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Report

Molecular Mobility of Supercooled Amorphous Indomethacin, Determined by Dynamic Mechanical Analysis

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Purpose. To determine the viscosity and the frequency-dependent shear modulus of supercooled indomethacin as a function of temperature near and above its glass transition temperature and from these data to obtain a quantitative measure of its molecular mobility in the amorphous state.

Methods. Viscoelastic measurements were carried with a controlled strain rheometer in the frequency domain, at 9 temperatures from 44° to 90°C.

Results. The viscosity of supercooled indomethacin shows a strong non-Arrhenius temperature dependence over the temperature range studied, indicative of a fragile amorphous material. Application of the viscosity data to the VTF equation indicates a viscosity of 4.5×10^{10} Pa.s at the calorimetric Tg of 41°C, and a T_0 of −17°C. From the complex shear modulus and the Cole-Davidson equation the shear relaxation behaviour is found to be non-exponential, and the shear relaxation time at Tg is found to be approximately 100 sec.

Conclusions. Supercooled indomethacin near and above its Tg exhibits significant molecular mobility, with relaxation times similar to the timescales covered in the handling and storage of pharmaceutical products.

KEY WORDS: amorphous state; molecular mobility; shear viscosity; viscoelastisity; relaxation time

INTRODUCTION

When a liquid is cooled, the transition to the crystalline solid can often be avoided and the system is found in the metastable supercooled liquid state. As a supercooled liquid the system is metastable with respect to the crystalline state and at small supercoolings the properties of the supercooled liquid are not drastically different from those expected for an equilibrium liquid. As the degree of supercooling becomes large, and if crystallization can still be avoided, most supercooled liquids will enter the glassy state. As a glass the system is metastable with respect to both the crystalline state and the "equilibrium" glassy state (the one that results after infinitely slow cooling of the supercooled liquid). By studying the viscoelastic properties of such amorphous materials information can be obtained about their molecular mobility under a variety of conditions. This is important because many molecular processes, such as those that occur during crystallization and chemical reactions in supercooled liquids and glasses, depend on the degree of mobility of the molecular species involved (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 amorphous indomethacin from 30 to 70°C and showed that crystallization occurred below Tg, on rather short time scales. It has been also 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 for both effects. Hancock *et al.* (5) conducted enthalpy relaxation experiments with dry indomethacin glass well below its Tg and concluded that indomethacin in the glassy state still exhibits significant molecular mobility.

In this paper we report measurements of the dynamic viscosity $\eta^*(\omega)$ and the frequency-dependent shear modulus $G^*(\omega)$ of indomethacin between 44 and 90°C. Both parameters will allow us to characterize the timescales for molecular motion of indomethacin in the amorphous state, and to better understand the role of its molecular mobility in solid state processes of pharmaceutical interest.

Theoretical Considerations

There is a vast literature in the subject of rheology, and various methods have been developed to measure viscosity and shear modulus (6). In our experiment we adopt a technique (6–7) where a sinusoidal steady state strain $\epsilon(\omega)$ of frequency ω is applied to the sample. The stress $\sigma(\omega)$, or the response to the strain is given by

$$\sigma(\omega) = G^*(\omega)\epsilon(\omega) \tag{1}$$

where $G^*(\omega)$ is the complex shear modulus. It has a real and an imaginary part,

$$G^*(\omega) = G'(\omega) + iG''(\omega) \tag{2}$$

The storage modulus $G'(\omega)$ is a measure of the energy stored and recovered, and the loss modulus $G''(\omega)$ is a measure of the energy dissipated or lost as heat. A frequency dependent complex viscosity $\eta^*(\omega)$ can be defined as the response of the sinusoidal steady state stress $\sigma(\omega)$ to the sinusoidal steady state rate of strain. From this definition it can be shown that

$$\eta^*(\omega) = \frac{G^*(\omega)}{i\omega} \tag{3}$$

The viscosity also has a real and an imaginary part,

$$\eta^*(\omega) = \eta'(\omega) + i\eta''(\omega) \tag{4}$$

It can be shown further that the relationship between the components of the modulus and the viscosity are

$$\eta'(\omega) = \frac{G''(\omega)}{\omega} \quad \text{and} \quad \eta''(\omega) = \frac{G'(\omega)}{\omega} \tag{5}$$

In the zero frequency limit, $\eta'(\omega)$ is the Newtonian zero shear viscosity η_0 (6).

