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On determining the relaxation time of glass and amorphous pharmaceuticals' stability from thermodynamic data

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ABSTRACT

Spontaneous relaxation of an amorphous solid changes its properties with time, as does its slow crystallization, both resulting from slow molecular diffusion that decreases its free energy. When the solid is a pharmaceutical, this occurrence decreases its solubility and hence bioavailability, thus decreasing its effectiveness during storage. Its stability against crystallization or "shelf-life" is currently modeled by calculating the relaxation time, τ_{glass}, by using the specific heat C_p and the enthalpy of melting data in the viscosity-configurational entropy relation. We consider merits of such calculations, and find that use of, (i) the excess C_p and its hyperbolic dependence on temperature, (ii) the enthalpy of melting, and (iii) the fictive temperature, is inconsistent with the glass relaxation phenomenology, and their use leads to overestimate of τ_{glass}, and thus to a longer than real shelf-life of an amorphous pharmaceutical. We also argue that τ_{glass} is not the same as the characteristic time of spontaneous structural relaxation of a glass, and would not determine the nucleation or crystal growth rate in it.

1. Introduction

Because of its higher free energy, the glassy state of a material has a higher solubility than its crystalline state [1]. This recognition has led pharmaceutical scientists to prepare molecular, and proteins-based drugs [2–11] in the glassy or otherwise amorphous states. Those with a commercial and medicinal points of view anticipate that, (i) higher solubility and faster dissolution rate of an amorphous pharmaceutical would increase its bioavailability, (ii) a large number of medicinally beneficial compounds that are rejected because of their extremely poor solubility can become useful in their amorphous state, and (iii) the use of amorphous state can reduce the amount of additives that are currently used, despite their side effects, to increase solubility of a curative drug. Clearly, for molecular pharmaceuticals of poor aqueous solubility, particularly those that are hydrophobic and contain few groups that are capable of forming hydrogen bonds with water, both the higher solubility and faster dissolution rate are important attributes.

An amorphous solid has two characteristic features that cause its properties to change with time and thereby limit its long terms use. Thermodynamically speaking, (i) it is metastable with respect to the crystal state and therefore it tends to crystallize during storage, and (ii) it is kinetically unstable with respect to its lower energy but still disordered state [12–17], and its structure relaxes during storage. In both cases its physical properties change with time, more on crystallization than on structural relaxation. The rate at which this change occurs is higher the higher is the temperature at which the solid is kept. At a fixed temperature this rate decreases with time. The extent of change in the properties of a glass sample depends upon the energy, state, structure and intermolecular interactions. For a given material, this extent and the rate of change depend upon the procedure used for producing an amorphous solid. When it is made by slowly cooling a melt, the excess free energies over the crystal state, $G_{\text{exc}}^{\text{cryst}}$, and that over the equilibrium state, $G_{\text{exc}}^{\text{equil}}$, are relatively small and therefore the change in properties on crystallization and structural relaxation is small and the rate of change is slow, and when it is made by hyperquenching of a melt, by lyophilizing, spray-drying, vapor deposition, drying of a gelled state, random mechanical deformation and pressure collapse, both $G_{\text{exc}}^{\text{cryst}}$ and $G_{\text{exc}}^{\text{equil}}$ are large. Therefore, the change in the properties on crystallization is large and the initial rate is fast. Since most annealed state of pharmaceuticals have T_g below 373 K, the effects are large when their state formed by rapid cooling or flocculation is stored at a temperature of 300–310 K.

Molecular self-diffusion coefficient, D, determines the rates of both crystallization and structural relaxation and hence the rates of decrease in $G_{\text{exc}}^{\text{cryst}}$ and $G_{\text{exc}}^{\text{equil}}$. In both cases, the rate at which the decrease occurs becomes slower with time. Although both $G_{\text{exc}}^{\text{cryst}}$ and $G_{\text{exc}}^{\text{equil}}$ are important and they decrease together spontaneously,

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$G_{\rm exc}^{\rm cryst}$ decreases more than $G_{\rm exc}^{\rm equil}$. Therefore, decrease in $G_{\rm exc}^{\rm equil}$ is neglected in considering the effect of crystallization.

The quantity D of a mono-component system is then related to the relaxation time, τ, by the apparently equivalent equations,

$$D = \frac{x^2}{2\tau} \tag{1}$$

where x is the "distance of an elementary diffusion jump". Eq. (1), which was obtained for self-diffusion in crystals, is used for glasses and ultraviscous liquids and instead of using D, the shear relaxation time $\tau_{\rm shear} = \eta/G_\infty$ is used, where η is the viscosity and G_∞ the shear modulus. D is also related to η and d_0 the diameter of a molecule (or the diameter of the mean building unit) in a liquid by, $D = k_BT/\eta d_0$ where $k_{\rm B}$ is the Boltzmann constant and T is the temperature. Although it is the D value that determines nucleation and crystal growth, the overall crystallization rate is related to $\tau_{\rm shear}$, a macroscopic property that is more easily determined by experiments than D. Moreover there are concerns that properties determined by rotational diffusion such as dielectric relaxation time differ from those that are determined by translational diffusion alone such as viscosity and if crystallization requires hydrogen bonding and/or removal of steric effects from packing of molecular shapes, the overall crystallization would not be entirely controlled by the effective D. Since the Adam and Gibbs [18] model was originally used to determine $\tau_{\rm shear}$ from configurational entropy, it is believed that thermodynamic data may be used to obtain the crystallization rate. This constitutes the basis for determining the rate at which an amorphous solid may crystallize. This rate is determined by taking into account the decrease in the fictive temperature, T_f, of a glass sample with time, and thus implicitly by taking into account the decrease in $G_{\rm exc}^{\rm equil}$ with time.

