Solid-State Characteristics of Amorphous Sodium Indomethacin Relative to Its Free Acid

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Purpose. Having previously studied the amorphous properties of indomethacin (IN) as a model compound for drugs rendered amorphous during processing, we report on the formation and characterization of its sodium salt in the amorphous state and a comparison between the two systems.

Methods. Sodium indomethacin (SI) was subjected to lyophilization from aqueous solution, rapid precipitation from methanol solution, and dehydration followed by grinding to produce, in each case, a completely amorphous form. The amorphous form of SI was analyzed using DSC, XRD, thermomicroscopy and FTIR. The method of scanning rate dependence of the glass transition temperature, *Tg*, was used to estimate the fragility of the SI system. Enthalpy relaxation experiments were carried out to probe the molecular mobility of the SI system below *Tg*.

Results. The amorphous form of SI formed by different methods had a *Tg* equal to 121°C at a scanning rate of 20°C/min. This compares with a *Tg* for indomethacin of 45°C. Estimation of fragility by the scanning rate dependence of *Tg* indicates no significant differences in fragility between ionized and unionized forms. Enthalpy relaxation measurements reveal very similar relaxation patterns between the two systems at the same degree of supercooling relative to their respective *Tg* values.

Conclusions. The amorphous form of SI made by various methods has a *Tg* that is about 75°C greater than that of IN, most likely because of the greater density and hence lower free volume of SI. Yet, the change of molecular mobility as a function of *temperature relative to Tg* is not very different between the ionized and unionized systems.

KEY WORDS: glass transition temperature; amorphous systems; molecular mobility; fragility; enthalpy relaxation.

INTRODUCTION

While a high degree of crystallinity is pursued by chemists in the synthesis of new drug molecules, disorder in the crystal lattice or the creation of an amorphous phase is often encountered intentionally or unintentionally due to pharmaceutical processing (1,2). If the drug lacks sufficient aqueous solubility to provide adequate bioavailability it can be prepared as an amorphous form (3–5), or with polymeric additives to enhance metastable solubility (6). If the drug is quite water-soluble but chemically unstable and an amorphous form is created inadvertently, there is the possibility of enhanced chemical instability in the solid-state (7,8). In both cases, the amorphous state might easily spontaneously crystallize on storage, which will be disadvantageous in the former case, but possibly advantageous in the latter case. Such issues indicate the need for studies concerned with the amorphous characteristics of drug molecules that might be subjected to some type of processing for solid dosage form development.

Previously in this laboratory, we have reported studies with the drug, indomethacin, using it as a model of a small relatively nonpolar organic carboxylic acid that can be easily rendered amorphous by processing (9). For this drug, we have characterized the glass transition temperature, *Tg*, fragility, molecular mobility, below (10) and above *Tg* (11,12), water vapor sorption (13), FT-IR and FT-Raman spectra (14) and the effects of temperature and relative humidity on crystallization kinetics and polymorphic selection (13,15). Although the sodium salt of indomethacin is not ordinarily used in solid dosage forms, it represents an excellent model for a variety of salt forms that are often prepared as oral solids and solids for reconstitution as injectables or oral liquids. Thus it seems useful to carry out selected studies on the amorphous form of sodium indomethacin and to compare these properties directly to those of the free acid form previously reported.

The glass transition temperature of an amorphous solid provides local structural information about the material, and therefore, often serves to reflect the chemical and physical stability and mechanical properties of the material (16). Amorphous indomethacin has a glass transition temperature of about 45°C. It has been shown that for the amorphous indomethacin system, significant molecular mobility occurs at temperatures at which typical pharmaceutical operations and storage are usually performed (10). This explains the occurrence of crystallization of indomethacin from the amorphous state even at ambient temperature (15). Spectroscopic analysis of amorphous indomethacin shows that the dimeric structure formed by H-bonding between the two acidic carboxylic groups, that exists in the crystalline state predominantly, remains in the amorphous state. A small portion also exists as chains formed by hydrogen bonds between carbonyl and carboxylic acid groups (14). By forming the amorphous sodium salt, we hypothesize that the replacement of H-bonding between the dimers with ionic interaction between sodium ion and indomethacin anion will increase its *Tg* by increasing its density, and hence decreasing free volume. To what extent the presence of the carboxylate groups, and sodium ion will impact on the structural relaxation (molecular mobility) and the temperature dependence of such molecular mobility, i.e., its fragility, is not clear, yet it is an important issue in assessing and predicting its solid-state physical and chemical instability. Therefore such measurements on sodium indomethacin have been made for comparison with its free acid form.

