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The use of thermal methods for predicting glass-former fragility

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Abstract

Glass-former fragility describes the changing dynamics of a supercooled liquid with temperature and so dictates the temperature of glass transition as well as the dynamics of the non-equilibrium glassy state. Fragility parameters can be calculated from either experimental relaxation time or viscosity data. Predictions of fragility can also be made using thermal methods. The objectives of this manuscript are to evaluate three thermal methods of fragility prediction and, using these methods, to predict the fragility of a number of pharmaceutical glass-formers.

Using differential scanning calorimetry, fragility predictions were performed by extrapolating configurational entropy to zero and by calculating an activation enthalpy of structural relaxation at the glass transition (ΔE_{T_g}) from the scanning rate dependency of the glass transition temperature, and glass transition width. On comparison with experimental Vogel–Tammann–Fulcher (VTF) fragility parameters for four glass-formers, all thermal methods were found to have reasonable predictive ability. Characterisation of pharmaceutical glass-formers by all thermal methods yielded predicted VTF D parameters in the range of 7–15. Predictions for a further 10 pharmaceutical glass-formers using only the configurational entropy method were within this range suggesting that moderately 'fragile' behaviour may be a common feature of such materials. © 2001 Elsevier Science B.V. All rights reserved.

Keywords: Fragility; Glass transition; Configurational entropy; Activation enthalpy of structural relaxation; Pharmaceutical glass-former

1. Introduction

The amorphous state is very relevant to the formulation of pharmaceuticals, both as a means of improving the bioavailability of poorly soluble materials and as a consequence of rigorous processing that can provide a focus for accelerated physical and chemical change [1]. Whether amorphous phase is introduced intentionally or unintentionally, it will commonly present stability problems [2,3] because greater molecular mobility in the amorphous state relative to the crystalline state often lowers the activation barriers for processes such as crystallisation and chemical degradation. It is of profound importance for the pharmaceutical scientist to understand how molecular mobility in the amorphous state changes with temperature. Such knowledge facilitates the selection of storage conditions that reduce the rates of detrimental changes to acceptable levels. Appropriate annealing conditions (that allow relaxation to increase glass stability) or ageing conditions (allowing recrystallisation of unwanted amorphous phase) can be selected based upon such information.

Measurement of relaxation behaviour following a perturbation from equilibrium allows direct assessment of molecular mobility. Powdered pharmaceutical materials are not always amenable to such measurements (e.g. dielectric spectroscopy or measurement of shear viscosity) as sample manipulation is often needed for analysis and long experiment times may

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result in unwanted physical or chemical change. Fortunately, thermal methods can be used to estimate the effect of temperature on the mean relaxation time, τ, in supercooled liquids and so a reasonable prediction of glass-former fragility can be made.

Different thermal methods of fragility prediction are described here. Section 3 offers an evaluation of each method using both new and existing data for well-characterised glass-formers. Particular attention is given to the validity of using such methods for small organic molecules of pharmaceutical interest as these methods were validated mainly using inorganic or polymeric glass-formers. In Section 4, fragility predictions for a range of pharmaceuticals are presented and some general observations made for this category of material. The prediction of molecular mobility below the glass transition is also discussed.

1.1. Liquid supercooling and glass formation

A liquid cooled to below its melting temperature is said to be supercooled. Although thermodynamically metastable with respect to the crystalline state, supercooled liquids can exhibit effective equilibrium behaviour as long as crystallisation is impeded. The viscosity of supercooled liquids undergoes substantial increase on temperature reduction that is accompanied by a large increase in the timescale of molecular rotational and translational motions. As a liquid experiences increased supercooling, the timescales of molecular motion will coincide with the experimental timescale which, inevitably, results in the loss of equilibrium. The system is now said to be in the glassy state, the viscosity of which is so great that solid behaviour is observed. The glass transition represents a change from equilibrium to non-equilibrium conditions on cooling or the reverse process on heating. The temperature at which glass transition takes place reflects the kinetic behaviour of the system and not a thermodynamically driven process. In this analysis, the experimental glass transition temperature (T_g) is defined as the extrapolated onset temperature measured on heating through the glass transition using differential scanning calorimetry (DSC).

Changes in enthalpy or free volume that occur on liquid supercooling and glass formation are shown graphically in Fig. 1. The lowest enthalpy crystalline state is also included in this schematic indicating the first-order melting transition at temperature T_m. Cooling a liquid to below T_m without crystallisation produces continuous changes in enthalpy and free volume, with departure from equilibrium at the glass transition causing a discontinuous change in these parameters. A broken line represents an equilibrium supercooled liquid that would form were it not for the intervention of the glass transition. Further cooling to below T_g would eventually yield a supercooled liquid equal in enthalpy to the crystalline state. The serious thermodynamic implications of this scenario were described by Kauzmann [4] in terms of entropy, as temperature decrease would eventually yield a disordered liquid state lower in entropy than the most ordered crystalline state, ultimately creating negative entropy. Fortunately, such an entropy ‘crisis’ is never encountered as T_g will always intervene at a higher temperature. The isoentropic point between a supercooled liquid and crystal is described as the Kauzmann temperature (T_K).

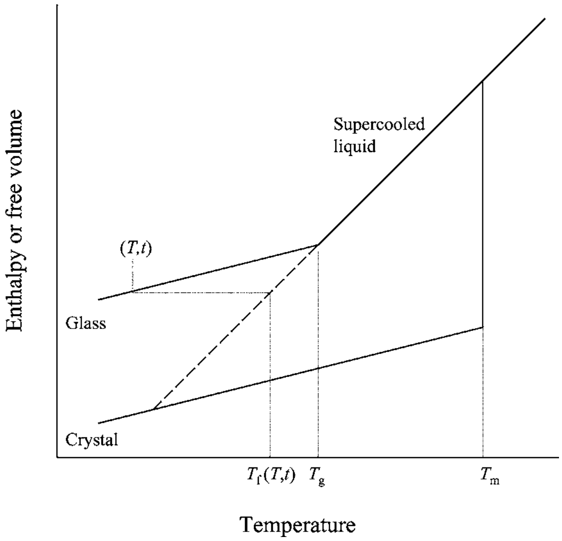

Fig. 1. The relationship between enthalpy/free volume and temperature for liquid, supercooled liquid, glass and crystalline phases.