MATERIALS

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 kept at this tempera-

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ture for 5 min and then quenched at room temperature in cylindrical aluminum molds to form well defined discs. Previous studies have shown that no chemical degradation occurs under these conditions (2). 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. The resulting glass discs were dried under vacuum for more than 96 hrs at 0% RH (P_2O_5), previously shown to produce very dry samples. The glass transition temperature Tg was measured by DSC at a heating rate of 1°C/min in a Seiko 220C DSC and found to be 41°C.

METHODS

Measurements were carried in a control strain rheometer (Bohlin Vor-Melt) with a high torque head (2000 gcm), a frequency range 10^{-3} to 20 Hz, and a shear strain range 2×10^{-5} to 1. The sample was placed between two parallel circular plates and was heated to 80°C. It was then brought to the temperature of interest (44°–90°C) and kept isothermally for the duration of the measurement under a stream of dry nitrogen gas. A constant very small normal force was applied during the measurement to ensure full contact of the sample with the plates. The lower plate applies a known periodic displacement and a transducer on the upper plate measures the periodic force. The displacement is proportional to the strain, and the force to the stress, so monitoring these periodic functions is equivalent to tracing out the periodic variation of stress and strain with time. The phase angle between the force and the displacement is the same as between the stress and the strain. The components of the shear modulus can be calculated if the peak values of the force and the displacement, and the dimensions of the sample, are known (6). The above analysis can only be applied when sample inertia effects are negligible (gap-loading conditions) (6). This is possible only when the sample thickness is small compared with the wavelength of the shear wave propagated through the sample (8). The sample thickness was always kept less than 2mm, which satisfied the gap-loading conditions for the frequency range of our measurements and the modulus values of the sample at all temperatures. Steel plates of 25mm diameter were used at the higher temperatures whereas 12mm diameter plates were used at lower temperatures to keep the torque within the dynamic range of the transducer. In order to use a strain that ensured linear response, strain sweep experiments were performed covering the full frequency range at each temperature.

Each data point reported is the average of at least three different samples measured on different days. Repetitive measurements on the same sample gave essentially the same results, which indicated that the measurement procedure had no effect on the sample properties in terms of structural damage or crystallization. Only at 90°C was a small amount of crystallization observed at the outer rim of most of the samples during the measurement. This resulted in a large sample-to-sample deviation at 90°C.

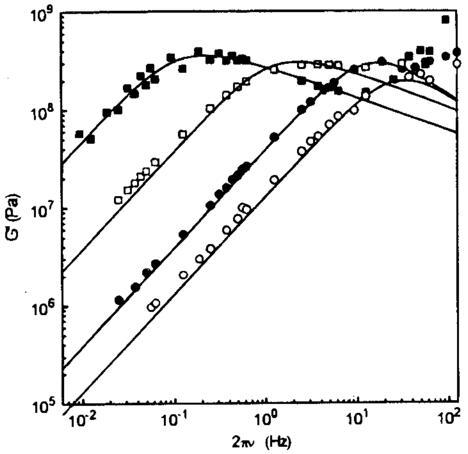

Fig. 1. The shear loss modulus G″ of amorphous indomethacin as a function of radian frequency $2\pi\nu$ at 44°C (■), 49°C (□), 54°C (●), and 56°C (○). The solid lines are the fits to the imaginary part of equation 8.

RESULTS AND DISCUSSION

In Figure 1 the loss shear modulus G″ is shown as a function of radian frequency ω at fixed temperatures. As the temperature increases the peak of the loss modulus moves to higher frequencies. Due to the limited width of our frequency window we cannot see the full shape of the loss modulus at temperatures higher than 56°C. However, it was possible to determine the viscosity values in the full temperature range from 44° to 90°C from linear regression at the $\lim_{\omega\to0}[G''(\omega)/\omega]$. We found that for the same data log G″(ω) vs log ω gave a straight line with slope 1 (Figure 1), and in addition, the linearity of plots of G′(ω) vs ω^2 at the limit of low frequencies was very good (data not shown). Both these criteria should be satisfied for the determination of the viscosity from the $\lim_{\omega\to0}[G''(\omega)/\omega]$ (6). The viscosity of supercooled indomethacin is shown in Figure 2 as an Arrhenius plot of log viscosity versus inverse temperature, the viscosity data are also presented in Table 1. From Figure 2 we can see that the viscosity of amorphous indomethacin has a very strong temperature dependence, in that for approximately every 6 K decrease in temperature, the viscosity increases by one order of magnitude. The solid line in Figure 2 is the fit of the data to the VTF equation (9),