MATERIAL AND METHODS

Materials

Crystalline sodium indomethacin (sodium 1-(p-chlorobenzoyl)-5-methoxy-2-methylindole-3-acetate) trihydrate was obtained as a gift from Merck & Co. and used as received. Karl Fisher titration (Aquastar Coulometric titrator C2000, EM Science, Cherry Hill, NJ) showed an average water content of 12.20 ± 0.06% (n = 6) as compared to the theoretical value of 12.45% for sodium indomethacin trihydrate. TGA (Netzsch TG 209) analysis also showed a one step weight loss of 12.50%

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at an onset temperature of 75°C, thereby confirming the trihydrate state of the sample. Crystalline anhydrous sodium indomethacin was produced by complete dehydration of the trihydrate. It has a melting point of 247°C followed by decomposition. Deionized water was used to make all of the aqueous solutions. Anhydrous methanol (Aldrich, water <0.005%) was used to prepare the amorphous form of sodium indomethacin by the precipitation method described below.

Methods

Formation of the Amorphous Form

Amorphous indomethacin was prepared by melting indomethacin in an aluminum weighing pan at 165°C, followed by quenching with liquid nitrogen. Preparation of amorphous sodium indomethacin was carried out by three procedures: freeze-drying, grinding and precipitation. Aqueous solutions of sodium indomethacin at various concentrations (0.5, 1.0, 2.0 and 5.0%, w/v) were freeze-dried using a FTS Dura-Stop tray drier (Dura-Stop, FTS Systems, Stone Ridge, NY) coupled with a condenser module (Dura-Dry-MP, FTS Systems, Stone Ridge, NY). The solution was placed into 10 mL scintillation vials and it was frozen at −40°C for 12 hr before a vacuum was applied. At a residual pressure of around 50 millitorr the temperature of the freeze-drier was then programmed to −25°C (48 hr), −10°C (48 hr), 0°C (24 hr), 25°C (24 hr) and 45°C (24 hr). Following this procedure, the amorphous form was dried under vacuum at 60°C for 48 hours to remove any residual water. Karl Fisher titration revealed less than 0.1% (w/w) water content.

To prepare mechanically ground amorphous samples, sodium indomethacin trihydrate crystalline powder was dried under vacuum at 80°C until Karl Fisher titration showed a water content of less than 0.2%. The dried powder was allowed to cool to ambient temperature and was handled in a glove box where relative humidity was kept below 10%. Two hundred (200) mg of the dried sample was weighed into the stainless steel mixing capsule of a Wig-L-Bug (Crescent Dental Mfg. Co., Lyons, IL) and the sample was ground with a steel ball for various lengths of time.

To prepare the precipitated amorphous form, dried sodium indomethacin was dissolved in anhydrous methanol (2 g/25 mL) in a round bottom flask at 65°C. Upon complete dissolution, the solvent was rapidly rota-evaporated under vacuum at 55°C. The resultant amorphous material was further dried overnight under vacuum at 60°C to remove residual methanol.

The formation of a completely amorphous form in all cases was confirmed by examination for the presence of crystallinity (i.e., presence of birefringence) using an Olympus BH-2 optical microscope equipped with a thermal hot stage and polarized light accessories, and by X-ray powder diffraction using a Scintag scanning powder diffractiometer (Scintag Inc., Santa Clara, California). In all cases, no crystallinity was detected.

Density measurements for crystalline and amorphous indomethacin and sodium indomethacin were carried out using helium pycnometry (Quantachrome Multipycnometer, Syosset, NY) at ambient temperature.

Thermal Analysis Studies

TGA Analysis. TGA (Netzsch TG 209) analysis was carried out for the amorphous materials made by the different procedures. In all cases, there was no significant weight loss, indicating the absence of water or methanol.

DSC Analysis. The glass transition temperature Tg, heat capacity ΔC_p of amorphous sodium indomethacin, and melting point of crystalline sodium indomethacin were measured using a Seiko 220C DSC (Seiko Instruments, Horsham, PA) and the data were analyzed using a coupled Seiko DSC 5200 Data Station. Samples of 5–10 mg were weighed into aluminum pans (TA Instruments, Mettler, Toledo) with a pinhole in the lid to allow removal of any residual water during the first scan. Dry nitrogen was used as the purge gas and liquid nitrogen as the coolant. When different scanning rates were used, high purity indium, gallium and biphenyl were used for temperature calibration. In all cases, the onset temperature for the glass transition is reported.

Determination of the Heating Rate Dependence of Tg *Using DSC.* Samples of amorphous sodium indomethacin made in the different ways were loaded into an aluminum DSC pan with a pin hole in the lid. The *Tg* of the sample was measured at the same cooling and heating rates of 5, 10, 20, 30 and 40°C /min.