1.2. Kinetic behaviour of supercooled liquids

The rate of change of viscosity (η) on liquid supercooling often deviates from the Arrhenius relationship. The magnitude of such deviation can be described using the fragility concept [5]. Supercooled

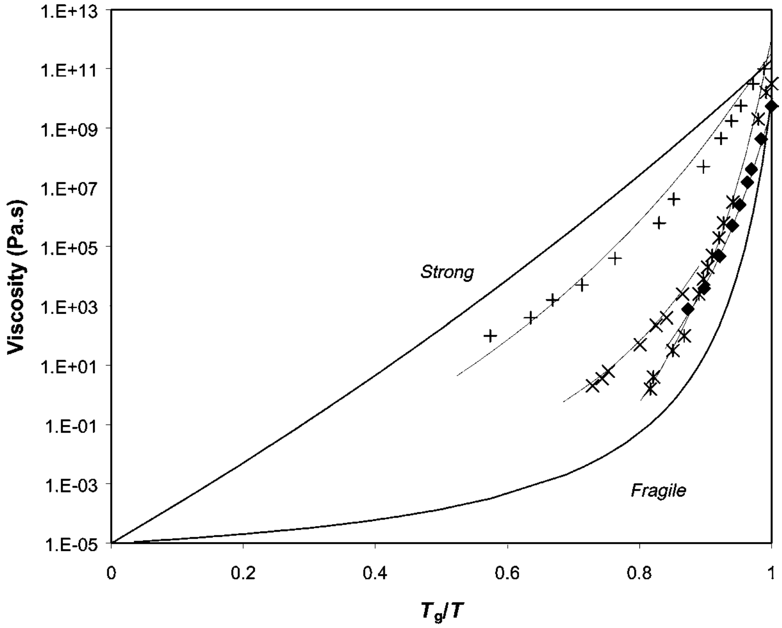

Fig. 2. Viscosity vs. temperature scaled to T_g for B_2O_3 (+); sorbitol (×), *o*-terphenyl (✳) and IMC (◆).

liquids exhibiting Arrhenius-like behaviour are classified as 'strong' liquids whereas 'fragile' liquids display marked non-Arrhenius behaviour. A useful method of depicting fragility is to plot η in an Arrhenius fashion, with temperature scaled to a fixed value at which η is known. Data for four glass-formers are presented in such a manner in Fig. 2 with temperature scaled to T_g, a temperature at which η reaches a relatively narrow range of 10^{10}–10^{12} Pa s. Extremes of fragility are also shown to demonstrate the limits within which liquid dynamics fall. Of the four model glass-formers included in Fig. 2, B_2O_3 shows the least deviation from Arrhenius behaviour so is a 'strong' glass-former. Conversely, sorbitol, *o*-terphenyl and indomethacin (IMC) all exhibit 'fragile' behaviour.

The Vogel–Tammann–Fulcher (VTF) equation [6–8] in the modified form describes the relationship between η and temperature (T) in the supercooled region:

$$\eta = \eta_0 \exp\left(\frac{DT_0}{T - T_0}\right) \tag{1}$$

where η_0, D and T_0 are constants. D is termed the strength parameter, with a large D value (>30) representing 'strong' behaviour and low D value (<10) representing 'fragile' behaviour. Changes in molecular dynamics can also be described using relaxation time (the timescale of equilibration following any perturbation). A distribution of relaxation times is invariably encountered at a given temperature, particularly in the supercooled liquid and glass regions, so a mean relaxation time (τ) is used. The implications of this behaviour are addressed in Section 4. Both η and τ exhibit a comparable relationship with temperature and so the VTF equation can also be presented in the following form (using a pre-exponential constant τ_0):

$$\tau = \tau_0 \exp\left(\frac{DT_0}{T - T_0}\right) \tag{2}$$

In addition to the ability to describe liquid dynamics in the supercooled region for a wide range of glass-formers, the VTF expressions also provide information of probable thermodynamic significance in the form of the constant T_0. Estimates of T_K via free volume calculations often match VTF T_0 with remarkable accuracy [9–11]. This relationship is not very surprising as T_0 represents the temperature at which either η or τ become infinite, a point which can be conceptually related to T_K.

Non-Arrhenius behaviour in the supercooled region can be accounted for by the presence of co-operative molecular motions [12]. Adam–Gibbs theory [12] defines the size of co-operatively rearranging regions using the configurational entropy (S_c) of a supercooled liquid via the Adam–Gibbs equation:

$$\tau = \tau_0 \exp\left(\frac{C}{TS_c}\right) \tag{3}$$

where C is a constant. This expression is of profound importance as it links supercooled liquid dynamics with the thermodynamic function S_c, that changes with temperature according to the following relationship:

$$S_c = \int_{T_2}^{T} \left(\frac{C_p^{conf}}{T}\right) dT \tag{4}$$

where C_p^{conf} represents the configurational heat capacity, i.e. the difference in heat capacity (C_p) between liquid and crystalline states, T_2 the temperature at which configurational entropy reaches zero so is taken to represent the Kauzmann temperature [4] ($T_2 \equiv T_K$). Adam–Gibbs theory [12] invokes a second-order transition at T_2 [13], an important consequence of which is that configurational entropy remains zero below T_2 and thus negative entropy is averted. Irrespective of the ongoing debate regarding the existence of such a transition [14], Eq. (3) accurately predicts supercooled liquid dynamics for a range of glass-formers [10,12].

The Adam–Gibbs model can be modified to describe non-equilibrium relaxation in the glassy state. A fictive temperature $T_{f(T,t)}$ has been used to account for the temperature and time dependence of the non-equilibrium glass structure [15]. $T_{f(T,t)}$ represents the temperature at which the equilibrium glass enthalpy equals that of the non-equilibrium glass at a given temperature and time, as depicted in Fig. 1. Modifying Eq. (3) with $T_{f(T,t)}$ creates the Adam–Gibbs–Vogel equation [15,16]:

$$\tau_{(T,t)} = \tau_0 \exp\left(\frac{DT_0}{T(1 - T_0/T_{f(T,t)})}\right) \tag{5}$$

Note that for an equilibrium supercooled liquid, $T_{f(T,t)}$ equals T and Eq. (5) equates to the VTF equation (Eq. (2)). $T_{f(T,t)}$ of a rapidly and freshly quenched glass will be close to the temperature at which equilibrium was lost, the glass transition temperature. In this instance, a constant $T_{f(T,t)}$ will result in Arrhenius behaviour in the glassy state. Various approaches for calculating the temperature and time dependence of $T_{f(T,t)}$ are also available [17,18].

Using both VTF and Adam–Gibbs relationships, data collected using thermal methods can be used to characterise how molecular dynamics change with temperature in both supercooled liquid and glassy states.