$$\eta = A \exp\left(\frac{DT_0}{T - T_0}\right) \tag{6}$$

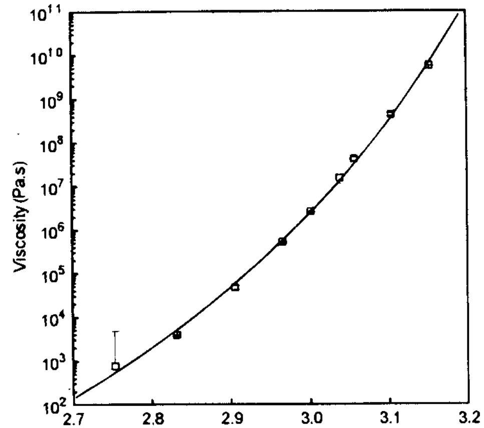

Fig. 2. Arrhenius plot of the viscosity of amorphous indomethacin as a function of temperature. The solid line is the fit to equation 6. The calorimetric Tg is 314 K.

Table 1. The Viscosity, Average Relaxation Times and the Cole-Davidson Parameter β for Amorphous Indomethacin, as a Function of Temperature

Temperature (°C)	Viscosity (Pa·s)	Average relaxation time (sec)	Parameter β
44	$5.51 \times 10^9 (1.53 \times 10^7)$	4.36(1.44)	0.35(0.08)
49	$4.27 \times 10^8 (2.90 \times 10^7)$	0.40(0.18)	0.38(0.09)
54	$4.12 \times 10^7 (3.81 \times 10^6)$	0.07(0.02)	0.55(0.08)
56	$1.48 \times 10^7 (3.69 \times 10^6)$	0.04(0.02)	0.70(0.10)
60	$2.54 \times 10^6 (7.90 \times 10^4)$		
64	$5.06 \times 10^5 (1.99 \times 10^4)$		
71	$4.64 \times 10^4 (4.44 \times 10^3)$		
80	$3.85 \times 10^3 (1.49 \times 10^2)$		
90	$7.65 \times 10^2 (4.00 \times 10^3)$		

Note: The sample standard deviations are given in parenthesis.

where A and D are material parameters and T_0 is the temperature where a special singularity in dynamics is anticipated, in that viscosity and relaxation times approach infinity. An equivalent expression is the WLF equation (10),

$$\log \eta = \log \eta_g - \frac{C_1 \times (T - T_g)}{C_2 + (T - T_g)} \tag{7}$$

where η_g is the viscosity at Tg, and C_1, C_2 are material parameters. In terms of the VTF equation $C_2 = T_g - T_0$, and $C_1 = (DT_0/(T_g - T_0)2.3)$. Both the VTF and WLF equations can be derived on the basis of free volume (6,11–13), and configurational entropy theories (14) of supercooled liquids. Based on the fit of the data to equation 6, for indomethacin the viscosity at Tg is estimated to have a value of 4.5×10^{10} Pa·s, which is less than the rule of thumb that assumes a value of 10^{12} Pa·s at Tg. However there are other examples in the literature with small organic glass formers where the viscosity at Tg is less than 10^{12} Pa·s (15–17). Also from the fit of the data to the VTF equation the temperature T_0 is estimated to be 256 K, approximately 58 K below the calorimetric Tg in agreement with the results for a number of organic glasses. The parameter D in equation 6 was found to have a value of 8.9, indicating that indomethacin is a fragile liquid according to Angell's classification (9). From the fit of the data to the WLF equation we found $C_1 = 17.2$ and $C_2 = 57.4$, both values being close to the universal WLF constants of 17.4 and 51.6 (6).

