Pharmaceutical Research, Vol. 23, No. 10, October 2006 (© 2006)
DOI: 10.1007/s11095-006-9071-9

Research Paper

A Calorimetric Method to Estimate Molecular Mobility of Amorphous Solids at Relatively Low Temperatures

Chen Mao,[1] Sai Prasanth Chamarthy,[1] Stephen R. Byrn,[1] and Rodolfo Pinal[1,2]

Received February 2, 2006; accepted May 22, 2006; published online August 24, 2006

Purpose. To present a calorimetry-based approach for estimating the initial (at the onset of annealing) relaxation time (τ^0) of organic amorphous solids at relatively low temperatures, and to assess the temperature where molecular mobility of the amorphous drug is reduced to a level comparable with the desired shelf-life of the product.
Materials and Methods. Values of τ^0 for six amorphous pharmaceutical compounds were estimated based on the nonlinear Adam–Gibbs equation. Fragility was determined from the scanning rate-dependence of the glass transition temperature (T_g). The initial enthalpic and entropic fictive temperatures were obtained from the T_g and the heat capacities (C_p) of the amorphous and crystalline forms.
Results. At a relatively low temperature (~40°C or more below T_g), τ^0 for the different compounds varies by over an order of magnitude. For some materials, the practical storage temperature at $T_g - 50$ K was found to be still too high to ensure long-term stability. The estimated τ^0 is highly sensitive to the fragility of the material and the C_p of the crystalline and amorphous forms. Materials with high fragility or greater C_p differences between crystalline and amorphous forms tend to have longer τ^0.
Conclusions. The proposed method can be used to estimate molecular mobility at relatively low temperatures without having to conduct enthalpy recovery experiments. An accurate τ^0 determination from this method relies on faithful fragility measurements.

KEY WORDS: amorphous; differential scanning calorimetry; fictive temperature; molecular mobility; relaxation; stability.

INTRODUCTION

The development of organic pharmaceutical compounds into amorphous formulations has become widely accepted as a potentially effective method for drug delivery with enhanced bioavailability. The important work in this area by George Zografi and coworkers, started in the early 1990s (1–3) and continued to date (4,5), has brought the notion of amorphous formulations into the mainstream of pharmaceutical research in two equally important respects. One is the advantageous formulation possibilities offered by drugs in the amorphous state. The other is the need for a fundamental understanding of organic amorphous solids, specifically, the relationship between molecular mobility and the physical and chemical stability of amorphous products. All with the ultimate goal of producing consistent and reliable amorphous drug products that are kinetically stable over their desired shelf life.

It is well known that the reduced stability of amorphous solids is, to a good extent, due to their greater molecular mobility relative to their crystalline form. The development of every pharmaceutical amorphous formulation presents the challenge of establishing the optimal processing and storage conditions where molecular mobility is minimized, so that the desired physical and chemical stability of the product can be attained. Thus, a reliable means of estimating molecular mobility of drug candidates under different but relevant sets of conditions is of vital importance for the successful development of amorphous drug products.

Molecular mobility in amorphous solids is usually evaluated by means of the structural relaxation time (τ). Among all available methods for estimating molecular mobility, thermal methods are most frequently employed in pharmaceutical development because of their applicability to powder samples, the ease of conducting the measurements and direct interpretation of the data. The current routine approach is the so-called "enthalpy recovery experiment" (1,6), in which amorphous samples are stored (annealed) below the glass transition temperature (T_g) for various lengths of time, followed by the measurement, using differential scanning calorimetry (DSC), of the corresponding enthalpy loss. With this method, the average τ value and a stretch parameter β can be obtained by fitting the data to the empirical Kohlrausch–Williams–Watts (KWW) equation:

$$\phi = 1 - \frac{\Delta H_{relax}}{\Delta H_\infty} = \exp\left(-\left(\frac{t}{\tau}\right)^\beta\right) \quad (1)$$

[1] Department of Industrial and Physical Pharmacy, Purdue University, 575 Stadium Mall Drive, West Lafayette, Indiana 47907, USA.
[2] To whom correspondence should be addressed. (e-mail: pinal@pharmacy.purdue.edu)

where ϕ is the extent of impending relaxation at the annealing temperature, ΔH_{relax} is the enthalpy recovered after isothermal annealing for a given time and ΔH_∞ is the total enthalpy available for relaxation at the annealing temperature. Enthalpy recovery experiments provide a convenient way for estimating molecular mobility in amorphous solids. However, the method presents some practical shortcomings and some theoretical limitations as well. From a practical point of view, the magnitude of the relaxation time serves as a measure of the shelf life of the product. Consequently, a viable pharmaceutical amorphous formulation should have a relaxation time of 2–3 years under the normal conditions intended for its storage. In order to achieve such shelf lives, it is necessary that amorphous products be maintained at a temperature that is roughly 50°C below their T_g (1,7). At such low (relative to the T_g) temperatures, molecular mobility is so sluggish that the very long relaxation times necessary for viable pharmaceutical products are attainable. But all this brings a practical issue, since it would require very long experiments. Therefore, in order to obtain the needed information, molecular mobility determinations are typically conducted at temperatures closer to the T_g, where the relaxation time falls within the time scale of the experiment, resulting in τ values obtained at temperatures different from the temperature of interest. Since the molecular relaxation of organic compounds very often follows non-Arrhenius behavior, there is no reliable method for estimating the relaxation time at say $T_g - 50$°C by extrapolating data obtained at higher temperatures.

