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Research Paper

Structural Relaxation of Acetaminophen Glass

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Purpose. The aim is to determine the structural stability of acetaminophen glass with time and temperature change, and to examine the merits of adapting the structural relaxation models of the glassy state for pharmaceuticals.
Methods. Differential scanning calorimetry technique has been used to study the acetaminophen glass after keeping the samples for various periods at fixed temperatures and after keeping at various temperatures for fixed periods.
Results. A general formalism for thermodynamic changes during storage in a temperature fluctuating environment is given and the kinetics of the enthalpy and entropy decrease determined. At a fixed temperature, the decrease occurs according to a non-exponential kinetics. For the same storage time, but at different temperatures, the enthalpy and entropy decrease rises to a maximum value at a certain temperature and then declines. The peak appears at the temperature at which the internally equilibrated state of the sample is reached for a fixed storage time. The change in the normalized heat capacity during the heating of acetaminophen has been analysed in terms of a non-exponential, non-linear enthalpy relaxation model.
Conclusion. A single set of parameters that fit the data for unannealed acetaminophen glass does not fit the calorimetric data for annealed glass. Since acetaminophen molecules form intermolecular hydrogen-bonds in the crystal state and likely to form such bonds more easily in the disordered state, effect of such bonds on structural relaxation is likely to be significant.

KEY WORDS: acetaminophen; enthalpy and entropy; glassy state; structural relaxation.

INTRODUCTION

The possibility that an amorphous pharmaceutical may have a much higher solubility, and hence enhanced bioavailability, than the crystalline form has focused investigations on its physical stability during storage. In these studies, available formalisms for a phenomenological description of the changes in the properties of amorphous polymers have been adapted for modeling the changes in physical properties of an amorphous pharmaceutical and extrapolating its physical stability during shelf life. Several reviews on this aspect have been published since 1997 (1–5).

It is well recognized that properties of a glass change with time, and for small molecular glasses, this change may lead to nucleation and crystallization. Because interest in amorphous or glassy pharmaceuticals is relatively new, it seems helpful to provide a brief introduction to this phenomenon and to the relevant thermodynamic theories, with relevant references. The glassy state of a material is produced by supercooling its melt until the melt's viscosity exceeds $10^{13.6}$ P, i.e., its shear relaxation time exceeds $10^{3.6}$ s, and it behaves as a rigid solid. (The glassy state differs from the amorphous state, which is obtained by lyophilization, vapor-phase deposition, chemical reactions, mechanical deformation of crystals, high energy particles irradiations, etc., but for discussion of structural relaxation, the two are not distinguished here.) The temperature at which a melt's viscosity becomes equal to $10^{13.6}$ P has been formally defined in the text books (6–11) as the glass formation temperature, T_g. Both the glass and the supercooled melt are metastable with respect to the crystal state, but a glass is in thermodynamic nonequilibrium, whereas a supercooled liquid is in (internal) thermodynamic equilibrium (8–21).

An amorphous solid or a glass is kinetically unstable with respect to its equilibrium liquid's disordered structure of lower energy, entropy, and volume, and its nonequilibrium structure tends to approach its melt's (equilibrium) structure spontaneously with time (12,21). This is known as structural relaxation. In polymer technology and the pharmaceutical industry, it is known as physical ageing, and in silicate glass technology, as annealing. It is a characteristic feature of nonequilibrium, kinetically unstable states, and it results from thermally activated slow molecular diffusion. During the structural relaxation, thermodynamic properties change: (a) the net enthalpy and entropy decrease and, according to

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the configurational entropy theory (22), the size of the co-operatively rearranging region increases and (b) the net volume decreases and, according to the free volume theory, the free volume decreases (23). The postulated co-operatively rearranging regions in the structure, which are separated from each other, apparently do not transform to a crystal nuclei or molecular-aggregate to a crystal-like form. Decrease in the free volume also neither leads to crystal nucleation nor crystallizes a glass. Crystal nucleation and growth require molecular diffusion, and there is a free energy barrier to this process. Structural relaxation is distinct from crystallization, which is driven by decrease in the enthalpy and entropy.

A faster process of localized motions, known as β-relaxation or the Johari–Goldstein relaxation, also persists in the ultraviscous liquid and rigid glassy states. More recently, it has been found to be capable of creating crystal nuclei whose finite—albeit small, and often difficult to measure—probability of growth can crystallize a glassy state with time. However, critical-size crystal nuclei formation is a probabilistic process, and therefore, observations of nucleation in the glassy state are often irreproducible. Recent studies of nucleation and crystallization in organic molecule glasses (24–26) have supported this view.

Structural relaxation also changes other physical properties and therefore has been studied by measuring, in addition to thermodynamic properties, spontaneous changes in dielectric, mechanical, optical, and related properties of the glassy material stored at a certain temperature with time (8,9,12–14,17,18,20,21,27–33). The observed changes have been modeled by using formalisms that express the change in the physical properties as a change in the fictive temperature with time. (The fictive temperature, T_f, is the temperature at which a glass would be in internal thermodynamic equilibrium.) However, structural relaxation under certain conditions may also lead to nucleation and crystal growth. When a pharmaceutical becomes amorphous during lyophilization, rapid dehydration, grinding of crystals, or by fast chemical reaction, the solid produced has a large frozen-in enthalpy and entropy and its T_f is high. It structurally relaxes faster than a usual glass, losing a large amount of enthalpy rapidly on heating, for example, up to 2.5 kJ/mol for vapor-deposited amorphous (small molecule) 1-butene (34). Because crystal nuclei may form and grow during such a rapid loss of enthalpy before T_g is reached, a high-enthalpy glass is structurally relaxed slowly at a low temperature before heating it through its T_g. Classic examples are hyperquenched glassy water (35–37) and metallic glasses (38) whose structural relaxation and crystallization exotherms partly overlap and whose T_g endotherm has been observed only after structurally relaxing their glassy state slowly at a low temperature.

Amorphous pharmaceuticals have relatively low T_gs, usually below 350 K. These are expected to structurally relax significantly during storage at ambient temperature and may even crystallize over long periods, thereby affecting their bioavailability. In contrast, the T_g of amorphous polymers (12–20, 39–43), inorganic network and linear chain structure glasses (27,29,44,45), and metallic glasses (30,31,46) is far above the ambient temperature, and therefore, loss of their beneficial property by structural relaxation or crystallization during storage is not of concern. It is however of concern for cryopreserved biopolymers (47–51) and small molecule glasses (12,21,29,32–34,52,53).

Here we report a detailed study of structural relaxation of acetaminophen glass by differential scanning calorimetry (DSC). Its molecular mobility (54) and its crystalline forms (55) have been studied by DSC. Heat capacity of acetaminophen glass and crystal forms measured by both DSC and adiabatic calorimetry has been reported (56), and heat capacity of its glass and ultraviscous liquid states measured by DSC has been reported and related to molecular mobility (57). For comparison, we have included references to structural relaxation studies on other glasses.

EXPERIMENTAL METHODS

Crystalline acetaminophen (4-acetamidophenol or 4′-hydroxyacetanilide, also known as paracetamol) was purchased from Sigma-Aldrich Chemicals (St. Louis, MO, USA). Molecular weight of acetaminophen is 151.17 Da and its stated melting point is 168–172°C (441–445 K). Glass formation of acetaminophen was explored by first melting in an oven in a 1-mm internal diameter glass vial. It was removed from the oven and allowed to cool to 298 K. The liquid sample gradually became viscous and finally became a transparent solid, which fractured on further cooling to 253 K.

