Pharm Res (2012) 29:271–284
DOI 10.1007/s11095-011-0540-4

RESEARCH PAPER

Role of Viscosity in Influencing the Glass-Forming Ability of Organic Molecules from the Undercooled Melt State

Jared A. Baird • Darlene Santiago-Quinonez • Carlos Rinaldi • Lynne S. Taylor

Received: 11 April 2011 / Accepted: 14 July 2011 / Published online: 22 July 2011

ABSTRACT

Purpose Understanding the critical factors governing the crystallization tendency of organic compounds is vital when assessing the feasibility of an amorphous formulation to improve oral bioavailability. The objective of this study was to investigate potential links between viscosity and crystallization tendency for organic compounds from the undercooled melt state.

Methods Steady shear rate viscosities of numerous compounds were measured using standard rheometry as a function of temperature through the undercooled melt regime. Data for each compound were fit to the Vogel-Tamman-Fulcher (VTF) equation; kinetic fragility via strength parameter (D) was determined.

Results Compounds with high crystallization tendencies exhibited lower melt viscosities than compounds with low crystallization tendencies. A correlation was observed between rate of change in viscosity with temperature and crystallization tendency, with slowly crystallizing compounds exhibiting larger increases in viscosity as temperature decreased below T_m. Calculated strength parameters indicated all compounds were kinetically fragile liquids; thus, kinetic fragility may not accurately assess glass-forming ability from undercooled melt state.

Conclusions A link was observed between the viscosity of a compound through the undercooled melt regime and its resultant crystallization tendency, indicating viscosity is a critical parameter to fully understand crystallization tendency of organic compounds.

KEY WORDS crystallization · fragility · glass-forming ability · viscosity

J. A. Baird · L. S. Taylor (✉)
Department of Industrial and Physical Pharmacy, College of Pharmacy
Purdue University
West Lafayette, Indiana 47907, USA
e-mail: lstaylor@purdue.edu

D. Santiago-Quinonez · C. Rinaldi
Department of Chemical Engineering
University of Puerto Rico-Mayagüez
PO Box 9000, Mayagüez, Puerto Rico 00681, USA

INTRODUCTION

Current high throughput screening and combinatorial chemistry methods employed for drug discovery have led to an increasing number of new chemical entities with poor aqueous solubility (1). To develop these compounds as solid oral dosage forms, enabling technologies, in particular amorphous formulations, are increasingly being applied to improve oral bioavailability (2). Melt extrusion, whereby the active pharmaceutical ingredient (API) is co-melted with polymers and/or other excipients and extruded to produce a homogeneous amorphous dispersion has become more commonplace (3–5). Although solid dispersion technology has been studied for more than 40 years (6), to date, relatively few drug products have been marketed as amorphous solid dispersions (7). Major issues limiting the use of amorphous solid dispersions as a formulation technique include challenges with scale-up, in addition to concerns about API crystallization during the product shelf life.

For amorphous solid dispersions, understanding the crystallization tendency of the API as a function of temperature and during storage is important for assessing whether a compound is a suitable candidate for an amorphous formulation. For melt extrusion, it is also particularly important to understand the crystallization behavior during the cooling step that occurs after exiting the extruder. In a recent study, the crystallization tendency from undercooled melts was evaluated for a large set of

organic molecules and separated into three separate classes —class (I), class (II), class (III)—based upon the presence (or absence) of crystallization during a controlled heating/cooling/heating cycle using differential scanning calorimetry (DSC) (8). From this study, a link between the physicochemical (molecular, thermal) properties of the compounds and their resultant crystallization tendency was established using principal component analysis (PCA).

However, one property that was not evaluated in the previous study was viscosity, which not only is a critical processing parameter for melt extrusion but also an important transport property influencing crystallization tendency between the melting temperature (T_m) and the glass transition temperature (T_g), commonly described as the undercooled melt regime. Viscosity is an internal property of a fluid that measures the resistance of the fluid to flow under an applied stress and is related to the molecular rotation time and hence mobility of a material above T_g. It can be measured as a function of temperature using various experimental techniques, most commonly standard rheometry, dynamic mechanical analysis (DMA), or thermomechanical analysis (TMA). However, there are relatively few studies (9–11) where the viscosity of pharmaceutically relevant pure amorphous materials or solid dispersions has been measured in the undercooled melt regime, with limited focus on evaluating potential relationships between viscosity and the inherent crystallization tendency of compounds.