On the assumption that dissolution and precipitation of an amorphous solid is a reversible process with an equilibrium, the solubility ratio of an amorphous solid to its crystal is given by, $(s_{\rm glass}/s_{\rm crystal}) = \exp(G_{\rm exc}^{\rm cryst}/RT)$ where s refers to the saturation solubility, R is the gas constant and T is the temperature. Thus, an amorphous solid has generally a higher solubility (and vapor pressure according to an analogous equation) than its crystal.

As mentioned earlier here, the enhanced solubility over their crystal form and higher vapor pressure makes the application of these concepts to development of amorphous solid pharmaceuticals especially beneficial. But when it slowly crystallizes during storage its $G_{\rm exc}^{\rm cryst}$ decreases and this reduces its saturation solubility and hence its bioavailability. Crystallization may also cause contraction in local regions of the initially amorphous solid, which in turn may produces internal (tensile) strains high enough to produce micro-cracks and to ultimately fracture its packaged form as a capsule or tablets intended for oral delivery, and it has been argued that spontaneous decrease in free energy of an amorphous pharmaceutical with time also decreases its chemical stability [17]. Accordingly, a pharmaceutical is more stable when it crystallizes more *slowly* at the storage temperature, and is less stable when it crystallizes relatively *rapidly*. Two reviews on the role of molecular motions on chemical [19] and physical [11] stabilities of amorphous pharmaceuticals have described some of these aspects.

In a detailed discussion of an amorphous pharmaceutical's stability against crystallization during storage, Shamblin et al. [20] used the Adam–Gibbs model, determined the relaxation time $\tau_{\rm glass}$ of the glassy state and provided a formalism for its temperature dependence, and used $\tau_{\rm glass}$ as a measure of the stability of a glass. Instead of using the configurational entropy, $S_{\rm conf}$, directly, they used the specific heat, C_p, and the enthalpy of melting of its crystal, ΔH_m, and obtained the plot of $\log_{10}(\tau_{\rm glass})$ against $1/T$. These plots were found to be curved, with slope increasing with increase in $1/T$ in a manner similar to the plots of $\log_{10}(\tau_{\rm liq})$ against $1/T$, but to a much lesser extent. The increasing slope of the curved plot of $\log_{10}(\tau_{\rm glass})$ against $1/T$ seems contrary to the general findings that such plots are straight lines, characteristic of the Arrhenius temperature dependence [13–16,21–24]. Shamblin et al. [20] have carefully described the assumptions made in determining $\tau_{\rm glass}$ for the purpose of estimating an amorphous solid's stability against crystallization, and their procedure has been used for discussing a pharmaceutical's shelf life [25,26]. More recently, Matteucci et al. [27] have used this procedure. Thus, it seems that physical stability of such solids could be modeled by using only the C_p and ΔH_m data.

As part of our studies of amorphous solids in general and of pharmaceuticals in particular, here we examine the relevance of the concepts of glass relaxation adapted by Shamblin et al. [20], and by others [25–27], for studying amorphous pharmaceuticals and modeling their physical stability. In particular, we inquire why their procedure led to $\tau_{\rm glass}$ values much larger than the value calculated by using the accepted methods in the study of glasses [21–24]. It turns out that the approximations made for estimating $\tau_{\rm glass}$ [20] has made their formalism inconsistent with the concept of the fictive temperature, T_f, of a glass as well as with the Adam–Gibbs model [18]. The findings also bear upon the use of C_p data for determining the variation of $\tau_{\rm liq}$ with T. Since an overestimate of the shelf-life of an amorphous pharmaceutical compromises with its effectiveness or bioavailability, it seems that, even if the Adam–Gibbs model has to be used, some of the approximations made in estimating $\tau_{\rm glass}$ should be eliminated. We also briefly review these, but in the context of amorphous pharmaceutical, because it appears that some of the features of the amorphous state are unfamiliar to most pharmaceutical scientists.

2. Molecular dynamics of glass and annealing effects

The rate of crystallization and its temperature dependence is usually estimated by measuring the spontaneous loss of the enthalpy by differential scanning calorimetry (DSC) [13–15], or by another technique that is sensitive to the change in the properties. When steric hindrance and hydrogen bonding needed for molecular packing are neglected, D determines the rate of crystallization. Since D is difficult to determine, one uses $\tau_{\rm shear}$ or the dielectric relaxation time, $\tau_{\rm diel}$, for this purpose. But variation of D with T differs from the variation of both $\tau_{\rm shear}$ and $\tau_{\rm diel}$. As a liquid is cooled, x decreases as the volume decreases and, according to Eq. (1), this decreases D in addition to the decrease caused by increase in $\tau_{\rm shear}$ and $\tau_{\rm diel}$. Thus, D in Eq. (1) varies with T implicitly as x varies with T. But the effect of change in T on τ is much greater than on x, and both τ and D of a solid of fixed structure, say a crystal in which the volume change is due to anharmonic forces and not due to random accumulation of volume resulting from structural fluctuations, follow the Arrhenius equation, i.e., τ (or D^{-1}) = $A \exp(E_A/RT)$, where A is a constant and E_A is the Arrhenius energy. The structure of an ultraviscous melt changes with T, as is known from direct studies of its radial distribution function and of its free volume and vibrational and configurational properties and this alters the variation of its $\tau_{\rm shear}$ and $\tau_{\rm diel}$ with T. Thus cooling increases $\tau_{\rm shear}$ and $\tau_{\rm diel}$ of an ultraviscous liquid beyond that expected from the Arrhenius temperature dependence, and a plot of $\ln(\tau)$ against $1/T$ becomes a curved line whose slope increases as $1/T$ increases. The plots *appear* to indicate that E_A of the Arrhenius equation is increasing with decreasing T.

