The Molecular Mobility of Supercooled Amorphous Indomethacin as a Function of Temperature and Relative Humidity

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Purpose. To determine the relaxation times of supercooled indomethacin as a function of temperature and relative humidity above Tg, and to analyze the results in the context of being able to predict such behavior at various storage conditions.

Methods. Dielectric relaxation times were measured in the frequency domain (12 to 10^5 Hz) for amorphous indomethacin equilibrated at 0, 56, and 83% relative humidity. The heating rate dependence of Tg for dry supercooled indomethacin was measured with differential scanning calorimetry and used to determine relaxation times. The results were compared with previously published shear relaxation times and enthalpy recovery data.

Results. Very good agreement was observed between dielectric and shear relaxation times, and those obtained from the heating rate dependence of the Tg, for dry indomethacin as a function of temperature above Tg. The introduction of water lowered the dielectric relaxation times of supercooled indomethacin without significantly affecting its fragility. The relaxation times below Tg, found to be lower than those predicted by extrapolation of the data obtained above Tg, were analyzed in the context of the Adam-Gibbs-Vogel equation.

Conclusions. The relaxation times of amorphous indomethacin obtained from the heating rate dependence of Tg were in good agreement with those obtained from shear and dielectric measurements, thus validating a relatively simple approach of assessing molecular mobility. The significant molecular mobility of amorphous indomethacin observed below Tg, and the significant plasticizing effects of sorbed water, help to explain why amorphous indomethacin crystallizes well below Tg over relatively short time scales.

KEY WORDS: amorphous state; dielectric relaxation; water; indomethacin.

INTRODUCTION

In recent years it has been increasingly recognized that the presence of an amorphous phase can have very important implications in the manufacturing, storage and use of pharmaceutical dosage forms through changes in their physical and chemical stability (1). In our laboratory we have used the drug, indomethacin, as a model substance for studying crystallization from the amorphous state. Yoshioka et al. (2) studied the isothermal crystallization of dry ground amorphous indomethacin and showed that crystallization occurred below Tg, on rather short time scales. It also has been found that the presence of coprecipitated poly(vinylpyrrolidone) greatly inhibits the crystallization of indomethacin from the amorphous state (3), whereas the presence of water increases crystallization rates (4). Changes in molecular mobility are believed to be responsible in part for both effects. Starting from this premise Hancock et al. (5) conducted enthalpy recovery experiments with dry amorphous indomethacin below its Tg and concluded that indomethacin in the glassy state still exhibits significant molecular mobility. In a previous paper (6) we presented data on the viscosity and shear relaxation times of dry supercooled indomethacin above its Tg and showed significant changes in molecular mobility with changing temperature, in agreement with the trend seen for other organic materials. In this paper we report measurements of the dielectric relaxation times of supercooled indomethacin equilibrated at 0, 56 and 83% RH, as a function of temperature, above its Tg. The dielectric relaxation method was chosen over the viscoelastic method (6) for these studies because control of the relative humidity was better accomplished inside the dielectric measurements setup. Both sets of data should help us analyze recent nucleation and crystal growth rate results (7) for supercooled indomethacin as a function of temperature and RH. The dielectric relaxation data also will enable us to access the rotational mobility of amorphous indomethacin in view of the hypothesis that this rotational mobility might be responsible for the crystallization of amorphous indomethacin close to its Tg (2). Relaxation times of amorphous indomethacin were also estimated from the heating rate dependence of its Tg according to the method of Moynihan (8–11), and a comparison of the relaxation times obtained from the three techniques was made.

MATERIALS AND METHODS

Determination of the Complex Dielectric Constant $\varepsilon^*(\omega)$ of Amorphous Indomethacin

Crystalline indomethacin (1-(p-chlorobenzoyl)-5-methoxy-2-methylindole-3-acetic acid), in the γ crystalline form, obtained from Sigma Chemical, was melted in an aluminum weighing pan at 165°C. The melt was then quenched at room temperature between two aluminum plates to form discs with approximately 20 mm diameter and 0.3 to 0.5 mm thickness. Attention was paid to assure that all the samples were free of bubbles and that the procedure was performed at less than 15% RH to minimize contact with water vapor. After preparation, the sample discs were dried at room temperature for more than 96 hrs over P_2O_5 (0% RH) under vacuum (10^{-2} Torr). Samples were also stored in desiccators containing saturated salt solutions of 56 and 83% RH., at 30°C, for 6–9 days to allow the samples to equilibrate with water vapor. All the samples were thus pre-equilibrated before dielectric measurements. The water vapor sorption isotherm at 30°C, and the effect of water content on the Tg of samples of amorphous indomethacin similar to the ones used in this study, have been previously determined (4). No crystallization was observed with X-ray diffraction during the time scale of this equilibration and previous studies have shown that no chemical degradation occurs under these conditions (4). Dielectric measurements were conducted with a parallel plate capacitor of the three-terminal guarded-circuit type. The capacitor was constructed based on the original design of McCammon et al. (12) with minimal changes. It has a solid upper electrode and a smaller