Crystallization from the Undercooled Melt State

Crystallization is a process that involves two separate but interdependent steps: nucleation followed by crystal growth. Within classical nucleation theory (CNT) (12), the steady-state homogeneous volume-based nucleation rate (I_{ss}) for a compound from the undercooled melt can be written as

$$I_{SS} = I_0 \exp\left[-\frac{W^* + \Delta G_\eta}{k_B T}\right] \quad (1)$$

where I_0 is a pre-exponential term, k_B is the Boltzmann constant, T is the temperature, and ΔG_η is the activation free energy for viscous flow, or the kinetic barrier for nucleation relating the activation energy for transfer of a molecule from the surrounding undercooled melt to the nucleus surface. Assuming spherical nuclei, the thermodynamic barrier for nucleation (W^*) can be written in terms of the specific free energy (interfacial tension) of the critical nucleus-melt interface (σ_{cm}) and the difference in free energies between the undercooled melt and the crystal on a per unit volume basis (ΔG_v):

$$W^* = \frac{16\pi\sigma_{cm}^3}{3\Delta G_v^2} \quad (2)$$

Assuming screw dislocation crystalline growth, the general growth rate (U) from undercooled melts can be described as follows:

$$U = f\frac{k_B T}{\lambda^2 \eta}\left[1 - \exp\left(\frac{\Delta G_v}{k_B T}\right)\right] \quad (3)$$

where f is the fraction of sites on the interface whereby molecules can be added or removed from the crystalline surface, λ is the distance advanced by the interface over a unit kinetic process (assumed to be equal to the molecular diameter), and η is the viscosity of undercooled melt (13). Equations 1–3 show that in addition to thermodynamic parameters, both nucleation and crystal growth are dependent on viscosity, whereby viscosity is used to represent the diffusion or rearrangement of molecules necessary either to form aggregates of molecules leading to stable nuclei or to attach to a growing crystal face. Clearly, viscosity is thus likely to be one of the key attributes governing the crystallization tendency of a compound from the undercooled melt state.

The purpose of this study was to investigate the potential link between viscosity and crystallization tendency for organic molecules from the undercooled melt state. Steady shear rate viscosities for 34 compounds from the original test set of 51 compounds evaluated in a previous study (8) were measured as a function of temperature in the undercooled melt regime, and potential links between the measured viscosities and the compound's crystallization classifications were sought. The measured viscosities as a function of temperature were then fit to the Vogel-Tamman-Fulcher (VTF) equation, and the kinetic fragilities were evaluated by comparison of the strength parameter, D.

MATERIALS AND METHODS

Materials

Benzocaine, dibucaine, lidocaine, miconazole, procaine, and tolbutamide were obtained commercially from Spectrum Chemical, Gardena, CA, USA. Loratadine and aceclofenac were obtained commercially from Attix Pharmachem, Toronto, ON, Canada. 4-biphenylmethanol, 4-biphenylcarboxaldehyde, acetaminophen, antipyrin, benzamide, bifonazole, chlorpropamide, cinnarizine, clotrimazole, fenofibrate, flufenamic acid, haloperidol, indomethacin, ketoprofen, nilutamide, nimesulide, phenacetin (*p*-acetophenetidide), probucol, and tolazamide were obtained commercially from Sigma-Aldrich Inc., St. Louis, MO, USA. Itraconazole, ketoconazole, and nifedipine were obtained commercially from Hawkins, Inc., Minneapolis, MN, USA. Ibuprofen was obtained commercially from

Albemarle Co., Baton Rouge, LA, USA. Felodipine was a generous gift from AstraZeneca, Södertälje, Sweden. Ritonavir was kindly provided from The Clinton Foundation, New York, NY, USA. Celecoxib was kindly supplied by Pfizer, Inc., Groton, CT, USA.