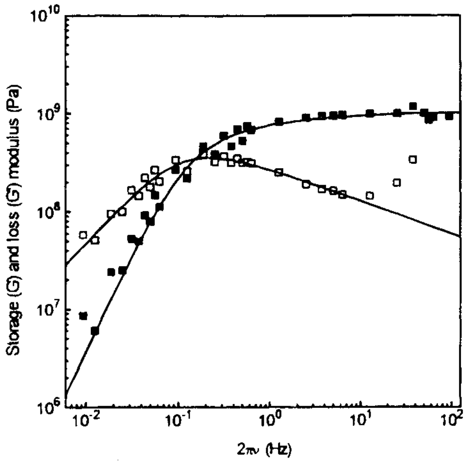

Fig. 3. The shear storage G′ (■) and loss (□) G″ modulus of amorphous indomethacin as a function of radian frequency 2πν at 44°C. The solid lines are the fits to the real and the imaginary parts of equation 8 respectively.

In Figure 3 the storage G′ and loss G″ shear modulus are shown at 44°C, as a function of radian frequency ω. The solid lines in Figures 1 and 3 are the fit of the data to the empirical Cole-Davidson equation (17–19),

$$G^*(\omega) = G_\infty\left(1 - \frac{1}{(1 + i\omega\tau_{CD})^{\beta}}\right) \tag{8}$$

where $G^*(\omega)$ is the complex frequency-dependent shear modulus, G_∞ is the high frequency limiting storage modulus, τ_{CD} is the Cole-Davidson relaxation time, and β is the Cole-Davidson width parameter. We can see in Figure 3 that the relaxation process observed in supercooled indomethacin (as in most supercooled liquids (9)) is considerably different than the relaxation of a Maxwell liquid (20). A Maxwell liquid is characterized by an exponentially relaxing process with a single relaxation time, its loss shear modulus G″ curve is symmetric and it has a width at half maximum of 1.14 decades in frequency. The corresponding loss shear modulus G″ for indomethacin in Figure 3 has a width at half maximum more than 4 decades in frequency, and it is asymmetric to the high frequency side. This non-exponential nature of the response of supercooled liquids to a perturbation can be explained with two fundamentaly different approaches (19,21). The first proposes that supercooled liquids are homogeneous and that each molecule relaxes nearly identically in an intrinsically non-exponential way, possibly the result of cooperative molecular motions (22). The second proposal is that a heterogeneous set of enviroments exist in a supercooled liquid; relaxation in any given environment is intrinsically exponential, but the relaxation time is different in different enviroments. The resulting superposition of exponential relaxations, with each one having its own relaxation time is seen experimentally as a non-exponential response by the system. It is not at present known which of the two approaches is more correct since the available experimental techniques observe only the *average*, of the simultaneous relaxation of *many* molecules. Thus as many other investigators we use the Cole-Davidson equation only as a fitting function, without proving that its underlying distribution of relaxation times is physically correct. Non linear curve fitting using our data was performed on both G′(ω) and G″(ω). From this curve fitting procedure the relaxation time τ_{CD}, the Cole-Davidson parameter β, and the high frequency limiting elastic modulus G_∞, were obtained.

In the Cole-Davidson equation, τ_{CD} is the maximum relaxation time considered to be present in the material under study. The average relaxation time can be determined from the distribution of relaxation times to be $\langle\tau_{CD}\rangle = \tau_{CD}\,\beta_{CD}$ (19). The average relaxation time $\langle\tau_{CD}\rangle$ as a function of temperature is shown in Figure 4 and Table 1, where we can see that the relaxation time at the calorimetric Tg approaches 100 sec according to a VTF equation extrapolation, and as expected theoretically (7). From an extrapolation of $\langle\tau_{CD}\rangle$ below Tg we would predict a $\langle\tau_{CD}\rangle$ of 3 years at 23°C.

The Cole-Davidson width parameter, β ($0 < \beta < 1$) in equation 8 determines the shape of the $G^*(\omega)$ curves in Figures

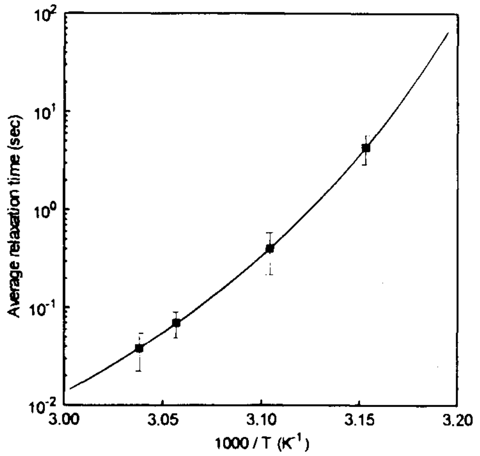

Fig. 4. Arrhenius plot of the average relaxation time for amorphous indomethacin as a function of temperature. The solid line is the fit to equation 6.