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central lower electrode circled by three concentric ring electrodes. The sample disc extends out to the first ring electrode, and its capacitance is measured only across the central measuring electrode (13,14). The capacitance of air is measured across one of the outer ring electrodes and is used to measure the sample thickness at any time (12). Both the sample measuring electrode and the gap electrode have their corresponding guard electrodes (13,14).

The sample capacitor was placed inside an aluminum cylindrical box to shield it from electrical noise. The aluminum box served also as the thermostat; its temperature was controlled with a band heater wound around it. The capacitor inside the box was continuously flushed with air of the desired RH. In addition to maintaining the desired RH inside the box, this flow of air was also responsible for the temperature equilibration of the sample and the capacitor. The sample temperature was measured by two thermocouples in close proximity, accurate to within ± 1.5 K. With our setup the sample could be maintained isothermally (±0.3 K) at the temperature of the experiment for extensive periods of time.

A GenRad 1689 RLC Digibrige in parallel circuit with the sample capacitor was used for measurements of the sample capacitance and the dissipation factor (tan δ) at each temperature in the frequency range from 12 Hz to 100 kHz. The real and the imaginary parts of the dielectric constant were calculated from the capacitance and the tan δ values according to known relations (15). Each data point reported corresponds to a different sample measured on a different day. Repetitive measurements on the same sample on the same day gave essentially the same results, for both the dry and the wet samples. This indicates that the measurement procedure had no effect on the sample properties in terms of structural damage or crystallization. It also indicates that for the samples equilibrated and measured at 56 and 83% RH no appreciable water loss occurred during the measurement.

Determination of the Heating Rate Dependence of Tg with DSC

The glass transition temperature of amorphous indomethacin was measured with a Seiko 220C DSC. High purity indium, gallium, and mercury were used for temperature calibration at every heating rate used. Crystalline γ indomethacin (5–10 mg) was loaded into aluminum DSC pans with a pin hole in the lid. The samples were melted in the DSC, cooled to a temperature well below Tg, and then heated at the same rate through Tg (8). Cooling and heating rates of 2, 5, 10, and 20°C/min were used. The onset temperature from the heating step is reported (average of 3 determinations).

RESULTS

In Figure 1 the imaginary part of the dielectric constant ε″ of amorphous indomethacin stored at 0% RH is shown at selective temperatures. We note here that preliminary experiments at a constant frequency of 40 Hz as a function of temperature between 10 and 80°C (data not shown) revealed only a single ε″ peak. Thus we believe that the peaks shown in Figure 1 represent the main dielectric relaxation process for amorphous indomethacin. The data were analyzed with the Cole-Davidson equation (16,17),

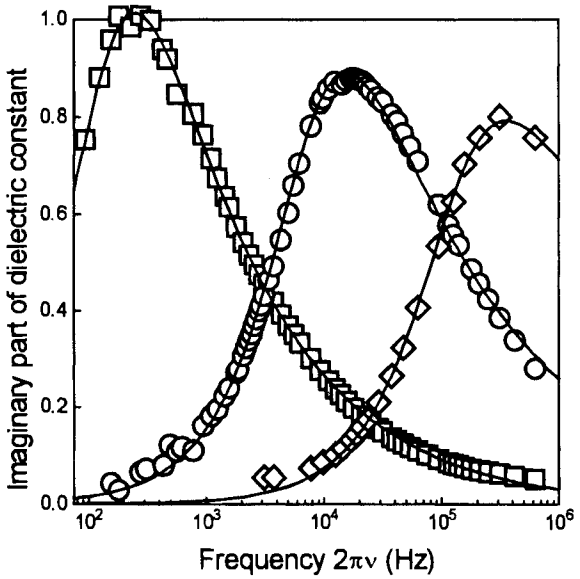

Fig. 1. The imaginary part (ε″) of the complex dielectric constant of amorphous indomethacin at 0% RH, as a function of frequency (ω = 2πν), at 60°C (□), 73°C(○), and 86°C (◇).