Vitrification (kinetic-freezing of a liquid's structure) occurs gradually over a narrow temperature range. All properties therefore show a gradual change through this range. In technology, vitrification temperature is (conventionally and precisely) defined as the temperature at which $\eta = 10^{13.3}$ Poise (or dPa s^{-1}) and it is denoted by T_g [28]. On heating, C_p shows the beginning of a sigmoid-shape increase at the temperature at which a glass softens (devitrifies to liquid). In academic discussion, this temperature is taken as T_g for heating at 10 or 20 K/min rate and the calorimetric relaxation time, τ_{cal}, is said to have decreased to 1 ks or 100 s at this T_g. (A melt may appear as a rigid glass on a short time scale of observation and a glass may appear as a liquid on a long time scale.) In the context of amorphous pharmaceuticals formed by vapor phase deposition, mechanical deformation, lyophilization, spray-drying, drying of a gel, pressure collapse of crystals or by chemical reactions, the definition of T_g in terms of η does not apply, nor does the definition of glass softening apply in terms of the rise in C_p, because the rise in C_p is compromised by rapid enthalpy relaxation effects. Nevertheless, the state of solid obtained is regarded as similar to the one that forms when hyperquenching of a melt kinetic-freezes it at $T \gg T_g$.

Since our interest is in the properties to amorphous pharmaceuticals, it would be helpful to provide a brief review of generally observed thermodynamics and dynamics features of glassy state. Irrespective of how an amorphous solid is formed, its specific heat $C_{p,\text{glass}}$, enthalpy H_{glass} and entropy S_{glass}, decrease on cooling most rapidly initially and then slowly, and the rate of decrease ultimately becomes comparable to that of a crystal. The initially rapid decrease is attributed to three occurrences:

(i) During the cooling at rate q, a glass structurally relaxes over a time interval of T/q and as the rate of structural relaxation decreases, its contribution to the decreasing $C_{p,\text{glass}}$, H_{glass} and S_{glass} becomes smaller. If the glass is kept at a fixed T, the contribution decrease with time [13–17], and $C_{p,\text{glass},}$ H_{glass} and S_{glass} measured on the cooling path from T_g become further different from those measured on the heating path toward T_g.

(ii) Faster modes of relaxation in the characteristically broad distribution of relaxation times, whether expressed in the form of sum of single relaxation times as done by Majumdar in 1971 [29], or in terms of heterogeneous dynamics as reviewed by Ediger [30], kinetically freeze gradually on cooling from T_g. It has been argued that faster modes of motion in a distribution of times that remain unfrozen at T below the calorimetric T_g and they contribute more to glass thermodynamics at T immediately below T_g than at lower T [31]. This has been evident from enthalpy relaxation studies in which a glass was thermally cycled between two temperatures both of which were below T_g. When a sample was annealed at $T < T_g$ and then heated to another temperature that was still below T_g, the enthalpy lost on annealing was recovered on heating [32,33]. The finding led to the conclusion that each mode of motion in the relaxation time distribution has its own mini-T_g [32,33].

(iii) Molecular motions in local regions in the structure of a glass [31,34,35], i.e., from the JG relaxation [36], are found to have a role in nucleation and crystallization of a glass. Their contribution to dielectric properties decreases on cooling as well as on annealing a glass [37] thereby suggesting that the number of molecules involved in this relaxation decreases. In a recent review on the subject Bhattacharya and Suryanarayanan [38] concluded that JG relaxation plays an important role in the stability of amorphous pharmaceuticals.

Contributions from (ii) and (iii) to $C_{p,\text{glass}}$, H_{glass} and S_{glass} are often ignored. As long as a glass does not structurally relax in the time taken to measure its properties, $\log_{10}(\tau_{\text{glass}})$ against T plot is linear, as for crystals. Thus, on cooling, the Vogel–Fulcher–Tammann [39–41] type variation of τ_{liq} with T,

$$\log_{10}(\tau_{\text{liq}}) = A_{VFT} + \frac{B_{VFT}}{(T - T_0)} \tag{2}$$

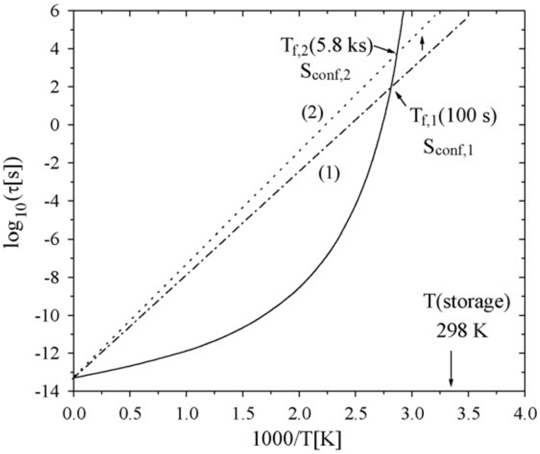

Fig. 1. An illustration for the logarithmic plot of τ_{diel} and τ_{shear} against the reciprocal temperature. The two straight line from the origin at $1/T = 0$ are for the Arrhenius plots with the energy that increases with decrease in the fictive temperature. Curve 1 is for the glassy state obtained by cooling at such a rate that its structure freezes at $T_{f,1}$ where its τ_{shear} is 100 s at $S_{\text{conf},1}$ and thereafter the plot become linear. Curve 2 is for the glassy state of obtained by cooling at such a rate that its structure freezes at $T_{f,2}$ where τ_{shear} is 5.8 ks at $S_{\text{conf},2}$. and thereafter the plot becomes linear. The small vertical arrow indicates the direction in which τ_{shear} would increase on structural relaxation during storage at 298 K. This would increase its stability against crystallization. The extrapolation limit is evident in the figure.