Measurement of Enthalpy Relaxation Below Tg. Enthalpy relaxation was assessed by subjecting amorphous samples to five storage temperatures, i.e., 16, 24, 32, 40 and 47°C below the *Tg* of sodium indomethacin for various lengths of time. These storage temperatures relative to *Tg* were chosen in accordance with the experimental conditions used in the enthalpy relaxation experiment conducted for indomethacin by Hancock *et al.* (10). Freeze-dried samples were used in this case, since it was possible to make large amounts of amorphous sample at one time, and because its properties were essentially identical to those of samples made by the other methods. The enthalpy that is lost due to relaxation of the glassy state during the aging process is recovered when the aged sample is heated through the glass transition to produce the supercooled liquid state, and is observed as a characteristic endotherm in the vicinity of *Tg*. The sample was first heated to 135°C to remove any residual water and then quench-cooled using a cooling rate of 40°C/min to 100°C below *Tg*. The temperature was then raised to the aging temperature desired and kept for a certain time before the aging process was terminated by cooling the sample at 40°C/min to 0°C. Enthalpy recovery was recorded as the area between the endothermic DSC peak at the glass transition and the extrapolated supercooled-liquid baseline. The chemical stability of sodium indomethacin at these aging temperatures was confirmed using a thin layer chromatography method (17). Enthalpy relaxation data for indomethacin using the same conditions were obtained directly from an earlier study (10).

Spectroscopic Analysis of Amorphous Indomethacin and Sodium Indomethacin

FT-IR absorbance spectra of amorphous indomethacin and sodium indomethacin were obtained on a Mattson Galaxy 5020

FTIR spectrometer with a DTGS detector. Amorphous samples were mixed with dry KBr at about 1% (w/w) before being pressed to form KBr pellets. For each sample, 64 scans were carried out at a resolution of 2 cm^{-1}, over the wavenumber region of 4000–400 cm^{-1}.

RESULTS

Glass Transition Temperature of Amorphous Sodium Indomethacin

The three methods used to make amorphous sodium indomethacin all resulted in complete formation of the amorphous form, as confirmed by the typical halo shaped X-ray powder diffraction pattern and a lack of birefringence using an optical microscope under polarized light. During the process of making ground amorphous sodium indomethacin from crystals, it was found that any water content that remained in the crystalline material tended to prevent the complete formation of the amorphous form upon grinding. In Fig. 1, it is shown that, when the same amount of crystalline materials with different water contents was ground, the trihydrate sample (with water content of 12.4%) was seen to remain considerably crystalline after grinding for up to 60 minutes, while for the vacuum oven dehydrated sodium indomethacin (with water content <0.2%), grinding for 15 minutes led to the formation of a completely amorphous form. It was also observed (data not shown) that dehydration of the crystalline trihydrate at a slow heating rate (<10°C/min) resulted in partial formation of amorphous material, as evidenced by a reduction in the intensity of the X-ray diffraction peak and a detectable glass transition. During dehydration at faster rates the crystalline state generally remained intact resulting in a crystal anhydrate form. These results show that the water of crystallization plays an important role in maintaining the crystal structure of sodium indomethacin trihydrate, reducing tendencies to form the amorphous state. Samples prepared by lyophilization from the four different initial solution concentrations also gave essentially the same *Tg* and ΔC_p, even though the pH of aqueous solution before freeze-drying changed from 6.67 to 8.36 between the lowest and the highest concentrations.

The amorphous form prepared in different ways exhibited very similar properties, including the glass transition temperature, *Tg*, and the change in heat capacity at the *Tg*, ΔC_p. The results determined at a scanning rate of 20°C/min are presented together with data for indomethacin from a previous study (10) in Table 1. It can be seen that the *Tg* of sodium indomethacin is 121°C, a difference in *Tg* from indomethacin of about 75°C. Similar differences in *Tg* were observed for scanning rates of 5 to 40°C/min (to be discussed later).

Densities of Amorphous and Crystalline Forms

The densities obtained for amorphous indomethacin (quench melt) and sodium indomethacin are 1.333 and 1.420 g/cm^3, respectively. For crystalline anhydrous sodium indomethacin (m.p. 247°C) obtained by heating the crystalline trihydrate in a vacuum oven at 80°C, the density is 1.466 g/cm^3, as compared to the value reported for the γ form of indomethacin, 1.372 g/cm^3 (18) (m.p. 161°C) (19).