$$\frac{\varepsilon^*(\omega) - \varepsilon_\infty}{\varepsilon_0 - \varepsilon_\infty} = \frac{1}{(1 + i\omega\tau_{CD})^\beta} \quad (1)$$

where ε*(ω) is the complex frequency-dependent dielectric constant, ε_∞ is the high frequency limiting value of the real part of the dielectric constant, and ε_0 is the low frequency limiting value of the real part of the dielectric constant. In the Cole-Davidson equation, τ_{CD} is the maximum relaxation time considered to be present in the material under study, and the width parameter, β ($0 < \beta < 1$), determines the shape of the ε*(ω) curves. Phenomenologically β is related to the spread of the distribution of relaxation times (as β becomes larger the distribution becomes narrower) (18,19). Since a small dc-conductivity, σ_{dc}, was observed for the samples equilibrated at 56 and 83% RH (data not shown) for these samples the following fit function was used (15),

$$\varepsilon''(\omega) = \frac{\sigma_{dc}}{\omega e_0} + Im\{\varepsilon^*_{CD}(\omega)\} \quad (2)$$

where e_0 is the permitivity of vacuum and $\mathrm{Im}\{\varepsilon^*_{CD}(\omega)\}$ denotes the imaginary part of the Cole-Davidson function. The relaxation times τ_{CD} as a function of temperature, for amorphous indomethacin stored at the 0, 56, and 83% RH, are shown as an Arrhenius plot in Figure 2. In Figure 3, the width parameter β is shown as a function of temperature for amorphous indomethacin stored at 0, 56, and 83% RH.

The effect of heating rate on the Tg of amorphous indomethacin is shown in Figure 4. The relaxation times for supercooled indomethacin as a function of temperature were obtained from the slope of the plot in Figure 4, based on the equations described in Appendix A.

DISCUSSION

The Relaxation Times of Dry Supercooled Indomethacin Above Tg

The dielectric relaxation times as a function of temperature for amorphous indomethacin stored at 0% RH are shown as an

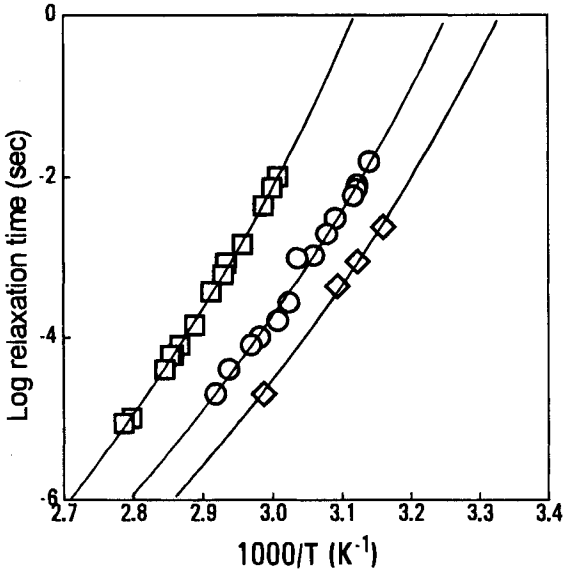

Fig. 2. Arrhenius plot of the dielectric relaxation times of amorphous indomethacin at 0% (□), 56% (○), and 83% (◇) RH. The lines are the fits to a modified VFT equation with τ_0 and D the same as for the dry indomethacin and with T_0 a function of RH.

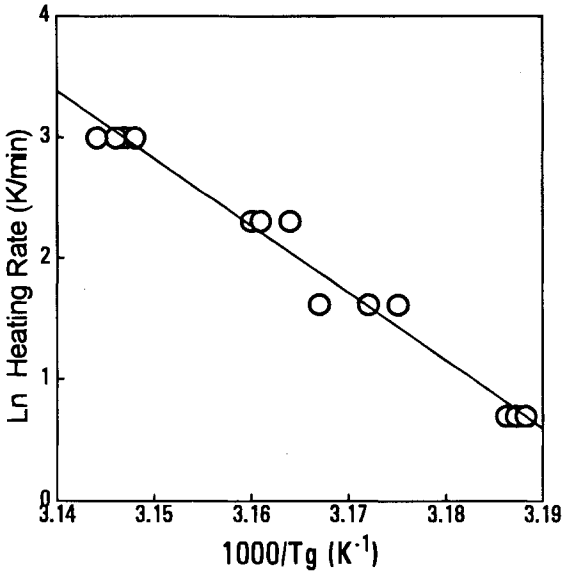

Fig. 4. The Tg of amorphous indomethacin as a function of heating rate.