Two calorimeters were used for the study. One was a differential scanning calorimeter (model Pyris Diamond; Perkin-Elmer, Boston, MA, USA) and the second was a thermal analyzer (model TA Q100; Thermal Analysis Instruments, New Castle, DE, USA). The instruments were calibrated with indium, water, and, *n*-dodecane by using their melting points and their enthalpy of melting. Argon was used as both a purge gas for the sample and a carrying gas for the intracooler with the Perkin-Elmer instrument, and nitrogen gas was used with the TA instrument. During the course of measurements on a sample, the baseline, temperature calibration, and stability of the equipment were frequently checked. An accurately weighed amount of the sample (nominally 4 to 12 mg) was contained in an aluminum pan and crimp-sealed. It was transferred to the instrument at ambient temperature. At least eight samples of different mass taken from the same stock of crystalline acetaminophen were studied. The DSC output in watts (joules per second) divided by the sample's mass was found to remain within 0.2%. This showed that the effect of the sample's mass on the measured values was negligible. The heating rate was 20 K/min, as in earlier studies of pharmaceutical glasses, and it served to enhance the features observed for glass softening and for structural relaxation over the features observed for the heating rates of 10 K/min or lower used generally for studying other glasses. All cooling and heating to reach a predetermined temperature of the sample were done at a rate of 40 K/min. This minimized the errors arising from structural relaxation that may have occurred during such cooling and heating. DSC scans were obtained for all thermal treatment, i.e., heating, cooling, and isothermally holding acetaminophen, but only the scans obtained during heating through the glass-softening range are shown here. The enthalpy and entropy changes were calculated accurately by transferring the data to Microcal Origin Software (Northampton, MA,

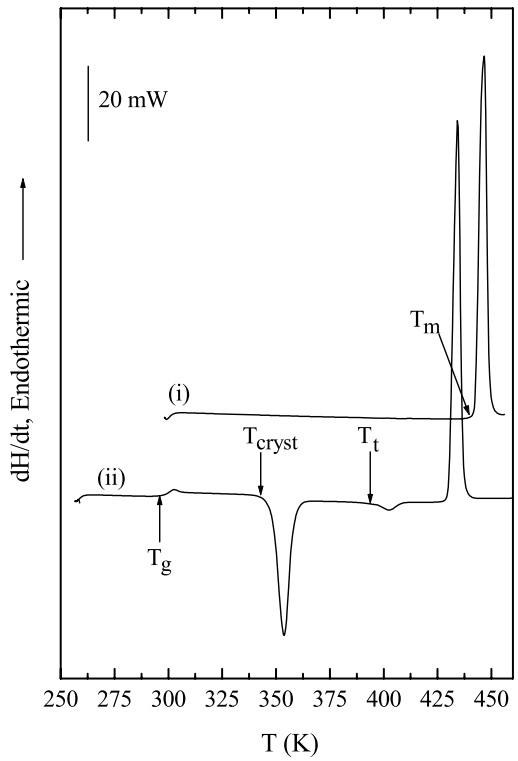

Fig. 1. The DSC scans for 6.27 mg of acetaminophen: (i) during the heating of the sample from 298 to 453 K at 20 K/min; (ii) during the reheating of the glassy state from 253 to 453 K at a rate of 20 K/min. The arrows indicate the onset temperatures of glass softening, T_g; the onset of cold crystallization, T_{cryst}; the onset of crystal–crystal phase transformation, T_t; and the onset of equilibrium melting, T_m.

USA) and performing all subtractions and integrations by using its mathematical procedure.

RESULTS

Crystalline acetaminophen contained in a crimp-sealed aluminum pan was first heated from 298 to 453 K at a rate of 20 K/min and kept for 1 min at 453 K to completely melt it. The DSC scan, shown in Fig. 1 curve (i), contains an endotherm with an onset temperature of 442.5 K for the melting point of the as-received acetaminophen. The melt was subsequently cooled from 453 to 253 K at 40 K/min, kept in its glassy state at 253 K, and allowed to thermally equilibrate by observing the change in temperature in the DSC display. It was then reheated to 453 K at 20 K/min and its DSC scan was obtained. It is shown in Fig. 1 as curve (ii), which contains (a) the sigmoid shape T_g-endotherm beginning at 297.4 K, which is a characteristic of the gradual softening of a glass to its ultraviscous equilibrium liquid state; (b) a deep exotherm on further heating beyond 347.6 K; (c) a small exotherm at ~396 K; and finally, (d) a melting endotherm with onset at 430.3 K. The two exotherms indicate that ultraviscous acetaminophen crystallizes to a certain phase at ~347.6 K, and the crystal phase then either transforms to another form at ~396 K or undergoes grain growth. The resulting crystals finally melt at 430.3 K. The onset temperature of the melting endotherm in curve (ii) is 12.2 K lower than that in curve (i). This indicates that the melting point of the new crystal phase formed is lower than that of the as-received acetaminophen crystals. In summary, curve (i) in Fig. 1 indicates only the equilibrium melting of acetaminophen, and curve (ii) indicates the onset of glass softening temperature, T_g; the onset of cold crystallization (i.e., crystallization occurring below the equilibrium melting/freezing temperature); an exothermic effect; and finally the melting of the crystals formed.

To determine the decrease in enthalpy by structural relaxation during annealing (or storage) of a sample or different times, t_{ann}, a procedure suggested by Lagasse (58) and used in previous studies (29,32,47–53) was also used here. In this procedure, the (equilibrium) ultraviscous liquid at a temperature, T_{max}, is cooled at a (chosen) high rate, q_c, to a temperature, T_{min}, which is 75 to 80% of the calorimetric T_g. It is then heated at a chosen rate, q_h, from T_{min} to T_{max}. The DSC scan obtained on heating in this case is for the unannealed sample, or $t_{ann} = 0$. The sample is cooled from T_{max} at the same rate, q_c, to T_{min} and then heated at the fastest rate to the chosen annealing temperature, T_{ann}, kept at T_{ann} for a period of t_{ann} min, cooled at the fastest rate to T_{min}, and then immediately heated to T_{max} at rate q_h and its DSC scan obtained. This scan is for the sample annealed t_{ann} min at T_{ann}. The procedure is repeated for different annealing periods, $t_{ann}(1)$, $t_{ann}(2)$, etc., for the same T_{ann}. It is also then repeated for a different T_{ann}.

We use this procedure also for determining the enthalpy decrease during a fixed t_{ann} at a selected T_{ann}, as follows: After the DSC scan has been obtained after annealing for a period of t_{ann} min at a chosen T_{ann} in the above-given sequence, the sample is cooled back to T_{min} and then immediately heated at the fastest rate to a new annealing temperature, say $T_{ann}(1)$, kept at $T_{ann}(1)$ for the same t_{ann} as at T_{ann}, cooled back at the fast rate to T_{min}, and then heated to T_{max} and the DSC scan obtained. The procedure is repeated for a fixed t_{ann} but for different T_{ann}. It is also then repeated for a different T_{ann}.

Crystalline acetaminophen was first heated at a rate of 20 K/min to a temperature 3–5 K above its T_m of 441–445 K and completely melted. The melt was then cooled at 40 K/min to T_{min} of 253 K. The first DSC scan was obtained on heating it from 253 K to T_{max} of 323 K where acetaminophen was an ultraviscous equilibrium liquid. The sample was then cooled from 323 to 253 K at a rate of 40 K/min. It was then heated to a chosen T_{ann}, at the nominal rate of 100 K/min and kept at T_{ann} for a chosen t_{ann}, recooled to 253 K (i.e., T_{min}) at 40 K/min and then immediately heated from 253 to 323 K at q_h of 20 K/min. The difference between the areas under the two DSC scans, one obtained for $t_{ann} = 0$ and the second obtained for $t_{ann} > 0$, is equal to $[(dH/dt)_{annealed} - (dH/dt)_{unannealed}]$ at T_{ann}. For structural relaxation at a fixed t_{ann} but different T_{ann}, the same procedure was adapted to obtain the difference scans.