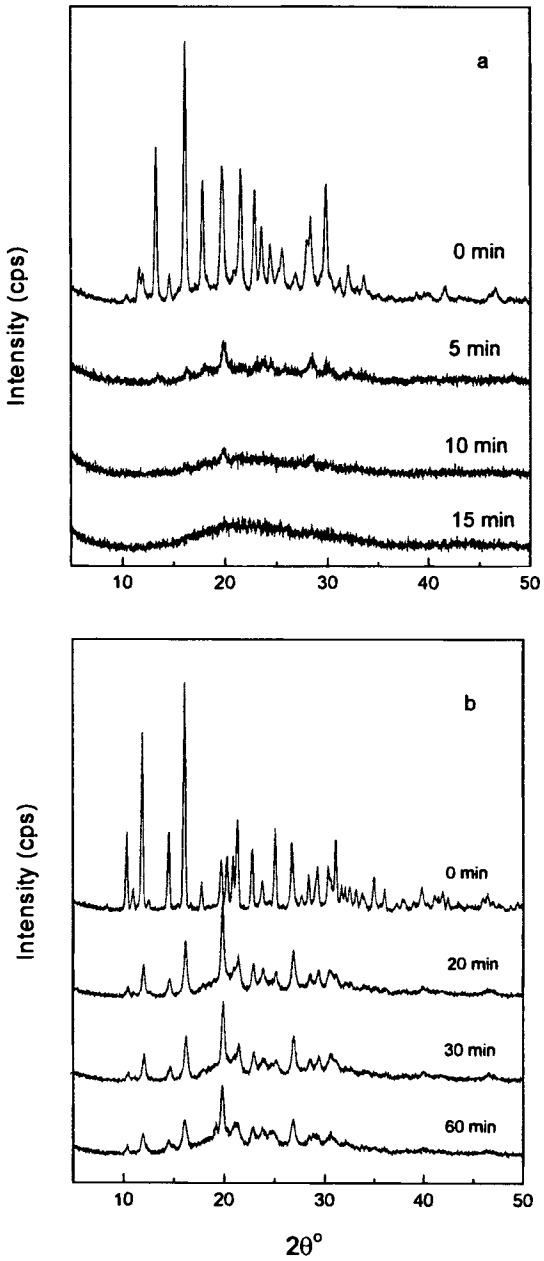

Fig. 1. Formation of amorphous sodium indomethacin by grinding its crystals for different amounts of time. (a): grinding oven-dried sodium indomethacin crystals. (b): grinding sodium indomethacin trihydrate crystals.

Table 1. Comparison of the Thermal Properties of Sodium Indomethacin and Indomethacin in the Amorphous Form (n ≥ 10)[a]

	Preparation method	Tg (°C)	ΔC_p (mJ/mg.K)
SI	grinding	121 ± 0.3	0.33 ± 0.03
	freeze-drying	121 ± 1.0	0.33 ± 0.03
	solvent evaporation	120 ± 0.7	0.32 ± 0.05
IN[b]	quench melt	44.7	0.47

Note: Scanning rate: 20°C/min.
[a] n = number of samples measured.
[b] From Ref. (10).

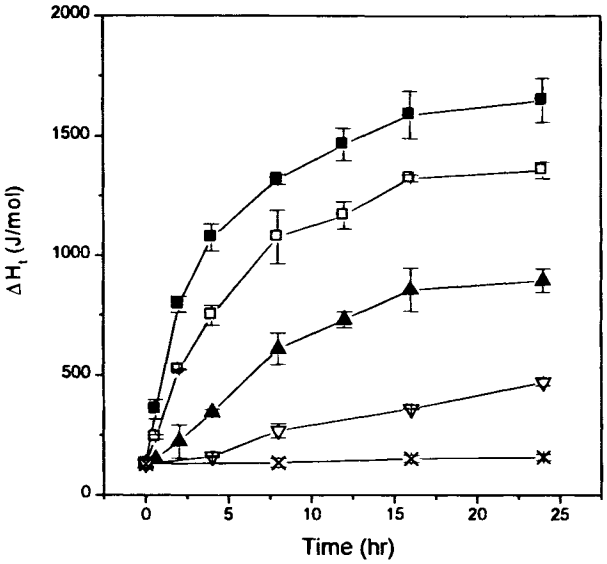

Fig. 2. Change of enthalpy relaxation (ΔH_t) of amorphous sodium indomethacin with time after storage at different temperatures. Aging temperature: *Tg*-16 (■), *Tg*-24 (□), *Tg*-32 (▲), *Tg*-40 (▽) and *Tg*-47 (×) °C.

Enthalpy Relaxation Determined by DSC

Enthalpy changes as a function of storage time for freeze-dried sodium indomethacin at temperatures below *Tg* (*Tg*-47, *Tg*-40, *Tg*-32, *Tg*-24 and *Tg*-16°C) are shown in Fig. 2. Samples stored at higher temperatures reach a plateau of enthalpy recovery faster than those stored at lower temperatures. Relaxation at *Tg*-47°C was too small to be detected over the experimental time scale.