The enthalpy recovery method commonly used presents also some theoretical limitations. First, the approach is built on the assumption that τ does not change significantly during the timescale of the annealing experiment. Such an assumption has been brought into question from both experimental and simulation studies (8,9). Second, since the τ value obtained from KWW approach is accompanied a degree of non-exponentiality of the relaxation, usually expressed by β, any direct comparison of two τ values is inconclusive at best unless the two relaxation processes share similar β (10). Third, a reliable estimation of τ from the KWW approach requires measurements from samples exhibiting extensive relaxation (approximately 80% of ΔH_∞) (6), which at 40 to 50°C below T_g could take months or years. This situation brings us back to the fact there is no method for accurately extrapolating relaxation time data from high temperature measurements to lower temperature conditions.

The aim of this study is to develop a calorimetric method for evaluating the molecular mobility of amorphous pharmaceutical solids at low temperatures (relative to T_g), where the relaxation process is too sluggish to be observed within the time scale of the experiment. In this method, the initial relaxation time of the amorphous material, $\tau^0(T)$ is evaluated. At temperatures well below the T_g, molecular mobility is very slow. In addition, under such conditions the change in τ over time also occurs very slowly. For this reason, at low temperatures (relative to T_g), the initial relaxation time, $\tau^0(T)$, can serve as an estimate of the average relaxation time over a time span comparable to the desired shelf life for amorphous products.

ESTIMATING INITIAL RELAXATION TIME

One widely accepted model for the structural relaxation time of amorphous solid below T_g is the nonlinear Adam–Gibbs (AG) equation, also known as the Adam-Gibbs-Vogel (AGV) equation. In one of its forms:

$$\tau = \tau_0 \exp\left(\frac{DT_0}{T(1 - T_0/T_f)}\right) \quad (2)$$

where T_f is the fictive temperature, *i.e.*, the temperature at which the observed configurational property (such as enthalpy or entropy) of a non-equilibrium state (glass) corresponds to that of the equilibrium one (liquid); τ_0 is a pre-exponential factor and is often taken as being of the order of the lifetime of atomic vibrations (10^{-14} s). The explicit form of the parameters D and T_0, derived from statistical thermodynamic considerations in the original Adam–Gibbs theory (11), can be obtained by assuming a hyperbolic temperature dependence of heat capacities (12,13). Above T_g, Eq. 2 is numerically indistinguishable from the Vogel-Tammann-Fulcher (VTF) equation, which describes the non-Arrhenius temperature dependence of relaxation of the glass-forming liquid:

$$\tau = \tau_0 \exp\left(\frac{DT_0}{T - T_0}\right) \quad (3)$$

The parameters D and T_0 describe the extent to which the relaxation time of the liquid deviates from the linear Arrhenius behavior as a function of temperature. Fragility is the term used to characterize the deviation from Arrhenius behavior in liquids as the temperature approaches T_g. The parameter D is a measure of fragility also termed strength parameter. Altogether, the relaxation time of an amorphous solid is determined from two sets of parameters: 1) those parameters that describe the relaxation time of the liquid as a function of temperature: fragility (D) and T_0, and 2) the instantaneous configurational property, entropy or enthalpy, that the amorphous solid possesses at any given temperature and time. Here the fictive temperature offers a convenient simplification because it replaces entropy or enthalpy as functions of both time and temperature for a temperature value, T_f.

A number of thermal methods for evaluating the fragility of organic glass formers have been proposed. A detailed description and comparison of these methods is provided in a review by Crowley and Zografi (14). In the present study, we estimate the parameters of the liquid (D and T_0) from the scanning rate dependence of T_g, to date, the most widely accepted and studied approach. It should be pointed out that its practical and theoretical merits notwithstanding, the method requires very careful experiments, as will be discussed later.

The fictive temperature reflects the instantaneous configurational property (entropy or enthalpy) of the glass. Currently, there is no method for the *a priori* estimation of T_f at any given time because of the continuous non-linear, non-exponential nature of the relaxation occurring in the glass. However, it is possible to calculate the initial fictive temperature, $T_f^0(T)$, defined as the fictive temperature of the newly prepared glass made by fast cooling the liquid from

above T_g. Under such conditions, $T_f^0(T)$ represents the configurational property of the amorphous solid prior to the onset of isothermal relaxation. The initial relaxation time $\tau^0(T)$ is therefore:

$$\tau^0 = \tau_0 \exp\left(\frac{DT_0}{T\left(1 - T_0/T_f^0\right)}\right) \quad (4)$$

It should be pointed out that both τ^0 and T_f^0 are temperature dependent, they vary according to the temperature chosen for isothermal annealing. However, the temperature dependence notation has been dropped in order to avoid cluttering of the expressions presented.