Steady Shear Rate Viscosities

Viscosities as a function of temperature were measured for all compounds using an Anton Paar MCR series 301 rheometer (Anton Paar, Ashland, VA, USA). Measurements were conducted using a 25 mm diameter parallel plate geometry with a 0.4 mm gap between the upper and lower plates. The temperature of the sample was controlled using Peltier plates inside a heating hood, resulting in a gradient-free temperature field. Each sample (~0.5 g) in powder form was loaded onto the lower plate at room temperature and heated at a rate of 10°C/min to 10°C above the melting temperature. The upper plate was then lowered to the experimental gap width (0.4 mm), excess molten material was trimmed along the edge of the plates, and the temperatures of both the lower and upper plates were allowed to equilibrate. The temperature of the sample was subsequently rapidly lowered to the melting temperature of the sample and allowed to equilibrate. Upon equilibration, a shear deformation at a rate of 30 s^{-1} was applied to the sample, and the shear viscosity of the material was recorded when a steady-state reading was observed. The sample was then reheated to 10°C above its respective melting temperature and held for 5 min to ensure melting of any nuclei or crystalline material formed during the viscosity measurement. The sample was then rapidly cooled to 5°C below the melting temperature, and the viscosity was measured. The above heating/cooling steps were further repeated at successively lower temperatures until the sample exhibited crystallization, as evidenced by an increase in viscosity with respect to time at a fixed temperature and shear rate.

RESULTS

Viscosity of Compounds

The constant shear rate viscosities at and below the melting temperature are shown in Fig. 1a–d for compounds classified as rapid crystallizers (class (I-A), class (I-B)), intermediate crystallizers (class II)), and slow crystallizers (class (III)) based on a previous study (8). In the presentation of results that follows, the compounds are compared in terms of the absolute value of the viscosity at the melting temperature (η_{melt}), the value of the viscosity on undercooling (η), and the relative change in viscosity on undercooling (i.e. η/η_{melt}). Some general trends can be noted from these data. As expected, the viscosity of all compounds increased as the temperature was decreased below the melting temperature (i.e. at increased degrees of undercooling). Additionally, the relative change in viscosity for each compound (Fig. 2a–d) as a function of temperature increased as the degree of undercooling increased, indicating a non-linear temperature dependency of viscosity as expected. Interestingly, there was significant variation in the viscosities at a given degree of undercooling for compounds within the same crystallization tendency classification, indicating that compounds with similar crystallization behavior from the undercooled melt state can exhibit quite different viscosities through the undercooled melt regime.

Class (I-A) Compounds

Figure 1a shows viscosity data for the undercooled melt regime for compounds with very rapid crystallization tendency (i.e. compounds which crystallize even during quench cooling in liquid N_2). For these compounds, it was not possible to obtain viscosity measurements at large degrees of undercooling due to sample crystallization. Given that these compounds crystallize upon quench cooling in liquid N_2, it can be surmised they all have very high nucleation and/or growth rates and that the temperature dependencies of these processes overlap significantly. Crystallization will be further facilitated during the viscosity measurement by the applied shear forces, which will promote heterogeneous nucleation at the interface between the upper plate and the sample. Thus, the temperature at which crystallization occurred was uniformly higher in the viscosity experiments relative to previously reported differential scanning calorimetry studies (8). Since the viscosities at which crystallization occurred for these compounds were fairly low (typically $<10^{-2}$ Pa-s), it is apparent that crystallization occurs in a temperature regime where it is primarily under thermodynamic control; in other words, the system has a high degree of mobility, but the thermodynamic driving force is low because the system is close to equilibrium (i.e. the melting temperature). The extent to which the samples could be undercooled prior to crystallization did, however, differ between the various compounds. For example, some compounds crystallized at temperatures very close to their melting points (at undercoolings of 5–10°C, 4-biphenylmethanol, phenacetin), while others could be cooled to higher degrees of undercooling before crystallization occurred (at undercoolings of 20–35°C, benzocaine, lidocaine). The differences in crystallization temperatures between the compounds give some insight into the temperature dependencies of their relative nucleation and/or growth rates. Thus, it can be inferred that the temperatures of maximum