gradually changes to the Arrhenius type variation of τ_{glass},

$$\log_{10}(\tau_{\text{glass}}) = A + \frac{E_A}{RT} \tag{3}$$

where A_{VFT}, B_{VFT} and T_0 in Eq. (2) are empirical constants for a material. The slope of the $\log_{10}(\tau_{\text{liq}})$ against $1/T$ plot increases with increasing $1/T$ until a liquid vitrifies and thereafter the slope of $\log_{10}(\tau_{\text{glass}})$ plot becomes fixed at E_A/R [13–16,21–24]. This latter plot is seen as an extension of a straight line drawn between $\log_{10}(A)$ and $\log_{10}(\tau_{\text{liq}})$ at which the glass structure kinetically froze. This is illustrated in Fig. 1, where the continuous lines denote the measured relaxation time and the broken line the extrapolation from the value of $\log_{10}(A)$ which is taken as −13.3 s. Increasing an experiment's time scale increases τ_{glass} at a given T and shifts the $\log_{10}(\tau_{\text{glass}})$ plot to higher $1/T$ as does isothermal annealing which is indicated by an arrow. The relaxation time and η of the state ultimately reached at T_{ann} is found to be the same as τ_{liq} at $T = T_{\text{ann}}$ [42]

The Arrhenius type τ_{glass}-T plots and increase in τ_{glass} on annealing has been observed usually by mechanical relaxation [24] and viscosity measurements [22,23]. More recently, it was also observed by two unusual techniques: (i) from measurements of the intensity of second harmonic generation in the rotational and reorientational dynamics in chromophore-doped polystyrene [43] and (ii) from dielectric measurements [44]. In the latter study [45], τ_{diel} of poly(vinylethylene) glass was found to agree with that calculated from Ngai's coupling model [45,46] according to which the α-relaxation time is determined by a combination of the JG relaxation time and the distribution parameter of the α-process. The value of E_A in Eq. (3) varies with the rate q at which the liquid has been cooled to vitrify it. When q is high, kinetic-freezing occurs at a high T, and τ_{shear} is shorter and E_A is low, as indicated for $T_{f,1}$, and when q is low kinetic-freezing occurs at a lower T, and τ_{shear} is long and E_A is high, as indicated by $T_{f,2}$ in the illustration in Fig. 1.

3. Fictive temperature, configurational entropy and relaxation time

We briefly recall the significance of T_f of a sample because, in combination with the Adam–Gibbs model, it was used for determining the stability of amorphous pharmaceuticals. T_f is defined as the temperature at which the measured or extrapolated physical property of a glass is the same as that of its supercooled liquid. Its value depends upon the property used to determine it. It is usually measured by extending a line drawn *parallel* to the H–T curve for the *glass* until the extended line meets the H–T curve for the liquid, as illustrated in Fig. 2A. To quote Moynihan et al. [14]: "As shown in Fig. 2, T_f *via* Eq. (2) is determined by the temperature of intersection with the equilibrium H–T curve of a line drawn through the (H, T) point of interest parallel to the glass H–T curve, i.e., the fictive temperature at point a on the cooling curve is $T_{f,a}$." (A similar definition appears in Fig. 9.3 of the monograph by Scherer [13] and in other papers and monographs on the subject [14–16,21–23].) More recent studies have shown that entropy consideration yield the same T_f as the enthalpy [47,48]. In summary, a glass at a temperature T has a frozen-in configuration of the liquid at T_f and its properties correspond to this configuration. At a fixed temperature it relaxes towards a structure of lower volume, C_p, H and S at a progressively slower rate. When T_f is higher than the actual temperature, properties change with time and T_f decreases. It is to be noted that stability of a non-crystallizing glass was originally considered in terms of change of the refractive index [49] with time, which led to the definition of T_f before it was defined in terms of a thermodynamic function. (It was later considered in terms of the density [50] and a different T_f corresponding to the state of a glass achieved by localized motions at $T \ll T_g$.) When the difference between the temperature of a sample and its T_f is less, the change in its properties with time is rapid and the net change is less, but when the difference is larger, the change is slow and the net change is larger. At the same T, the T_f value of a sample on the cooling path differs from the T_f value on the heating path.

Although T_f was defined in thermodynamic terms, it is also discussed in terms of the relaxation time. It is regarded as the temperature at which the $\log_{10}(\tau_{\text{liq}})$ against $1/T$ plot changes from the Vogel–Fulcher–Tammann to the Arrhenius type as shown in Fig. 1. Structural relaxation decreases T_f with time, increases τ_{glass} towards τ_{liq} and lowers the temperature at which the slope of the plot changes [13,16,22,23].