For all structural relaxation experiments, it is required that the DSC scans obtained for different t_{ann} at a fixed T_{ann} should meet (i.e., have the same (dH/dt) value) at T_{min} and also meet at T_{max}. If any crystallization occurs during the annealing, cooling, and heating, the scans would not meet. Furthermore, partial crystallization of a sample would reduce

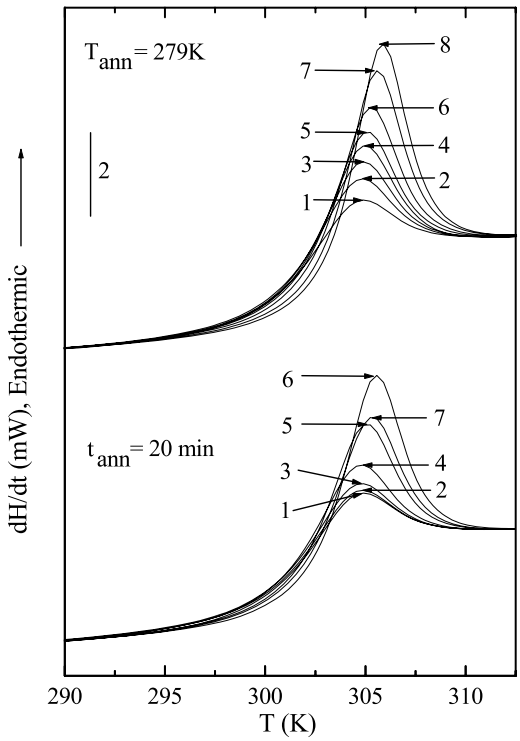

Fig. 2. The DSC scans of 10.14 mg of acetaminophen. Set 1 was obtained for different t_{ann} at a fixed 279 K and set 2 at different T_{ann} for a fixed period of 20 min. In set 1, curve 1 is for the unannealed sample, and curves numbered in sequence from 2 to 8 are for samples annealed for 5, 10, 15, 20, 30, 50, and 70 min. In set 2, curve 1 is for unannealed sample, and curves numbered 2 to 7 are for samples annealed sequentially for 20 min at temperatures 262, 267, 273, 279, 284, and 289 K, respectively. Note that the scans in each set merge both at the low temperature in the glassy state and at the temperature in the equilibrium liquid state, thus indicating that the acetaminophen sample did not crystallize on thermal cycling or on annealing.

the (dH/dt) value much more at T_{max}, at which the state is expected to be equilibrium liquid than at T_{min}, at which it is expected to be a glass. The DSC scans for different t_{ann} at a fixed T_{ann} of 279 K as well as at different T_{ann} for a fixed t_{ann} of 20 min over a temperature range of 290 to 312.5 K provided in Fig. 2 show clearly that this requirement has been met and there was no crystallization. These scans also show that the usual procedure for obtaining T_g by intersection of the two lines, one extrapolated from the glass state and the other drawn as a tangent at the point of inflexion of the sigmoid-shape curve, would not yield the same T_g value, an aspect often overlooked in DSC studies.

The (dH/dt) value in the DSC scan was multiplied by the molecular weight of acetaminophen and divided by the mass of the sample and by the heating rate, q_h. This converted it to (dH/dT) in units of joules per mole Kelvin. Typical plots of (dH/dT) for acetaminophen for T_{ann} of 284 K are shown in Fig. 3A. The first scan for t_{ann} = 0 min is labeled 0, and the scans obtained after annealing at 284 K for different periods are labeled according to the t_{ann} values. The difference between the DSC scan at $t_{ann} > 0$ and at $t_{ann} = 0$, i.e., $[(dH/dT)_{annealed} - (dH/dT)_{unannealed}]$ is plotted against T in Fig. 3B and is also labeled according to t_{ann}. Similar experiments were performed for T_{ann} of 279 and 289 K.

To investigate the effect of T_{ann}, a second set of experiments on acetaminophen was performed in which t_{ann} was fixed and T_{ann} was varied. The sample was annealed at six chosen T_{ann} for a fixed t_{ann} of 15 min, and the same heating and cooling rates were used as for the scans in Fig. 3. The (dH/dT) plots obtained are shown in Fig. 4A. The curve labeled 0 is for the unannealed sample. The difference curves between the unannealed and annealed samples were obtained for each T_{ann}, and these are shown in Fig. 4B. These also correspond to $[(dH/dT)_{annealed} - (dH/dT)_{unannealed}]$ but for varying T_{ann}. Experiments were repeated for t_{ann} of 5 and of 20 min, while keeping the same set of six T_{ann}s.

DISCUSSION

Thermodynamic Functions and Structural Relaxation

We recall that structural relaxation is part of the definition of the amorphous state, and it causes thermodynamic functions to become time- and temperature-dependent. The net enthalpy, entropy, and volume of a glass decrease with

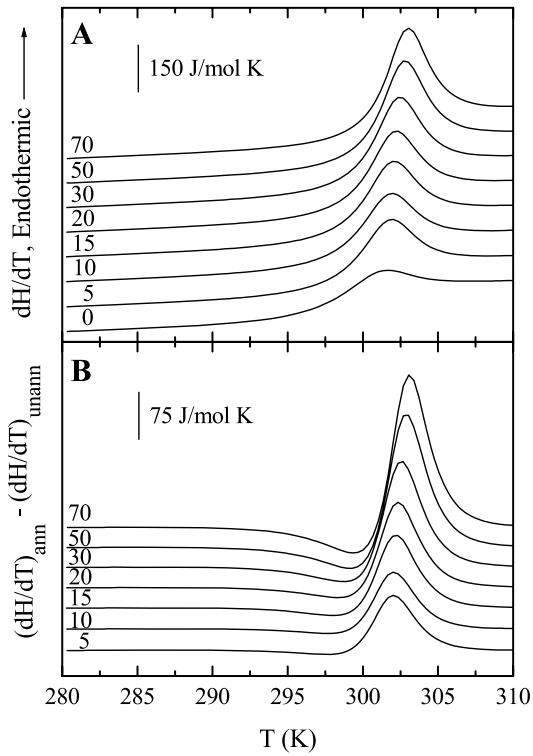

Fig. 3. (A) The dH/dT (joules per mole Kelvin) plots for acetaminophen. The sample was cooled from 343 to 253 K at a rate of 40 K/min, heated to the annealing temperature, T_{ann}, of 284 K at 100 K/min, kept at T_{ann} for an annealing period t_{ann}, and recooled to 253 K at 40 K/min, and the final DSC scan was obtained on heating from 253 to 343 K at a rate of 20 K/min. Curve (0) is for the unannealed sample (t_{ann} = 0 min), and the numbers next to the subsequent curves refer to the annealing time in minutes. (B) The difference curves for acetaminophen obtained by subtracting the DSC scan of the unannealed sample (curve 0) from the DSC scan of the annealed samples. The numbers refer to t_{ann} for the annealed samples as in Fig. 3(A).

