landel-Ferry (WLF) equation (23) above Tg (when C_1 = B/(T-C) and C_2 = (T-C)) (16). The VFT equation can also be equated to the widely used Adams-Gibbs equation with appropriate assumptions and approximations (24). Previous workers have observed that above Tg the VFT constant C often appears to correspond to a temperature about 50K below Tg and the value of constant B can be related to the fragility of the system being studied (a typical value for fragile materials is 10 × (Tg-50)) (22). Constant A has also been related to a hypothetical relaxation time constant for an unrestricted molecule and thus usually has a very low value ($\ll 10^{-9}$ hours) (22).

The three amorphous pharmaceutical systems considered in this work might be expected to show some noticeable differences in their glass forming behaviour because of their widely different chemical structures. Based on Tm/Tg and ΔCp criteria both sucrose and indomethacin would be expected to be fragile glass formers (Table I), with sucrose being slightly more fragile (The β values determined in this study were too scattered for a reliable ranking to be made on this criteria.). PVP would be expected to be a slightly stronger glass former because of its polymeric nature (21). In Fig. 9 the relaxation time constants determined for these materials below Tg are plotted versus Tg/T, with the best fit of the empirical VFT equation to these data. In our analyses we used initial VFT constant values of A = 10^{-9}, B = 10 × (Tg-50) and C = Tg-50, and the optimised values of these constants obtained by non-linear curve fitting (see earlier) are given in Table II. It can be seen that each set of data in Fig. 9 follows a non-linear relationship, presumably indicating some degree of fragility for all the materials. There also appear to be some small differences in the changes in molecular mobility of the glasses with temperature, presumably indicating the structural response to temperature change is slightly different for each molecular species even in a corresponding glassy state. The values of the VFT constant C obtained below Tg (Table II) all coincide with a temperature about 50K below Tg whereas the B values are all slightly lower than those typically obtained for fragile glass formers above Tg (20). For PVP and sucrose the A constant is of the order normally reported above Tg, but for the indomethacin the A constant is much larger. Until now the physical significance of these constants has only been discussed for systems above Tg because of difficulties in interpreting relaxation time data collected for non-equilibrium materials below Tg. Even in the region above Tg the interpretation of these constants is somewhat uncertain. A detailed analysis of the behaviour of systems below Tg clearly requires much more data than is currently available and is beyond the scope of this work. However such an analysis should eventually increase our understanding of the glassy state, provided sufficient care is taken to control the effect of sample history in the amorphous structure below Tg.

CONCLUSIONS

We have used experimental techniques which measure enthalpic and volumetric relaxation to estimate the extent of molecular mobility and to calculate molecular relaxation times for three typical pharmaceutical glasses below their respective glass transition temperatures. For each material the relaxation time constants calculated from DSC data ranged from a few minutes at Tg to many years at about 50K below Tg, and in the intermediate temperature range it was noted that significant numbers of molecular motions would occur over the lifetime of a typical pharmaceutical product. Extensive analysis of the data indicated that the techniques used may provide a practical means of studying the structural properties of pharmaceutical glasses and also of predicting the temperature stability of some glassy pharmaceutical products.

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