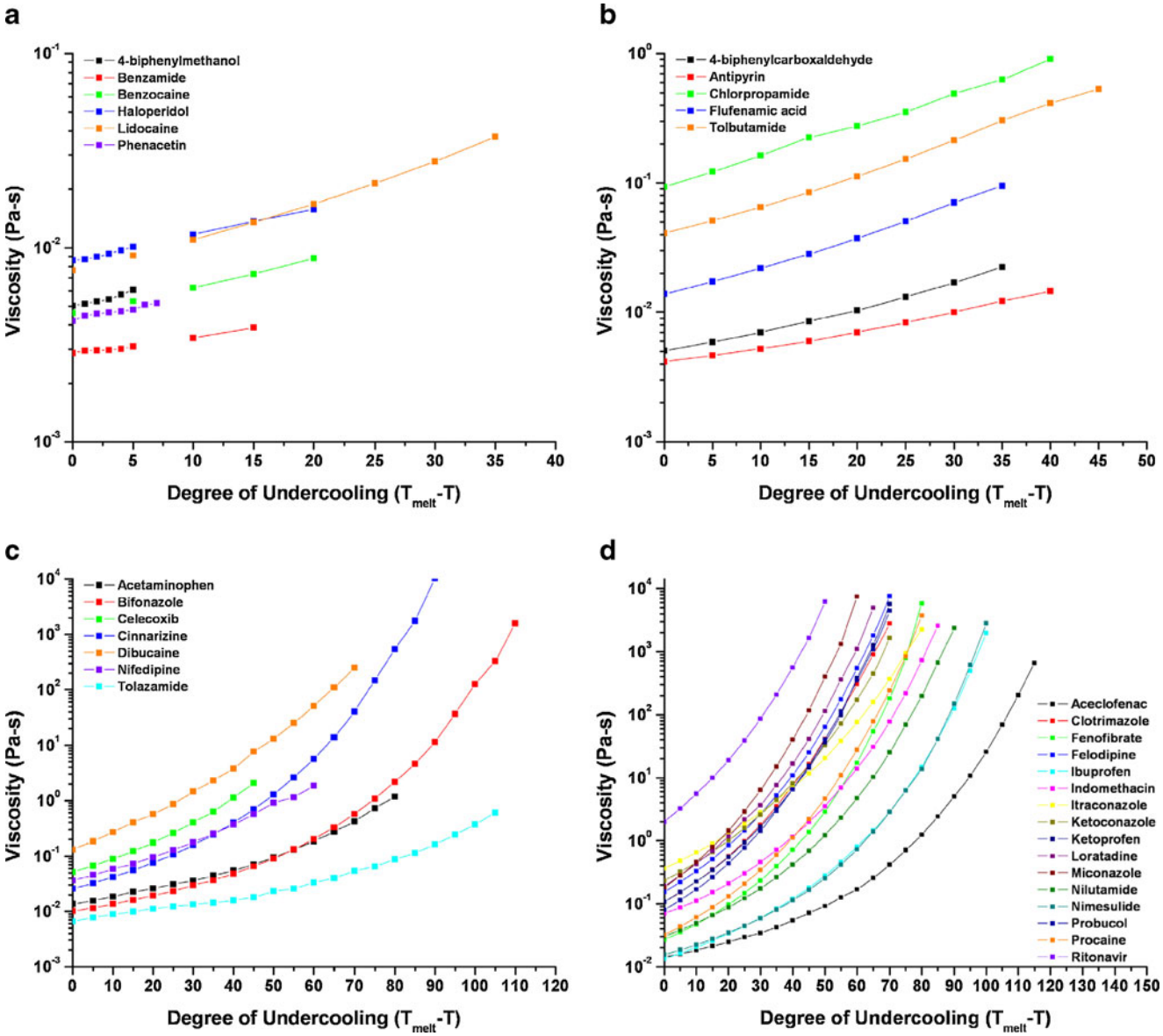

Fig. 1 Measured equilibrium viscosity of compounds as a function of temperature through the undercooled melt regime. (**a**) Class (I-A) compounds; (**b**) class (I-B) compounds; (**c**) class (II) compounds; (**d**) class (III) compounds.

heterogeneous nucleation and/or growth rates most likely occur at lower degrees of undercooling for compounds such as 4-biphenylmethanol compared to lidocaine; therefore, it is necessary to cool the latter compound to a lower temperature before the crystallization rate becomes fast enough to interfere with the experimental measurement.