If the glass is assumed to follow Arrhenius behavior, T_f^0 can be estimated as being equal to T_g (5,15). However, although convenient and applicable in some cases, such an approximation can never be exactly true because it would require that the heat capacities of the glass and crystal forms be identical. Graphically, this would correspond to a horizontal line for the glass in Fig. 1. Since the heat capacity of the glass is often somewhat greater than that of the corresponding crystalline form, the very act of cooling the glass involves a net loss (relative to the crystal) on configurational properties (even before isothermal relaxation starts), in other words, it involves a decrease of T_f^0 (Fig. 1). The magnitude of this decrease depends on the difference between the glass and crystalline heat capacities, which may differ significantly for different compounds (16).

The value of T_f^0 can be obtained if the heat capacities of the different forms of the compound are known. As shown in Fig. 1, the total enthalpy available for relaxation (ΔH_∞) for a freshly made amorphous solid at the annealing temperature T_1, can be expressed in two alternative ways, either in terms of T_g or in terms of T_f^0:

$$\Delta H_\infty(T_1) = \int_{T_1}^{T_g}\left(C_p^l - C_p^g\right)dT = \int_{T_1}^{T_f^0}\left(C_p^l - C_p^x\right)dT \quad (5)$$

where C_p is the constant pressure heat capacity, and the superscripts l, g and x denote liquid, glass and crystal, respectively. Assuming (consistent with Eq. 2) a hyperbolic temperature dependence of C_p, T_f^0 can be calculated by rearranging Eq. 5 as follows:

$$T_f^0 = T_g^\gamma \cdot T_1^{(1-\gamma)} \quad (6)$$

where

$$\gamma = \left.\frac{\left(C_p^l - C_p^g\right)}{\left(C_p^l - C_p^x\right)}\right|_{T_g} \quad (7)$$

Equations 6 and 7 show that regardless of the annealing temperature, the condition $T_f^0 \approx T_g$ requires the heat capacities of the glass and crystalline forms to be very close to each other. In fact, this rarely happens for organic molecules. Shamblin *et al.* (16) measured the heat capacity of different forms of four organic compounds and obtained γ values ranging from 0.61 (sorbitol) to 0.92 (indomethacin). Combining Equations 4 and 6, the following expression for initial relaxation time is obtained:

$$\tau^0 = \tau_0 \exp\left(\frac{DT_0}{T - T_0(T/T_g)^\gamma}\right) \quad (8)$$

The preceding discussion presents the methodology for estimating the initial molecular mobility of organic amorphous compounds. A synopsis of the corresponding experimental method is presented in Table I. The table shows the different parameters necessary for the complete calculation of the fragility parameters necessary in the approach presented here. A detailed discussion on the origin, values and significance of such parameters is provided elsewhere (9).

In some instances, such as in the case of solid dispersions consisting of drug-polymer mixtures, the crystalline form to use in the proposed method may not be readily available. In

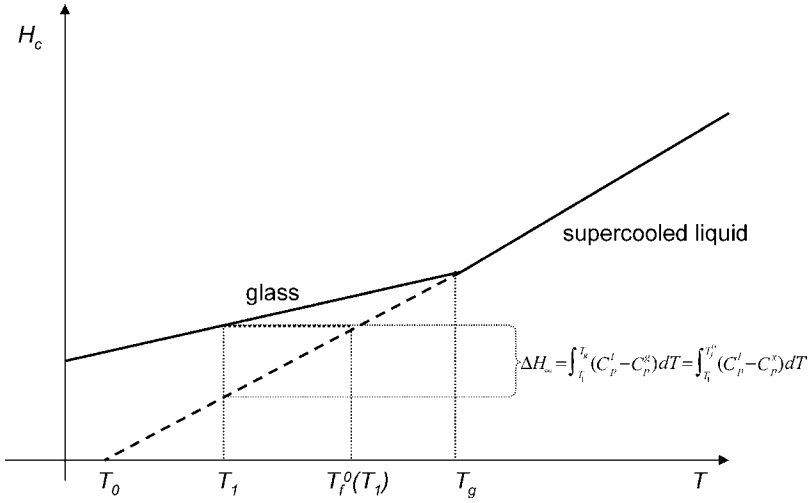

Fig. 1. Schematic diagram depicting the changes of configurational enthalpy (H_c) with temperature (T) and the determination of the enthalpic initial fictive temperature $T_f^0(T_1)$ for an amorphous material annealed at temperature T_1.