1.3. Thermal methods of fragility prediction

1.3.1. Extrapolation of configurational entropy to zero

The configurational entropy, S_c, of a supercooled liquid can be extrapolated to zero ($\equiv T_K$) using the relationship between C_p^{conf} and temperature defined in Eq. (4). Assuming that the entropy change on melting, ΔS_m, represents S_c at T_m:

$$\Delta S_m = \int_{T_K}^{T_m} \left(\frac{C_p^{conf}}{T}\right) dT \tag{6}$$

The simple relationship '$C_p^{conf} = \text{constant}/T$' has been shown to be valid for many organic glass-formers [11,18]. Consequently, C_p^{conf} calculation at a single temperature such as T_g allows estimation of T_K using the following relationship:

$$\frac{1}{T_K} = \frac{1}{T_m}\left(1 + \frac{\Delta H_m}{C_p^{conf} T_g}\right) \tag{7}$$

where ΔH_m represents the enthalpy of melting. Shamblin et al. [18] stress that ΔC_p at T_g measured in a single DSC analysis does not represent C_p^{conf} but rather the difference in C_p between the supercooled liquid and glass. Therefore, C_p measurements are required for both the crystalline and supercooled liquid in order to calculate C_p^{conf}.

Based on the assumption that T_K and T_0 are synonymous, the strength parameter D can be calculated using the VTF equation because both η and τ at T_g can be approximated; τ at T_g is approximately 10^2 s when measured by thermal analysis at a heating rate of 10 K/min [19]. With τ_0 representing the timescale of vibrational motions (approximately 10^{-14} s), D can be calculated via Eq. (2).

1.3.2. ΔE_{T_g} calculation using the scanning rate dependency of T_g

As discussed above, glass transition occurs in the temperature region where a supercooled liquid deviates from or returns to equilibrium and so reflects the relationship between relaxation time and temperature. It follows that the glass transition temperature will depend upon the experimental heating or cooling rate (q), a relationship that can be used to calculate the activation enthalpy of structural relaxation at T_g (ΔE_{T_g}) as follows [20]:

$$\frac{-\Delta E_{T_g}}{R} = \frac{d(\ln q)}{d(1/T_g)} \tag{8}$$

where R is the gas constant. Glass transition temperature measurement can be made either on cooling or heating by DSC with the more abrupt change in heat flow found on heating usually offering greater reproducibility. When conducting this experiment in heating mode, the cooling rate used for glass formation must equal that used on subsequent heating or else an erroneous activation enthalpy is obtained [19–21]. Other requirements are that cooling must begin from well above T_g and continue to well below T_g. The scanning rate dependency of T_g is usually measured using cooling/heating rates within the range of 2.5–40 K/min as either poor sensitivity or significant temperature lags are encountered beyond each extreme. The non-Arrhenius behaviour of fragile glass-formers close to T_g produces a large ΔE_{T_g} and thus a less pronounced effect of q on T_g. Consequently, greater error is encountered when calculating ΔE_{T_g} for fragile materials by this method. Of the eight glass-forming liquids studied by Moynihan et al. [22], only the most fragile material gave significant error between ΔE_{T_g} and an apparent activation enthalpy for viscosity close to $T_g(\Delta E_\eta)$. Data for fragile materials is scarce so the accuracy of this method for predicting such behaviour has not been conclusively demonstrated.

ΔE_{T_g} can be linked to the VTF relationship using an expression describing the temperature dependence of an apparent activation enthalpy ΔE^* across a wide temperature range:

$$\frac{\Delta E^*}{R} \equiv \frac{d(\ln \tau)}{d(1/T)} = \frac{DT_0}{(1 - T_0/T)^2} \tag{9}$$

By replacing ΔE^* with ΔE_{T_g} at a single temperature, an alternative fragility parameter m is defined by:

$$m \equiv \left.\frac{d\log\tau}{d(T_g/T)}\right|_{T=T_g} = \frac{\Delta E_{T_g}}{(\ln 10)RT_g} \tag{10}$$

which can be related to the VTF parameters by using Eq. (9):

$$m = \frac{DT_0/T_g}{(\ln 10)(1 - T_0/T_g)^2} \tag{11}$$

From Eq. (10), it is apparent that a large m value indicates rapidly changing dynamics at T_g which equates to 'fragile' behaviour. To solve Eq. (11), the minimum value of m ($m_{\min}$) must first be defined:

$$m_{\min} = \log\left(\frac{\tau(T_g)}{\tau_0}\right) = \left(\frac{D(T_0/T_g)}{(\ln 10)(1 - T_0/T_g)}\right) \tag{12}$$

Making the same assumptions for $\tau(T_g)$ and τ_0 as in Section 1.3.1, we find that $m_{\min} = 16$. Combining Eqs. (11) and (12) yields

$$D = \frac{(\ln 10)m_{\min}^2}{m - m_{\min}} \tag{13}$$

1.3.3. ΔE_{T_g} calculation using glass transition width

A highly supercooled liquid often possesses a distribution of relaxation times, a property that is retained on glass formation [23]. An important consequence of such a distribution is that glass transition either on heating or cooling takes place over a range of temperatures and so an experimental glass transition temperature width can be measured. Considering the different kinetic behaviour of supercooled liquids, it follows that differences in fragility will be reflected in the width of the glass transition. A 'strong' glass-former will not exhibit rapid changes in τ with temperature and so a large glass transition width is observed. Conversely, the non-Arrhenius changes in τ that define fragile behaviour produce a more narrow glass transition temperature region. The temperature width of the glass transition measured by DSC in heating mode has been used as a measure of glass fragility [24]. Importantly, a wide range of fragilities can be described using a single expression [25]. Both investigators used the extrapolated onset (T_g) and extrapolated offset following enthalpy relaxation (T_g^{off}) temperatures to measure glass transition width as shown using a specimen DSC heating scan in Fig. 3. An expression relating DSC glass transition width to ΔE_η has been proposed [22]:

$$\left(\frac{\Delta E_\eta}{R}\right)\left(\frac{1}{T_g} - \frac{1}{T_g^{\text{off}}}\right) = \text{constant} \tag{14}$$

