Determination of the Viscosity of an Amorphous Drug Using Thermomechanical Analysis (TMA)

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Purpose. To evaluate thermomechanical analysis (TMA) as a technique for determining the viscosity of amorphous pharmaceutical materials. This property of amorphous drugs and excipients is related to their average rate of molecular mobility and thus to their physical and chemical stability.

Methods. Indomethacin was selected as a model amorphous drug whose viscosity has previously been reported in the literature. A Seiko TMA 120C thermomechanical analyzer was utilized in isothermal penetration mode to determine the viscosity of the amorphous drug over the maximum possible range of temperatures.

Results. Using a cylindrical penetration geometry it was possible to accurately determine the viscosity of amorphous indomethacin samples by TMA over the temperature range from 35 to 75°C. The results were consistent with those reported in the literature using a controlled strain rheometer over the range 44–75°C. The limiting lower experimental temperature for the TMA technique was extended to significantly below the calorimetric glass transition temperature ($T_g \approx 42$°C), thus allowing a direct experimental determination of the viscosity at T_g to be made.

Conclusions. Thermomechanical analysis can be used to accurately determine the viscosity of amorphous pharmaceutical materials at temperatures near and above their calorimetric glass transition temperatures.

KEY WORDS: viscosity; glass; amorphous; thermomechanical analysis; TMA.

INTRODUCTION

The type and rate of molecular motions within amorphous pharmaceutical materials are crucial factors controlling their long term physical and chemical stability (1). Such motions may be experimentally monitored in a variety of ways, for example, by solid state nuclear magnetic resonance (NMR) experiments (2) or by isothermal microcalorimetry (3). For many amorphous materials the rate of molecular or atomic reorientation can be determined from measurements of the viscosity of the system (4,5). Viscosities are usually between 10^{-4} and 10^{12} Pa.s in the equilibrium super-cooled liquid state (at temperatures between the melting point and the glass transition temperature (T_g)), and greater than 10^{12} Pa.s for glassy amorphous materials (at temperatures below the glass transition temperature). These viscosities typically correspond to mean molecular relaxation times (τ) of about 10^{-14} to 10^{2} seconds in the supercooled liquid, and greater than 10^{2} seconds in the glass. Detailed information of this type can be used to determine the effect of different storage conditions on the mobility/reactivity/stability of amorphous materials (1,6), and may help in establishing meaningful shelf-life criteria for amorphous pharmaceutical systems (1,7).

Very little data exists for the viscosity of amorphous pharmaceutical materials, probably because of the specialized instrumentation required for its determination and/or the complexity of the experimental procedures involved (8–10). Recently there have been several reports of the successful use of thermomechanical analysis (TMA) techniques to measure the viscosity of glass forming materials (11–13). TMA is a simple technique which is widely available in many pharmaceutical laboratories and may be automated for routine experimental use. In the recently published work (12,13) conventional penetration experiments were used to determine viscosities of inorganic glasses between 10^{8} and 10^{12} Pa.s.

The objective of the work described herein was to assess the utility of TMA experiments for determining the viscosity of amorphous pharmaceutical materials. Of particular interest were the ability of this technique to reproduce data from well established experimental methods and its potential for determining viscosities at temperatures near to the glass transition region. This region is of great interest because it is usually where the greatest alterations in molecular motion occur with changing temperature, and also because it is often a difficult region to study with other techniques due to the very high viscosities encountered.

MATERIALS AND METHODS

The material chosen for study was anhydrous indomethacin (1-[*p*-chlorobenzoyl]-5-methoxy-2-methylindole-3-acetic acid). The amorphous form of this compound has been extensively characterized and it is known to be physically and chemical stable when freshly prepared and stored under controlled conditions (14). Viscosity data for amorphous indomethacin between 44 and 90°C obtained using a conventional torsional rheometer have been reported (10), thus allowing a direct comparison between data from an established technique and that proposed herein.

Disc shaped samples (≈ 6 mm diameter; ≈3.5 mm thick) of amorphous indomethacin were prepared using a reproducible melt-quench cool technique (10). The samples were stored in glass desiccators at room temperature (approximately 20°C below the glass transition temperature) for at least 48 hours before testing to minimize the effects of immediate sample history on the measured viscosity. Each sample was used for only one test and after testing it was examined using polarized light microscopy, differential scanning calorimetry (DSC) and/or X-ray powder diffraction techniques to determine if any change in the sample (*e.g.*, crystallization) had taken place prior to or during TMA testing. The geometry of the sample was also determined using a micrometer before and after testing to ensure that no dimensional changes (*e.g.*, compression) were caused by the test procedure.