The data shown in Fig. 1a indicate that there is no direct correlation between viscosity and crystallization behavior for compounds within this crystallization class. For example, the viscosity of benzamide immediately prior to crystallization was an order of magnitude lower than the viscosity of lidocaine at its crystallization temperature. Furthermore, benzamide has a lower viscosity as a function of temperature compared to either 4-biphenylmethanol or phenacetin, yet benzamide could be cooled to a lower temperature relative to its melting temperature before crystallization occurred compared to these two compounds. This observation lends support to the contention that crystallization is under thermodynamic control. Interestingly, although the compounds exhibited different viscosities at their respective melting temperatures, the relative increase in viscosity for each compound as the temperature decreased was similar, as indicated by the measured viscosities remaining relatively parallel to each other (Fig. 1a). This was further confirmed by plotting the viscosity ratio (η/η_{melt}) for each compound as a function of degree of undercooling (Fig. 2a), whereby only small differences were observed between the compounds,

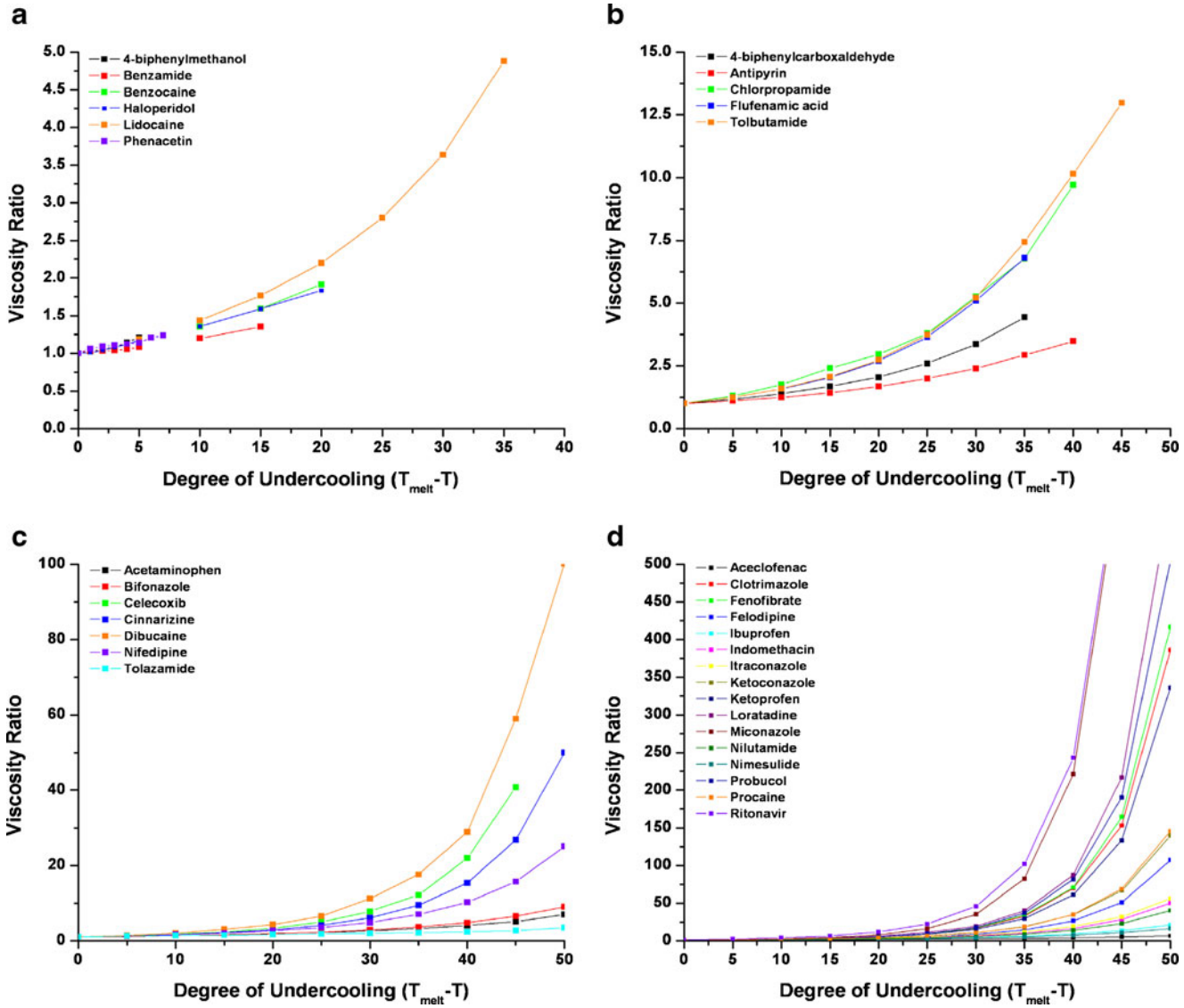

Fig. 2 Relative change in viscosity as a function of temperature (viscosity ratio, η/η_{melt}) through the undercooled melt regime. (**a**) Class (I-A) compounds; (**b**) class (I-B) compounds; (**c**) class (II) compounds; (**d**) class (III) compounds.

particularly at small degrees of undercooling. Furthermore, with the exception of lidocaine, when crystallization occurred, the viscosities had increased by less than a factor of 2. Thus, for these compounds with a very high crystallization tendency from the undercooled melt state, it is clear that viscosity is sufficiently low close to the melting point to facilitate crystallization and that the thermodynamic factors important for crystallization are sufficiently favorable to overcome the nucleation barrier even at low degrees of undercooling.

Class (I-B) Compounds