FT-IR Spectroscopy

In Fig. 3, we see the characteristic peak for the carboxylic acid dimers (1710 cm^{-1}) of amorphous indomethacin, as previously described in great detail (14), and we note that for sodium indomethacin this dimer peak has been eliminated. Also absent is the shoulder at 1735 cm^{-1} that occurs because of the vibration of the non-hydrogen bonded carbonyl on the end of a chain. Indeed, even in the anhydrous and trihydrate crystal forms sodium indomethacin also lacked any peaks associated with dimer formation, as found in various forms of indomethacin (14) (data not shown). The ionization of the carboxyl group and its electrostatic interaction with a sodium ion would be expected to interfere with such dimer formation.

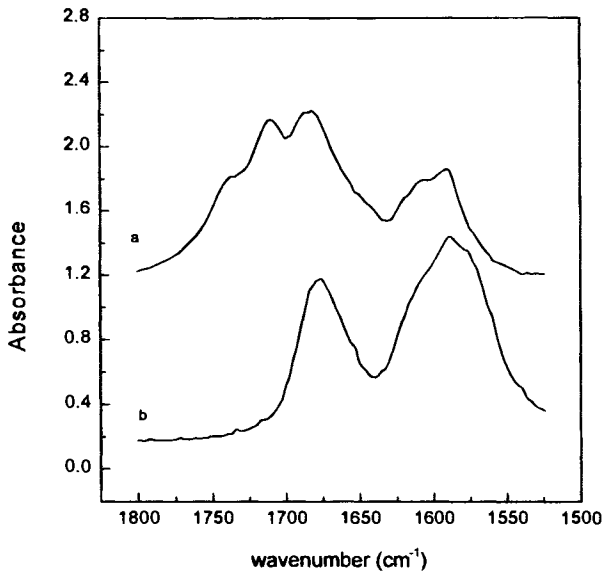

Fig. 3. FT-IR spectra for (a) amorphous indomethacin and (b) amorphous sodium indomethacin.

DISCUSSION

From the results of this study we can give a number of important insights into the properties of amorphous sodium indomethacin relative to those of its free acid form, indomethacin. By creating the ionized form, there is an increase in *Tg* of about 75°C over that of the free acid. From the FT-IR measurements (Fig. 3), we see that the characteristic peak associated with carboxylic acid dimers (1710 cm^{-1}) (14) is missing with the sodium salt. Presumably the much higher temperature required for the glass transition arises from the electrostatic interactions that must occur between the sodium ion and the indomethacin carboxylate anion. The stronger molecular interaction in the salt form can be reflected by the much higher melting point (247°C) of the crystalline salt form relative to the free acid form (161°C). Also we see a correspondingly reduced free volume of the amorphous salt form relative to carboxylic acid dimers in the amorphous free acid form, as indicated by the increase in density of amorphous sodium indomethacin relative to amorphous indomethacin (from 1.335 to 1.420 g/cm^3).

To gain some further understanding of how the presence of the sodium salt might influence the amorphous properties of indomethacin, it is useful to explore the fragility of sodium indomethacin relative to that of indomethacin. The classification of *strong* and *fragile* glasses, as described by Angell *et al.* (20–22), serves to differentiate the way in which the structural relaxation of the amorphous state responds to temperature changes above *Tg*. Materials that are *fragile* generally exhibit non Arrhenius behavior with regard to viscosity or relaxation time vs. temperature, whereas *strong* glasses, usually existing in some type of tetrahedrally coordinated network structure, exhibit Arrhenius behavior. *Strong* glasses tend to exhibit smaller heat capacity changes at *Tg* and to have ratios of melting temperature to *Tg* greater than 1.5. *Fragile* materials generally exhibit large heat capacity changes and have ratios of melting temperature to *Tg* less than 1.5.

One way to examine such behavior is to apply the Vogel-Tamman-Fulcher (VTF) equation in terms of τ, the mean relaxation time at temperature *T*:

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

where τ_0 is the relaxation time at a high temperature limit, which is of the order of vibrational lifetimes ($10^{-14} \sim 10^{-15}$ sec). T_0 is the temperature (in Kelvin) where molecular mobility becomes negligible (it is also called the ideal glass transition temperature). *D* is a parameter related to the fragility of the material. *D* values from 3 to 7 represent very fragile glasses, whereas values above 30 indicate very strong glasses (20).