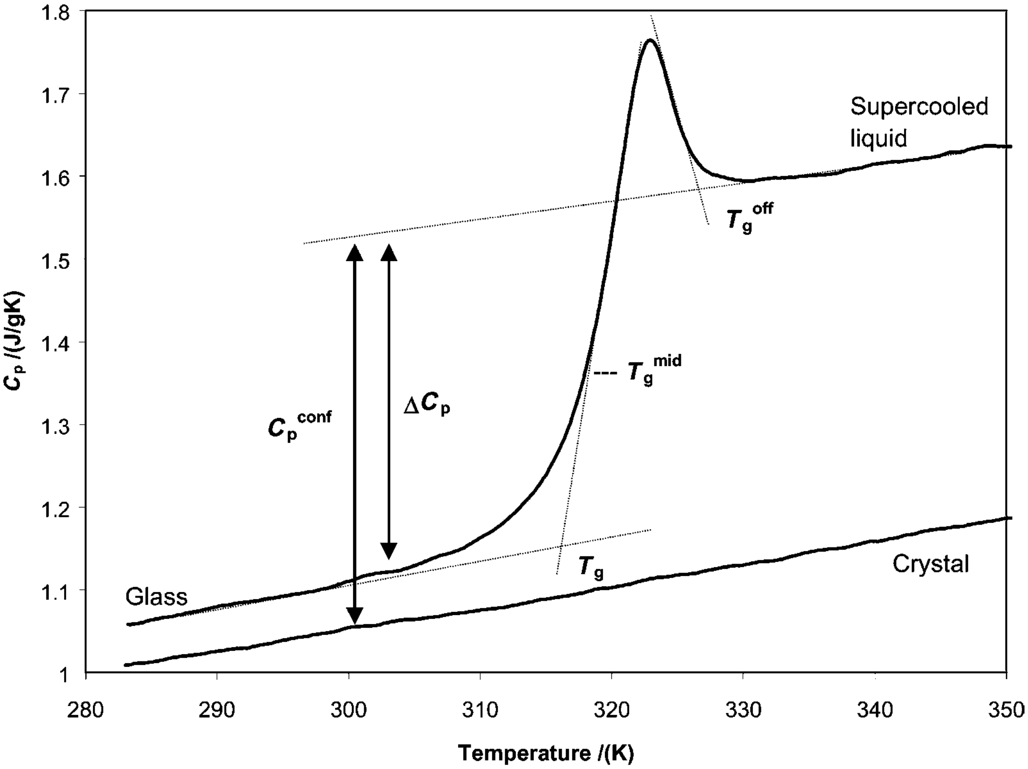

Fig. 3. Crystalline (stable γ-polymorph) and amorphous IMC heat capacity data, also indicating methods of T_g, T_g^{mid}, T_g^{off}, ΔC_p and C_p^{conf} measurement.

Using experimental ΔE_η values for 22 'strong' glass-formers, an empirical constant of 5 ± 0.5 with no physical significance was identified [22]. Assuming equivalence of ΔE_η and ΔE_{T_g}, the fragility parameter *m* and strength parameter *D* can be estimated using the procedure described in the preceding section.

2. Experimental

Thermal analysis was used to characterise the well-studied glass-former *o*-terphenyl (99% purity, Aldrich, Milwaukee, WI) and the following pharmaceutical glass-formers obtained from Sigma (St. Louis, MO): indomethacin (IMC), probucol (PBL) and ursodeoxycholic acid (UDCA). Sodium indomethacin (NaIMC) was a gift from Merck Frosst Canada (Kirkland, Canada).

A Seiko SSC220C DSC instrument (Haake, Paramus, NJ) with controlled liquid N_2 cooling was used with a 100 ml/min N_2 gas purge. A two-point calibration was carried out at each heating rate using the extrapolated onset of melting temperature (T_m) and enthalpy of melting (ΔH_m) of indium and gallium. T_m was calibrated to within 0.1 K and ΔH_m to less than 5% of the literature values. All thermal data is the average of three measurements with standard deviation given where appropriate.

About 5–6 mg crystalline study materials were accurately weighed into aluminium pans (SSCE030, Haake) and compressed with crimped lids. A 10 K/min heating ramp was used for T_m and ΔH_m measurements to a temperature 20 K above T_m. A rapid cooling ramp at 40 K/min was then used to lower the temperature to 50 K above T_g to minimise chemical degradation in the melting region. In situ glass formation was carried out at cooling rates of 5, 10, 20 and 30 K/min to temperatures of at least 50 K below T_g. Finally, T_g was measured at a heating rate that equalled the cooling rate of glass formation along with T_g^{mid}

(the temperature at which ΔC_p at T_g is 50%) and T_g^{off} as indicated in Fig. 3. An exception was made for NaIMC due to sample instability in molten form. NaIMC was made amorphous by freeze drying as described by Tong and Zografi [26]. In order to limit glass processing history, amorphous NaIMC was heated to 418 K ($T_g + 29$ K) at 10 K/min before in situ glass formation at the desired cooling rate.

C_p measurements were made by DSC using the conventional three-step approach [27]. Firstly, heat flow was measured for empty pans followed by a 10 mg sapphire standard and, finally, a study material accurately weighed in the range of 9–10 mg. For the purpose of data normalisation, a 10 min isothermal hold preceded the 10 K/min heating or cooling ramps used for C_p data collection. The temperature programme used for melting and in situ glass formation was as described above. For NaIMC, heat capacity was first measured for amorphous material formed on cooling at 10°C/min as previously described followed by in situ recrystallised material. Lids were not used for C_p measurement but sample was firmly compacted in the pan to improve heat transfer. Due to the low T_g of PBL, C_p data for this material were collected using a cooling ramp because baseline displacements occurred during the isothermal hold at 50 K below T_g that affected calculation of C_p from heating data. Cooling data was not affected by such anomalies in the temperature region of interest.

Normalised heat flow was converted to C_p versus temperature plots using sapphire data. C_p at T_g was recorded for the crystalline material and extrapolated to T_g for the quenched glass and supercooled liquid using linear portions of the C_p signal before and after the glass transition region, as indicated in Fig. 3.

3. Results

Three thermal methods were used to predict the fragility of three non-pharmaceutical glass-formers, B_2O_3, sorbitol and *o*-terphenyl, and four pharmaceutical glass-formers, IMC, NaIMC, PBL and UDCA. Predicted fragility was compared to experimental VTF parameters for B_2O_3, sorbitol, *o*-terphenyl and IMC, for which viscosity data in the temperature range close to T_g are available. These data were included in Fig. 2 and experimental VTF parameters are listed in Table 1.

3.1. Extrapolation of configurational entropy to zero

T_g, T_m, C_p^{conf} and ΔH_m literature values were used for predicting VTF fragility parameters for B_2O_3, sorbitol and *o*-terphenyl and measured by DSC for

Table 1
Experimental VTF parameters calculated using viscosity data close to T_g for B_2O_3, sorbitol, *o*-terphenyl and IMC

Material	T_g (K)	T_0 (K)	D	η_0 (Pa s)	Temperature range (T_g/T)	Reference
B_2O_3	554	299	33	1.1×10^{-5}	0.8–1	[24]
Sorbitol	267	215	8	2.8×10^{-5}	0.72–0.86	[32]
o-Terphenyl	249	200	10	1.1×10^{-8}	0.81–1	[52]
IMC	318	256	9	2.7×10^{-7}	0.87–0.99	[33]

Table 2
Predicted fragility by extrapolating configurational entropy to zero for non-pharmaceutical and pharmaceutical glass-formers

Material	T_g (K)	T_m (K)	T_g/T_m	C_p^{conf} (J/g K)	ΔH_m (J/g)	T_K (K)	D	Reference
B_2O_3	554	700	0.79	0.56	339	333	24	[53–55]
Sorbitol	272	367	0.73	1.28	162	249	3	[18]
o-Terphenyl	249	329	0.76	0.49	75	199	8	[56]
IMC	318	434	0.73	0.46	110	248	10	Current work
NaIMC	389	542	0.72	0.27	ΔH_{cr}, 37 (T_{cr}, 444)[a]	327	7	Current work
PBL	295	399	0.74	0.29	69	222	12	Current work
UDCA	379	478	0.79	0.46	94	311	8	Current work

[a] T_{cr} and ΔH_{cr} used due to degradation on melting.

the model pharmaceuticals IMC, NaIMC, PBL and UDCA. Predicted T_0 and D values are given in Table 2.

