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Thermochimica Acta 380 (2001) 95–107

thermochimica acta

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Molecular mobility of amorphous pharmaceuticals determined using differential scanning calorimetry

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Abstract

Amorphous pharmaceutical materials have received considerable attention in recent years because of their unique handling, processing and stability characteristics. A key question that arises with such materials is "what is the molecular mobility of the material, and how does this influence its performance?". In this manuscript, the use of differential scanning calorimetry (DSC) to characterize the molecular mobility of amorphous pharmaceutical materials is reviewed, and several applications of the data for the qualitative and quantitative prediction of their performance are presented. © 2001 Elsevier Science B.V. All rights reserved.

Keywords: Amorphous; Molecular mobility; Relaxation time; Differential scanning calorimetry; Stability; Glass transition temperature; Fragility

1. Introduction

Amorphous forms of pharmaceutical materials occur commonly and they are in widespread commercial usage, albeit sometimes unknowingly. They have different physical properties than their corresponding crystalline forms, in particular, their kinetic solubility, their stability, and their mechanical properties. These property differences are usually quite large and more marked than, for example, the differences between the properties of different crystalline polymorphs. As a consequence of these features, it can be highly advantageous to use an amorphous form of a drug or an excipient to capitalize upon its unique physicochemical properties and functionality.

It is possible to deliver amorphous drugs and excipients to the body in a physically stable state, although there are significant challenges involved in doing this. There is often an underlying tendency for the crystallization of amorphous pharmaceutical materials that needs to be circumvented through the selection of appropriate processing and storage conditions. Despite their thermodynamic metastability, many amorphous systems are kinetically stable for much longer than the expected lifetime of a drug product, and there are examples of amorphous materials that have been found intact after many hundreds or thousands of years [1–3].

In cases where the crystallization kinetics of amorphous pharmaceutical materials are reasonably slow at room temperature, these materials can be treated as pseudo-equilibrium systems, and this permits their detailed characterization on normal experimental timescales. This has been demonstrated by several research groups for one model drug substance, indomethacin, and has allowed this material's physical stability and performance to be understood in some detail [4–10]. The results of the published work indicate that one can study the stability of amorphous

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PII: S0040-6031(01)00663-3

pharmaceutical materials in a similar way to conventional crystalline drug substances.

The study of stability in crystalline systems often utilizes 'thermal techniques' (i.e. studies at elevated temperatures) to understand the rates of transformation processes and the energetic barriers between forms, and an analogous approach is most appropriate for studying the stability of amorphous materials. The temperature dependencies of physical transformation processes and the thermal barriers between forms can be quite different in magnitude than for chemical reactions since typically no covalent bonds are being broken, but identical general approaches apply. Elevated temperatures are used to increase the rate of transformations and variable temperature studies are used to determine the temperature dependence of molecular interactions, and to permit the prediction of performance at experimentally inaccessible or impractical temperatures. The average rate of molecular motions at any given temperature is probably the most important parameter to know for amorphous pharmaceutical materials, and it can be used to explain and even predict the stability of many such systems [9,11–14].

The goal of this manuscript is to review the available approaches for measuring the molecular mobility of amorphous pharmaceutical materials using differential scanning calorimetry, and to provide a perspective on the use of the data from these techniques for predicting the stability and performance of amorphous pharmaceutical materials. The manuscript starts with a brief introduction to the concepts of molecular motion in amorphous pharmaceuticals and a description of how relaxation time data can be used to characterize the performance of such materials. The article concludes with a description of experimental approaches that may be used to characterize molecular motions in these systems.

2. Molecular mobility in amorphous pharmaceutical systems

At any given moment in time, an amorphous material can be described using a schematic free energy diagram, such as that in Fig. 1. This "thermodynamic snapshot" indicates that the amorphous form only exists below the crystalline melting temperature (T_m) and is really a "supercooled" liquid form. As one cools far below T_m, the metastability of the amorphous form increases and in a characteristic temperature region called the glass transition (T_g), the properties of the amorphous material diverge from those of the extrapolated supercooled liquid form. This occurs because the molecular motions in the amorphous material become increasingly limited in their rate and extent upon cooling and in the glass transition region they go from being faster that the experimental cooling rate to being slower than the experimental cooling rate. When this happens, the amorphous form falls out of equilibrium with its surroundings and takes on some unique qualities. The amorphous material below T_g is said to be in the "glassy state" and almost all of its physical properties continue to change slowly with time as it tries to re-establish energetic equilibrium with its surroundings. The location of the glass transition temperature is obviously a function of the experimental cooling rate and of the energetic history of the glassy material. Thus, T_g values reported in the literature should be expected to vary from laboratory to laboratory, and even somewhat from experiment to experiment. This is an indication that all is well in the amorphous state!

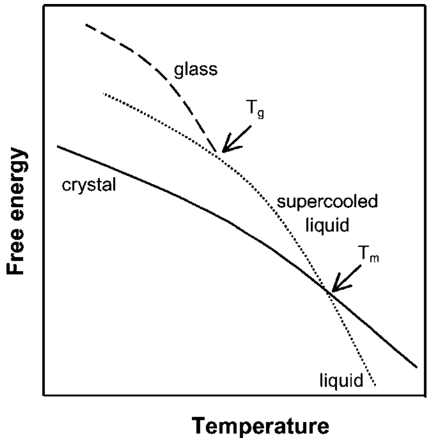

Fig. 1. Schematic free energy vs. temperature plot.

The temperature dependence of the duration of molecular motions (τ) at any point in time is a very important characteristic of an amorphous pharmaceutical material, and it will vary according to whether the material is in the glassy or supercooled liquid states (Fig. 2). At temperatures above T_g, τ typically follows a non-Arrhenius temperature dependence that may

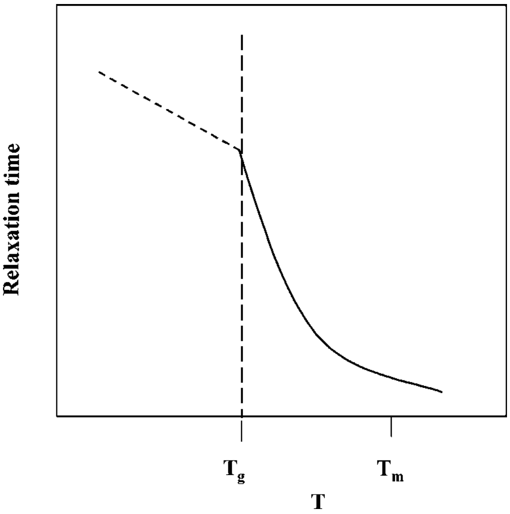

Fig. 2. Diagram showing the dependence of the average molecular relaxation time on experimental temperature.

permit a 10-fold increase in molecular mobility for as little as 3–5 K rise in temperature in the region just above T_g [15]. At T_g, τ is typically about 100–200 s [15]. At temperatures below T_g, the apparent activation energy for molecular rearrangement will vary according to the history of the sample, but it is typically significantly less than that above T_g [12]. In this instance, any measured value for τ should be regarded as an instantaneous measure of molecular mobility for the sample being considered and not an equilibrium value.