As mentioned earlier, Shamblin et al. [20] determined τ_{glass} from the Adam–Gibbs [18] relation between η and S_{conf}, and used it as a measure of the stability of a glass. It is worth noting that only in studies of ultraviscous liquids has an equilibrium thermodynamic property been quantitatively related to the rate of molecular motions – such properties are not related to chemical reaction or nucleation and crystallization rates. Moreover, there are both analytical and fundamental concerns on the use of Adam–Gibbs model for determining the temperature dependence of τ_{liq}. Laughlin and Uhlmann [51] who tested this model by using η–T variation of several molecular liquids pointed out its weakness; Mazurin [52] discussed the shape of the η–T plots obtained and the possibility of $\eta \to \infty$, Johari [53,54] critically discussed it on mechanistic grounds; Ngai [55] argued that the model ignores both the distribution of relaxation times and occurrence of the JG relaxation, both recognized as characteristics of ultraviscous melts and Dyre et al.'s [56] analysis has put into question its prediction of the manner of progressively rapid increase in τ_{diel} on cooling. Nevertheless, its wide use owes to its satisfactory fit of τ_{diel} and η against T plots over a wide range.

According to the Adam–Gibbs model, S_{conf} decreases on cooling until the liquid vitrifies and thereafter does not change on further cooling. The glassy sample formed is termed iso-configurational (fixed structure) state, but τ_{glass} increases on cooling. This seems consistent with the observed change from the temperature dependence of τ_{liq} in Eq. (2) to that of τ_{glass} in Eq. (3). Accordingly, the variation of τ_{glass} with T was written as [20],

$$\tau_{\text{glass}} = A_{AG} \exp\left(\frac{C}{TS_{\text{conf},T_f}}\right) \tag{4}$$

where C is a material's constant and S_{conf,T_f} is the value of S_{conf} at T_f. The pre-exponential term A_{AG} is taken to be the same as the term A_{VFT} in Eq. (2) and also the same as the term A in Eq. (3). For convenience, it is accepted that $T_f = T_g$ when $q = 10$ K/min. In contrast, $T_f > T_g$ when $q > 10$ K/min, and $T_f < T_g$ when $q < 10$ K/min, as is also the case for an annealed glass. Note that A_{AG} and the constant C cannot be determined *a priori*, and therefore the Adam–Gibbs equation does not yield values of either τ_{liq} or τ_{glass} – it only yields its dependence on T. Since the equation was developed for viscosity, it also does not account for the distribution of relaxation times.

Since S_{conf,T_f} in Eq. (4) is fixed, the plot of $\log_{10}(\tau_{\text{glass}})$ against $1/T$ has a slope of $C/2.303S_{\text{conf},T_f}$. This slope would be equal to E_A of Eq. (2). When q is low, T_f and S_{conf,T_f} of the glass formed are low and E_A is high, and when q is high, T_f and S_{conf,T_f} of the glass formed are high and E_A is low. This is also illustrated in Fig. 1. On isothermal annealing, S_{conf} is known to decrease and this is equivalent to saying that S_{conf,T_f} decreases as T_f decreases. Hence, E_A would increase with time until it becomes equal to $C/2.303S_{\text{conf}}$, S_{conf} referring to the supercooled liquid value. At $T < T_0$, τ_{liq} is seen to be formally infinite, but Dyre et al. [56] argue that it may not be so. In contrast, τ_{glass} remains finite at $T < T_0$. It is relatively low when T_f and S_{conf,T_f} are high. E_A is given by the slope of the straight line between two points, $\log_{10}(A)$ at $1/T = 0$ and $\log_{10}(\tau_{\text{liq}})$ at $1/T = 1/T_f$ and τ_{glass} lies on an extension of this line to $T < T_f$, as also illustrated in Fig. 1.

Fictive temperature is also an integral part of the Tool-Narayanaswamy–Moynihan model for non-exponential, non-linear enthalpy relaxation of a glass [14,57,58],

$$\tau(T, T_f) = \tau_0 \exp\left(\frac{x\Delta h^*}{RT} + \frac{(1-x)\Delta h^*}{RT_f}\right) \tag{5}$$

where τ_0 is the pre-exponential factor, x is the non-linearity parameter, Δh^* is the activation energy and R is the gas constant. For a fixed T_f, the second term in brackets is constant and therefore $\ln(\tau_{\text{glass}})$ varies according to the Arrhenius equation with E_A equal to $x\Delta h^*/R$ and the intercept equal to $(\ln(\tau_0) + (1-x)\Delta h^*/RT_f)$, instead of $\ln(\tau_0)$. For using the Adam–Gibbs model for ultraviscous liquids [18], Eq. (5) was modified to [58],

$$\tau(T, T_f) = \tau_0 \exp\left(\frac{DT_0}{T - (T/T_f)T_0}\right) \tag{6}$$

where A_{VFT} of Eq. (2) has been replaced by τ_0, and B_{VFT} by DT_0. Eq. (6) takes into account the increase in both τ_{liq} and τ_{glass} with decrease in T, as well as with decrease in T_f. When T_f of a glass decreases with time at a fixed T, τ_{glass} increases formally as the term T/T_f in the denominator of Eq. (6) increases. For a fixed T_f,

$$\tau_{\text{glass}}(T) = \tau_0 \exp\left(\frac{DT_0}{T - \phi T}\right) \tag{7}$$

where ϕ is a constant equal to T_0/T_f. Thus, $\log_{10}(\tau_{\text{glass}})$ varies as $1/(T - \phi T)$. It is evident that Eq. (7) does not correspond to the Arrhenius variation of τ_{glass} with T, while Eq. (5) does. In this respect, it differs from Eq. (5). It is also to be noted that experimental data on the temperature dependence of η and τ_{diel} [13–16,22–24,43,44] have also been found to deviate from the prediction of Eq. (7).