Let us first consider materials for which viscosity data are available. Predicted D values are in good agreement with viscosity data for IMC and *o*-terphenyl but are appreciably lower than viscosity data for B_2O_3 and sorbitol. It has been previously reported that extrapolating S_c to zero for both B_2O_3 and sorbitol yields VTF parameters that differ from experimental viscosity parameters [28,29]. This discrepancy is likely due to the error associated with extrapolating both viscosity and calorimetric data over many orders of magnitude. In addition, non-conformational contributions to C_p^{conf} and ΔS_m have been reported that will compromise Eqs. (6) and (7) [29–31].

For NaIMC, degradation occurs in the melting region [26] so the use of ΔH_m was prevented. Non-isothermal crystallisation of freeze-dried NaIMC produced a single sharp exothermic DSC peak in a narrow and reproducible temperature range resulting in a reproducible peak temperature (T_{cr}) of 444 K (standard deviation, $\sigma_{n-1} = 0.2$ K) and enthalpy of crystallisation (ΔH_{cr}) of 37.1 J/g (σ_{n-1}, 0.7 J/g). T_{cr} and ΔH_{cr} data were used in place of T_m and ΔH_m in Eq. (7) making the assumption that ΔS_{cr} equals the configurational entropy at T_{cr}. D values for the remaining pharmaceuticals NaIMC, PBL and UDCA were predicted in the range 8–12 indicating moderately 'fragile' behaviour.

3.2. ΔE_{T_g} calculation using the scanning rate dependency of T_g

Experimental ΔE_η and calculated ΔE_{T_g} from the scanning rate dependency of T_g are listed in Table 3 for all study materials along with predicted m and VTF parameters. Moynihan et al. used strong glass-formers including B_2O_3 to validate ΔE_{T_g} calculation [19,20] with close agreement between ΔE_{T_g} and ΔE_η reported. This method has also been used for ΔE_{T_g} calculation for sorbitol and IMC [32,33]. For these two fragile glass-formers, the choice of experimental glass transition temperature had a large effect on ΔE_{T_g}, with the extrapolated onset temperature (T_g) producing the largest ΔE_{T_g} and also that closest to ΔE_η [32,34]. Angell et al. [32] noted that such an effect is expected for 'fragile' glass-formers due to the return of non-Arrhenius behaviour that takes place as ergodicity is regained at the glass transition. The greater error associated with using this method for 'fragile' glass-formers has been described in Section 1. The discrepancy between ΔE_{T_g} and ΔE_η for both sorbitol and IMC emphasises the need for caution when using this method to characterise 'fragile' glass-formers. Despite the differences between ΔE_{T_g} and ΔE_η, predicted D values are in reasonable agreement with experimental viscosity values for all materials listed in Table 1.

A plot of ln q versus reciprocal T_g for *o*-terphenyl, PBL and UDCA is presented in Fig. 4 for both T_g and T_g^{mid} data. Higher activation energies were calculated when using T_g as opposed to T_g^{mid}, an immediate indicator that *o*-terphenyl, PBL and UDCA are 'fragile' glass-formers. Good agreement between ΔE_{T_g} and ΔE_η for *o*-terphenyl (320 and 305 kJ/mol) offers some validation of this method for a 'fragile' glass-former. It is possible that use of a fictive temperature (not to be confused with T_f discussed earlier) to define glass transition temperature would offer more accurate determination of ΔE_{T_g} by this method [35]. Fictive temperature is obtained by matching the enthalpy change on structural relaxation during glass transition

Table 3
Predicted fragility using ΔE_{T_g} calculated from the scanning rate dependency of T_g for non-pharmaceutical and pharmaceutical glass-formers

Material	T_g (K)	ΔE_η (kJ/mol)	ΔE_{T_g} (kJ/mol)	m	T_0 (K)	D	Reference
B_2O_3	554	385	385	36	310	29	[22]
Sorbitol	267	503	389	76	211	10	[45,32]
o-Terphenyl	249	307	320	67	189	12	Current work, [52]
IMC	318	396	464	77	250	10	[33]
NaIMC	389	–	609	81	316	10	[26]
PBL	295	–	326	58	213	14	Current work
UDCA	379	–	725	100	318	7	Current work

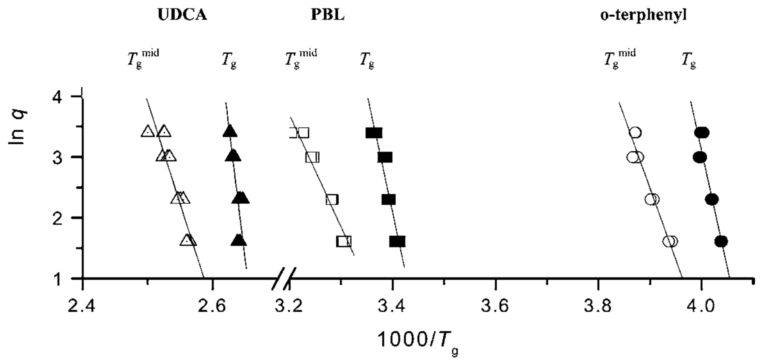

Fig. 4. A plot of heating rate (ln q) vs. reciprocal T_g for o-terphenyl, PBL and UDCA to calculate the activation enthalpy of structural relaxation at the glass transition, ΔE_{T_g}. Both T_g and T_g^{mid} data are given for each glass-former.

and the relaxation endotherm that accompanies glass transition, a method that removes errors associated with hysteresis between cooling and heating data. However, the glass transition of 'fragile' glasses yield comparable extrapolated onset and fictive temperatures [36]. For the purpose of this analysis, only the extrapolated onset temperature (T_g) was employed for ΔE_{T_g} calculation.

Predicted D values for PBL and UDCA of 7 and 14 were of a similar magnitude to the D values of 10 and 12 previously predicted for IMC and NaIMC by this method [26,33]. Thus, moderately 'fragile' properties are predicted for all pharmaceutical glass-formers investigated in this study.