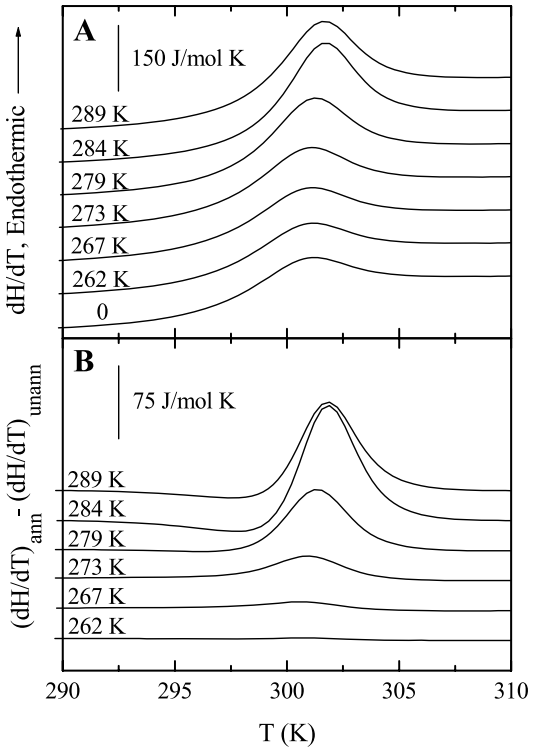

Fig. 4. (A) The dH/dT (joules per mole Kelvin) plots for acetaminophen. The sample was cooled from 343 to 253 K at a rate of 40 K/min, heated to the annealing temperature, T_{ann}, of 262 K at 100 K/min, kept at T_{ann} for an annealing period of 15 min, and recooled to 253 K at 40 K/min, and the final DSC scan was obtained on heating from 253 to 343 K at a rate of 20 K/min. Curve (0) is for the unannealed sample (t_{ann} = 0 min), and the numbers next to the subsequent curves refer to T_{ann}. (B) The difference curves for acetaminophen obtained by subtracting the DSC scan of the unannealed sample (curve 0) from the DSC scan of the annealed samples. The numbers refer to T_{ann} for the annealed samples as in Fig. 4(A).

time; the frequency of vibrational modes increases, as evident from the blue-shift of the far-infrared spectra; and the energy of the electronic transition levels increases, as evident from the increase in the refractive index. (It is significant to note in this context that structural relaxation is distinguished from ageing, such as that of commercial silicate glasses whose density and refractive index increase by an extremely small amount over a time period of 10 to 50 years when the glass is kept at a temperature nearly half of its T_g or lower. Such ageing was first reported by James Prescott Joule who had observed that the zero temperature point of a gas thermometer made from a silicate glass shifted with time over a period of 38.5 years (59). For details, a recent paper on the ageing of sodium–calcium silicate glasses (60) may be consulted where this ageing effect at temperatures far below T_g is shown to be mechanistically different from the structural relaxation, annealing, or physical ageing effects.)

For analyzing the time- and temperature-dependence of thermodynamic functions, we use a formal expression and not the phenomenological models of the types used for polymers and inorganic glasses (61–74). (See also "Nonexponential Nonlinear Models for Structural Relaxation" section in this paper.) Strictly speaking, the decrease in enthalpy on structural relaxation is the sum of all the changes that occur with time and during the cooling and heating of a glass. This decrease may be formally written as the sum of four contributions:

$$d\Delta H_{ann} = \left(\frac{\partial \Delta H_{ann}}{\partial t_{ann}}\right)_{T_{ann},q_h,q_c} dt_{ann} + \left(\frac{\partial \Delta H_{ann}}{\partial T_{ann}}\right)_{t_{ann},q_h,q_c} dT_{ann} + \left(\frac{\partial \Delta H_{ann}}{\partial q_c}\right)_{T_{ann},t_{ann},q_h} dq_c + \left(\frac{\partial \Delta H_{ann}}{\partial q_h}\right)_{T_{ann},t_{ann},q_c} dq_h \quad (1)$$

In Eq. (1), $d\Delta H_{ann}$ is the difference between the enthalpy of the material before and after the annealing experiment, q_h is the heating rate and q_c the cooling rate, and all other notations are as defined before. The corresponding decrease in the entropy is given by:

$$d\Delta S_{ann} = \left(\frac{\partial \Delta S_{ann}}{\partial t_{ann}}\right)_{T_{ann},q_h,q_c} dt_{ann} + \left(\frac{\partial \Delta S_{ann}}{\partial T_{ann}}\right)_{t_{ann},q_h,q_c} dT_{ann} + \left(\frac{\partial \Delta S_{ann}}{\partial q_c}\right)_{T_{ann},t_{ann},q_h} dq_c + \left(\frac{\partial \Delta S_{ann}}{\partial q_h}\right)_{T_{ann},t_{ann},q_c} dq_h \quad (2)$$

where the terms have the same meaning as in Eq. (1). (Note that the prefix Δ is used to maintain that the quantities determined by experiments are: $H - H$ (0 K) and $S - S$ (0 K), and not the absolute values of H and S. Hence, Eqs. (1) and (2) include the effect of structural relaxation on the 0-K values of the enthalpy and entropy.)

Magnitude of the first term in Eqs. (1) and (2) may be determined from the plots in Fig. 3, and that of the second term may be determined from the plots in Fig. 4. Because q_c and q_h in both sets of experiments have been kept constant, the magnitudes of the third and the fourth terms are zero. All four terms in Eqs. (1) and (2) are of practical significance because they describe the changes in the thermodynamic state of a glassy material when fluctuations in the ambient temperature during its storage occur at different rates and over different temperature ranges.

Enthalpy and Entropy Decrease

The first and second coefficients of Eqs. (1) and (2) have been determined (29,32,42,47–49,53,58) from the area under the difference curves in Figs. 3B and 4B or from the area under the endothermic peak in the difference curves, which yields the enthalpy regained on heating the annealed sample. Law of energy conservation requires that this value be the same as the enthalpy decrease on structural relaxation at a chosen T_{ann} and t_{ann}. To determine the entropy decrease on structural relaxation, the difference $[(dH/dT)_{annealed} - (dH/dT)_{unannealed}]$ is plotted against $\ln(T)$ instead of against T, and the area under the difference curve in the plot gives the entropy regained on heating. If an exothermic dip-like feature also appears prior to the appearance of the broad peak in the difference curve, as in curves labeled 30, 50, and

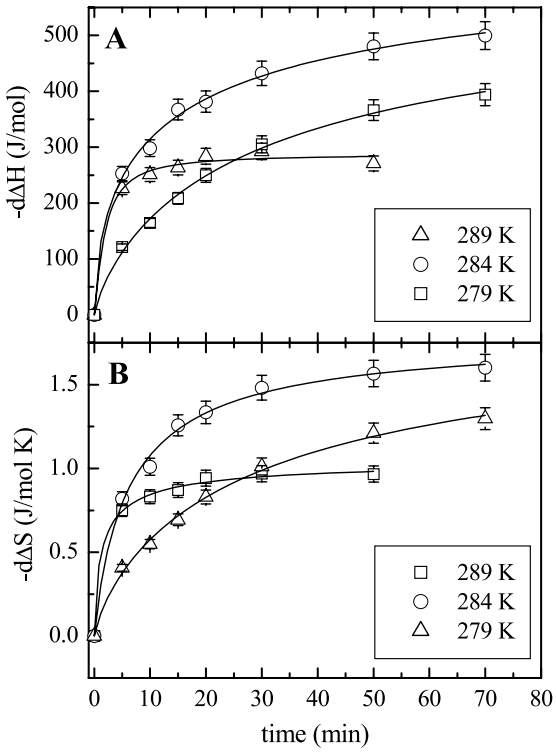

Fig. 5. (A) The enthalpy lost on structural relaxation of acetaminophen annealed for different periods at the indicated T_{ann} is plotted against the annealing time. (B) The corresponding plots of the entropy lost on structural relaxation of acetaminophen. The error bars for the data are shown.

70 in Fig. 3B and 284 and 289 K in Fig. 4B, the area of the dip should be subtracted from the total area, i.e., a baseline at $dH/dT = 0$ is to be used. Thus the area of the broad peak minus the area of the exothermic dip is equal to the true decrease in ΔH and ΔS that occurred during the annealing at T_{ann} before the sample was heated. (Note that an exothermic dip-like feature in the DSC scans of annealed samples appears when the heating rate is less than the cooling rate. It is an indication of a further enthalpy loss as a result of structural relaxation *during* the heating of the sample (15). It appears when T_{ann} is such that the characteristic relaxation time of the material is less than that which corresponds to the inverse of the heating rate.)