For pharmaceutical systems, one may desire a strong or a weak dependence of τ on temperature, according to the application and circumstances at hand. For example, when trying to stabilize a material by reducing its temperature (e.g. refrigerated storage) a strong dependence of τ on temperature might be seen as desirable to enable a greater stabilization to be achieved for each degree of cooling. However, such a material's properties would change quite significantly with small fluctuations in temperature during storage and there would be a need for very tightly controlled storage conditions to be maintained to prevent variations in product properties. There is a clear trade-off in instances such as this between the desire to be able to influence a product's molecular mobility by changing its preparation and storage conditions and the need for the properties of a product to remain unchanged with changes in the environment that are encountered during normal use.

An empirical equation known as the Vogel–Tamman–Fulcher (VTF) equation is most commonly used to quantitatively describe the temperature (T) dependence of molecular motions in amorphous materials [15]:

$$\tau(T) = A \exp\left(\frac{B}{T - C}\right) \tag{1}$$

where A, B and C are arbitrary fitting parameters. There have been many proposals to assign physical significance to the VTF parameters for common materials in their supercooled liquid state: A is usually considered to represent the time needed for a molecular to move in an open space (τ_0) ($\sim 10^{-14}$ s) [15], B is related to the temperature dependence of τ at T_g (also known as the "fragility" of an amorphous material [16]), and C is said to be the temperature at which the average molecular mobility approaches zero (T_0) ($\sim$50 K below T_g). Alternate equations and more detailed interpretations of the VTF constants have been proposed (e.g. Angell's D parameter [16,17]), however, none provides any better or more widely applicable physical interpretation of the temperature dependence of molecular motions in the various amorphous regions.

The true importance of the molecular relaxation rate under any given conditions can only be properly appreciated with a knowledge of the appropriate reference time frame. This could be just a few hours for a sample used in a laboratory experiment, or as long as several years for a drug product being stored in the neighborhood pharmacy. Perhaps the key question to ask here is "what is the longest lifetime that is required for the amorphous material being considered?". With a knowledge of this expected product lifetime, the proposed storage or processing conditions, and the temperature and structure dependence of the molecular relaxation times, it should be possible to make a reasonable qualitative prediction of the performance and stability of the amorphous material at hand. As will be described at the end of this manuscript, with additional data, such as the heat capacity of crystalline and amorphous samples and the distribution of molecular relaxation times, a quantitative estimate of the product's behavior upon storage can also be attempted.

It is worth noting at this juncture that molecular motions in amorphous materials can influence both chemical and physical transformation processes. In each of these instance, a "coupling" between the molecular motion that is of interest (e.g. a carbonyl stretch required for a chemical reaction to occur) and the relaxation time that can be measured experimentally is required for experimental estimates of τ to be useful and meaningful. Such "coupling" is often quite difficult to prove, and the identification of experimental procedures that are sensitive to the precise molecular motions of interest can be a considerable challenge. It should also be remembered that all molecular motions in amorphous materials will exhibit a distribution of relaxation times due to the dynamically heterogeneous nature of the amorphous state. Because of this, it is important to consider which region of the relaxation time distribution is of relevance when attempting to predict the performance of amorphous pharmaceutical materials. For example, a bulk phenomenon, such as volume contraction (e.g. shrinkage of a freeze-dried cake) may be predicted adequately by an average relaxation time, whereas the initiation of chemical degradation processes that occur preferentially in the fastest moving regions of an amorphous material might be more accurately predicted from estimates of the most rapid rate of molecular motion in the material. For more details on how to interpret relaxation time distributions, and for practical advice on how to relate them to the performance of amorphous pharmaceuticals, the reader is referred to our previous work [11].

There are many experimental methods available for the characterization of molecular motions in amorphous materials (e.g. dielectric relaxation, dynamic mechanical analysis, etc.). Some of these techniques are only suitable for use at temperatures above the glass transition region where many pharmaceutical materials are chemically or physically unstable. Differential scanning calorimetry (DSC) is frequently used by pharmaceutical scientists because of its convenience, speed, small sample requirements, and because it can be effectively used at temperatures below the glass transition temperature. In some small pharmaceutical laboratories, it may be the only technique available for estimating molecular relaxation time values. As with many analytical techniques, the results obtained by DSC somewhat reflect the choice of method and instrumentation, and they will not correspond exactly with results from other techniques. This is especially true when studying amorphous systems below their glass transition temperature since they are not truly at equilibrium with their experimental surroundings. As always, it is preferable to utilize several complementary analytical tools to study the system of interest rather relying on a single measuring technique. Example applications of non-DSC techniques for studying amorphous pharmaceutical systems can be found in [18–20]. In the remainder of this article, approaches for using differential scanning calorimetry to estimate the timescales for molecular motions in amorphous pharmaceutical systems will be reviewed and then details of how such estimates can be used to anticipate the performance of amorphous pharmaceutical materials will be described. The section starts by outlining the simplest, quickest and crudest approaches, and progresses through to the more lengthy, complex and comprehensive ways of characterizing molecular motions in amorphous pharmaceutical systems.

3. DSC methods for estimating molecular mobility

3.1. Qualitative approaches

In the early stages of working with an amorphous pharmaceutical material, it is often sufficient to have an order-of-magnitude estimate of how the material will perform at any given experimental temperature. In such instances, there are several simple approaches that can be used to characterize the molecular mobility of an amorphous drug or excipient.

Over a long period of time, it has been observed that the glass transition region occurs in a temperature range that is approximately two-third of the melting point in Kelvin. This observation may be used to estimate the location of T_g from T_m, or vice versa. If both these properties are known then it is possible to estimate the "deviation from the two-thirds rule", which is thought to reflect the temperature dependency of molecular motions in the region just above T_g. If T_g/T_m is significantly greater than 2/3, then the material is likely to have a greater than average temperature dependence of its molecular mobility in the region of T_g, and in the terminology of Angell and co-workers [15,16] and [21], it can be said to be 'fragile'. Conversely, a material with a T_g/T_m ratio of much less than 2/3 probably has a less than average temperature dependence of its molecular motions between these two temperatures. Unfortunately, there is currently no simple method by which to estimate the temperature dependence of molecular motions in temperature region below T_g where a considerable proportion of amorphous pharmaceutical materials are processed and stored.