In previous studies it was possible to prepare amorphous indomethacin in forms (discs) that could be used to obtain τ and hence D and T_0 in Eq. 1 from thermomechanical and dielectric analysis (11,12). However, in the present study this was not possible since anhydrous crystalline sodium indomethacin showed some decomposition at its melting point. An alternative approach, originally proposed by Moynihan (23), can be used to estimate D and T_0 through the VTF equation. Use of this approach to estimate the fragility of indomethacin produced results in excellent agreement with those obtained from thermomechanical and dielectric relaxation measurements (12). Here one starts with the definition of a dimensionless term fragility, m, which is defined as the slope at Tg of the plot of log τ vs. the reciprocal of temperature scaled to Tg (both in Kelvin):

$$m = \left.\frac{d\log\tau}{d(Tg/T)}\right|_{T=Tg} \tag{2}$$

At temperatures above Tg, it is possible to approximate the relaxation of both *strong* and *fragile* supercooled liquids using the Arrhenius equation if the temperature change is small enough, using a temperature dependent apparent activation enthalpy ΔH:

$$m = \frac{\Delta H|_{Tg}}{2.303RTg} \tag{3}$$

A simple way to estimate m is to use the activation energy for viscous flow, ΔH^*, a term which is experimentally indistinguishable from the apparent activation enthalpy ΔH. Moynihan *et al.* (23–25) had shown that ΔH^* can be obtained from the scanning rate dependence of Tg (in Kelvin), based on the following equation:

$$\frac{\Delta H^*}{R} = -\frac{d \ln q}{d(1/Tg)} \tag{4}$$

where q is the cooling/heating rate. Therefore, ΔH and m can be obtained from the slope of the plot of ln q vs. $1/Tg$ using Eq. 3 and 4, as shown in Fig. 4. The strength parameter D and ideal glass transition temperature T_0 can be related to m (12) as:

$$D = \frac{2.303 \times 17^2}{m - 17} \tag{5}$$

and

$$T_0 = Tg\left(1 - \frac{17}{m}\right) \tag{6}$$

where an assumption is made that the relaxation time for supercooled liquids changes by 17 orders of magnitude upon glass formation ($\tau_{Tg} \approx 100$ sec while τ_0 approaches 10^{-15} sec). The fragility term, m, and other parameters that describe the strength/fragility of the sodium indomethacin amorphous system are tabulated in Table 2. Interestingly, from Table 2, we can see that, despite the significant difference in the values of Tg, the temperature dependence of molecular mobility in the vicinity of Tg, reflected in fragility m, is essentially unchanged going from the free acid to sodium salt. Thus we can conclude that no significant network structure, characteristic of a *strong* glass, is introduced when the sodium salt is formed as an amorphous solid.