Arrhenius plot in Figure 5, along with the previously obtained shear relaxation-time data for dry supercooled indomethacin (6). In the same figure the relaxation times obtained from the heating rate dependence of Tg are also included. The solid lines 1 and 2 in Figure 5 are the fit of the VTF equation (19),

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

to the shear and dielectric relaxation times. In the VTF equation, τ_0 is the relaxation time at the high temperature limit, D is a material parameter related to the fragility of the material (see Appendix A), and T_0 is the temperature where the relaxation

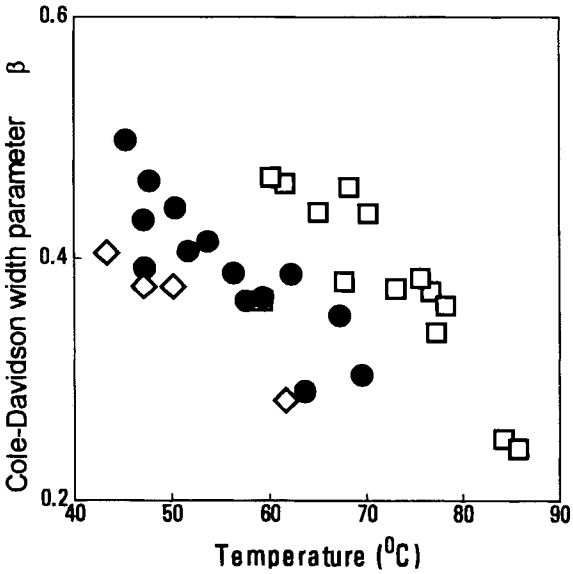

Fig. 3. The Cole-Davidson parameter for amorphous indomethacin at 0% RH (□), 56% RH (●), and 83% RH (◇).

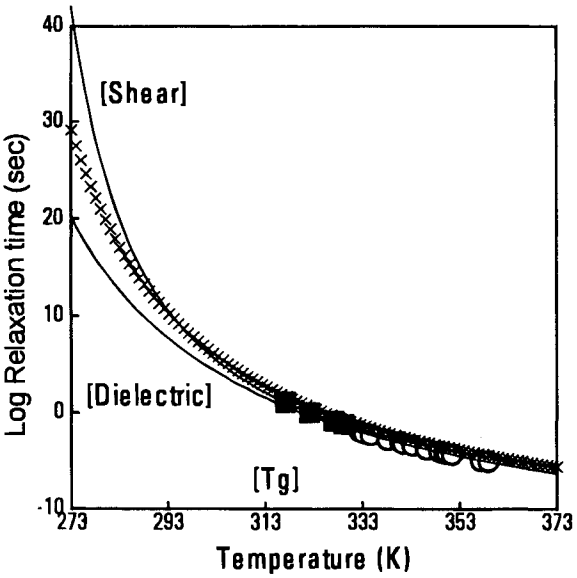

Fig. 5. Comparison of the shear (■), dielectric (○), and the relaxation times of supercooled indomethacin obtained from the heating rate dependence of Tg (×) as described in Appendix A. The lines are the VTF fits as explained in the text.

times will tend towards infinity. In Table I we present all the VTF equation parameters obtained from the fitting of the data from the different experiments. Small differences in the obtained VTF parameters are obvious from Table I. For example we see that the D parameter varies between 6.9 and 14.4 and the T_0 varies between 233 and 259 K. However, despite the different VTF parameters in Table I, as can be seen in Figure 5, above Tg, the shear, the dielectric, and the relaxation times of supercooled indomethacin obtained from the heating rate dependence of Tg, have very similar temperature dependencies, with the actual relaxation times practically agreeing within the width of their distributions. This suggests that all the measured relaxation times are coupled to the same fundamental molecular

Table I. The VTF Equation Parameters for Dry Amorphous Indomethacin Obtained from the Different Experiments

	Viscosity	Shear relaxation	Dielectric relaxation	Heating rate
η_0	2.7×10^{-7}	—	—	—
τ_0	—	4.3×10^{-13}	1.8×10^{-17}	1×10^{-15}
B	2281	1791	3361	2743
D	8.9	6.9	14.4	11.1
T_0	256 K	259 K	233 K	246 K

Note: The shear viscosity data are from Ref. (6).

motion that is responsible for the relaxation behavior of amorphous indomethacin. It also suggests that crystallization of amorphous indomethacin close to Tg cannot be attributed to a presumably faster rotational motion of the indomethacin molecule.