4. Use of specific heat and enthalpy of melting for calculating the relaxation time

At mentioned earlier here, τ_{glass}, was taken to be equal to the reciprocal of the overall crystallization rate [20,27], and used for estimating the stability of a pharmaceutical during storage. To recall, Shamblin et al. [20] combined Eq. (2) with the Kauzmann temperature T_k, i.e., the temperature at which the extrapolated entropy of a supercooled liquid seems to become equal to the entropy of its crystal [59], and thus they [20] related τ_{liq} and τ_{glass} to C_p and the enthalpy of melting of its crystal state, ΔH_{m}. In doing so, they assumed that, (i) S_{conf} is equal to the excess entropy of the liquid over the crystal state, i.e., the configurational specific heat, $C_{p,\mathrm{conf}}$ is equal to the difference between $C_{p,\mathrm{eq\,liq}}$ and $C_{p,\mathrm{cryst}}$, where $C_{p,\mathrm{eq\,liq}}$ in their terminology, which we retain here, is the specific heat of the equilibrium supercooled liquid, and, (ii) the temperature dependence of $(C_{p,\mathrm{eq\,liq}} - C_{p,\mathrm{glass}})$, like that of $(C_{p,\mathrm{eq\,liq}} - C_{p,\mathrm{cryst}})$, is hyperbolic. Thus they defined a term γ_{C_p} as [20],

$$\gamma_{C_p} = \frac{C_{p,\mathrm{eq\ liq}} - C_{p,\mathrm{glass}}}{C_{p,\mathrm{eq\,liq}} - C_{p,\mathrm{cryst}}} \tag{8}$$

The term γ_{C_p} was then used to characterize the variation of $\log_{10}(\tau_{\mathrm{glass}})$ with T. Thus, T_g, T and γ_{C_p} became related to T_f by,

$$\frac{1}{T_f} = \frac{\gamma_{C_p}}{T_g} + \frac{1-\gamma_{C_p}}{T} \tag{9}$$

With γ_{C_p} and T_g becoming known, Eq. (9) could be used to determine T_f of a glass as a function of T. To use Eqs. (6) and (7) where T_f appears in the denominator, one also requires T_0. They assumed that $T_0 = T_k$, and estimated T_k from the equation [20],

$$\frac{1}{T_k} = \frac{1}{T_m}\left(1 + \frac{\Delta H_m}{K}\right) \tag{10}$$

where T_m is the melting temperature. The quantity K was defined as,

$$(C_{p,\mathrm{eq\ liq}} - C_{p,\mathrm{cryst}}) = \frac{K}{T}; \quad K = T(C_{p,\mathrm{eq\ liq}} - C_{p,\mathrm{cryst}}) \tag{11}$$

Eq. (11) was used to determine K which on substitution in Eq. (10) yields T_k. By using the T_k value for T_0, and T_f determined from Eq. (9), the plots of $\log_{10}(\tau_{\mathrm{glass}})$ against $1/T$ were calculated from Eq. (6). Thus they found that for the condition $0 < \gamma_{C_p} < 1$, the slope of the $\log_{10}(\tau_{\mathrm{glass}})$ against $1/T$ plot increased as $1/T$ increased [20].

The characteristic structural relaxation time determined from enthalpy loss measurements by DSC was found to be within an order of magnitude of the estimate of τ_{glass} of indomethacin and sucrose [20]. They also concluded that while T_k represents the temperature below which molecular motions in the supercooled liquid are negligible on any time scale, T_k of real glass represents a temperature below which the time scale for structural relaxation is of the order of years. It is known that molecular mobility of a glass at T_k is *not* zero and also that on annealing a glass at T_k the mobility would be too slow for its structure to reach equilibrium.

5. A conflict between glass relaxation and use of specific heat data

To determine whether the use of C_p and ΔH_{m} data for calculating the τ_{glass} is consistent with the glass phenomenology or not, we consider the approximation made in deducing Eq. (9), as follows:

(1) In the Adam–Gibbs' description, the vibrational part of $C_{p,\mathrm{eq\,liq}}$ is taken to be equal to $C_{p,\mathrm{glass}}$ and therefore [18] S_{conf} is written as,

$$S_{\mathrm{conf}}(T) = \Delta C_p \ln\left(\frac{T}{T_2}\right) \tag{12}$$

where ΔC_p (= $C_{p,\mathrm{eq\,liq}} - C_{p,\mathrm{glass}}$) is the configurational part, $C_{p,\mathrm{conf}}$ and T_2 is the temperature at which the extrapolated S_{conf} of ultraviscous liquid would become zero. For determining the temperature dependence of viscosity they [18] used a constant value of ΔC_p. Others who use the Adam–Gibbs equation in their discussion of τ_{liq} use a temperature dependent ΔC_p which is determined from the experimental values of $C_{p,\mathrm{eq\,liq}}$ and extrapolated values of $C_{p,\mathrm{glass}}$.In contrast for determining K from Eq. (7), Shamblin et al. [20] used $C_{p,\mathrm{conf}}$ as equal to $C_{p,\mathrm{exc}}$ (=$C_{p,\mathrm{eq\,liq}} - C_{p,\mathrm{cryst}}$), and hence making S_{conf} equal to S_{exc}. But this is usually not the case, and later analyses have shown $C_{p,\mathrm{cryst}} < C_{p,\mathrm{glass}}$, because phonon frequencies are lower for a glass than for its crystal (glasses are usually bulkier than their crystals) and anharmonic forces associated with vibrations would usually contribute more to $C_{p,\mathrm{glass}}$ than to $C_{p,\mathrm{cryst}}$ [60–62]. Therefore, use of $C_{p,\mathrm{exc}}$ in place of $C_{p,\mathrm{conf}}$ yields inaccurate values of S_{conf} and thus inaccurate values for both τ_{liq} and τ_{glass}. (We note that it has also been conjectured that $S_{\mathrm{conf}} = 0.7S_{\mathrm{exc}}$ [63], or, depending upon the liquid, S_{conf} may be even less than $0.7S_{\mathrm{exc}}$ particularly when $C_{p,\mathrm{conf}}$ is much less than $C_{p,\mathrm{exc}}$ [63]. Such approximations seem now unnecessary because the vibrational part of C_p of a liquid can be determined by temperature-modulated calorimetry, thus allowing one to obtain $C_{p,\mathrm{conf}}$ by an experiment [64,65].) As mentioned earlier here, estimates of $C_{p,\mathrm{conf}}$ would include contributions from the distribution of relaxation times at $T < T_g$ and from the JG relaxation also at $T > T_g$. These contributions become negligibly small only at T far from T_g.