The quantity $d\Delta H_{ann}$ was determined from the difference curves shown in Fig. 3B. For T_{ann} of 279, 284, and 289 K, it is plotted as a negative quantity against t_{ann} in Fig. 5A. The corresponding $d\Delta S_{ann}$ was similarly determined from the difference curves in $\ln(T)$ plane, and the corresponding $-d\Delta S_{ann}$ values are plotted against t_{ann} in Fig. 5B. Similarly, $d\Delta H_{ann}$ and $d\Delta S_{ann}$ were obtained from experiments described in Fig. 4B and from similar experiments performed at different annealing temperatures but for a fixed t_{ann}. The $-d\Delta H_{ann}$ is plotted against T_{ann} in Fig. 6A for three sets of t_{ann} values, 5, 15, and 20 min, as is indicated. The corresponding plots for $-d\Delta S_{ann}$ are shown in Fig. 6B. Both the $-d\Delta H_{ann}$ and $-d\Delta S_{ann}$ values plotted in Figs. 5 and 6 include the decrease in the respective 0-K enthalpy and entropy of acetaminophen that occurred on annealing. These quantities have been determined on the premise that the ratio of the heat flow (in joules per second) to the heating rate, i.e., $[(dH/dt)/q]$, is *the time- and temperature-dependent, apparent* C_p of acetaminophen. It includes the thermal effects of structural relaxation.

Variation of ΔH and ΔS with Temperature During Structural Relaxation

We now deduce the shape of the enthalpy and entropy against T plots during heating of acetaminophen glass. To do so, we integrate the plots of (dH/dT) against T at different T in the range T_{ann} and $T_{equilibrium\ liquid}$ for the enthalpy, and the plots of (dH/dT) against $\ln(T)$ at different T in the range T_{ann} and $T_{equilibrium\ liquid}$ for the entropy and use for this purpose the data of curves in Figs. 3 and 4 and the relations:

$$\Delta H(T) = \Delta H(T_{ann}) - \int_{T_{ann}}^{T} \left(\frac{dH}{dT}\right) dT \tag{3}$$

and

$$\Delta S(T) = \Delta S(T_{ann}) - \int_{T_{ann}}^{T} \left(\frac{dH}{dT}\right) d\ln T. \tag{4}$$

Because ΔH and ΔS of an equilibrium liquid are independent of the path by which the liquid is reached from the glassy state, the $\Delta H(T)$ and $\Delta S(T)$ plots against T for all t_{ann} and T_{ann} conditions would merge when the equilibrium liquid state is reached. The integration end point, i.e., $T_{equilibrium\ liquid}$, was taken as 311 K, and $\Delta H(T_{ann})$ and $\Delta S(T_{ann})$

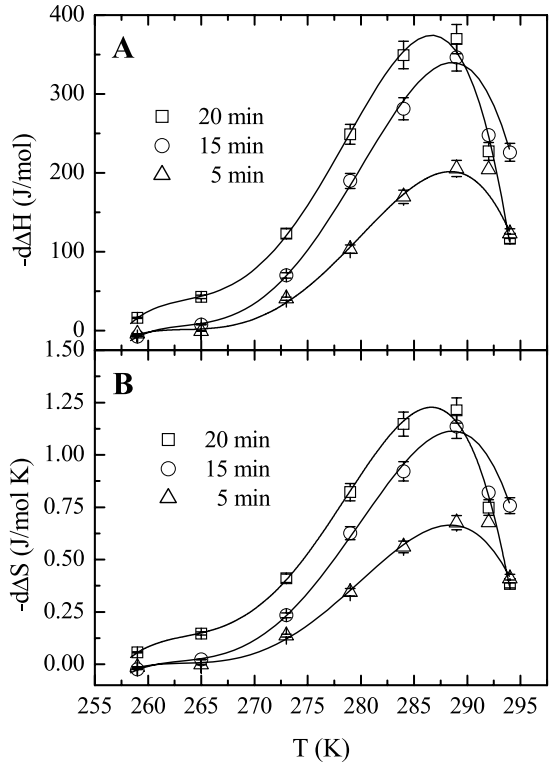

Fig. 6. (A) The enthalpy lost on structural relaxation of acetaminophen annealed for 5, 15, and 20 min at different temperatures is plotted against the annealing temperature. (B) The corresponding plots of the entropy lost on structural relaxation of acetaminophen. The error bars for the data are shown. The line is a guide showing the shape of the curves.

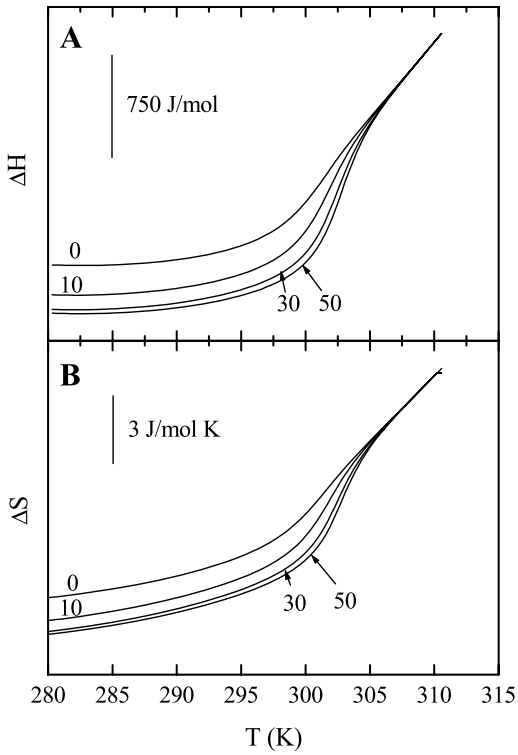

Fig. 7. (A) The relative enthalpy of acetaminophen. Curve (0) is for the unannealed state. Subsequent curves are for the states obtained after annealing at 284 K for the indicated time. (B) The corresponding relative entropy of acetaminophen.

values at 311 K were taken from Fig. 2. The ΔH and ΔS plots were calculated from Eqs. (3) and (4) by using the data provided in Figs. 3 and 4. These are presented in Fig. 7A and B for T_{ann} of 284 K. The curve for the unannealed sample is labeled as 0, and the curves for the annealed samples for t_{ann} of 10, 30, and 50 min are labeled as 10, 30, and 50. This integration does not yield the absolute values of the enthalpy or the entropy but is useful in determining the manner in which these changes occur.

The corresponding plots for the second set of experiments on acetaminophen, for fixed t_{ann} and varying T_{ann}, are shown in Fig. 8. The curve for the unannealed sample is labeled as (1) and the curves for the samples annealed for a period of 15 min at T_{ann} of 279, 284, and 289 K are labeled as (2), (3), and (4), respectively, and marked by an arrow.

Time and Temperature Effects on Structural Relaxation

We begin our analysis by using the simplest equations that fit the measured data, instead of the available models. We find that the simplest equations that fit the plots of ΔH and ΔS against t_{ann}, in Fig. 5, are:

$$\Delta H_{ann}(t_{ann}, T_{ann}) = [\Delta H(t_{ann} = 0, T_{ann}) - \Delta H(t_{ann} \to \infty, T_{ann})] \times \left[1 - \exp\left\{-\left(\frac{t_{ann}}{\tau(T_{ann})}\right)^{\beta}\right\}\right] \quad (5)$$

$$\Delta S_{ann}(t_{ann}, T_{ann}) = [\Delta S(t_{ann} = 0, T_{ann}) - \Delta S(t_{ann} \to \infty, T_{ann})] \times \left[1 - \exp\left\{-\left(\frac{t_{ann}}{\tau(T_{ann})}\right)^{\beta}\right\}\right] \quad (6)$$

where τ is the characteristic time for structural relaxation and β is a fitting parameter, which is equal to 1, for an exponential process. It has been argued (15) that Eqs. (5) and (6) have limited validity, an aspect we will discuss later here. For the best fit of Eqs. (5) and (6) to the data for acetaminophen annealed at 279 K, we obtain, $\Delta H\,(t_{ann} = 0, T_{ann}) - \Delta H\,(t_{ann} \to \infty, T_{ann}) = 463$ J/mol and $\Delta S(t_{ann} = 0, T_{ann}) - \Delta S(t_{ann} \to \infty, T_{ann}) = 1.51$ J/mol K, $\tau =$ 28.33 min and $\beta = 0.74$. Similar expressions have been found to fit the data on enthalpy relaxation of one polymer (42), hydrated DNA (48,49), and 2-methyl-3-heptanol (53), an alcohol in which intermolecular H-bonding produces apparently nonpolar dimers (52).