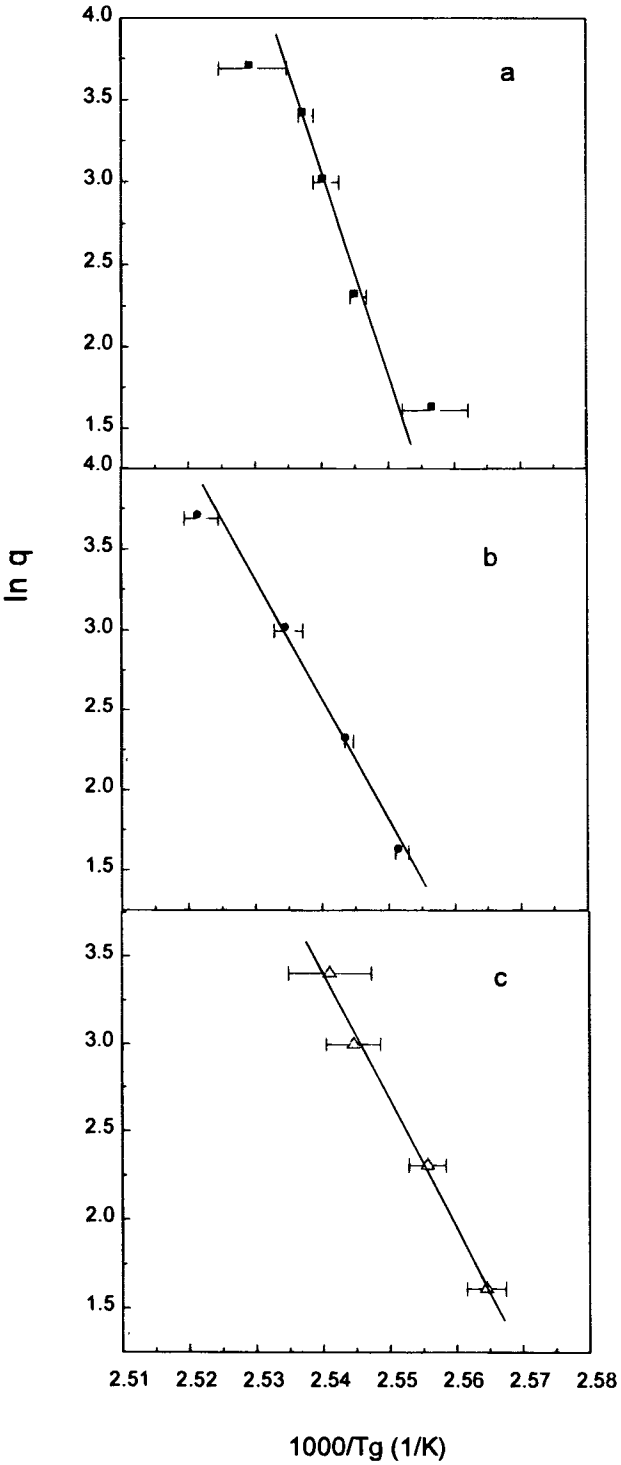

Fig. 4. Plots of *ln* scanning rate, q, vs. reciprocal of Tg for amorphous sodium indomethacin made in different ways: (a) ground , (b) freeze-dried and (c) solvent-evaporated.

To further probe the amorphous behavior of sodium indomethacin relative to indomethacin, we can examine relaxation behavior below Tg by an analysis of the enthalpic relaxation measurements described in the methods section and shown in Fig. 2. To estimate τ below Tg, we can use the Kohlrausch-Williams-Watts (KWW) stretched exponential expression (26)

Table 2. The Strength/Fragility Parameters for Amorphous Sodium Indomethacin and Indomethacin

	SI			
	Freeze-dried	Ground	Solvent evaporated	IN[a] quench cooled
T_m/Tg	1.32	1.32	1.32	1.37
T_0 (K)	311	319	310	246
ΔH^* (kJ/mol)	609	677	609	464
m	81	90	81	77
D	10	9	10	11

[a] From reference (12).

that is commonly used to describe the mean relaxation time and distribution of molecular motions of an amorphous material:

$$\phi(t) = \exp\left(-\left(\frac{t}{\tau}\right)^{\beta}\right) \quad (7)$$

where $\phi(t)$ is the extent of relaxation at time t, τ is the mean relaxation time and β is a constant that describes the distribution of relaxation processes.

At temperatures below *Tg*, amorphous solids are non-equilibrium liquids with extremely large viscosities ($\geq 10^{12}$ Pa.s) and therefore they will tend to relax constantly toward equilibrium at a characteristic rate, eventually reaching a maximum enthalpy change equal to ΔH_∞. The value of ΔH_∞ can be estimated using the following equation:

$$\Delta H_\infty = \Delta C_p\,(Tg - T) \quad (8)$$

which has been confirmed by long term studies with indomethacin and other materials (10). The extent of enthalpy relaxation $\phi(t)$ at each storage temperature T can be calculated based on ΔH_t, the experimentally measured enthalpy recovery at any given time t, and the calculated ΔH_∞ using the following equation:

$$\phi(t) = 1 - \left(\frac{\Delta H_t}{\Delta H_\infty}\right) \quad (9)$$

By fitting the KWW equation (Eq. 7) to the data, the mean relaxation time τ can be estimated for sodium indomethacin as was done for indomethacin in a previous study (10). Such values are plotted in Fig. 5, for both sodium indomethacin and indomethacin. In both cases, down to 32°C below *Tg* we see very similar relaxation behavior. At lower temperatures, the estimation gets much poorer due to the accuracy of the technique, as indicated by the large error bars.

As has been shown for indomethacin by Andronis *et al.* (12), the real relaxation times for amorphous material below *Tg* are usually smaller than the equilibrium times estimated from extrapolations below *Tg* using the VTF equation. This is because at temperatures below *Tg*, the configurational entropy does not decrease to the extent predicted by the VTF equation (27). To complete our analysis, taking this into account, as has been shown previously with indomethacin, we can use the *D* and T_0 values shown in Table 2 and the VTF and Adam-Gibbs-Vogel (AGV) (27) equations to construct an expected plot of τ vs. *T/Tg* for temperatures above and below *Tg*, respectively. The AGF equation takes the form of:

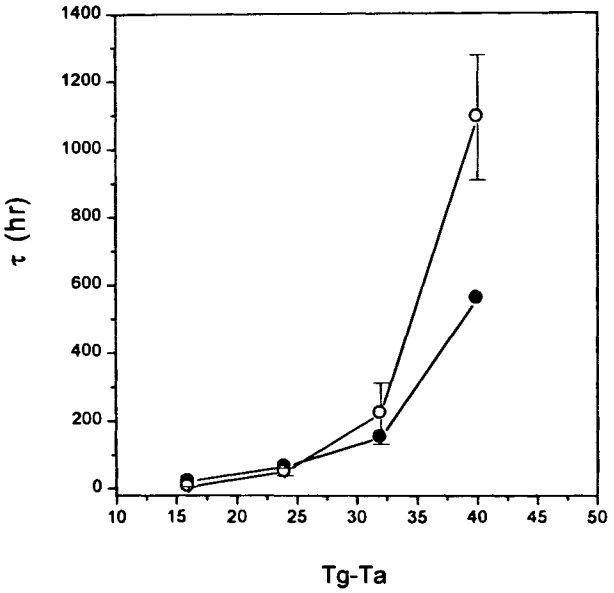

Fig. 5. Relaxation time τ for indomethacin (●) and sodium indomethacin (○) at storage temperatures up to 40°C below their *Tg* values.

$$\tau = \tau_0 \exp\left(\frac{DT_0}{T(1 - T_0/T_f)}\right) \quad (5)$$

where T_f, the fictive temperature, is defined as the temperature at which the non-equilibrium value of some macroscopic property would be the equilibrium one. As a starting point for a plot of τ vs. *T/Tg* using the AGF equation, we can assume that T_f is equal to *Tg* (12) and obtain the generally expected rate of change for τ vs. *T/Tg* at temperatures below *Tg*. At temperatures *T* above *Tg*, $T_f = T$, therefore above *Tg* Eq. 5 becomes Eq. 1, the VTF equation.

In Fig. 6, using the respective values of *Tg*, *D*, T_0, τ and T_f for sodium indomethacin and indomethacin, we can plot the theoretically expected fits to the VTF and AGV equations normalized to their respective *Tg* values. Here, we see that above *Tg* the mean relaxation times predicted for both substances using parameters estimated from the scanning rate dependence of *Tg* are very close, indicative of similar fragilities. The temperature dependence below *Tg*, assuming T_f equal to *Tg*, agrees well with the expected linear Adam-Gibbs behavior, i.e., lower relaxation times than predicted from the VTF equation. Furthermore, experimental relaxation times below *Tg* are essentially the same for sodium indomethacin and indomethacin, changing at a rate predicted from the AGV equation.

CONCLUSIONS

Sodium indomethacin can be made amorphous by freeze-drying its aqueous solutions, by mechanically grinding the dried crystalline powder or by rapid evaporation of solvent from its methanol solution under reduced pressure. The glass transition temperature of the amorphous forms made in different ways is 121°C, which is about 75°C higher than the corresponding free acid form. This is believed to be due to a strong ionic interaction between the sodium and indomethacin ions giving a reduced free volume, relative to the less dense indomethacin system. The temperature dependence of molecular mobility, as reflected by

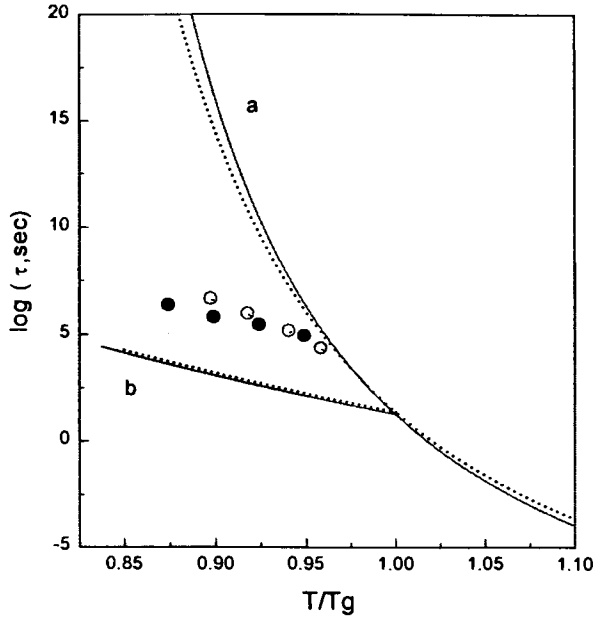

Fig. 6. Relaxation time for indomethacin (●) and sodium indomethacin (○) obtained from the scanning rate-dependence method. Lines are fits for (a) VTF and (b) AGV equations as indicated in the text. Solid lines are for sodium indomethacin and dotted lines for indomethacin.

the scanning rate-dependence of *Tg* for the ionized and unionized forms, however, shows that both forms are fairly *fragile*. The molecular mobility of the two systems below *Tg*, as estimated by enthalpy relaxation recovery measurement, also revealed similar relaxation patterns relative to their *Tg*. It can be concluded that salt formation for indomethacin mostly likely will enhance its physical and chemical stability relative to its free acid form, due to a significantly raised *Tg*, and hence a raised T_0, and its reduced molecular mobility at comparable temperatures.

ACKNOWLEDGMENTS

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