Table I. Step By Step Description of the Methodology for Estimating Initial Relaxation Time As Described in this Study

No.	Step	Remark
1	Measure T_g as a function of heating rate (q)	
2	Plot ln q *vs* $1/T_g$ (K)	Obtain the slope of the fitted line
3	Calculate activation enthalpy	$\Delta H^*(T_g) = 8.314 \times \text{slope}$
4	Calculate the fragility index:	$m = \Delta H^*(T_g)/(2.303 \times 8.314 \times T_g)$
5	Calculate D and T_0:	$D = (2.303 \times m_{min}^2)/(m - m_{min})$ $T_0 = T_g \times (1 - m_{min}/m)$
6	Measure C_p of the liquid (l), glass (g) and crystalline (x) forms	
7	Calculate the γ parameter	$\gamma = \frac{(C_p^l - C_p^g)}{(C_p^l - C_p^x)}\Big\vert_{T_g}$
8	Calculate the initial relaxation time, τ^0:	$\tau^0 = \tau_0 \exp\left(\frac{DT_0}{T - T_0(T/T_g)^\gamma}\right)$

The T_g measured at 10°C min^{-1} is used for calculations requiring a single T_g value. A value of m_{min} = 16 and $\tau_0 = 10^{-14}$ s were used in the calculations. For details on the theoretical basis for use of these parameters, see (9).

such cases, the glass form may be regarded as the apparent stable form and a quick estimation of the initial molecular mobility can be performed by assuming $\gamma = 1$. However, one should always bear in mind that this is an approximation necessary by virtue of the nature of the formulation. This type of simplification should not be necessary during solid state characterization studies aimed at assessing the suitability of drugs as potential candidates for development as amorphous formulations.

MATERIALS AND METHODS

Materials

Indomethacin, felodipine, griseofulvin and citric acid were purchased from Sigma Aldrich (St. Louis, MO). Ketoconazole was purchased from Spectrum Chemical and Laboratory Products, Inc. (Gardena, CA). Nifedipine was purchased from Hawkins, Inc. (Minneapolis, MN). All compounds were obtained by selecting the highest available grade and used as received.

Differential Scanning Calorimetry (DSC)

All calorimetric experiments were performed using a Perkin Elmer DSC 7 differential scanning calorimeter (Norwalk, CT), equipped with a refrigerated cooling accessory. The amorphous forms of the compounds were prepared in the DSC by quench cooling the melt. The lack of crystallinity was confirmed by the complete absence of melting endotherm at the corresponding melting temperature. The samples were analyzed using aluminum pans hermetically sealed under dry nitrogen purge. The cell constant and temperature calibration was conducted using indium and zinc as standards. The thermal history of the amorphous materials was standardized by heating the samples to 5°C above T_g, followed by an isothermal hold for 3 min, and cooling the sample to 50°C below T_g, both at 10°C·min^{-1}.

Heat Capacity Measurements

The constant pressure heat capacities of the amorphous and crystalline forms of the model compounds were measured using DSC in accordance with the ASTM method (E1269-04). Sapphire was used as a heat capacity standard. The C_p measurements involve three DSC runs: a baseline was obtained by heating the empty sample pan and a reference pan of equivalent weight through the temperature range of interest, bracketed by isothermal hold steps to establish equilibrium. The NIST sapphire standard was placed in the sample pan and subjected to same temperature program as the baseline. A third identical run was conducted with the sample. The heat capacity of the sample was obtained by referencing the baseline-corrected, weighted heat flow data with the published NIST values of sapphire heat capacity. The heat capacity values for all the amorphous samples were measured in a range from 30–40°C below T_g to approximately 15–20°C above T_g. Data used in the study were averaged from a minimum of three runs.

Scanning Rate Dependence of T_g

The scanning rate (q) dependence of T_g was performed using the method originally proposed by Moynihan *et al.* (17). The mid-point T_g was measured during the second scan after a first scan to 10 °C above T_g and a subsequent cooling to 50°C below T_g at the same rate. The T_g at five different heating rates (1, 2, 5, 10 and 20°C·min^{-1}) was measured in triplicate. For all heating rates, good linearity (correlation coefficient > 0.98) was obtained for the ln q *vs*. $1/T_g$ plot.

RESULTS AND DISCUSSION

The T_g and fragility data of six amorphous organic compounds are given in Table II. The D values of these compounds fall in the range of 8–15, indicating that typical small molecule organic compounds are relatively "fragile" materials (if $D < 30$, the compound is generally considered fragile) (14). The γ values of these materials estimated from Eq. 7 using carefully measured heat capacity data of crystalline and amorphous forms, are also shown in Table II. The heat capacities of glass and liquid at T_g were obtained by linearly extrapolating their corresponding values prior to the onset of the glass transition (see Fig. 2).