The fact that different sets of VTF parameters can result in very similar relaxation times originates from the reality that only the effective VTF activation energy (given in equation 4) is tightly constrained by the experimental data over narrow temperature ranges,

$$\frac{\Delta H_{VTF}}{R} = \frac{\partial ln\tau}{\partial 1/T} = \frac{BT^2}{(T - T_0)^2} \quad (4)$$

thus the VTF parameters D and T_0 can vary within fairly wide limits, with ΔH_{VTF} still being a constant (20). As we can see from Figure 5, such variations in D and T_0 are not apparent over narrow experimental temperature ranges. However when the fits to the VTF equation are extrapolated below Tg, they each predict relaxation times that differ by orders of magnitude. Below Tg, the *equilibrium* shear relaxation time is estimated to be 3 days at 30°C, and 3 years at 22°C, whereas the *equilibrium* dielectric relaxation time is estimated to be 4 hours at 30°C, and 92 days at 22°C. Extrapolation of the relaxation times of supercooled indomethacin obtained from the heating rate dependence of Tg below Tg results in intermediate values for the relaxation times. The disagreement in the values of τ much below Tg, predicted by the different experiments, is the result of extrapolating over many orders of magnitude in time. In this case small differences in the VTF parameters can lead to widely different relaxation times as seen in Figure 5. Fortunately, as we will explain later the predicted relaxation times much below Tg are not very important for practical reasons, however this is not true for the VTF parameters (see the following discussion of the AGV equation) that have to be as accurate as possible to have any practical significance. For this to happen the VTF parameters have to be obtained from data covering as wide a time (or frequency) scale as possible. From these results, it also can be concluded that the heating rate method is a fair alternative method for the estimation of the temperature dependence of relaxation times, especially since it is much faster, more convenient than the direct viscoelastic or dielectric methods for determination of relaxation times, and requires only a DSC instrument, generally available in most industrial laboratories.

Dielectric Relaxation of Supercooled Indomethacin as a Function of Relative Humidity

In Figure 2 we presented the Arrhenius plot of the dielectric relaxation times of amorphous indomethacin stored a 0, 56, and 83% RH. It can be seen that at a certain temperature increasing water content significantly lowers the relaxation time of amorphous indomethacin. The VTF equation was fitted to the data of Figure 2 by assuming that D and T_0 are the *only* composition dependent VTF parameters. This is justifiable since the high temperature limit of the relaxation time, τ_0, most likely does not change with water content. The results of the non-linear fitting are shown in Table II, where beyond the expected decrease of T_0 we do not see any extensive change in the values of D as a function of water content. In addition the values of D at 56 and 83% RH are within error of the value at 0% RH. If however a very small effect of water on the fragility of amorphous indomethacin were to exist our data may not be accurate enough to resolve such difference. We will conclude on this basis that in this concentration range, water does not have any significant effect on the fragility of amorphous indomethacin. Although the question of the effect of water on the fragility of amorphous materials is an important one (21), we do not know of any other study that has focused on a hydrophobic material such as indomethacin. From data available for hydrophilic molecules it seems that water has some effect on their fragility but it is observable only if wide concentration ranges for water are studied (22,23).

As is seen in Figure 3 the Cole-Davidson width parameter β decreases with increasing temperature at a constant RH. Also in Figure 3 it can be seen that, at a constant temperature, an increased water content results in a decrease in the value of β. This suggests that the distribution of the dielectric relaxation times becomes wider as the temperature and water content increase. This result is opposite to what we found for the temperature dependence of β from shear relaxation of amorphous indomethacin (6) and from the trend seen with many organic glass formers (19). However, Nagel and coworkers have observed similar behavior, as in this study, with the effect of temperature on the distribution of relaxation times of supercooled di-n-butylphthalate (24), and Johari and coworkers (25) have observed similar results in their dielectric study of glucose-water mixtures. These observations suggest that for amorphous indomethacin decreasing relaxation times (with increased temperature or water content) result in an increased non-exponentiallity of the dielectric relaxation process. We think that this effect may be related to the intermolecular H-bonding behavior of amorphous indomethacin. This was recently studied with FT-IR and FT-Raman spectroscopy (26), and it was shown that, in the supercooled state indomethacin to a large extent consists of inter-molecular ring dimers formed by H-bonding of the carboxylic groups of two neighbor molecules. In terms of dielectric relaxation behavior it is known (27) that in simple acids that form such dimers in the liquid state (acetic acid for example), the dipole moments of the two monomers cancel each other, with resulting dielectric constants characteristic of non-polar liquids.