The next simplest approach for characterizing the molecular motions within amorphous pharmaceutical materials is to use conventional DSC data to construct a semi-quantitative diagram of the excess enthalpy (relative to the crystalline state) versus temperature, such as that shown in Fig. 3a. The most easily obtained parameters on this plot are the melting point (T_m) and the calorimetric glass transition temperature (T_g), followed by the enthalpy of fusion (ΔH_f) and the apparent heat capacity change at T_g ($\Delta C_p^{T_g}$) (Fig. 3b). These parameters can all be measured experimentally from conventional DSC heating scans of the crystalline and amorphous materials. For thermally stable materials, they can often be determined in a single experiment if the crystalline material is first melted in the DSC and then supercooled in-situ to produce the amorphous form which is characterized using a second heating scan. Heating and cooling rates of 20 K/min or greater may be required so that the glass transition event can be easily detected. During the second heating scan, there may be a crystallization event soon after the glass transition event, and this typically manifests itself as a broad exotherm (ΔH_c) which is followed by fusion of the crystalline material at the normal melting temperature. These data can also be used in the construction of the simple enthalpy–temperature plot, as can data from any other independent measure of the enthalpy change between the crystalline and amorphous forms (e.g. solution calorimetry experiments) [22–24].

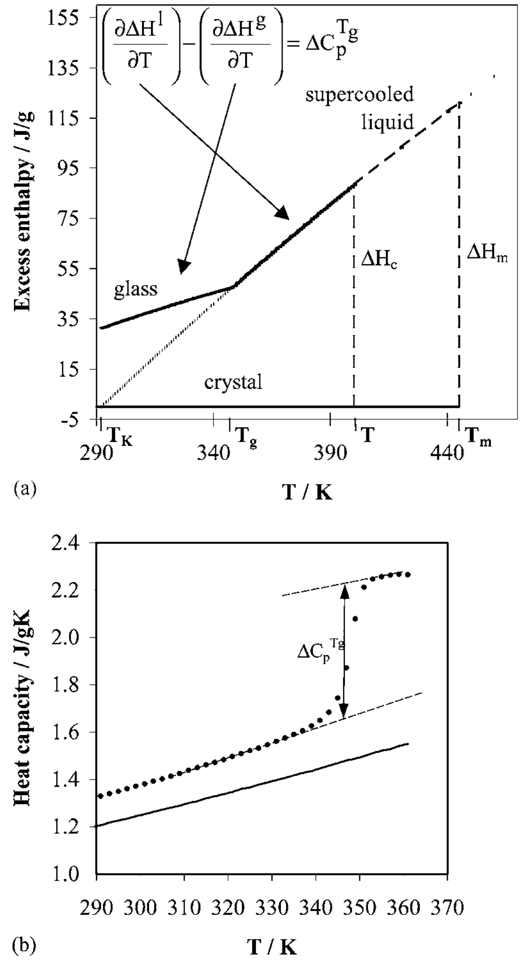

Fig. 3. (a) Excess enthalpy vs. temperature for sucrose (data from [9]). (b) Heat capacity vs. temperature for amorphous and crystalline sucrose (data from [9]).

In order to use just the values of T_m, T_g, ΔH_m, ΔH_c and $\Delta C_p^{T_g}$ to construct a rough enthalpy–temperature diagram, some assumptions regarding the heat capacity ($d(\Delta H)/dT$) of the crystalline, liquid and amorphous forms are needed [9,14]. Typically, the heat capacities of the crystalline and glassy forms are assumed to be similar and small relative to the liquid form, and approximately linear over narrow temperature ranges ($\Delta T = 50-100$ K). The extrapolated enthalpy of the supercooled liquid form may also be presumed to coincide with that of the crystal at a theoretical temperature (T_K) [25],[1] which can be roughly estimated from $(T_g)^2/T_m$. Using such approximations, a

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[1] The coincidence of the extrapolated thermodynamic properties of the supercooled liquid with those of the crystal at some temperature (T_K) was first described by Kauzmann [25]. The exact value of T_K is different depending upon which property (*H*, *S* or *V*) is evaluated [14]. The T_K values so obtained have been used as a measure of the temperature where the molecular mobility of the supercooled liquid is equal to that of the crystal (i.e. limited primarily to vibrational modes of motion).

semi-quantitative excess enthalpy versus temperature plot, such as that in Fig. 3a can be constructed and the magnitude of the temperature dependence of the thermodynamic properties at any given temperature can be determined for each new material. The simple excess enthalpy–temperature diagram will indicate whether the amorphous material has a glass transition temperature that is above or below normal storage and processing temperatures, and where the theoretical excess enthalpy is equal to zero (T_K). For materials where both these parameters are significantly above (>50 K) normal operating temperatures, there should be a reasonable chance of being able to produce and retain a stable amorphous material [12]. In contrast, materials which have both T_g and T_K values below ambient temperature are often hard to produce and maintain in an amorphous state in any significant quantity.

3.2. Quantitative approaches

Quantitative measurements of molecular mobility in amorphous materials can be made using a DSC that has been carefully calibrated for temperature, enthalpy and heat capacity measurements. This is most simply achieved by constructing a quantitative excess enthalpy versus temperature plot similar to that described above. Such an approach is especially effective when the heat capacities of both the crystalline and supercooled liquid forms (C_p^x, C_p^l) can be directly measured since these data permit the configurational heat capacity ($C_p^l - C_p^x$) in the equilibrium state above T_g to be determined. The magnitude of this quantity can be related to the temperature dependence of molecular motions in the supercooled liquid [26]. Using the same data, it is also possible to calculate the excess entropy and free energy between the crystalline and supercooled liquid forms as a function of temperature (e.g. Fig. 4), and these data can provide a direct indication of the molecular mobility differences between these two forms between T_g and T_m.

Alternative experimental approaches are required at temperatures below T_g to account for the non-equilibrium nature of the glassy amorphous material. The most widely used method is known as an enthalpy relaxation (or enthalpy recovery) measurement [3,12,27,28]. This technique is usually only practical on normal experimental timescales in the temperature range between T_g and $T_g - 40$ K and for broader temperature ranges it maybe necessary to operate the DSC so that the apparent heat capacity of the glass can be determined over a wide range of temperatures. In such instances, an in-depth thermodynamic analysis is required to effectively quantify the molecular mobility of the amorphous sample [9], as will be described later.