The evolution of the initial relaxation time τ^0 estimated from Eq. 8 is shown on Fig. 3 for all six compounds investigated. At T_g, all materials share the same magnitude of relaxation time (in the order of 100 s). As the temperature

Table II. The Calorimetrically Determined Values of T_g, D, T_0, and γ for the Amorphous Model Compounds

	T_g (K)[a]	D	T_0 (K)	γ	τ^0 (T_g − 50 K) (days)
Indomethacin	317.8	10.6	246.7	0.96	3
Ketoconazole	316.9	11.4	242.0	0.89	20
Felodipine	317.0	9.2	253.4	0.87	88
Nifedipine	318.4	8.8	257.1	0.87	105
Griseofulvin	363.5	10.2	285.0	0.80	77
Citric acid	282.4	15.0	200.7	0.91	25

[a] T_g values are measured from 10 K·min^{-1} heating run using DSC.

falls below T_g, the τ^0 values for the different compounds begin to diverge as the result of the compounds' different properties. At a relatively low temperature (40–50°C below T_g), the values of τ^0 for the different compounds vary by more than one order of magnitude, as seen in Fig. 3. This observation suggests that the distance between the storage (annealing) temperature and the T_g alone is not sufficient to provide a general description of the molecular mobility of amorphous solids. In order to compare the KWW approach with the method proposed in this study, the relaxation times for indomethacin obtained from fitting the KWW Eq. 9 are also shown in Fig. 3. As can be seen, the τ values evaluated from KWW approach are approximately one order of magnitude greater than the estimation from the proposed method at the same temperature. This is an expected result because the method proposed here provides the initial relaxation time, i.e., right at the onset of isothermal relaxation, whereas the KWW approach gives the relaxation time averaged over the relaxation process of the entire experiment. As the annealing process progresses, the relaxation time changes (increases), such that changes in τ over more than an order of magnitude could happen (9). The higher the annealing temperature, i.e., the closer to T_g, the faster the change in τ. However, when the storage (annealing) temperature is well below T_g, as would be the desired case for many pharmaceutical formulations, the change in τ takes place very slowly and the initial relaxation time (τ^0) becomes more important. The value of τ^0 obtained with the method presented here provides an estimate of the molecular mobility when the storage temperature is significantly (~40 K or more) below T_g. Under such conditions, structural relaxation is so sluggish that τ^0 becomes a meaningful estimate of the average molecular mobility.

It is worthwhile to mention that four of the tested materials, indomethacin, ketoconazole, felodipine and nifedipine exhibit very similar T_g, yet the corresponding τ^0 do not share this similarity. A useful rule-of-thumb is that when amorphous solids are stored 50 K below their T_g, their molecular motion can be considered negligibly slow over the lifetime of the corresponding drug products (1,7). Consequently, these four materials would be stable if their storage temperature is controlled at about −6°C. However, the results of this study suggest that this temperature may not be low enough to suppress the molecular motion to ensure long-term stability for all materials. As shown in Table II, the initial relaxation times of some compounds (such as indomethacin) at 50 K below T_g are one or more orders of magnitude shorter than the typical lifetime of the drug products. Therefore, at 50 K below T_g, it is still possible for some amorphous solids to exhibit molecular dynamics strong enough for unwanted physical or chemical transformations in the solid state. If amorphous drugs are regarded as being feasible for product development when their relaxation times

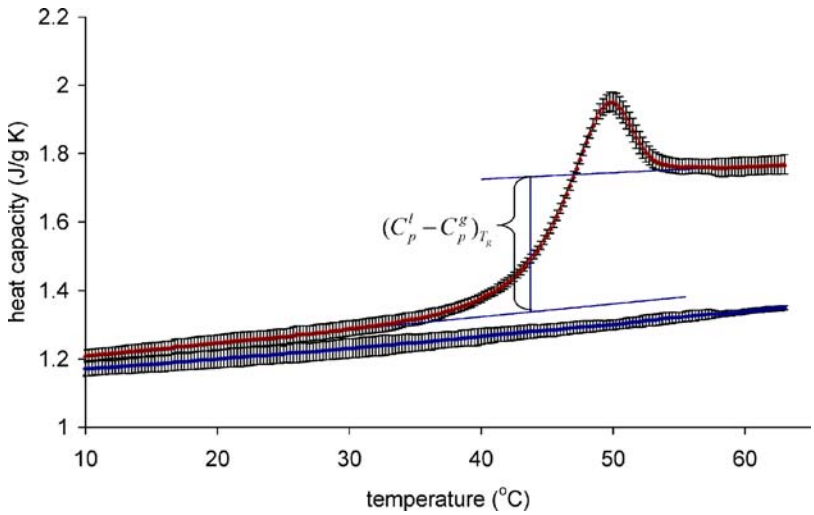

Fig. 2. Constant pressure heat capacities of crystalline and amorphous felodipine, measured by DSC (ASTM E1269-04). The heat capacity difference between liquid and glass heat capacity at T_g is determined through linear extrapolation.