Table II. VTF Equation Parameters from Dielectric Relaxation of Amorphous Indomethacin Equilibrated at the Various RH

	0% RH	56% RH	83% RH
τ_0	1.8×10^{-17}	1.8×10^{-17}	1.8×10^{-17}
D	14.4	16.1	15.6
T_0 (K)	233	216	210

The dielectric constant of amorphous indomethacin was found from our measurements to be approximately 6 and we found that it did not change much in the temperature and RH range of our experiments. This is not uncommon considering the narrow range of our measurements, and it means that most likely increasing temperature or water content does not result in a total elimination of the ring dimers. However increased temperature or water content can probably partially destabilize these dimers and thus increase the non-exponentiallity of the dielectric relaxation process. It is interesting that Johari (28) in his dielectric study of various isomeric octanols, found that octanols that form such ring dimers are characterized by a wider distribution of relaxation times than octanols that do not form such cyclic dimers, and that the introduction of ions increases the distribution of relaxation times for all octanols, presumably due a destabilization of the H bonding structure.

Beyond the fundamental reasons for the dependence of the distribution of relaxation times on temperature and water content, our results clearly indicate that the time-temperature-RH superposition principle (29) does not hold for amorphous indomethacin.

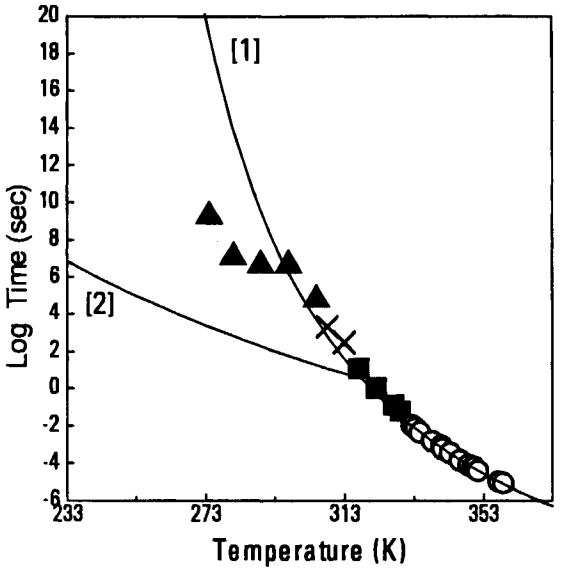

Fig. 6. Shear (■) and dielectric (○) relaxation times, $t_{\Delta H\infty}$ (×) (Ref. (30)), and $t_{\Delta H\infty}$ (▲) (Ref. (5)) times for amorphous indomethacin. Line 1 is the fit of the VTF equation to the dielectric relaxation times. Line 2 is the prediction of the AGV equation as described in the text.

Relaxation Times Below Tg

Fukuoka et al. (30) and Hancock et al. (5) measured the effect of isothermal storage of amorphous indomethacin below Tg on the subsequent enthalpy recovery during heating in the DSC. The time, $t_{\Delta H\infty}$, required for the enthalpy to reach its final equilibrium value, $\Delta H\infty$, in the enthalpy relaxation experiments (see ref (31)) is by definition important because it signifies the time that is required for equilibrium to be attained. Values for the characteristic times $t_{\Delta H\infty}$ were obtained directly from the published plots, at 40 and 35°C from Ref. (30), and at 32°C from Ref. (5). At the lower temperatures, the data of Hancock et al. (5) were fitted to the KWW equation (17) in order to obtain an estimate of the value of $t_{\Delta H\infty}$. All the $t_{\Delta H\infty}$ data along with our shear and dielectric relaxation times are shown in Figure 6. We can see that very close to the Tg the time required for ΔH to reach its equilibrium value practically is the same as the equilibrium relaxation times obtained from extrapolations below Tg with the VTF equation. This suggests that the *real* relaxation times of indomethacin below the Tg are much smaller than the equilibrium relaxation times. The observation is more obvious at the lowest temperatures where the $t_{\Delta H\infty}$ times are sometimes orders of magnitude lower than the equilibrium relaxation times. It is clear, therefore, that in the glassy state indomethacin possesses relaxation times much smaller than the equilibrium relaxation times. The fact that relaxation times in the glassy state are much shorter than equilibrium extrapolations below Tg is well known and studied in the field of glasses and polymers (see references (20) and (32)).