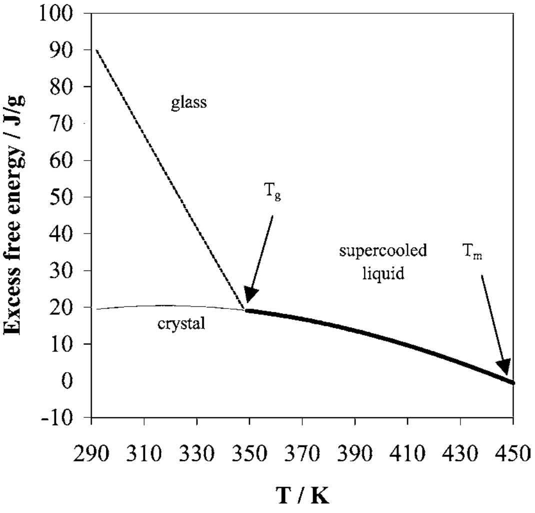

Fig. 4. Excess free energy vs. temperature for sucrose (data from [9]).

3.2.1. Enthalpy relaxation measurements below T_g

Enthalpy relaxation (or enthalpy recovery) experiments can be performed by the careful operation of a conventional DSC, however, it should be noted that these experiments take a longer time than typical pharmaceutical DSC experiments (hours rather than minutes). In these experiments, an amorphous material is first held for several minutes in the DSC at a temperature just above T_g to ensure that it is in thermal equilibrium with its surroundings. It is then cooled under carefully controlled conditions to the temperature of interest and permitted to remain at that temperature for a fixed length of time (typically many hours). The sample is then re-heated through T_g and the form of the DSC trace at T_g is analyzed (Fig. 5). Depending upon the equilibration time (t) and temperature (T), there will usually be an endotherm of varying magnitude in the region of the glass transition event. The endothermic process is the recovery of the

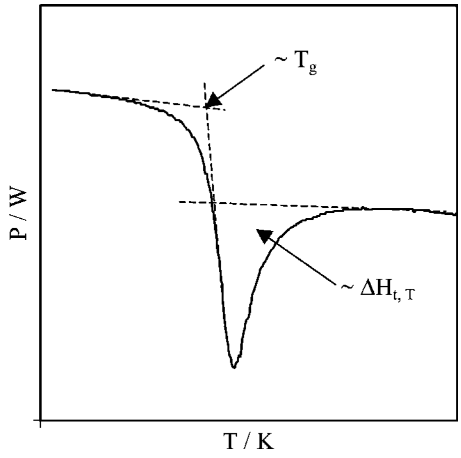

Fig. 5. Typical DSC thermogram from an enthalpy recovery ('relaxation') experiment.

enthalpy that was lost by structural relaxation during the storage below T_g (also known as 'aging'). The enthalpy associated with this endotherm ($\Delta H_{t,T}$) can be quantified in most cases by careful subtraction of the response for a non-aged sample with an identical thermal history. Alternatively, it can be estimated by using the extrapolated supercooled liquid response to define an approximate baseline response as shown in Fig. 5. Some authors have advocated the use of temperature modulated DSC to more easily resolve the endothermic change, but the influences of the associated cyclic thermal history on the already complex relaxation behavior of amorphous samples are still not sufficiently well understood for this approach to be widely accepted [29,30].

The enthalpy change indicated by the measured endotherm corresponds to the extent that the sample was able to 'relax' under the chosen storage time and temperature conditions. This enthalpy relaxation is directly related to the "average" molecular mobility of the material under those conditions. This "average" is a crude macroscopic measure of the molecular mobility occurring in all regions of the material during the entire experiment, and it should be remembered that a distribution of relaxation times in both time and space occurs in reality. By repeating the experiment using a range of storage times, it is possible to determine the enthalpy change versus storage time, and from these data, the average molecular relaxation time can be estimated at any given temperature.

To determine the average relaxation time from the enthalpy change versus storage time data, it is necessary to know the extent to which the glass has relaxed at each time point. This requires the estimation of the maximum possible enthalpy recovery at each temperature ($\Delta H_{\mathrm{max},T}$) using the following equation:

$$\Delta H_{\mathrm{max},T} = \Delta C_{\mathrm{p}}^{T_{\mathrm{g}}}(T_{\mathrm{g}} - T) \tag{2}$$

where $\Delta C_{\mathrm{p}}^{T_{\mathrm{g}}}$ is the heat capacity change at T_g and T is the storage temperature. The enthalpy change at each time point can then be expressed as a fraction of the total potential enthalpy relaxation, or the fraction relaxed $\Delta H_{t,T}/\Delta H_{\mathrm{max},T}$. Next, the fraction relaxed is plotted as a function of storage time and in most cases a fit to the empirical Kohlrausch–Williams–Watts (KWW) equation (Eq. (3)) is used to estimate the average relaxation time (τ) and the corresponding distribution parameter (β) (Fig. 6).

$$\frac{\Delta H_{t,T}}{\Delta H_{\mathrm{max},T}} = 1 - \exp\left(-\frac{t}{\tau}\right)^{\beta} \tag{3}$$

For this curve fitting procedure to provide meaningful data, at least five or six data points are needed, and more are desirable. In addition, enthalpy changes that cover the range from 10–80% of the fully-relaxed enthalpy change are required for meaningful values of τ and β to be obtained.

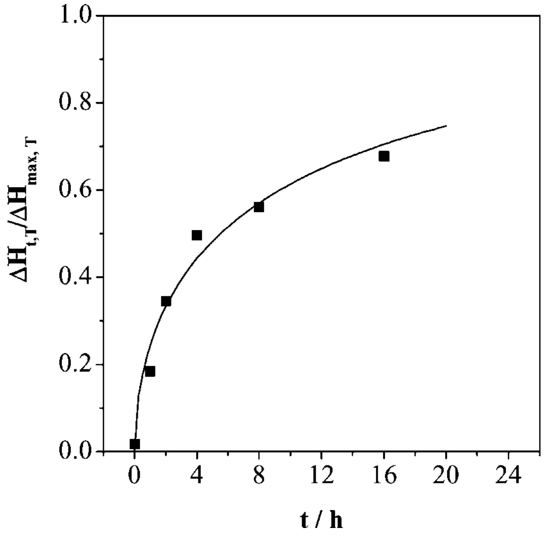

Fig. 6. Fraction recovered enthalpy vs. time for quench-cooled amorphous sucrose at 333 K. Line represents fit to the Kohlrausch–Williams–Watts equation.