The magnitude of the second term on the right-hand side of Eqs. (1) and (2), i.e., the effect of T_{ann}, is indicated by the manner in which the area under the peaks seen in Fig. 4B changes with change in T_{ann}. When acetaminophen glass was annealed at selected T_{ann}s for a fixed period of 15 min, $d\Delta H$ and $d\Delta S$ reached a maximum negative value at 289 K in Fig. 6. This maximum appears as a result of two competing effects: The first dominates at low T_{ann} at which τ is long, and therefore, the decrease in ΔH and ΔS over a fixed t_{ann} is too small to be measurable. As T_{ann} is increased, τ decreases rapidly, and there is a progressive

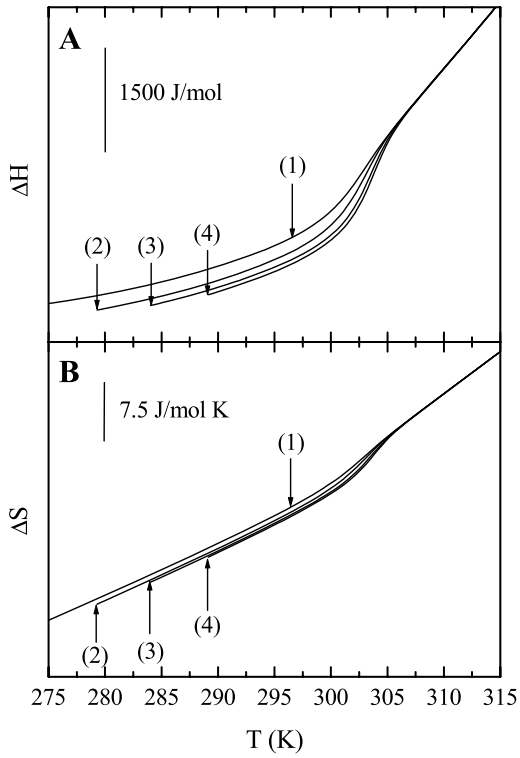

Fig. 8. (A) The relative enthalpy of acetaminophen. Curve (1) is for the unannealed state. Subsequent curves are for the states obtained after annealing for 15 min at the indicated temperatures. (B) The corresponding relative entropy of acetaminophen.

increase in the negative values of ΔH and ΔS. The second dominates when T_{ann} is high and structural relaxation is complete within the fixed t_{ann}. In this case, the magnitude of the quantities $[\Delta H(t_{ann} = 0, T_{ann}) - \Delta H(t_{ann} = \infty, T_{ann})]$ and of $[\Delta S(t_{ann} = 0, T_{ann}) - \Delta S(t_{ann} = \infty, T_{ann})]$ decreases as T_{ann} approaches the equilibrium liquid temperature. Thus the shape of the plot in Fig. 6 is determined by two processes: (a) a kinetically limiting process that increases the spontaneous loss of the enthalpy and entropy as T_{ann} is increased and t_{ann} is kept fixed, and (b) a thermodynamically limiting process that decreases $[\Delta H(t_{ann} = 0, T_{ann}) - \Delta H(t_{ann} = \infty, T_{ann})]$ and $[\Delta S(t_{ann} = 0, T_{ann}) - \Delta S(t_{ann} = \infty, T_{ann})]$ as T_{ann} is increased. The peaks in $d\Delta H_{ann}$ and $d\Delta S_{ann}$ appear at a T_{ann} when effect (b) begins to dominate the thermodynamic changes during structural relaxation.

Molecular Processes and Structural Relaxation

Because an acetaminophen molecule contains both donor and acceptor sites for hydrogen bonds in the –OH, = O, and –NH– groups, it is likely that its molecules are intermolecularly hydrogen bonded in the molten state. (This aspect will be detailed with experimental evidence in the "Conclusions" section here.) In that case, the spontaneous decrease in the enthalpy and entropy on its structural relaxation is to be seen as a combined effect of three occurrences:

(a) Decrease in the configurational enthalpy and entropy as a result of structural rearrangement when long-range molecular motions have occurred within an unspecified degree of freedom in the disordered structure.

(b) Decrease in the excess magnitude of enthalpy, entropy, and volume, and increase in the elastic modulus, etc., determined by the molecular and atomic vibrations or electronic transitions over the value for the lowest energy state. It is due to the fact that the phonon frequencies change with change in the density, so that the enthalpy difference between the nonequilibrium and equilibrium glassy state is not only due to the attainment of configurationally low energy state but also due to the vibrationally different, less anharmonic (low-energy) states of lower heat capacity.

(c) Increase in the number of intermolecular hydrogen bonds (an exothermic process), when the reaction quotient for the hydrogen-bond formation approaches the equilibrium constant value at a fixed T_{ann} with time as a result of localized molecular diffusion. This process also has an effect on the properties associated with vibrations and anharmonic effects.

Effects (a) and (b) are physical effects and are common to all glasses. Effect (c) is specific to hydrogen-bonded substances and is seen as a chemical effect. Amongst these, the magnitude of effect (b) is usually ignored, but it does remain finite because configurational states of high energy also have low vibrational frequencies and hence a large vibrational contribution. Therefore, the results given in Figs. 5, 6, 7, and 8 show changes in the net enthalpy and entropy with changes in t_{ann} and in T_{ann}, when 1) displacement (diffusion) of the entire molecules occurs during structural relaxation and 2) hindered rotations of the acetyl ($COCH_3$) group about the NH–C bond, of the $NHCOCH_3$ group about the C–NH bond, and of the –OH group about the O–C bond occur in an intermolecular environment and when the number of hydrogen bonds increases.

Non-Exponential Non-Linear Models for Structural Relaxation

The phenomenon of overall spontaneous changes in the properties of glassy material has been described in several review articles (12,15,16,18–20,30,43,58,62) mostly in terms of enthalpy and volume relaxations (12–14,18,19,27,61,62), mechanical modulus (18,19,61,74,75), and dielectric properties (76–78). A variety of models have been developed for fitting to the DSC scans, and all these models admit to a structural relaxation phenomenology that is based upon the original observations of Winter-Klein (79) and Tool (63) and a mathematical treatment introduced by Narayanaswamy (64). The model was applied to the DSC scans of a variety of substances originally by Moynihan and coworkers (28), and an algorithm for fitting to the DSC scan was developed by Hodge and Berens (39), who used it to simulate the DSC scans for amorphous polymers.

To examine the validity of such models, we proceed to fit the often-used Tool-Narayanaswamy-Moynihan-Hodge model to our DSC data. According to this model (28,39):

$$\tau = A \exp\left[\frac{x\Delta h^*}{RT} + \frac{(1-x)\Delta h^*}{RT_f}\right] \tag{7}$$

where τ is the characteristic relaxation time, Δh^* is the activation energy, A is a parameter equal to τ when both T and T_f are formally infinity, and x is an empirical parameter referred to as the nonlinearity parameter, whose value is between 0 and 1. The normalized relaxation function is written as $\phi = \exp\left[-(t/\tau)^{\beta_{KWW}}\right]$, where β_{KWW} is the stretched exponential (Kohlrausch-Williams-Watts) parameter and t is the macroscopic time. The details of the equation and the manner of data fitting may be found in (15,39,44).