A Seiko TMA/SS 120C thermomechanical analyzer was used in isothermal penetration mode with a cylindrical shaped quartz probe (11–13) (Fig. 1a). The instrument was calibrated for temperature relative to the melting points of pure indium (155.0°C) and galium (29.8°C), and a dry nitrogen purge was

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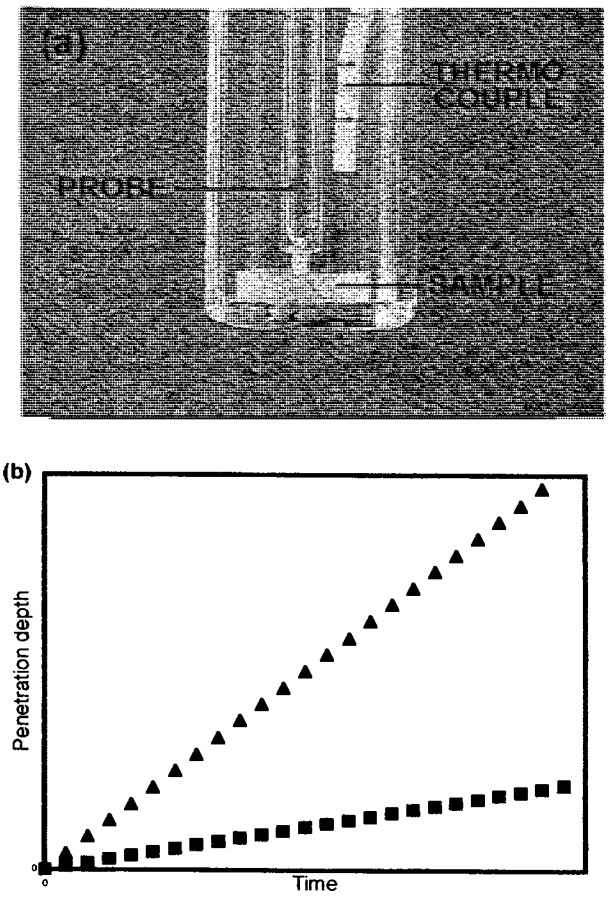

Fig. 1. The use of the thermomechanical analyzer for the viscosity measurements (a) experimental set-up, (b) typical probe penetration data at two temperatures.

employed to ensure sample dryness (~50 ml/minute). After equilibrating each sample in the instrument at the desired temperature for at least three hours a load of between 1 and 100 g was applied to the sample via the probe. After a short initial lag period steady state penetration was observed and the rate of the probe penetration was recorded (Fig. 1b). The applied load was selected so that the experimental time was typically of the order of several hours, thereby giving an approximately zero shear rate viscosity that could be compared with previous data.

RESULTS AND DISCUSSION

All the samples of amorphous indomethacin were carefully examined after testing to determine if the test procedures had induced any changes in their physical properties. No crystallization of the samples could be detected by polarized light microscopy, differential scanning calorimetry or X-ray powder diffraction, even after the longest experiments and at the highest temperatures (4200 minutes and 75°C respectively). There were no significant dimensional changes induced in the samples by the test procedures, and the hole dimensions were typically regular and similar indicating that there was gradual, controlled penetration of the probe into the test samples. The midpoint of the glass transition temperature (T_g) for the samples used in this work, determined by DSC at a heating rate of 1°C/minute, was 42°C, in good agreement with the value of 41°C reported by previous workers for samples prepared and tested under similar conditions (10).

The viscosities of amorphous indomethacin samples could be determined between 35 and 75°C using the TMA. This range of temperatures was primarily determined by the loading capability of the instrument. The effects of using different probe loads on the measured viscosity are illustrated in Table I where data generated at 50°C using three different loads are presented. There were no obvious differences between the results generated using these different loads, hence at other temperatures the probe loads were selected to maintain the experimental time between 2 and 4200 minutes.