3.3. ΔE_{T_g} calculation using glass transition width

Table 4 summarises ΔE_{T_g} calculated using glass transition width for all model glass-formers along with predicted m and VTF parameters. A constant of 5 was used in Eq. (14) [22]. Data for three 'fragile' glass-formers sorbitol, o-terphenyl and IMC listed in the current work offered the opportunity for modification of the constant to encompass both 'strong' and 'fragile' glass-formers. However, there was no consistent discrepancy between ΔE_{T_g} and ΔE_η for these materials so constant 5 was retained.

ΔE_{T_g} calculation using glass transition width yielded predicted D values in excellent agreement with experimental viscosity data for sorbitol and o-terphenyl, and in reasonable agreement with B_2O_3 and IMC experimental data. It appears that the current method can predict fragility with reasonable accuracy for both 'strong' and 'fragile' glass-formers. A correlation between T_g width and fragility for a range of glass-formers encompassing both strong and fragile behaviour has also been demonstrated using an alternative fragility parameter, $F_{1/2}$ [25]. $F_{1/2}$ measures the magnitude of deviation from Arrhenius behaviour via a single dielectric measurement and has been put forward as the most appropriate descriptor of fragility [37]. In view of the current observations for sorbitol, o-terphenyl and IMC, and the findings of Ito et al. [25], we have greater confidence when interpreting the data

Table 4
Fragility prediction from ΔE_{T_g} using glass transition width for non-pharmaceutical and pharmaceutical glass-formers

Material	T_g (K)	T_g^{off} (K)	ΔE_{T_g} (kJ/mol)	m	T_0 (K)	D	Reference
B_2O_3	557	591	404	38	320	27	[22]
Sorbitol	269.8 (0.2)	277.4 (0.2)	409	84	214	9	[57]
o-Terphenyl	248.8 (0.1)	256.2 (0.3)	355	74	195	10	Current work
IMC	317.5 (0.1)	328.8 (1)	384	63	237	13	Current work
NaIMC	388.7 (0.4)	404.7 (0.9)	408	55	276	15	Current work
PBL	294.8 (0.3)	304.7 (0.1)	378	67	224	12	Current work
UDCA	378.5 (0.5)	392.1 (0.7)	454	63	282	13	Current work

for the pharmaceutical materials under investigation, for which moderately 'fragile' behaviour has been predicted by other thermal methods. D values predicted for IMC, NaIMC, PBL and UDCA ranged from 12 to 15, providing further suggestion of moderately 'fragile' behaviour.

4. Discussion

4.1. Evaluation of different thermal methods of fragility prediction

Viscosity data for B_2O_3, sorbitol, *o*-terphenyl and IMC and corresponding calculated VTF parameters listed in Table 1 enable the evaluation of different thermal methods of fragility prediction. Data for the only 'strong' glass-former, B_2O_3, demonstrated lower predicted D values by all methods (24–29) compared to the viscosity D value of 33. Small changes in D in the 'fragile' region reflect larger changes in dynamic behaviour compared to numerically equivalent differences in D in the 'strong' region. Thus, the difference between predicted and experimental D values for B_2O_3 does not have a dramatic effect on T_0 (299–333 K) when the large temperature range between T_g and T_0 is considered.

Predicted VTF parameters for sorbitol, *o*-terphenyl and IMC were in good agreement with experimental data with some exceptions. The configurational entropy method offered excellent prediction for two materials but error was encountered for sorbitol. The deleterious effect of non-conformational contributions on T_K extrapolation is the greatest potential shortfall for this method. ΔE_{T_g} calculation using the scanning rate dependency of T_g offered excellent fragility prediction for the three 'fragile' glass-formers with predicted D values only 1 or 2 units above experimental values. The use of glass transition width for ΔE_{T_g} calculation was also found to offer good prediction of D, with excellent accuracy for sorbitol and *o*-terphenyl and an error of 4 units for IMC. It is noted that both methods of calculating ΔE_{T_g} predict values at or above the experimental value, i.e. a higher strength parameter than is found experimentally. To summarise, these data do not indicate the superiority of one thermal method of fragility prediction over another. In terms of experimental duration and ease, calculating ΔE_{T_g} via glass transition width would appear to be an appropriate first-choice method.

All methods of fragility prediction by thermal methods depend upon data extrapolation over many orders of magnitude and fixing values of τ at T_g and τ_0. Error arises when comparing predicted and experimental D and T_0 values because the experimental τ at T_g and τ_0 can vary. The temperature range of interest to the pharmaceutical scientist is usually close to T_g (above and below). It may be appropriate to quote only the salient data generated by each thermal method, namely, T_K in the case of the configurational entropy method and ΔE_{T_g} in the case of both scanning rate dependency of T_g and glass transition width methods.

A consideration when using viscosity data for validating thermal methods of fragility prediction is the temperature range of data used to calculate either VTF fragility parameters or ΔE_η. Abrupt changes in supercooled liquid dynamics can be encountered (e.g. B_2O_3, [38]) that will affect the fit to the VTF equation. Thus, there are no 'universal' VTF parameters for a glass-former. Another consideration is that different α-relaxation processes often exhibit different temperature relationships, particularly at large supercooling [14] and so the relaxation mode chosen for investigation can be important. For the purposes of the current work, viscosity data obtained in the vicinity of T_g were considered an appropriate starting point for validating the thermal methods under investigation. We hope that further validation of the thermal methods presented will be carried out in the immediate future with a larger number of glass-formers and with consideration of different relaxation modes.

4.2. Fragility of pharmaceuticals predicted by thermal analysis

Some general observations will now be made based upon the fragility predictions by thermal methods for four pharmaceutical glass-formers IMC, NaIMC, PBL and UDCA that have T_g values in the range 222–311 K. All model pharmaceuticals exhibited moderately 'fragile' behaviour. D values predicted using all thermal methods varied from 9 to 15, a range that incorporates the error and bias of each method and so represents a conservative attempt to classify these materials. This range is depicted graphically in Fig. 5.