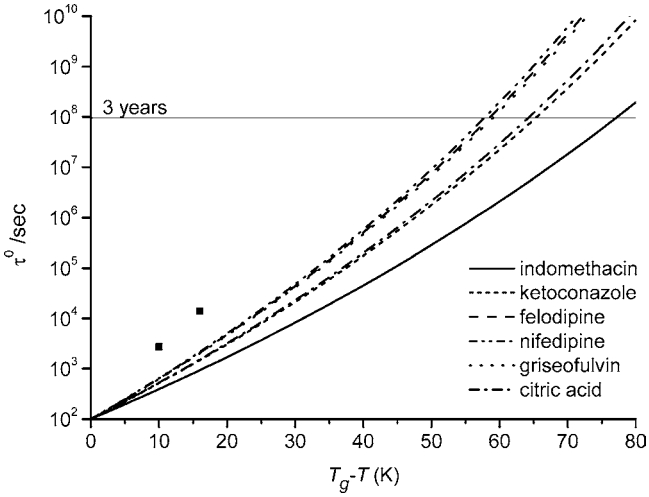

Fig. 3. Estimated initial relaxation times (τ^0) of amorphous indomethacin, ketoconazole, felodipine, nifedipine, griseofulvin and citric acid as the function of $T_g - T$. The *symbols* represent the average relaxation time of indomethacin obtained with the KWW approach (9).

are comparable to their shelf life (e.g., 3 years), then based on this study, the highest storage temperatures for our model compounds range from $T_g - 58$ K (nifedipine) to $T_g - 78$ K (indomethacin). It is important to point out that even though the type of cooperative mobility manifested as the relaxation time is a very important factor for physical stability, it is not necessarily the only one. The data in Table II suggest that indomethacin should have a greater tendency toward crystallization than nifeditpine. However, it has been established (5,18) that under similar annealing conditions, nifedipine has a greater crystallization tendency than indomethacin. NMR studies by Aso *et al.* (18) show that the high crystallization tendency of amorphous nifedipine is consistent with higher residual mobility of functional groups in the molecule. This type of localized mobility could certainly affect the physical stability of the amorphous drug without necessarily being reflected on the relaxation time. Another factor to consider is the thermodynamic driving force for crystallization of amorphous materials. The difference in free

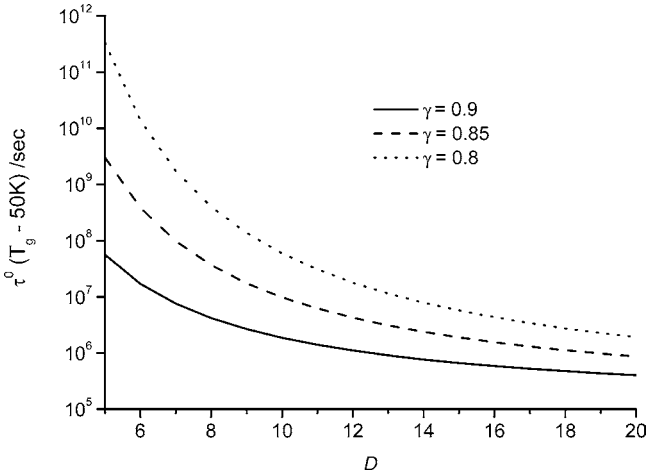

Fig. 4. Comparison of changes in initial relaxation time (τ^0) for amorphous solids with equal T_g (45°C) but different D and γ values.

energy between the amorphous and crystalline forms could also affect the crystallization tendency of amorphous materials independently of the relaxation time. Nevertheless, Studies by Zhou *et. al.* (19) on five structurally different amorphous compounds show that crystallization is more closely related to configurational entropy and relaxation times than other thermodynamic driving forces. Considering the fact that relaxation times are strongly configurational entropy dependent (based on Adam–Gibbs theory), it is more pertinent to treat configurational entropy as a measure of molecular mobility, rather than a thermodynamic barrier. Some important exceptions notwithstanding, one can conclude that molecular mobility is one of the most important factors controlling physical stability of pharmaceutical glasses.

Effect of D and γ on Molecular Mobility

Table II shows that amorphous solids sharing similar T_g can exhibit considerably different molecular mobility at low temperatures, even though they all belong to relatively "fragile" materials, and their γ values are only moderately different. It is therefore necessary to investigate how significantly, changes in fragility and γ, could affect the storage temperature favoring a stable amorphous drug product. Figure 4 shows how changes in D and γ affect the initial relaxation time for a compound with a T_g of 45°C. The D values chosen for the estimation (from 5–20) cover the fragility range for the vast majority of drugs. Figure 4 indicates that for an amorphous solid with a given T_g, the more fragile a glass former, i.e., the smaller the D value, the slower the molecular mobility (greater initial relaxation times) when annealing. Molecular mobility is also sensitive to the heat capacity difference between the crystalline and amorphous forms, with higher value of γ resulting in lower relaxation time at a given annealing temperature. This is so because the closer the heat capacities of the glass and crystal, (i.e., as $\gamma \rightarrow 1$), the smaller the loss of configurational enthalpy and entropy produced upon cooling of the glass, and consequently, the higher the degree of molecular mobility that the material will be able to retain. Like with D, the effect of γ is more pronounced for the most fragile materials. When $D \leq 8$, a small change in γ can lead to a significant increases in the relaxation time, whereas when $D \geq 15$, the same change in γ brings a considerably smaller effect on τ^0. These observations suggest that when dealing with very fragile materials, a relatively small margin of error in heat capacity measurements could lead to a greater variation in the estimated relaxation time. In other words, the quality of the estimates of initial relaxation time depends very much on the quality of the calorimetric determinations. The uncertainty about C_p values would be greatly reduced if measurements were done using adiabatic calorimetry instead of DSC. However, the latter technique is the one available in just about every pharmaceutical research facility. DSC is, and will be in the foreseeable future, the main calorimetric technique used for characterization studies of amorphous pharmaceutical compounds.