Typical plots of the TMA results for probe penetration depth versus experimental time are shown in Fig. 1b. Several approaches exist for calculating viscosities from such penetration data, based on either empirical or theoretical perspectives (11–13). Each of these approaches shows the viscosity (η) to be a simple function of the probe diameter (d), the applied load (F) and the experimentally determined penetration rate (v):

$$\eta = k.\ F/d \cdot v \qquad (1)$$

with the value of the proportionality constant (k) being between 2.5 and 4.0 depending upon the assumptions used to derive equation 1 from the various models. The viscosities of the amorphous indomethacin samples were calculated using both the maximum and minimum reported values of the constant k, and the results are plotted as a function of the experimental temperature in Fig. 2a. The results at each temperature represent the mean of three or more determinations.

The results of the viscosity determinations using the thermomechanical analyzer followed the trends expected for materials in the amorphous state, with viscosity values varying with temperature over many orders of magnitude in a non-linear manner. Specifically, the measured viscosity varied over about eight orders of magnitude between approximately 10^4 Pa.s at 75 °C and 10^{12} Pa.s at 35 °C. At the calorimetric glass transition temperature the viscosity of the amorphous indomethacin was determined to be approximately 10^{10} Pa.s, as reported previously (10). The two different methods of calculating viscosity from the penetration data did not provide significantly different results from one another since the experimental viscosity values were very large (10^{12} to 10^4 Pa.s) and varied logarithmically with the temperature. Under such circumstances it is the order of magnitude of the proportionality constant which is critical, and this was effectively constant from 2.5 to 4.0. In order to simplify subsequent analyses the method of Yang *et al* (k = 4.0) was selected as the preferred method because of its more rigorous theoretical derivation.

A comparison of the data collected in this work with that previously published is shown in Fig. 2b. Whilst the data are

Table I. Viscosity of Amorphous Indomethacin Samples at 50°C (323 K) Measured Using Different TMA Loads

Load applied (g)	Mean viscosity (n = 2–4) (Pa.s)	Standard deviation (Pa.s)
5	2.1×10^8	6.2×10^7
10	2.4×10^8	3.3×10^7
20	1.4×10^8	5.7×10^7

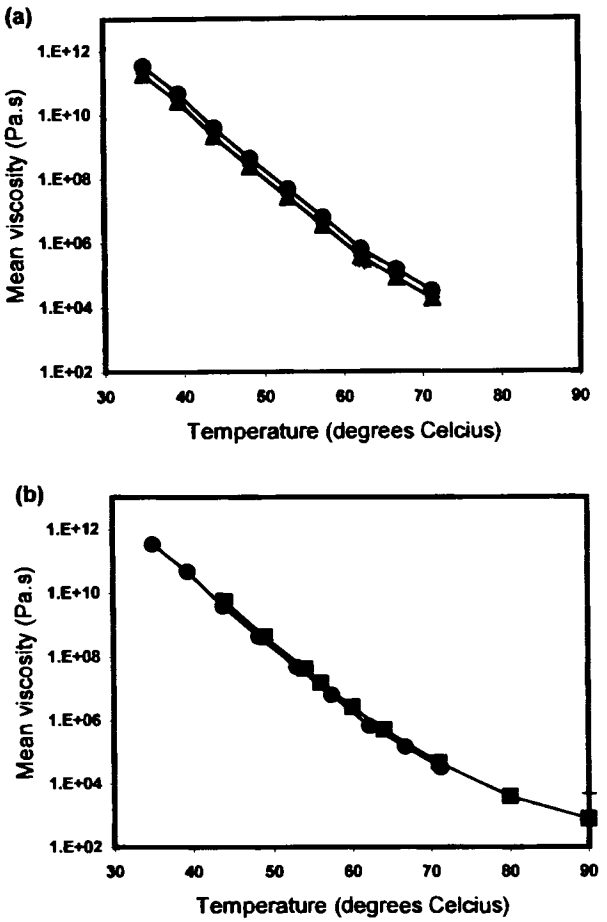

Fig. 2. The viscosity of amorphous indomethacin as a function of temperature (a) ● calculated using k = 2.5 (12); ▲ calculated using k = 4.0 (13) (b) ● this work (k = 4.0); ■ previous work (10).