Enthalpy recovery experiments provide an estimate of the average molecular mobility that is associated with enthalpy changes in the sample, and other techniques (e.g. dielectric relaxation experiments) may provide slightly different absolute estimates of the average molecular relaxation time under similar time and temperature conditions. In all cases, the distribution parameter (β) indicates the extent to which the data deviate from a true exponential function, with a value of unity corresponding to an exponential function. Meaningful comparisons of average relaxation times from different experiments can only be made when the values of β are comparable (say, ± 0.1) or when the impact of the non-exponential behavior on the average value of τ is fully understood. It should also be noted that comparison of material properties should only be made using data generated under similar experimental conditions (e.g. maximum storage time). When assuming that the cause of non-exponential relaxation behavior ($\beta < 1$) is a distribution of relaxation times, it is also important to consider the underlying distribution of relaxation times for the sample being studied. This is because the application of the KWW equation to certain types of distribution functions (e.g. normal) has some significant limitations. The reader is referred to our previous work for further details [11].

Once average values of τ have been estimated from enthalpy relaxation experiments, their magnitude can be compared to the appropriate reference timeframe to provide a perspective on the material's likely performance characteristics. For example, if an amorphous drug has an average relaxation time of 10^5 s ($\sim$28 h) at ambient conditions, it may not experience significant changes in structure and performance during a short laboratory experiment, such as a simple dissolution test. However, it will certainly be structurally unstable when subjected to typical pharmaceutical storage stability stress testing conditions (e.g. 40°C for 6 months). If the temperature dependence of τ indicated by the enthalpy relaxation experiments is very high (e.g. an order of magnitude reduction in τ for every 5 K change in temperature), then, reducing the storage temperature by refrigeration should provide a sufficient reduction in molecular mobility for this particular amorphous material to withstand storage at this temperature for several years without any noticeable changes in structure.

3.2.2. Estimating average relaxation times below T_g using apparent heat capacity data

The models typically used to describe the temperature dependence of molecular relaxation times do not account for deviations from equilibrium behavior and thus they cannot be used to precisely describe molecular motions in glasses (i.e. below T_g). However, a model proposed by Adam and Gibbs [26], which describes the temperature dependence of molecular mobility above T_g, has been extended into the glassy state [9,31,32]. In the original theorem developed by Adam and Gibbs, motions requiring diffusion or rotation were assumed to cease below T_K and the configurational entropy was assumed to be zero below T_K. These authors also assumed that glasses had a small and constant configurational entropy below T_g. These assumptions were quite reasonable when the mobility at temperatures above T_g was of interest, but they imply a constant level of molecular motion in glasses at all temperatures below T_g. It is in fact known that molecular mobility is finite and varies with temperature in real glasses and this is critical to their observed behavior [12].

By accounting for the excess configurational entropy that is present in real glasses at different temperatures, the average relaxation times for several pharmaceutical glasses have been estimated using Eq. (4), which was adapted from Adam–Gibbs model:

$$\tau(T, T_f) = \tau_0 \exp\left(\frac{DT_0}{T - (T/T_f)T_0}\right) \tag{4}$$

where $\tau_0 = A$, $T_0 = C$, $D = B/C$ and the parameters A, B and C have the same meaning as in the VTF equation (Eq. (1)). The term T_f is the 'fictive temperature', which defines the instantaneous properties of a glass in terms of the equilibrium supercooled liquid having the same configurational entropy [33]. The value of T_f for a glass can be estimated from Eqs. (5) and (6):

$$\frac{1}{T_f} = \frac{\gamma_{C_p}}{T_g} + \frac{1 - \gamma_{C_p}}{T} \tag{5}$$

where

$$\gamma_{C_p} = \frac{C_p^l - C_p^g}{C_p^l - C_p^x} \tag{6}$$

and C_p^l and C_p^x are the constant pressure heat capacities of the supercooled liquid and crystalline states evaluated at T_g. C_p^g represents the apparent heat capacity of the glass,[2] also evaluated at T_g. The values of τ_0, D and T_0 in Eq. (4) are usually obtained from measurements of relaxation time above T_g (e.g. dielectric relaxation or viscosity), and for more details on the derivation of this equation, the reader is referred to our previous work [9].

Accurate estimates of mean relaxation times in glasses using Eq. (4) require measurements of apparent heat capacities which are precise enough to differentiate between the crystalline and glassy amorphous phases. The determination of such heat capacity data can be difficult and time consuming even for experienced thermal analysts with state of the art equipment. For sucrose and indomethacin (two materials for which relaxation times have been previously measured by enthalpy relaxation measurements [12]), the relaxation times estimated from high quality apparent heat capacity data using Eqs. (4)–(6) are observed to agree reasonably well with the experimental relaxation times [9], validating the utility of this experimental approach. The most important feature of Eq. (4) is the value of T_f, which is a measure of the additional configurational entropy and thus, enhanced mobility of the glass relative to the corresponding supercooled liquid. The concept of fictive temperature is discussed in more detail in the following section. The modified Adam–Gibbs model is particularly powerful since it quantifies how the excess thermodynamic properties of a glass translate into an enhanced degree of mobility relative to the crystal and the supercooled liquid states. This point is well illustrated in Fig. 7 where the configuration entropy and the predicted relaxation times of amorphous sucrose are shown over a range of temperatures below T_g. Clearly the relaxation times for the real glass (square symbols) are significantly shorter than those of the supercooled liquid extrapolated below T_g, and quite close to values estimated using Eq. (4).