Enthalpic- *vs.* Entropic-Based Fictive Temperature

It is important to point out that the nonlinear AG equation used to estimate molecular mobility is of entropic

Table III. The Initial Enthalpic (H) and Entropic (S) Fictive Temperatures and the Corresponding Initial Relaxation Times at $T_g - 50$ K for the Amorphous Model Compounds

	$T^0_{f,H}$ (K)	$T^0_{f,S}$ (K)	$\tau^0_{f,H}$ (days)	$\tau^0_{f,S}$ (days)
Indomethacin	315.7	315.5	3	4
Ketoconazole	311.0	310.5	20	26
Felodipine	310.0	309.4	88	128
Nifedipine	311.5	311.0	105	156
Griseofulvin	352.9	352.3	77	112
Citric acid	277.5	277.0	25	30

origin, i.e., the relaxation time of a glass is controlled by the configurational entropy available. The reader will notice from Eqs. 5 and 6 that the fictive temperature T_f^0 used here is derived from the configurational enthalpy, rather than from the entropy. The change is based on the assumption that the degree of relaxation is the same whether viewed from an entropic or enthalpic point of view. Numerically, the enthalpic fictive temperature can be used without generating significant error. When the temperature interval between the annealing temperature and T_g is relatively small (~50°C), the integrals of ΔC_p and $\Delta C_p/T$ are nearly proportional, so that the enthalpic and entropic T_f^0 values are very similar. In fact, using a treatment analogous to that leading to Eq. 6, the initial the entropic fictive temperature $T^0_{f,S}$ can be obtained (16):

$$\frac{1}{T^0_{f,S}} = \frac{\gamma}{T_g} + \frac{1-\gamma}{T_1} \tag{9}$$

Comparison of the initial enthalpic and entropic fictive temperatures and the corresponding relaxation times at $T_g - 50$ K for the model compounds is given in Table III. For all compounds, the two fictive temperatures differ by less than one degree, and the estimated relaxation times are in good agreement. The data in Table III show that either choice of fictive temperature would lead to similar conclusions about the molecular mobility of the drug in question.

Comment on Calorimetric Fragility Determinations

It is evident from the foregoing discussion that an accurate quantification of the fragility parameter D is critical for the reliable estimation of molecular mobility. In practical terms, the experimental error of D determination should be kept to a minimum (ideally within one unit) when the nonlinear Adam–Gibbs approach is applied, since small variations in D may lead to pronounced changes in the resulting relaxation time. Unlike T_g for example, fragility cannot be measured directly, and there is significant variation among fragility values reported in the literature for the same material, even if using the same experimental method. For example, reported values of D for indomethacin, using the scanning rate dependence of T_g, vary from 9.6 to 14.7 (14,20). Different D values are obtained with changes in experimental setup and data analysis, such as selection of heating or cooling curves (20), or by different choices of T_g from the DSC thermogram (21). Since fragility is a fundamental concept that describes the temperature dependence of liquid properties, small variations in glass properties or slight experimental modifications should have little effect on the quantification of fragility. The observed inconsistencies among reported fragility measurements should therefore be due to the type of experiments involved. As sound as the underlying principle is, if different laboratories obtain slightly different slopes when plotting ln q *vs.* $1/T_g$ for example, considerably different fragilities can be expected. To the best of our knowledge, no round robin study has been conducted in order to address this question, and the publication of this issue of *Pharmaceutical Research* ought to be a good occasion to propose one.

CONCLUSIONS

A calorimetric method is proposed to evaluate the molecular mobility of organic amorphous solids at relatively low temperatures without the need of carrying out enthalpy recovery experiments. Based on the Adam–Gibbs theory, the method provides an estimate for the temperature at which a given relaxation time is considered adequate to maintain the stability of the amorphous drug over its anticipated lifetime. This approach requires a careful experimental determination of the fragility of the glass former. The heat capacities of the crystalline, glass and liquid forms at T_g are also needed in order to obtain the fictive temperature. Methods for obtaining both enthalpic and entropic fictive temperatures are provided and they are shown to give very similar results. Therefore both routes can be used to provide reliable estimation of molecular mobility. The experimental procedure of this method is quite simple, involving only DSC measurements. Since variations are projected exponentially, the accuracy of DSC measurements is critical.