Compounds within this class crystallize from the undercooled melt state at modest cooling rates (20°C/min), but can be trapped in the amorphous state by quench cooling in liquid N_2. Thus, according to the classification system, class (I-B) compounds have a lower crystallization tendency from the undercooled melt state compared to class (I-A) compounds. Hence, it was pertinent to compare the viscosities for compounds between these two classes to elucidate what role (if any) mobility of the undercooled melt may have on differences in crystallization tendency observed. Measured viscosities for compounds within this class (Fig. 1b) exhibited much larger variation compared to class (I-A) compounds, with over an order of magnitude difference between the melt viscosities of antipyrin ($\eta_{melt} = 4.18 \times 10^{-3}$ Pa-s) and chlorpropamide ($\eta_{melt} = 9.32 \times 10^{-2}$ Pa-s). Moreover, with the exception of antipyrin and 4-biphenylcarboxaldehyde, the melt viscosities of class (I-B) compounds were all greater than 10^{-2} Pa-s, compared to class (I-A) compounds in which no compound had a melt

viscosity above this threshold. Thus, based only upon consideration of viscosity at the melting point and through the undercooled melt regime, it appears that the increased viscosity of class (I-B) compounds may contribute to their decreased crystallization tendency compared to class (I-A) compounds.

In general the viscosities of class (I-B) compounds could be measured at higher degrees of undercooling before crystallization occurred compared to class (I-A) compounds. The relative changes in viscosity for class (I-B) compounds are shown in Fig. 2b, where it can be seen that similar to class (I-A) compounds, the relative change in viscosity for these compounds at small degrees of undercooling (<15°C) was small; however, at larger degrees of undercooling, the viscosity increases rapidly. This trend of rapidly increasing viscosity as the crystallization temperature is approached most likely explains why class (I-B) compounds can be captured as glasses when the cooling rate is sufficiently rapid.