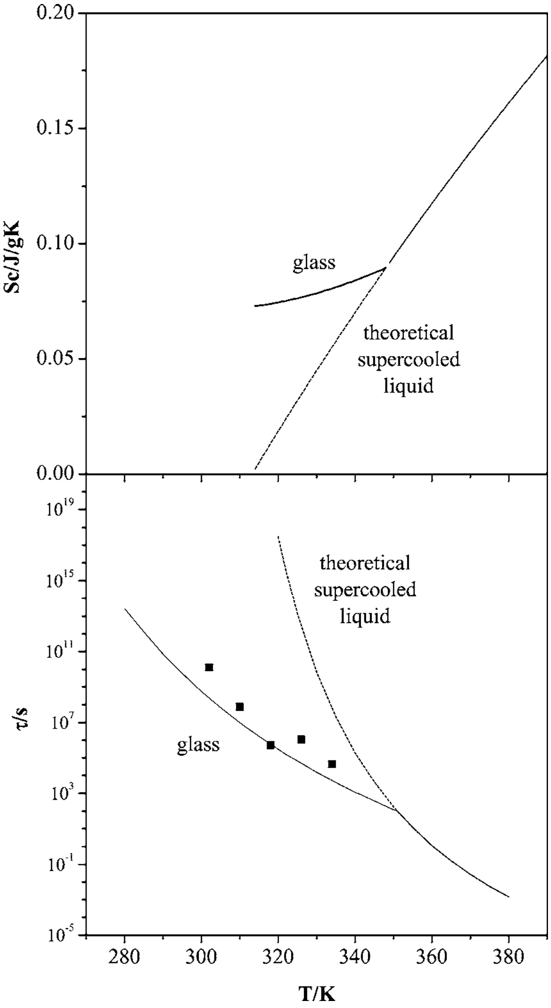

Fig. 7. Entropy and relaxation times of amorphous sucrose vs. temperature. Lines in lower portion were obtained using Eq. (4) (data from [9]) and symbols represent data measured by enthalpy relaxation experiments [12].

At this juncture, it is important to point out that in our previous work we have described the temperature T_K as the lower temperature limit for molecular motion in amorphous materials [25]. This interpretation is based on the assumption that the disappearance of configurational entropy in the supercooled liquid at T_K translates into a degree of mobility equal to that in the crystal. Thus, at T_K, the average relaxation time is assumed to be infinitely long. This assumption is valid for the theoretical supercooled liquid which is in equilibrium with its surroundings, however, it clearly underestimates the true degree of molecular mobility of real glasses. In reality, at T_K the value of τ for the sucrose glass is predicted to be finite (Fig. 7). Thus, for most real glasses (rather than theoretical supercooled liquids), a more appropriate estimate for the temperature at which the instantaneous relaxation

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[2] The apparent heat capacity measured for a glass reflects the thermal and processing history of the non-equilibrium material.

time approaches infinity would be that temperature where the fictive temperature of the particular glass in question is equal to T_K.

3.2.3. Characterizing molecular mobility in glasses using fictive temperatures

An alternative approach for estimating the degree of mobility in a glass is to determine its fictive temperature. This may be particularly helpful for those materials for which the values of τ_0, D and T_0 are not known. The concept of a fictive temperature was first introduced by Tool [33] to characterize the instantaneous structure of a glass undergoing structural rearrangement. The advantage of the fictive temperature is that it allows the properties of a glass (which are time-dependent) to be described in terms of a reference state (the supercooled liquid) whose properties are dependent only on temperature. This is shown schematically in Fig. 8 where T_f defines the glass at point "A" in terms of the corresponding supercooled liquid which is in equilibrium with its surroundings and has the same degree of configurational entropy. If desired, the fictive temperature of a glass can be defined based on other thermodynamic properties (e.g. free volume, excess enthalpy) making this parameter a particularly useful means of characterizing the properties of glasses [34].

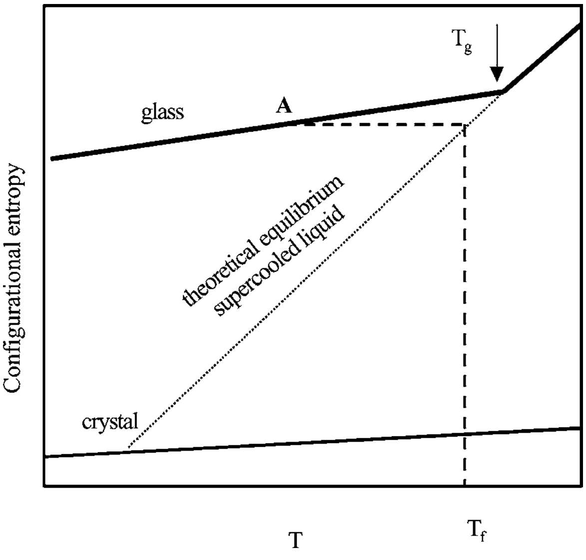

Fig. 8. Schematic representation of configurational entropy as a function of experimental temperature.

The most straightforward approach to determining fictive temperature of glasses is to use a quantitative enthalpy–temperature or entropy–temperature diagram. Using this approach, T_f is used to describe the glass in terms of either its excess enthalpy or its configurational entropy depending on which type of graph is used. T_f can also be determined from heat capacity data using Eqs. (5) and (6) given earlier. Each of these approaches relies on knowing how the temperature dependence of the thermodynamic properties (i.e. enthalpy, entropy or volume) of the glass and the theoretical supercooled liquid diverge below T_g.

Another common approach for estimating the fictive temperatures using DSC is to numerically simulate the heat capacity curves in the region of the glass transition temperature using the Tool–Narayanswamy–Moynihan (TNM) equation (Eq. (7)) [35]:

$$\tau(T, T_f) = \tau_0 \exp\left(\frac{x\Delta h^*}{RT} + \frac{(1-x)\Delta h^*}{RT_f}\right) \tag{7}$$

The TNM equation describes the temperature dependence of τ in terms of T_f, τ_0, Δh^* and x, where τ_0 is a pre-exponential constant, Δh^* an activation energy and x is a "non-linearity" parameter that partitions the activation energy into temperature and structure dependent terms. Briefly, this approach for determining T_f as a function of temperature involves measuring the heat capacity of a well defined glass while heating it through the glass transition region, and then fitting the heat capacity curve with an expanded form of Eq. (7) to obtain values of τ_0, Δh^* and x. The reader is referred to [35,36] for details on using this approach to determine T_f values in glasses. One of the limitations of this approach for determining the fictive temperature of glasses is the uncertainty in interpreting the values of τ_0, Δh^* and x which are obtained for pharmaceutical materials [31,36].