This behavior has been explained with equations based on the configurational entropy model of Tg (33,34). In a seminal paper, Gibbs and DiMarzio (33) developed a statistical mechanical quasilattice theory of amorphous phases and suggested that molecular mobility involves the cooperative rearrangement of increasingly large numbers of molecules as temperature is decreased. They also showed the existence of a second order transition at a temperature T_2 where the configurational entropy vanishes; configurational entropy is that part of the entropy due to configurational rather than vibrational degrees of freedom.

Adam and Gibbs (34) modeled the temperature dependence of relaxation times in terms of the temperature dependence of the size of cooperatively rearranging regions. The size of these cooperatively rearranging regions was shown to be determined by configurational restrictions and is expressed in terms of the configurational entropy. The quantitative result of the model is,

$$\tau = \tau_0 exp\left(\frac{C}{TS_c}\right) \tag{5}$$

where τ_0 and C are constants, and S_c is the macroscopic configurational entropy of the liquid. The general validity of the AG equation has been well demonstrated previously (35,36). Note that for a constant S_c the AG equation transforms to an Arrhenius type equation. The macroscopic configurational entropy of the liquid S_c is given as (37),

$$S_c(T) = \int_{T_2}^{T} \frac{\Delta C_p}{T}\, dT \tag{6}$$

where ΔC_p is the difference in heat capacity between the liquid and the glass. For ΔCp with a hyperbolic temperature dependence (38),

$$\Delta Cp = \frac{K}{T} \tag{7}$$

where K is a constant, the VTF equation is obtained with T_2 identified with T_0. Scherer (37) has expressed equation 6 as,

$$S_c(T) = \int_{T_2}^{T_f} \frac{\Delta C_p}{T}\, dT \tag{8}$$

where in the upper limit of the integral the temperature T has been substituted with the fictive temperature T_f. The basis behind the use of T_f is that in the glassy state the configurational entropy depends on the existing frozen-in structure rather than on the equilibrium structure and that the fictive temperature T_f

is a measure of the configurational entropy. For materials above Tg the fictive temperature T_f is the same as the experimental temperature (39) while for materials below Tg, T_f is defined as the temperature at which the nonequilibrium value of some macroscopic property would be the equilibrium one. Immediately after formation of a glassy material T_f is the best measure of Tg (39). Nevertheless since the material below Tg is out of equilibrium, T_f will evolve as a function of time to the temperature of isothermal storage. For ΔCp with a hyperbolic temperature dependence the Adam-Gibbs-Vogel (AGV) equation is obtained (40),

$$\tau = Aexp\left(\frac{B}{T(1 - T_2/T_f)}\right) \quad (9)$$

The equation has been found to describe well experimental data below Tg (37,39,41). In the equilibrium state above Tg, where $T_f = T$, the equation assumes the VTF form, whereas below Tg, where $T_f = Tg$ = constant, the equation takes the Arrhenius form. Line 2 in Figure 6 represents the *non-equilibrium* values of the relaxation times of indomethacin below Tg determined from the AGV equation using the values of τ_0, B, and T_0 obtained from the fit of the VTF equation to the dielectric data, and taking T_f as 44.7°C, the same as the calorimetric Tg at 20°C/min the cooling rate used in Ref. (5). It represents the relaxation times of amorphous indomethacin immediately after it is cooled through Tg, at a cooling rate of 20°C/min. In this case supercooled indomethacin will fall out of equilibrium at 44.7°C, and this is the fictive temperature T_f.