Class (II) Compounds

Compounds within this crystallization class failed to crystallize even at relatively slow cooling rates (<5°C/min) from the undercooled melt state; however, they did crystallize upon reheating from the amorphous or glassy state back through the undercooled melt regime. One can see from Fig. 1c that the lower crystallization tendency of these compounds allowed viscosity of the undercooled melts to be measured to much higher degrees of undercooling compared to class (I-A) and class (I-B) compounds, accessing temperature regions for some compounds much closer to their glass transition temperatures. It should be noted, however, that four class (II) compounds (acetaminophen, celecoxib, nifedipine, tolazamide) crystallized during the viscosity measurements, while the viscosities of bifonazole, cinnarizine, and dibucaine were measured until the shear rate no longer remained constant during the experiment. Similar to class (I-B) compounds, there was significant variation in the measured melt viscosities for class (II) compounds, with over an order of magnitude difference between the compound with the lowest melt viscosity (tolazamide, $\eta_{melt} = 6.61 \times 10^{-3}$ Pa-s) and that with the highest (dibucaine, ($\eta_{melt} = 1.31 \times 10^{-1}$ Pa-s). Interestingly, although tolazamide exhibited almost an order of magnitude lower melt viscosity compared to either celecoxib or nifedipine, the viscosity for this compound could be measured at much higher degrees of undercooling before crystallization occurred. Similarly, bifonazole has a much lower melt viscosity than either celecoxib or nifedipine, yet this compound could be cooled to more than 100°C below its melting temperature without crystallizing. These observations indicate that differences in viscosity cannot be used to explain the variation in crystallization tendency observed *within* this class of compounds. Comparison of the melt viscosities for class (II) compounds to those of both class (I-A) and class (I-B) compounds indicated that the melt viscosities of class (II) compounds were much higher than those measured for class (I-A) compounds, with only one compound (tolazamide) exhibiting a melt viscosity below 10^{-2} Pa-s. However, class (II) compounds exhibited similar ranges in melt viscosities to class (I-B) compounds.

Examination of Fig. 2c shows that unlike class (I-A) and class (I-B) systems where most compounds exhibited similar changes in viscosity within a class as a function of temperature, there were much larger differences between class (II) compounds. This can be illustrated by comparing the viscosity ratios for the compounds at a degree of undercooling equal to 45°C. Three of the compounds (acetaminophen, bifonazole, tolazamide) exhibited similar changes in viscosity (viscosity ratios ≈ 5), while the other four compounds evaluated (celecoxib, cinnarizine, dibucaine, nifedipine) had viscosities at least one order of magnitude (viscosity ratio = 10) greater than their melt viscosities. Further examination of the properties of class (II) compounds indicates that at this relative degree of undercooling (45°C), the compounds with the higher viscosity ratios were in fact closer to their respective glass transition temperatures. Hence, these differences in relative viscosities as a function of undercooling arise, in part, because T_g/T_m is not a constant with a value of 2/3 (≈ 0.66) but varies between 0.65 and 0.76; hence, the temperature span of the undercooled region (T_m-T_g) varies between compounds.

Moreover, one can see that although the measured melt viscosities were similar between class (II) and class (I-B) compounds (Fig. 1b, c), differences could be observed in their relative change in viscosities. This can be illustrated by comparing the viscosity ratios of chlorpropamide (class (I-B), (T_m-T_g) = 108°C) and celecoxib (class (II), (T_m-T_g) = 105°C) at a degree of undercooling equal to 40°C. Since these two compounds have similar undercooled melt ranges (T_m-T_g), a direct comparison between the temperature dependency of their viscosities can be made. The viscosity ratio for chlorpropamide at 40°C below its melting temperature is ≈ 10, while for celecoxib at the same temperature relative to its melting temperature the viscosity ratio is ≈ 20, indicating celecoxib viscosity has a much stronger temperature dependence compared to that of chlorpropamide. The same trend was observed comparing other class (I-B) and class (II) compounds with similar (T_m-T_g) ranges (flufenamic acid and cinnarizine, tolbutamide and nifedipine), whereby the class (II) compounds had higher relative changes in viscosities at a given degree of undercooling compared to the class (I-B) compounds. The greater temperature dependency on viscosity for class (II) compounds compared to class (I-B) could play a role in

their observed lower crystallization tendency by hindering the diffusion of molecules together to form nuclei or to a growing crystalline surface, especially at higher degrees of undercooling.

Class (III) Compounds

From a previous study (8), class (III) compounds were differentiated from the other classes of compounds by their very low crystallization tendency, whereby crystallization was not observed either upon slow cooling (2°C/min) or during subsequent slow reheating (2°C/min) from the glass to the melting temperature. Thus, no crystallization was observed for any class (III) compounds during the viscosity experiments, in contrast to class (I-A), (I-B), and (II) compounds, where some or all of the compounds crystallized. From Fig. 1d one can see that similar to class (I-B) and class (II) compounds, there was a large variation in the melt viscosities (over an order of magnitude) within class (III) compounds. Interestingly, one compound (ritonavir) had a melt viscosity (1.99 Pa-s) almost an order of magnitude higher than any other compound. Furthermore, from the data collected it can be observed that the melt viscosities of class (III) compounds in general were higher than for compounds from other crystallization classes. Using a viscosity value of 10^{-2} Pa-s as a benchmark, clear differences can be seen between the classes, especially between class (I-A) and class (III) compounds, where none of the class (I-A) compounds had melt viscosities above 10^{-2} Pa-s, while all class (III) compounds had melt viscosities above 10^{-2} Pa-s.