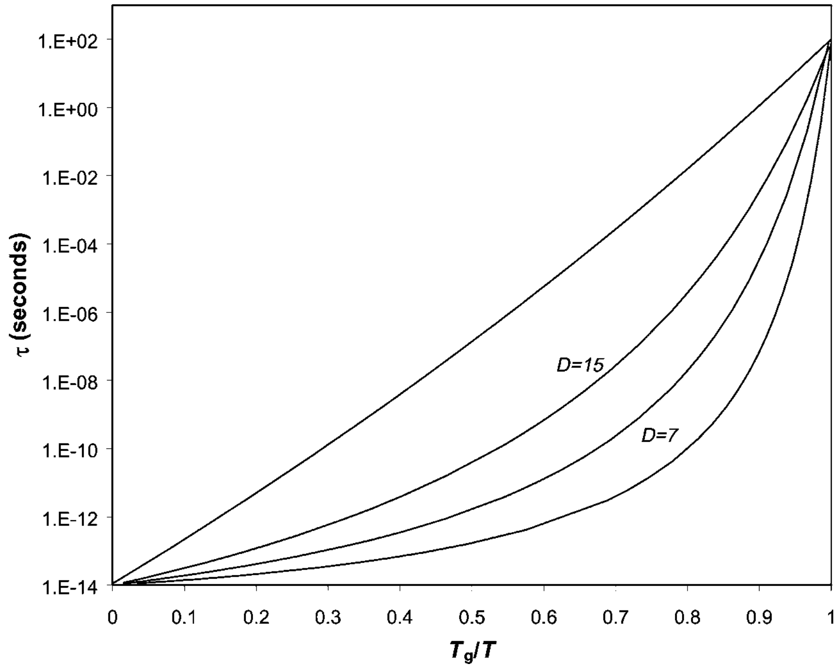

Fig. 5. Relaxation time vs. temperature scaled to T_g, indicating the range of supercooled liquid dynamics described by VTF D values from 7 to 15, a range found to encompass predicted fragilities of pharmaceutical glass-formers studied in this work. Extremes of fragility are also shown.

In order to establish whether the prediction of moderately 'fragile' behaviour is a common feature of pharmaceutical materials, predictions were made for another 10 materials using the configurational entropy method. C_p^{conf} was not available for these materials so ΔC_p at T_g was used, a value that will under-estimate C_p^{conf}. The consequence of this substitution will be to raise predicted D values in accordance with Eq. (6). Examination of heat capacity data for IMC, NaIMC, PBL and UDCA (Table 5) indicated a consistent difference between ΔC_p and C_p^{conf} as shown by the ratio $\Delta C_p/C_p^{conf}$ equalling 0.90 (σ_{n-1}, 0.02).

Table 5
Measured heat capacity (J/g K) of liquid (C_p^{liq}), glass (C_p^{glass}) and crystal (C_p^{cryst}) phases, ΔC_p ($C_p^{liq} - C_p^{glass}$) and C_p^{conf} ($C_p^{liq} - C_p^{cryst}$) at T_g for IMC, NaIMC, PBL and UDCA

	IMC	NaIMC	PBL	UDCA
C_p^{liq}	1.56 (0.04)	1.48 (0.06)	1.64 (0.04)	2.19 (0.08)
C_p^{glass}	1.15 (0.03)	1.24 (0.04)	1.37 (0.04)	1.77 (0.09)
C_p^{cryst}	1.10 (0.04)	1.21 (0.03)	1.35 (0.04)	1.73 (0.08)
ΔC_p	0.41 (0.02)	0.24 (0.02)	0.27 (0.004)	0.42 (0.01)
C_p^{conf}	0.46 (0.02)	0.27 (0.03)	0.29 (0.02)	0.46 (0.02)

Fragility predictions for 10 pharmaceutical materials recorded in Table 6 yield D values ranging from 9 to 15. Assuming comparable discrepancies between ΔC_p and C_p^{conf} using the ratio 0.90, corrected D values lie in the region 7 to 13. These predictions are very rough estimates due to the assumption that $\Delta C_p/C_p^{conf}$ will be constant. Nevertheless, it is interesting to find that they compare favourably with the D values predicted earlier for IMC, NaIMC, PBL and UDCA by the same method. These data lend weight to the generalisation that pharmaceutical glass-formers may possess comparable fragility, a suggestion that contradicts the observation of Li et al. [39]. In their work, D values predicted using the scanning rate dependency of T_g ranged from 11 to 133 for six pharmaceutical glass-formers, but an erroneous ΔE_{T_g} was used as cooling and heating rates were not matched. The activation enthalpy value will be lower than ΔE_{T_g} and therefore yield reduced m and increased D value predictions [21].

The ratio T_g/T_m for all pharmaceuticals listed in Tables 2 and 6 varied between from 0.71 to 0.86. This range is consistent with previous observations made

Table 6
Predicted fragility by extrapolating configurational entropy to zero (with C_p^{conf} replaced with ΔC_p) for a range of pharmaceutical glass-formers

Material	T_g (K)	T_m (K)	T_g/T_m	ΔH_m (J/g)	ΔC_p (J/g K)	T_K (K)	D	Reference
Glibenclamide	331	450	0.74	108	0.45	261	10	[58]
Griseofulvin	364	494	0.74	107	0.36	272	12	[58]
Hydrochloro-thiazide	385	547	0.70	104	0.31	292	12	[58]
Polythiazide	346	493	0.70	97	0.34	270	10	[58]
Nifedipine	322	445	0.72	110	0.27	228	15	[59,60]
Phenobarbital	319	448	0.71	120	0.46	246	11	[59,60]
Flopropione	335	452	0.74	160	0.7	269	9	[59,60]
Diazepam	315	398	0.79	86.7	0.46	249	10	[44]
Temazepam	339	392	0.86	90.9	0.42	239	15	[44,61]
Felodipine	317	416	0.76	87	0.40	247	10	[62]

for pharmaceutical glass-formers [40,41] and offers a useful ‘rule of thumb’ for these materials. There does not appear to be a straightforward relationship between T_g/T_m and fragility as exemplified by the fact that B_2O_3 possesses a similar value to the more ‘fragile’ glass-formers presented in this work. Investigation of homologous series of simple organic glass-formers have shown T_g/T_m to be sensitive to subtle functional group substitutions that affect intermolecular interactions [42]. However, these changes do not necessarily have great impact on the fragility of simple organic glass-formers. We conclude that important structural information may be gained by considering T_g/T_m values particularly within a group of chemically-related glass-formers but such differences may not be indicative of differences in fragility.

4.3. Relationship between relaxation below T_g and fragility

An important challenge facing the pharmaceutical scientist is ensuring sufficient glass stability to guarantee a long product shelf-life. As can be seen in Tables 2 and 6, drug molecules often possess T_g values close to room temperature and so are commonly stored at temperatures close to the glass transition. Consequently, we have an intense interest in either measuring or predicting relaxation behaviour below T_g and relating this to physical and chemical processes dependent upon molecular mobility.