Briefly, the DSC data were transformed into a normalized heat capacity:

$$C_{p,norm} = \left(\frac{C_{p,meas}(T) - C_{p,glass}(T)}{C_{p,equilibrium\,liquid}(T) - C_{p,glass}(T)}\right) \tag{8}$$

where $C_{p,meas}(T)$ is taken as the measured dH/dT, i.e., the measured dH/dt in a DSC scan divided by the heating rate, $q = dT/dt$ (15,28,39). (For a fixed heating rate, dH/dt is proportional to dH/dT.) Figure 9A shows the normalized DSC scans obtained for acetaminophen. Curve 1 is for a sample cooled at 20 K/min and heated at 20 K/min, curve 2 for that cooled at 5 K/min and heated at 20 K/min, and curve 3 is for that cooled at 40 K/min and heated at 20 K/min, without annealing in all cases. The fit to these scans was obtained with a least-squares Marquardt algorithm by using temperature step of 0.5 K and annealing time step of at least 1 s (for $t_{ann} > 2$ ks, the annealing time step was equal to t_{ann} / 2000). The best-fit parameters obtained for curve 1 are: $\ln A = -158.7$, $x = 0.46$, $\beta_{KWW} = 0.67$, $\Delta h^* = 400$ kJ/mol. The calculated curves from these parameters are shown by continuous lines.

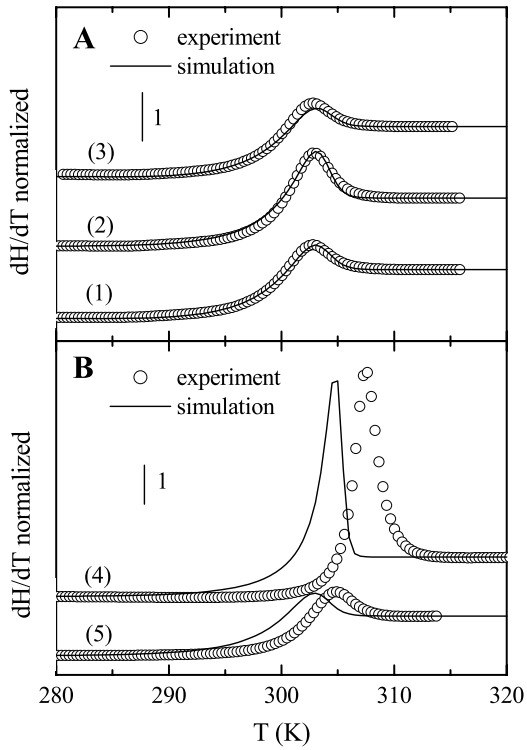

Fig. 9. (A) The DSC data obtained for acetaminophen by cooling at 20 K/min and heating at 20 K/min without annealing (curve 1), that obtained by cooling at 5 K/min and heating at 20 K/min without annealing (curve 2), and that obtained by cooling at 40 K/min and heating at 20 K/min without annealing (curve 3). (B) The DSC scans for the samples annealed for a period of 5 min at 279 K (curve 5) and for the samples annealed for a period of 360 min (the longest t_{ann}) at 279 K (curve 4). Full lines are the curves calculated from Eqs. (7) and (8) by using $\ln A = -158.7$, $x = 0.46$, $\beta_{KWW} = 0.67$, $\Delta h^* = 400$ kJ/mol, as obtained from the best to experimental data in curve (1).

Figure 9B shows the DSC data for annealed samples of acetaminophen. Curve 5 is for a sample cooled at 40 K/min, annealed for a period of 5 min at 279 K, and then heated at 20 K/min; and curve 4 is for the sample cooled at 40 K/min, annealed for a period of 6 h at 279 K, and then heated at 20 K/min. The scans simulated by using the above-given $\ln A = -158.7$, $x = 0.46$, $\beta_{KWW} = 0.67$, $\Delta h^* = 400$ kJ/mol values are shown by continuous lines for these conditions. The simulations are in reasonable agreement for curves 1, 2, and 3, but deviate too strongly for curves 4 and 5 obtained for an annealed sample. To express the fit of the equations to the experimental data in an alternative manner, we have calculated the relaxation time, τ, from the simulated plots in Fig. 9. It is plotted logarithmically (to the base 10) against the reciprocal temperature in Fig. 10A and, for clarity, against the temperature in Fig. 10B. The plot in Fig. 10A is linear at $T > T_g$, which is characteristic of an Arrhenius temperature dependence and as expected from Eq. (7) when $T = T_f$ in the equilibrium state. (Note that the plot against T in Fig. 10B is not linear, but seems so over a small temperature range.)

Unfortunately, there is no independent manner of determining τ from the DSC data that would allow a comparison of the calculations. Nevertheless, it is qualitatively evident that τ for the annealed sample cannot be reliably estimated from the parameters that fit the experimental data for an unannealed sample. We will discuss this subject in detail after performing DSC experiments on a series of pharmaceuticals. In summary, the discrepancy between the DSC data and the calculated curves for the annealed samples in Fig. 9 shows that the fit parameters do not yield reliable value for the enthalpy regain on heating annealed acetaminophen. For that reason, the poor fits also underscore the need for use of Eqs. (1) and (4) for describing structural relaxation, rather than a structural relaxation model.

It is worth noting that there are at least nine different mathematical models, either empirical or based on a particular concept, for structural relaxation, and all apparently fit a set of DSC data. These models have been based on the description of (a) enthalpy (28), (b) configurational entropy (64,65), (c) distribution of relaxation times (66,67), (d) defects diffusion (19,68), (e) distribution of free volume (69), (f) fractal lattice fluctuation (71), (g) a multiparameter description known as the Kovacs-Aklonis-Hutchinson-Ramos (KAHR) model (13,14), (h) a different multiparameter description given by Rekhson (72), and (i) density fluctuation interpolation model (73). The fitting of the data to almost all models requires four parameters that are self-consistent, but their values for a particular relaxation process are not measurable by an independent method. Furthermore, it has been found (18) that the values of the parameters required to fit the DSC data differ remarkably from the values

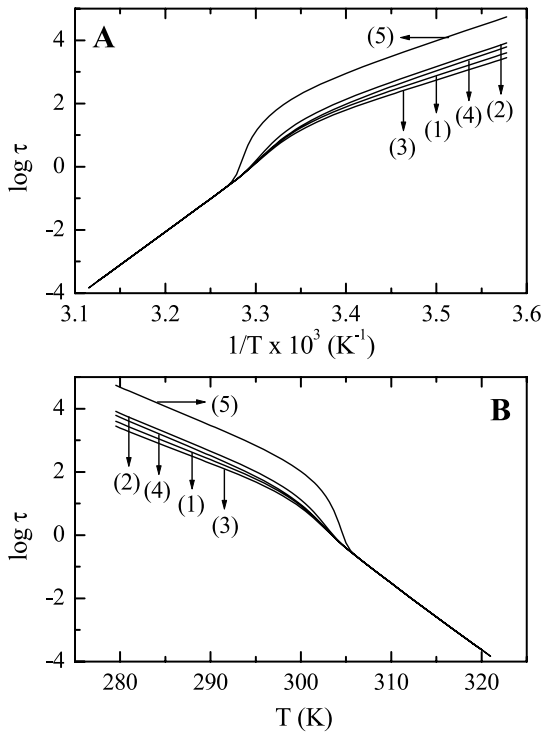

Fig. 10. (A) The relaxation time calculated from Eq. (7) by using $\ln A = -158.7$, $x = 0.46$, $\beta_{KWW} = 0.67$, $\Delta h^* = 400$ kJ/mol, as obtained from the best to experimental data in curve (1) in Fig. 9 and used to obtain the simulated curves 2, 3, 4, and 5 also in Fig. 9, is plotted against the reciprocal of temperature. (B) The same relaxation time is plotted against the temperature. The logarithm is to the base 10 in both plots. Here curve 4 corresponds to curve 5 in Fig. 9(B) and curve 5 to curve 4 in Fig. 9(B).

that fit the dielectric, mechanical, or volume relaxation data. This may be rationalized on the grounds that the regions of the spectra probed by different techniques differ, as do the molecular groups and size of the molecular regions in a material. Furthermore, the choice of the empirical parameters used for fitting the nine models differ, even when each model provides an acceptable simulation of the data. Therefore, it seems that caution is required in deducing molecular information from the parameters of these model-fittings.