ACKNOWLEDGMENTS

The financial support from the Purdue–Michigan Joint Program on the Chemical and Physical Stability of Pharmaceutical Solids is acknowledged.

REFERENCES

1. B. C. Hancock, S. L. Shamblin, and G. Zografi. Molecular mobility of amorphous pharmaceutical solids below their glass-transition temperatures. *Pharm. Res.* **12**:799–806 (1995).
2. B. C. Hancock and G. Zografi. The relationship between the glass-transition temperature and the water-content of amorphous pharmaceutical solids. *Pharm. Res.* **11**:471–477 (1994).
3. B. C. Hancock and G. Zografi. Characteristics and significance of the amorphous state in pharmaceutical systems. *J. Pharm. Sci.* **86**:1–12 (1997).

4. P. Tong and G. Zografi. Effects of water vapor absorption on the physical and chemical stability of amorphous sodium indomethacin. *Aaps Pharmscitech* **5**: Art. No. 26 (2004).
5. V. Andronis and G. Zografi. The molecular mobility of supercooled amorphous indomethacin as a function of temperature and relative humidity. *Pharm. Res.* **15**:835–842 (1998).
6. B. C. Hancock and S. L. Shamblin. Molecular mobility of amorphous pharmaceuticals determined using differential scanning calorimetry. *Thermochim. Acta* **380**:95–107 (2001).
7. S. R. Byrn, W. Xu, and A. W. Newman. Chemical reactivity in solid-state pharmaceuticals: formulation implications. *Adv. Drug Deliv. Rev.* **48**:115–136 (2001).
8. K. Kawakami and M. J. Pikal. Calorimetric investigation of the structural relaxation of amorphous materials: evaluating validity of the methodologies. *J. Pharm. Sci.* **94**:948–965 (2005).
9. C. Mao, S. P. Chamarthy, and R. Pinal. Time-dependence of molecular mobility during structural relaxation and its impact on organic amorphous solids: an investigation based on a calorimetric approach. *Pharm. Res.* **23**:1906–1917 (2006).
10. S. L. Shamblin, B. C. Hancock, Y. Dupuis, and M. J. Pikal. Interpretation of relaxation time constants for amorphous pharmaceutical systems. *J. Pharm. Sci.* **89**:417–427 (2000).
11. G. Adam and J. H. Gibbs. On temperature dependence of cooperative relaxation properties in glass-forming liquids. *J. Chem. Phys.* **43**:139–146 (1965).
12. G. W. Scherer. Use of the Adam–Gibbs equation in the analysis of structural relaxation. *J. Am. Ceram. Soc.* **67**:504–511 (1984).
13. I. M. Hodge. Enthalpy relaxation and recovery in amorphous materials. *J. Non-Cryst. Solids* **169**:211–266 (1994).
14. K. J. Crowley and G. Zografi. The use of thermal methods for predicting glass-former fragility. *Thermochim. Acta* **380**:79–93 (2001).
15. I. M. Hodge. Strong and fragile liquids — a brief critique. *J. Non-Cryst. Solids* **202**:164–172 (1996).
16. S. L. Shamblin, X. L. Tang, L. Q. Chang, B. C. Hancock, and M. J. Pikal. Characterization of the time scales of molecular motion in pharmaceutically important glasses. *J. Phys. Chem. B* **103**:4113–4121 (1999).
17. C. T. Moynihan, A. J. Easteal, J. Wilder, and J. Tucker. Dependence of Glass-transition temperature on heating and cooling rate. *J. Phys. Chem.* **78**:2673–2677 (1974).
18. Y. Aso, S. Yoshioka, and S. Kojima. Relationship between the crystallization rates of amorphous nifedipine, phenobarbital, and flopropione, and their molecular mobility as measured by their enthalpy relaxation and ^{1}H NMR relaxation times. *J. Pharm. Sci.* **89**:408–416 (2000).
19. D. L. Zhou, G. G. Z. Zhang, D. Law, D. J. W. Grant, and E. A. Schmitt. Physical stability of amorphous pharmaceuticals: importance of configurational thermodynamic quantities and molecular mobility. *J. Pharm. Sci.* **91**:1863–1872 (2002).
20. J. J. M. Ramos, R. Taveira-Marques, and H. P. Diogo. Estimation of the fragility index of indomethacin by DSC using the heating and cooling rate dependency of the glass transition. *J. Pharm. Sci.* **93**:1503–1507 (2004).
21. I. Weuts, D. Kempen, K. Six, J. Peeters, G. Verreck, M. Brewster, and G. Van den Mooter. Evaluation of different calorimetric methods to determine the glass transition temperature and molecular mobility below T-g for amorphous drugs. *Int. J. Pharm.***259**:17–25 (2003).