very similar there was a small systematic difference between the two data sets, with the current data set being very slightly lower than the published data. This difference can be easily understood when it is realized that the accuracy of the temperature calibration for the two techniques is typically only ±1°C, and the viscosity of most amorphous systems alters significantly even over such a narrow temperature range. An identical range of viscosity values (about eight orders of magnitude) could be monitored using the two experimental techniques, but the limiting viscosities which could be probed using the TMA technique were slightly different from those reported using the conventional controlled strain rheometer (10). Specifically, both the low and high viscosity limits were shifted to higher viscosities with the TMA. For amorphous indomethacin this shift meant that the region around calorimetric glass transition temperature was encompassed. This may represent an advantage for the TMA technique over other experimental methods which cannot probe very high viscosities and where the viscosity at T_g usually has to be determined by extrapolation. Notably the viscosity of the amorphous indomethacin below the calorimetric T_g simply extended the trend from temperatures above T_g, and thus short extrapolations from higher temperatures which have been used by previous workers (10) were confirmed to be accurate and meaningful for this material.

The viscosities of typical amorphous materials at temperatures up to 100°C above their glass transition temperature are expected to vary in a non-Arrhenius manner (6,7). This was the case for the data collected using the TMA (Fig. 3), and also for the previously reported results. Non-Arrhenius models and equations are often used to describe such data, with the WLF and VTF approaches being the most popular (1,6). The fit of the data to these equations usually involves iterative procedures with two or three curve-fitting parameters. For the current data set it was found that such procedures were extremely unreliable, with the fitted parameters being highly sensitive to the initial parameter estimates and to the step size chosen for the iterative procedure. This was due primarily to the limited range of temperatures studied (less than one order of magnitude) and the relatively small degree of non-linearity in the plots (Fig. 3). A similar phenomenon has been previously reported (15), and it is noted again here as a caution against the inappropriate determination of WLF and VTF constants from limited experimental data sets.

It was finally of interest to determine the practicality of estimating molecular relaxation times (τ) from the viscosities measured using the TMA, particularly in the region around T_g. By using the limiting storage modulus (G_∞) reported by Andronis and Zografi (10) ($\approx 1.22 \times 10^9$ Pa) average values of τ were estimated from the TMA viscosity data near T_g using the well known Maxwell equation (16):

$$\tau_{average} = \eta/G_\infty. \quad (2)$$

At 44°C the average relaxation time was estimated to be about 3 seconds, at 39°C it was 37 seconds, and at 35°C (7°C below T_g) a value of approximately 270 seconds was calculated. It is clear from these values that the mean relaxation time for amorphous indomethacin at its calorimetric T_g is about an order of magnitude less than that which is typical for other amorphous materials ($\sim 10^2$ seconds). Such "enhanced molecular mobility" in the region of T_g is consistent with the reported physical instability of indomethacin glasses at temperatures as much as 50 K below T_g (1,17). These calculations illustrate the potential for molecular relaxation times to help in the identification of appropriate storage conditions for amorphous pharmaceutical materials, and they also emphasize the importance of developing

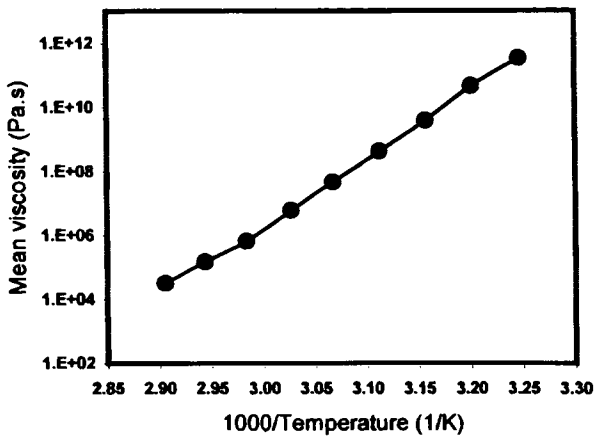

Fig. 3. A reciprocal temperature plot for the indomethacin viscosities measured by TMA.

techniques such as TMA for determining the rate of molecular motions in such systems.

CONCLUSIONS

The use of thermomechanical analysis (TMA) as a technique for determining the viscosity of amorphous pharmaceutical materials has been evaluated. Data generated for a well characterized anhydrous amorphous drug were consistent with those reported using conventional and well established rheological testing techniques (10). By using TMA the viscosity at the glass transition temperature could be directly determined.

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