It seems that the limitations of these models stem from the approximations made in developing and in using them. Firstly, calculation of $C_{p,norm}$ from Eq. (8) is a serious approximation, because although $C_{p,glass}$ is subtracted from $C_{p,meas}$, both $C_{p,equilibrium\ liquid}$ and $C_{p,glass}$ are obtained from a linear extrapolation. $C_{p,equilibrium\ liquid}$ is extrapolated from $T >> T_g$ to $T << T_g$, and $C_{p,glass}$ is extrapolated from $T << T_g$ to $T >> T_g$. However, $C_{p,glass}$ increases nonlinearly with T because $C_{p,glass}$ has contributions from anharmonic forces of the potential function and from localized molecular motions (referred to as the Johari-Goldstein relaxation), both of which increase rapidly with increase in T, and the slope of $C_{p,glass}$ against T plots is progressively higher as T_g is approached on heating, which makes its extrapolation to the equilibrium liquid state uncertain. Furthermore, plots of $C_{p,equilibrium\ liquid}$ against T for ultraviscous liquids at $T > T_g$ are curved. The curvature is such that $C_{p,equilibrium\ liquid}$ decreases with increase in T (i.e., $dC_{p,equilibrium\ liquid}/dT$ is negative for, as for 1-butene (80), the N-type liquids) or $C_{p,equilibrium\ liquid}$ increases with increase in T (i.e., $dC_{p,equilibrium\ liquid}/dT$ is positive as for *o*-terphenyl (80), a P-type liquid). Therefore, there is no *a priori* manner of determining how extrapolation of $C_{p,glass}$ and $C_{p,equilibrium\ liquid}$ can be done for use in such models. The combined effects of this assumption may be minor, but they are worth maintaining in a discussion of such analyses.

Secondly, the quantity dT_f/dT of an equilibrium liquid in these models is taken to be equal to 1, i.e, the T_f against T plot has a slope of 1. This means that, on extrapolation to lower temperatures, T_f would reach zero at $T > 0$ K. At still lower temperatures, the normalized C_p of the equilibrium liquid or dT_f/dT would remain zero (39). This too is perhaps a minor concern, but because most analyses of a supercooled liquid's thermodynamic properties have been based on this assumption, it is worth discussing it here briefly, as follows: By an extrapolation of an equilibrium liquid's entropy to T below T_g, Kauzmann (81) had suggested that the entropy of the equilibrium liquid may become equal to that of a crystal at T_K or T_2. This extrapolation forms the basis of several models that rely on the resolution of Adam and Gibbs (22) of the "Kauzmann paradox" that conjectures that configurational entropy of an equilibrium liquid, which is taken as equal to a liquid's excess entropy over the crystal phase, would become zero at T_K (8,65,66). Now apart from the fact that configurational entropy differs from the excess entropy, properties of an equilibrium liquid cannot be measured near T_K, T_2, or 0 K, and therefore, the validity of such conjectures can only be reasoned. It now seems that the T_K and T_2 conditions are inconsistent with our basic understanding. An alternative to the Kauzmann extrapolation has been discussed (82,83) in a manner different from that of Simon (84) and others (9,85–87), and it has been concluded that the entropy of an equilibrium liquid will remain above that of its crystal phase when both are cooled toward 0 K. This is because contributions from anharmonic forces remain higher in an equilibrium liquid than in a crystal phase (82,83,85), and there are additional configurational contributions from motion of atoms and molecular segments occupying higher volume sites in the glass structure. Results of a recent analysis of the C_p data of amorphous polyethylene claim to provide support for the absence of the T_K or T_2 (88), and an analysis of the DSC data on a polymer (89) has suggested a similar absence of T_K. The implications of this suggestion for our data analysis is that dT_f/dT would not become zero at $T > 0$ K. Rather, it would decrease slowly from its value of 1 to zero at 0 K. The plot of T_f against T would flatten out as $T \rightarrow 0$ K.

Thirdly, the most significant parameter, β, a measure of the distribution of relaxation times, is assumed to remain constant with t_{ann} and with change in T_{ann} and in T in these models, although it is acknowledged that β is expected to change. The study here and earlier (32,33,45) however show that β may change, thus confirming a 30-year old finding (90) that β changes with t_{ann} (91).

Nevertheless, these models may still seem adequate for fitting a DSC scan over a narrow temperature range of glass softening, particularly when combined effects of the above-given approximations become insignificant in comparison with the experimental errors, even allowing that some structural relaxation must occur in all experiments because the heating rate is never high enough to avoid it completely. For acetaminophen, Eqs. (7) and (8) seem unsatisfactory when samples are structurally relaxed for a long time. We prefer not to develop an empirical model for fitting to the data because it would require more experimentally unverifiable parameters.

CONCLUSIONS

The enthalpy and entropy decrease on structural relaxation of acetaminophen differs from those of polymers and inorganic glasses. A nonexponential, nonlinear structural relaxation model that has been used for polymers and inorganic glasses seems inconsistent with the calorimetric studies of acetaminophen.

Acetaminophen contains various groups with H, N, and O atoms, and, as for most liquids containing such groups, it is likely that its molecules form intermolecular hydrogen bonds. Fourier transform infrared spectra (92) of acetaminophen crystals have shown that its molecules form intermolecular hydrogen bonds, and these bonds persist in the liquid and glassy states. To elaborate, the 3163 cm^{-1} band in the acetaminophen crystal has been attributed to the intermolecularly hydrogen-bonded OH stretching vibration plus other combination bands (92). In the melt, this band became broad and merged with the neighboring bands, as is usually found for liquids, whose spectra show only broad features. Furthermore, the peak positions of the C=O stretching band shifted from 1653 cm^{-1} in the crystal to 1668 cm^{-1} in the melt at $T > 438$ K, and the N–H bending band shifted from 1564 cm^{-1} in the crystal to 1539 cm^{-1} in the melt. It shifted to 1545 cm^{-1} in the ultravisocous liquid at 298 K, i.e, at T near T_g. This shift was attributed to breaking of intermolecular hydrogen bonds resulting from the increase

in the temperature of the melt and to formation of hydrogen bonds on cooling the melt to 298 K. Intermolecular hydrogen bonds have been seen to be weaker in the melt at $T > 438$ K and stronger at 298 K (see (92) for further details). Similar observations have been made by Raman spectroscopy (93). Moreover, compressibility of the intermolecular hydrogen bonds NH–O and OH–O in crystalline acetaminophen has been measured, and the NH–O bonds have been found to be slightly more compressible than OH–O bonds in the hydrogen-bond network (93). This provides adequate evidence for intermolecular hydrogen bonds in acetaminophen's crystal and liquid states.

We propose that as acetaminophen structurally relaxes and densifies, two processes occur: (a) the number of intermolecular hydrogen bonds increases, and this adds to the decreases in the enthalpy and entropy because hydrogen bonding is an exothermic process; and (b) the disordered structure as a whole approaches the equilibrium state of lower enthalpy and entropy. Because molecular rearrangement in a hydrogen-bonded structure can occur only after an intermolecular hydrogen bond breaks, the molecule diffuses and then reforms a hydrogen bond with the same or a different molecule, and the enthalpy and entropy decrease on structural relaxation would be affected by the strength of the hydrogen bonds and the hydrogen bond equilibrium. It is recognized that the majority of pharmaceuticals contain hydrogen-bonding sites, and therefore, it would be important to investigate structural relaxation of more pharmaceuticals to determine whether the effect observed here is specific to them.

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