The practical utility of characterizing a glass in terms of its fictive temperature is that it allows the molecular mobility to be estimated from the excess enthalpy or entropy present in a glass. This is best explained with an example. In Fig. 9, the fictive temperature for a glassy indomethacin sample [9] as it is cooled below T_g is plotted as a function of temperature. Above T_g, the value of T_f and the experimental temperature are equal since the system is in equilibrium with its surroundings. Below T_g, the instantaneous value of T_f and the experimental temperature diverge

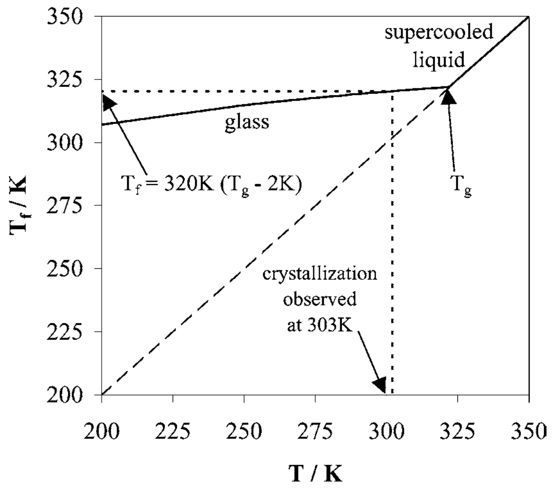

Fig. 9. Fictive temperature vs. temperature for amorphous indomethacin (data from [9]).

and T_f is always greater than the experimental temperature. This temperature difference ($T_f - T$) is a measure of the configurational entropy of the system, and thus, the enhanced mobility of the glass relative to the supercooled liquid. It has been observed that amorphous indomethacin often crystallizes at temperatures below T_g and this can be easily rationalized using the data in Fig. 9. At a storage temperature 20 K below T_g, the value of T_f is only 2 K below T_g indicating that under these storage conditions the glass still has a considerable degree of configurational entropy. Assuming that this configurational entropy translates into significant molecular mobility, it is not surprising that crystallization of indomethacin is observed at temperatures as far as 20 K below its T_g.

For equilibrium supercooled liquids, the dependence of molecular mobility on temperature has been characterized using the concepts of fragility (see earlier). It has been suggested that it may be possible to use a similar approach for ranking the extent to which the molecular mobility varies with thermal history in real glasses [32]. In a previous article, we reported the values for the apparent constant pressure heat capacities for a series of glasses having the same thermal treatment. When evaluated relative to the corresponding heat capacities for the crystalline and supercooled liquid states, these apparent heat capacities reflect the temperature dependence of the excess configurational entropy of these particular glasses as they are cooled to lower temperatures. These values are related to one another in the γ_{C_p} parameter in Eq. (6), which is used in the estimation of fictive temperature. The value of γ_{C_p} is measure of how much excess configurational entropy is present in the glass, and can range from 0 to 1. When the apparent heat capacity of the glass is close to that of the crystal, $\gamma_{C_p} \rightarrow 1$, the configurational entropy of the glass at T_g does not change upon further cooling. In this case, the variation of structure and mobility with temperature is minimal. At the other extreme, when the apparent heat capacity of the glass is close to that for the supercooled liquid, $\gamma_{C_p} \rightarrow 1$ and the excess entropy of the glass will be dependent on the temperature to which the glass is cooled. The values of γ_{C_p} for four glasses, sorbitol, sucrose, indomethacin and trehalose, having the same thermal history [9] are listed in Table 1. The average degree of mobility apparently varies most with temperature for sorbitol at temperatures just below T_g, whereas for indomethacin, the average degree of molecular mobility is seemingly much less sensitive to temperature. By applying the concept of fragility that is used to characterize the temperature dependence of supercooled liquid molecular mobility above T_g, the sorbitol sample may be said to be the "most fragile" while the indomethacin sample appears the "least fragile". The utility of this type of analysis in the context of pharmaceutical stability is illustrated as follows: if it is assumed that all of the materials have a similar average relaxation time at T_g, a "more fragile" glass like sorbitol would achieve an average relaxation time that is longer than the expected storage time at a temperature closer to its T_g, in comparison to a "less fragile" glass like indomethacin, which would require a greater degree of undercooling for the average relaxation time to exceed the expected storage time.

Table 1
The γ_{C_p} values for several pharmaceutical glasses with the same thermal history (data from [9])

Material	γ_{C_p}	Interpretation
Sorbitol	0.61	Greatest temperature dependence of τ
Sucrose	0.76	
Trehalose	0.80	
Indomethacin	0.92	Least temperature dependence of τ