(2) As a liquid is cooled toward T_2 ($S_{\mathrm{eq\,liq}} - S_{\mathrm{glass}}$), approaches zero in the Adam–Gibbs model [18]. In contrast, when it is cooled toward T_k, S_{exc} (=$S_{\mathrm{eq\,liq}} - S_{\mathrm{cryst}}$) approaches zero. In terms of the relevant C_p values, one assumes that ($C_{p,\mathrm{eq\,liq}} - C_{p,\mathrm{cryst}}$) has a hyperbolic dependence on T which implies that its value would approach infinity as $T \to 0$. This approximation has a significant effect on calculation of temperature dependence of τ_{liq}. But when ($C_{p,\mathrm{eq\,liq}} - C_{p,\mathrm{glass}}$) in the numerator of Eq. (8) is also assumed to have a hyperbolic dependence on T, it seems inappropriate to calculate the ratio γ_{C_p} from Eq. (8) and to then use its value to estimate ultimately τ_{glass} from Eq. (7).

(3) In modeling the equilibrium dynamics of a pharmaceutical melt and non-equilibrium dynamics of its glass, T_f was estimated by drawing a straight line parallel to *the temperature-axis* as given in Fig. 1, Ref. [25] and the same equations as in Ref. [20]. When T_f was needed to calculate τ_{glass} from Eq. (7) it was estimated, as is illustrated in Fig. 2B, by drawing a straight line parallel to the *H*–*T* plot for a crystal in Fig. 6 of Ref. [20], and it was stated: "Since T_f relates configurational entropy of an equilibrium supercooled liquid to that of a non-equilibrium system having a configurational entropy of equal value at a *lower* temperature, the S_c of a glass can be described by Eqs. (10), 13–14 at temperatures which *actually* fall below T_k (e.g., when $T_f = T_k$)." Now, T_f is usually determined by extending the *H*–*T* curve linearly for the glassy to the liquid state, and by drawing a line that is parallel to this line when the sample has been annealed [13–16,22–24]. It can be equivalently done for the *S*–*T* plots. But if we use a line parallel to the plot for crystal state, we would obtain a lower T_f than the true value, as shown in Fig. 2B. If this lower value were used in Eq. (7), it would lead to higher than the real value of τ_{glass}. It seems that using inaccurate value of T_f and determining τ_{glass} by using Eqs. (9)–(11) would lead to overestimate of a pharmaceutical's shelf life.

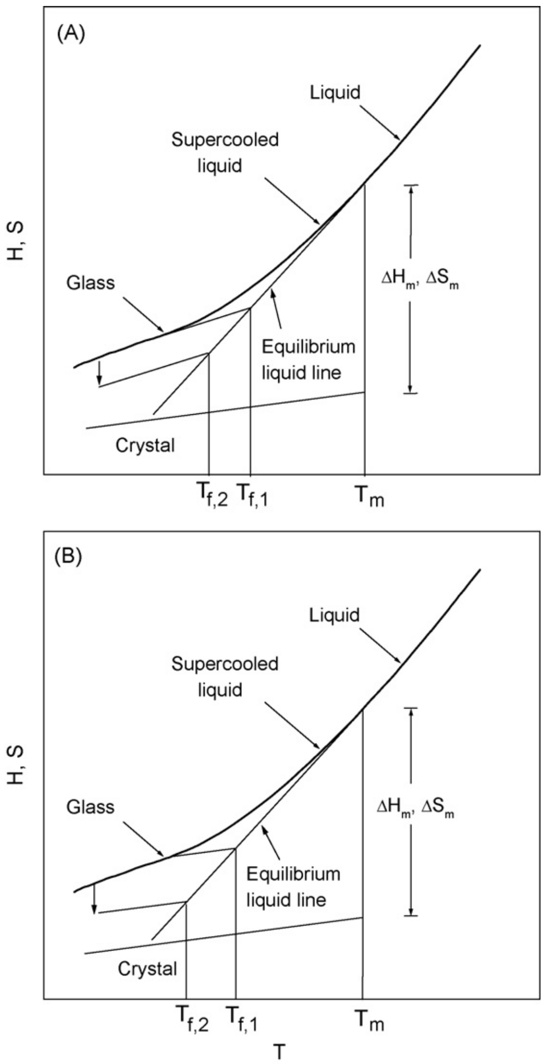

Fig. 2. An illustration of the decrease in the enthalpy and entropy of a liquid against the temperature during cooling and of that of the glass formed. Vertical arrow indicates the decrease on annealing due to structural relaxation with time. $T_{f,1}$ is the fictive temperature of a glass formed by cooling at a certain rate and $T_{f,2}$ is the fictive temperature of a glass after annealing for a certain time. It is the temperature at which a liquid would have kinetically frozen were it cooled slowly enough to yield a glass of the same property as that obtained on annealing. Panel A shows the accepted method for determining the fictive temperature. To obtain $T_{f,1}$, the plot for the glass is extended to the equilibrium liquid line. To obtain $T_{f,2}$, a line drawn parallel to the curve for the *glass* is extended to meet the equilibrium liquid line. Panel B is an illustration after Fig. 6 in Ref. [20], where the total enthalpy and entropy (and not, as stated, the configurational enthalpy and entropy), were plotted. Here $T_{f,1}$ and $T_{f,2}$ were determined by extending the lines drawn parallel to the curve for the *crystal phase*. In Fig. 1, Ref. [25], $T_{f,1}$ and $T_{f,2}$ were also determined differently, in their case by drawing lines parallel to the *axis*. Such plots yield incorrect values of $T_{f,1}$ and $T_{f,2}$.