Based upon data presented for 14 pharmaceutical glass-formers in this paper, we have suggested that these materials exhibit moderately ‘fragile’ behaviour. If such a generalisation is valid, we may anticipate comparable relaxation behaviour below T_g as well (assuming similar methods of glass formation). To probe this hypothesis, enthalpic relaxation times measured in the region from $T_g - 10$ to $T_g - 50$ for a range of pharmaceutical glass-formers [26,43,44] are gathered in a single plot scaled to T_g (Fig. 6). Close data inspection indicates that some materials exhibit Arrhenius-like behaviour whilst others deviate from Arrhenius behaviour even within the narrow temperature range. Despite these differences, the range of relaxation times remains relatively constant at all temperatures and the general trend is close to Arrhenius temperature dependence. Apparent activation enthalpies (ΔE^*) for these five glass-formers gave an average of 203 kJ/mol (±41). It is not surprising to find that the activation barrier for enthalpic relaxation below T_g falls within a relatively narrow range for a group of materials that have comparable predicted fragility above T_g. The moderately ‘fragile’ glass-former sorbitol has an ΔE^* for α-relaxations of 192 kJ/mol below T_g [45]. Thus, a ΔE^* of approximately 203 kJ/mol may serve as a useful starting point for predicting relaxation times of pharmaceuticals below T_g using τ at T_g of 100 s as a reference.

Some cautionary notes are now given in relation to this generalisation. Firstly, enthalpy relaxation data was obtained for glasses prepared by quenching at different rates and so differences in relaxation behaviour below T_g are expected. The average ΔE^* value of 203 kJ/mol does not apply to glasses prepared by different methods as each system will exhibit unique relaxation behaviour. Secondly, the suggestion that moderately ‘fragile’ behaviour may be a common property of pharmaceutical glass-formers infers that

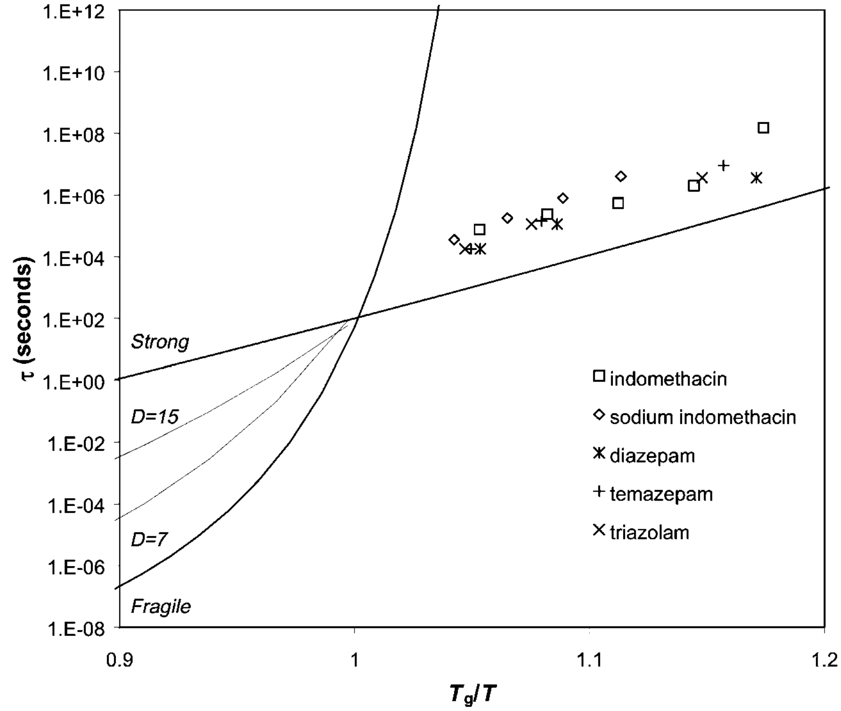

Fig. 6. Relaxation time vs. temperature scaled to T_g, extending the equilibrium behaviour of strong and fragile glass-formers to $T_g/T > 1$. Published experimental enthalpy relaxation times are given for a range of pharmaceutical glass-formers [26,43,44].

co-operative motions will be abundant close to T_g [14]. The measured relaxation process in a 'fragile' material at a temperature close to T_g will exhibit marked non-exponentiality that can be described using the Kohlrausch–Williams–Watts (KWW) expression [46]:

$$\phi_{(t)} = \exp\left(-\left(\frac{t}{\tau}\right)^{\beta}\right) \qquad (15)$$

The extent of relaxation $\phi_{(t)}$ at time t is determined by τ and β, with β defining the magnitude of deviation from exponential behaviour ($\beta < 1$ signifies varying levels of non-exponentiality). It is likely that measured non-exponential behaviour arises from a combination of exponential relaxation processes present in a spatially heterogeneous system [47], in which case a 'fragile' system is likely to possess a large distribution of relaxation times. Accordingly, we would predict a large distribution of relaxation times to be present in moderately 'fragile' pharmaceutical glass-formers in the vicinity of T_g. Values of β calculated for the enthalpy relaxation of pharmaceutical glasses included in Fig. 6 ranged from 0.27 to 0.6 [43,44,48] confirming the existence of a large distribution of relaxation times. Such a distribution has significant implications when attempting to correlate molecular mobility via τ to stability in pharmaceutical systems [49]. Closer examination of the distribution of relaxation times in pharmaceutical glass-formers and how the distribution changes with temperature will hopefully strengthen our ability to understand and predict the effect of molecular mobility on physical and chemical processes in the amorphous state.

5. Conclusion

Prediction of fragility parameters using thermal methods allows the equilibrium dynamics of supercooled liquids and non-equilibrium dynamics of glasses to be evaluated. Such information is valuable for stability assessment of glassy pharmaceuticals, which regularly exhibit T_g values close to room temperature and so possess significant molecular mobility. Three thermal methods were found to predict the fragility of four well-characterised glass-formers with reasonable accuracy. An optimal thermal method was not readily apparent although calculating ΔE_{T_g} using glass transition width has the advantage of being the least demanding experimentally. Anomalies were seen for fragility predictions by the configurational entropy approach for two model glass-formers. However, the opportunity to evaluate the changing dynamics of an ageing glass by this method offers clear advantages where appropriate [18]. ΔE_{T_g} calculation using the scanning rate dependency of T_g incorporates greater error for fragile materials and so must be used with caution with pharmaceuticals.

Four pharmaceutical glass-formers characterised by each thermal method were predicted to exhibit moderately 'fragile' behaviour, a finding that extended to a further 10 materials studied using the configurational entropy method. Tentatively, we propose that a range of VTF D values from 7 to 15 encompasses the majority of pharmaceutical glass-formers. Based upon the suggestion of moderately 'fragile' behaviour in the supercooled region, commonalities may also be inferred in the glassy region so long as the method of glass formation remains the same. It is stressed that this statement may not be valid for glasses prepared by different methods and possessing different histories [50,51]. Predicting dynamics in the glassy state remains a significant challenge but inferences can be made based on fragility parameters that serve as a useful starting point for understanding how methods of glass formation and ageing affect glassy state dynamics.

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