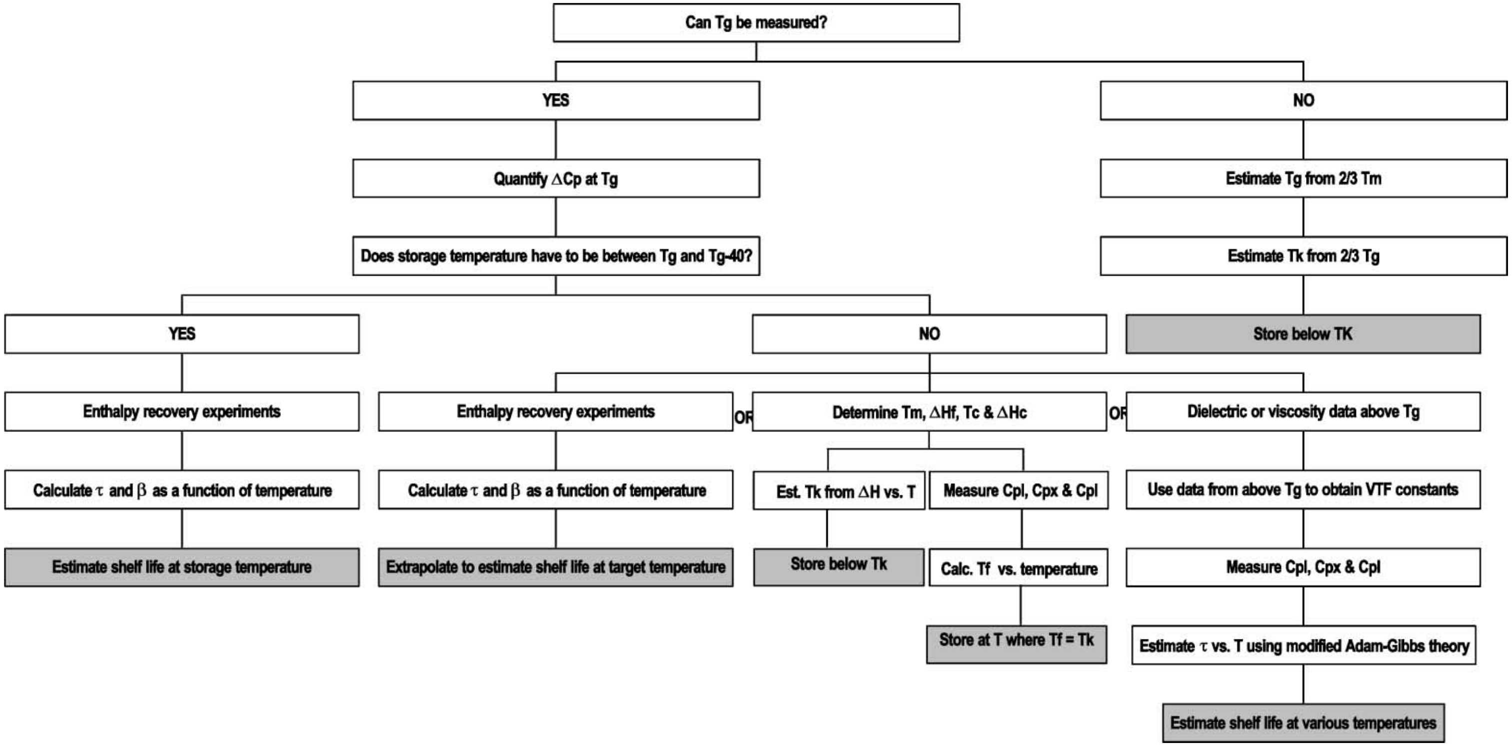

Fig. 10. Decision tree summarizing the approaches available for assessing the molecular mobility of amorphous pharmaceutical materials.

3.3. Summary of DSC methods for estimating molecular mobility

We have described a number of ways of characterizing the degree of molecular mobility in amorphous materials. The methods include very rough estimates of mobility ("what is the magnitude of T_g relative to the operational temperature?") as well as more sophisticated approaches which involve experimental and theoretical techniques for calculating average molecular relaxation times as a function of temperature. Which of these approaches is preferred will clearly depend upon the application for which the amorphous material is intended. In an attempt to guide the pharmaceutical scientist who is interested in characterizing the molecular mobility of amorphous materials, we have outlined these approaches in the form of a decision tree (Fig. 10). Upperbranches highlight the simpler approaches that involve a minimum number of experiments and provide only a limited description of the degree of molecular mobility. Such approaches may be adequate when it is of interest to know if it is possible to produce and maintain an amorphous form of a material under normal operating conditions. The lower branches of the figure show approaches that are more sophisticated and may involve more intricate experiments (e.g. careful heat capacity measurements) or require data which cannot be obtained by DSC alone. When it is possible for average relaxation time values to be accurately measured or estimated it is possible to make the most meaningful predictions of the chemical and physical stability of an amorphous material under normal handling and storage conditions.

Acknowledgements

The mentoring of Professors George Zografi and Mike Pikal is gratefully recognized.

References

[1] E.D. Zanotto, Am. J. Phys. 66 (1998) 392.
[2] E.D. Zanotto, P.K. Gupta, Am. J. Phys. 67 (1999) 260.
[3] L.C.E. Struik, Physical Aging in Amorphous Polymers and Other Materials, Elsevier, New York, 1978.
[4] V. Andronis, M. Yoshioka, G. Zografi, J. Pharm. Sci. 86 (1997) 346.
[5] V. Andronis, G. Zografi, J. Non-Cryst. Solids 271 (2000) 236.
[6] V. Andronis, G. Zografi, Pharm. Res. 15 (1998) 835.
[7] V. Andronis, G. Zografi, Pharm. Res. 14 (1997) 410.
[8] B.C. Hancock, Y. Dupuis, R. Thibert, Pharm. Res. 16 (1999) 672.
[9] S.L. Shamblin, X. Tang, L. Chang, B.C. Hancock, M.J. Pikal, J. Phys. Chem. B 103 (1999) 4113.
[10] M. Yoshioka, B.C. Hancock, G. Zografi, J. Pharm. Sci. 83 (1994) 1700.
[11] S.L. Shamblin, B.C. Hancock, Y. Dupuis, M.J. Pikal, J. Pharm. Sci. 89 (2000) 417.
[12] B.C. Hancock, S.L. Shamblin, G. Zografi, Pharm. Res. 12 (1995) 799.
[13] B.C. Hancock, C.R. Dalton, M.J. Pikal, S.L. Shamblin, Pharm. Res. 15 (1998) 762.
[14] B.C. Hancock, K. Christensen, S.L. Shamblin, Pharm. Res. 15 (1998) 1649.
[15] M.D. Ediger, C.A. Angell, S.R. Nagel, J. Phys. Chem. 100 (1996) 13200.
[16] C.A. Angell, Curr. Opin. Solid State Mater. Sci. 1 (1996) 578.
[17] C.A. Angell, Polymer 38 (1997) 6261.
[18] T.R. Noel, R. Parker, S.G. Ring, Carbohydrate Res. 329 (2000) 839.
[19] Y. Aso, S. Yoshioka, S. Kojima, J. Pharm. Sci. 89 (2000) 408.
[20] C.A. Oksanen, G. Zografi, Pharm. Res. 10 (1993) 791.
[21] B.C. Hancock, G. Zografi, J. Pharm. Sci. 86 (1997) 1.
[22] D.P. Miller, J. de Pablo, J. Phys. Chem. B 104 (2000) 8876.
[23] D. Gao, J.H. Rytting, Int. J. Pharm. 151 (1997) 183.
[24] G. Salvetti, E. Tognoni, E. Tombari, G.P. Johari, Thermochim. Acta 285 (1996) 243.
[25] W. Kauzmann, Chem. Rev. 43 (1948) 219.
[26] G. Adam, J.H. Gibbs, J. Chem. Phys. 43 (1965) 139.
[27] I.M. Hodge, J. Non-Cryst. Solids 169 (1994) 211.
[28] M.J. Richardson, M. Susa, K.C. Mills, Thermochim. Acta 280/281 (1996) 383.
[29] G.P. Johari, C. Ferrari, E. Tombari, G. Salvetti, J. Chem. Phys. 110 (1999) 11592.
[30] S.L. Simon, G.B. McKenna, Thermochim. Acta 307 (1997) 1.
[31] J.M. Hutchinson, S. Montserrat, Y. Calventus, P. Cortes, Macromolecules 33 (2000) 5252.
[32] I.M. Hodge, J. Non-Cryst. Solids 202 (1996) 164.
[33] A.Q. Tool, J. Am. Ceram. Soc. 29 (1946) 240.
[34] J. Malek, Macromolecules 31 (1998) 8312.
[35] C.T. Moynihan, P.B. Macedo, C.J. Montrose, P.K. Gupta, M.A. DeBolt, J.F. Dill, B.E. Dom, P.W. Drake, A.J. Easteal, P.B. Elterman, R.P. Moeller, H. Sasabe, J.A. Wilder, Ann. New York Acad. Sci. 279 (1976) 15.
[36] I.M. Hodge, Mater. Res. Soc. Symp. Proc. 215 (1991) 11.