6. Crystallization rate and relaxation time

Lastly we consider whether the overall crystallization rate may be related to the inverse of τ_{glass}. It is not generally recognized that there are two types of molecular mobilities in a glass. These are distinguished not only by their dynamics but also by the consequences they have for the properties of a glass. One type of mobility is random or Brownian self-diffusion. Its characteristic time is determined by an experiment in which an external stress is applied to bias the direction of self-diffusion and then measuring the time it takes to return to random diffusion after removing the stress. Its characteristic time is τ_{glass} that follows the Arrhenius equation. The second is the already "biased-diffusion" that leads to structural relaxation towards the equilibrium value with time and which is observed as a decrease in its volume, C_p, H and S. Its characteristic time, $\tau_{\text{struc irrev}}$, is determined by measuring the change in these and other physical properties with time at a fixed T. With time $\tau_{\text{struc irrev}}$ increases as a result of "biased-diffusion" and T_f decreases. Clearly, $\tau_{\text{struc irrev}}$ is not the same as τ_{glass}.

When supercritical nuclei already exist in a glass structure, crystallization becomes (Brownian) diffusion-controlled. Its rate is determined by D (η according to the Stokes–Einstein equation) or equivalently τ_{shear}. The value of τ_{shear} is generally taken to be equal to $\tau_{\text{cal},}$ τ_{diel} or the relaxation time determined from nmr experiments. In regard to pharmaceuticals, it was found that τ_{glass} calculated from Eq. (6) agrees with the measured $\tau_{\text{struc irrev}}$ for indomethacin and sucrose within a factor of ten (see Fig. 8, Ref. [20]). But it is difficult to see this agreement as a justifiable support for estimating τ_{glass}. It may be that the approximations made for determining both τ_{glass} and $\tau_{\text{struc irrev}}$ led to a similarly approximate agreement between the two.

7. Conclusions

A set of assumptions and approximations made for determining the configurational entropy contribution from the specific heat data seems to lead to unreliable estimates of the relaxation time of the glassy state of pharmaceuticals. Further complications in such estimates arise from use of a differently determined fictive temperature. Some of the same assumptions have been made in describing the sensitivity of the relaxation time to changing T by using a quantity m that is equal to the value of the slope of the Oldekop plot [21] at $T = T_g$. Therefore, such estimates of m may also be subject to a justifiable scrutiny. As discussed before [53–56,60,64], the apparent correlation between thermodynamics and molecular dynamics of even viscous liquids remains controversial, and the balance of evidence is that such a correlation is generally not valid for all substances. Accurate values of the vibrational and configurational heat capacity measured by using temperature-modulated calorimetry [65–68] may help examine the merits of the entropy model.

The characteristic time for spontaneous structural relaxation is not the same as the characteristic time for Brownian diffusion or molecular relaxation. They correspond to different processes, and Brownian diffusion is known to determine nucleation and crystal growth rates. Commercial and medicinal concerns require that experimental studies be used for determining the shelf life of an amorphous pharmaceutical in terms of its bioavailability. It is also academically important because molecule-specific properties often determine the nucleation and crystallization rates.

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A glass formed by rapidly cooling a liquid has a high T_f, which decreases rapidly with time until the equilibrium state is reached. When the structure does not change with T and time, T_f does not change. When it changes with T faster than the time taken to measure a property, T_f is the same as T. Theories of such changes have been well accepted, and the properties of a glass and its thermal history are described by its T_f. Once the glass structure remains fixed with changing T, T_f of a non-equilibrium (real) glass does not change, and its τ varies according to Eq. (3) given here. Either T_f of a glass does not vary with T or only slightly decreases, i.e., $\mathrm{d}T_f/\mathrm{d}T$ is zero or slightly negative (see description and Fig. 9 in Ref. [14]) After a structurally relaxed sample is heated, T_f crosses the equilibrium liquid line (for which $T_f = T$) in its plot against T and T_f becomes less than T. It then increases in a sigmoid shape manner and meets the equilibrium liquid line from below.

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The quantity γ_{C_p} was called "fragility". $\gamma_{C_p} = 1$, corresponded to a "strong" glass, or Arrhenius type dependence of τ_{glass} on T, and $\gamma_{C_p} = 0$ corresponded to "fragile" glass, or a Vogel–Fulcher–Tammann type dependence of τ_{glass} on T. For $\gamma_{C_p} = 0$, $C_{p,\mathrm{eq.liq}} = C_{p,\mathrm{glass}}$, and for $\gamma_{C_p} = 1$, $C_{p,\mathrm{glass}} = C_{p,\mathrm{cryst}}$. The real glasses were said to fall in between the two behaviors. For $\gamma_{C_p} = 0$, T_f is generally equal to T, i.e., the liquid does not kinetically freeze and there would be no change in C_p on cooling. Note that the "strong and fragile" terminology is also used for equilibrium liquids.

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