1 and 3. Phenomenologically β is related to the spread of the distribution of relaxation times (as β becomes larger the distribution becomes narrower), but has also been interpreted as a measure of the non-exponential character of the relaxation function (9). In Figure 5, β is shown to be increasing with increasing temperature. This result is consistent with similar results on a number of organic glasses (9), although there are some exceptions (17). From a rough extrapolation it appears that β approaches a value of 1, characteristic of a single relaxation time (or a very narrow distribution of relaxation times), at 60 to 70°C.

From the fitting of the G′ data to the Cole-Davidson equation (Figure 3) we found the value of G_∞ the high frequency limiting storage modulus to be approximately 1.22×10^9 Pa, which is similar with the values reported for a number of organic glasses (20).

Finally, our results have some implication with respect to the separation of rotational and translational time scales reported for other supercooled liquids (23). As shown in Figures 1 and 3, the fits to the Cole-Davidson equation are satisfactory except at higher frequencies where G″ doesn't follow the equation. In Figure 1 we see that a high frequency diverging tail of G″ persists even at 54°C, and it is marginally seen at 56°C. The high frequency tail is present in all the samples and after close examination of our experimental procedures it does not appear to be an experimental artifact. Nonetheless, we are not aware of similar data (obtained with the same experimental approach namely viscoelastic measurements) with other supercooled liquids. To the contrary Menon *et al.* (17) searched for but didn't find such a feature in their study of the dynamic viscosity of di-n-butylphthalate. Theoretically, a peak of G″ indicates the presence of a stress relaxation mechanism that dissipates energy. Based on our data we therefore can speculate on the existence of a second relaxation mechanism with a shorter time scale. It is possible for example, that in indomethacin rotational and translational motions decouple as the temperature approaches the glass transition temperature Tg, therefore two different mechanisms exist for stress relaxation, causing G″ to bifurcate into two peaks. It appears from the relative values for G″ of the two peaks that both mechanisms (translation and rotation) are equally responsible for stress relaxation. Within the precision of the data it also appears that the shorter time scale relaxation peak has a very weak temperature dependence opposite to that which we see for the primary longer time scale peak (the α-peak), and it seems that it disappears inside the α-peak with increasing temperature.

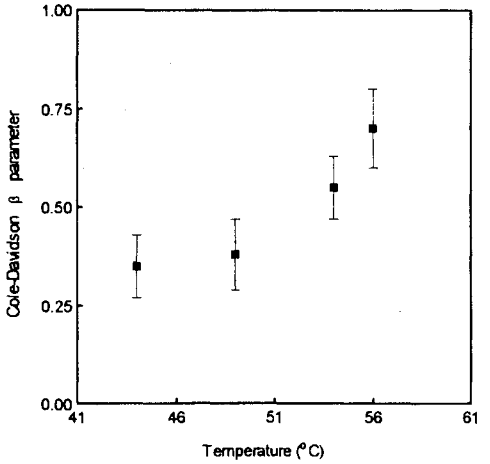

Fig. 5. The Cole-Davidson parameter β (equation 8 in text) for amorphous indomethacin as a function of temperature.

CONCLUSIONS

In this study we have shown that indomethacin in the amorphous form has a high degree of molecular mobility around its Tg, with a viscosity of 4.5×10^{10} Pa·s and an average relaxation time of 100 sec at Tg. Both viscosity and relaxation times are very sensitive to temperature in the range of 44° to 90°C, approximately changing by an order of magnitude for a change of 6°C. Viscosity shows a non Arrhenius temperature dependence with apparent activation energies on the order of 220 KJ/mol at the highest temperatures, and 410 KJ/mol close to the glass transition temperature. Fit of the viscosity data to the VTF equation indicates that indomethacin is a fragile glass former with $D = 8.9$ and $T_0 = 256$ K or 57° below Tg. The relaxation behaviour around Tg is highly non-exponential, with the Cole-Davidson β parameter having a value of 0.35 at 44°C. The relatively short timescales for molecular mobility in the region of Tg can explain the significant rate of crystallization of indomethacin from the amorphous state, previously described (2,4,24–25).

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