From a pharmaceutical perspective, an analysis based on the AGV equation is important for practical reasons. As can be seen in Figure 6 the temperature T_0 is characteristic of the equilibrium liquid only, and not of any real glass formed with a finite cooling history. For amorphous indomethacin for example, from the activation energy of viscosity near Tg, the cooling rate required so a Tg of 233 K is reached is calculated to be 10^{-30} K/sec. Even if such a cooling rate was technically possible the time required for this is about 10^{13} times the age of earth. For real glasses at any temperature below Tg according to the AG theory the relaxation times depend only on the "frozen in" configurational entropy. The amount of Sc "frozen in" in turn depends on the temperature at which the material went out of equilibrium and the method used to form the amorphous glass (42), and it is independent of the subsequent storage temperature below Tg (since according to the AG theory below Tg the configurational entropy is invariant with respect to temperature). The AGV equation provides a simple way to determine the relaxation times of materials immediately after glass formation since the AGV parameters can be calculated from experiments in the equilibrium state above Tg. From line 2 in Figure 6 we found that glassy indomethacin immediately after formation will have a relaxation time of about 10^6 sec or 12 days at 233 K. During storage below Tg molecular relaxation will result in a decreasing Sc and thus increasing relaxation times. These relaxation times eventually will approach the values characteristic of the equilibrium supercooled liquid, however, at temperatures close to T_0 this process literally will take infinite time. In fact at the lowest temperature of Figure 6 the time to equilibrium, $t_{\Delta H\infty}$, is approximately 80 years. It is obvious that stability predictions for pharmaceutical products cannot simply be based on the value of T_0 and that the early stages of an amorphous product's life are very important in determining its stability; since in the early stages all glassy materials will possess relaxation times far less than we might have thought. One way to minimize such effects is to resort to methods of preparing amorphous materials that least energize the amorphous state of the material. For example, a slow cooling through Tg will result in a smaller T_f and thus higher initial relaxation times. Of course the final storage temperature of the drug product should be as low as possible. A more rationale selection of storage temperature would be possible only if the time evolution of the relaxation times during sub-Tg storage could be predicted. Unfortunately at the present moment whereas phenomenological descriptions exist for the time dependence of the Sc (or T_f) below Tg, a prediction is not always possible and many theoretical problems still exist (20,32,43). Even if such a prediction was possible, a prediction of physical stability is generally impossible without some application of the general theory of phase transformation by nucleation and crystal growth (7).

CONCLUSIONS

The relaxation times of amorphous indomethacin above its Tg obtained from shear and dielectric relaxation and from the heating rate dependence of Tg were found to be in very good agreement. Water was found to have a very significant effect in lowering the relaxation times of amorphous indomethacin, without significantly changing its fragility. Amorphous materials below Tg, especially immediately after their preparation, are characterized by much shorter relaxation times than simple extrapolation of the equilibrium relaxation times obtained above Tg would suggest. This behavior should be taken into account when processing and storage conditions for amorphous pharmaceuticals are selected, so their physical and chemical stability can be optimized.

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APPENDIX A

It is well known that the relaxation times of most supercooled liquids show significant deviations from Arrhenius behavior as a function of temperature (44),

$$\tau = \tau_0 exp\left(\frac{\Delta H}{RT}\right) \quad (A1)$$

These deviations can be described by a temperature dependent apparent activation enthalpy ΔH. The apparent activation

enthalpy at Tg scaled by the thermal energy at Tg has been defined as the fragility, m (45), given by,

$$m = \left.\frac{d\ log\ \tau}{d(T_g/T)}\right|_{T=T_g} = \frac{\Delta H|_{T_g}}{2.303RT_g} \quad \text{(A2)}$$

since in small temperature intervals the relaxation times always can be described by the Arrhenius equation. It can be shown further (46) that the parameters D, and T_0 of the VTF equation are related to the fragility m as follows,

$$D = \frac{2.303m_{min}^2}{m - m_{min}} \quad \text{(A3)}$$

and

$$T_0 = T_g\left(1 - \frac{m_{min}}{m}\right) \quad \text{(A4)}$$

where m_{min} is given by,

$$m_{min} = log\left(\frac{\tau_{Tg}}{\tau_0}\right) \quad \text{(A5)}$$

For most supercooled liquids m_{min} takes values between 16 and 17 since the relaxation time τ at Tg is usually about 100 sec and τ_0 is of the order of vibrational lifetimes ($\approx 10^{-14}$ sec) (46). This was found to hold also for supercooled indomethacin, since from the fit of the VTF equation to experimental data for amorphous indomethacin we found that m_{min} is 16.54 for shear viscosity, 13.67 for shear relaxation times, and 17.56 for dielectric relaxation times. Moynihan et al. (8,9,11) have shown that the activation enthalpy for relaxation ΔH^* can be determined from the dependence of Tg on heating or cooling rate q,

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

If we assume that $\Delta H^* = \Delta H$, the parameters of the VTF equation can be calculated for amorphous indomethacin. A value for ΔH^* of 464 kJ/mol was determined for indomethacin from equation A6 and the slope of Figure 4. The fragility m was then determined to be 76.7 from equation A2 where the value of Tg was taken as 43.1°C the value measured at a heating and cooling rate of 10°C/min

The VTF parameters of D = 11.15 and T_0 = 246 were determined from equations A3 and A4 with m_{min} taken as 17, and Tg taken as 43.1°C. Finally by simply assuming that $\tau_0 = 10^{-15}$ sec, the relaxation times were calculated from the VFT equation.

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