Thus, it seems that there is some trend between a compound's crystallization tendency (as determined by its classification) and the viscosity at the melt and of the undercooled liquid, whereby compounds with higher crystallization tendencies tend to have a lower viscosity. This trend is best illustrated by comparing the average viscosities for each class of compound as a function of degree of undercooling (Fig. 3a). Here it is clear that even at low degrees of undercooling (<20°C), class (III) compounds on average have a higher viscosity while class (I-A) compounds on average have lower viscosity compared to the other classes. Although differences in the average viscosities are observed between class (I-B) and class (II) compounds, these differences are small and not statistically significant. The error bars reflect the large variations in viscosity within each class between compounds.

The calculated viscosity ratios for class (III) compounds (Fig. 2d) show that the viscosities of most compounds exhibit a strong temperature dependence, with the majority of compounds having viscosity ratios greater than 100 at large degrees of undercooling. Comparing the average change in viscosity ratio (Fig. 3b) between the classes of compounds shows that *on average* class (I-A) compounds have the weakest temperature dependence on viscosity, while class (III) compounds exhibit the strongest temperature dependence. This trend can be exemplified by comparing the viscosity ratio of dibucaine, a class (II) compound, to several class (III) compounds (felodipine, ketoprofen, loratadine, probucol, procaine) with similar (T_m-T_g) ranges (≈ 100°C) at a degree of undercooling equal to 40°C. At this degree of undercooling dibucaine had a calculated viscosity ratio of ≈ 29, the highest value for any class (II) compound. However, this ratio was lower than the viscosity ratios calculated for the selected class (III) compounds (felodipine = 71, ketoprofen = 61, loratadine = 87, probucol = 82, procaine = 35). Furthermore, ketoconazole is a class (III) compound with a similar (T_m-T_g) to both chlorpropamide (class I-B) and celecoxib (class II), yet exhibited the highest calculated viscosity ratio among the three compounds (36) at a degree of undercooling equal to 40°C. Thus, similar to measured viscosities, a trend between crystallization tendency from the undercooled melt state and the temperature dependence of viscosity was observed, indicating that mobility of the undercooled melt state likely plays a role in determining crystallization tendency.

One interesting trend that was observed from the data collected was the apparent relationship between the temperature range of the undercooled melt state (T_m-T_g) and the measured melt viscosity for compounds *within* the same crystallization classification (Tables 1, 2, 3 and 4). For example, antipyrin had the largest calculated (T_m-T_g) range and the lowest measured melt viscosity, while chlorpropamide had the smallest calculated (T_m-T_g) and the highest melt viscosity for class (I-B) compounds (Table 2). The same trend was observed for class (II) and class (III) compounds (Tables 3 and 4), whereby tolazamide (class (II)) and aceclofenac (class (III)) had the largest (T_m-T_g) ranges and the lowest measured melt viscosities compared to dibucaine (class (II)) and ritonavir (class (III)), which had the smallest (T_m-T_g) ranges and the highest observed melt viscosities. However, as mentioned above, this trend was not observed when comparing compounds from *different* classes. Furthermore, the average (T_m-T_g) range for class (I-A) compounds was 123 (±11°C) compared to class (I-B) compounds (119 (±11°C)), class (II) compounds (126 (±20°C)), and class (III) compounds (108 (±16°C)). These differences are not statistically significant and indicate that (T_m-T_g) is not strongly correlated with the melt viscosity across the entire group of organic compounds studied.

DISCUSSION

Viscosity is an internal property of a fluid that measures the resistance of the fluid to flow under an applied stress (14). At a molecular level, the viscosity of a liquid can be regarded

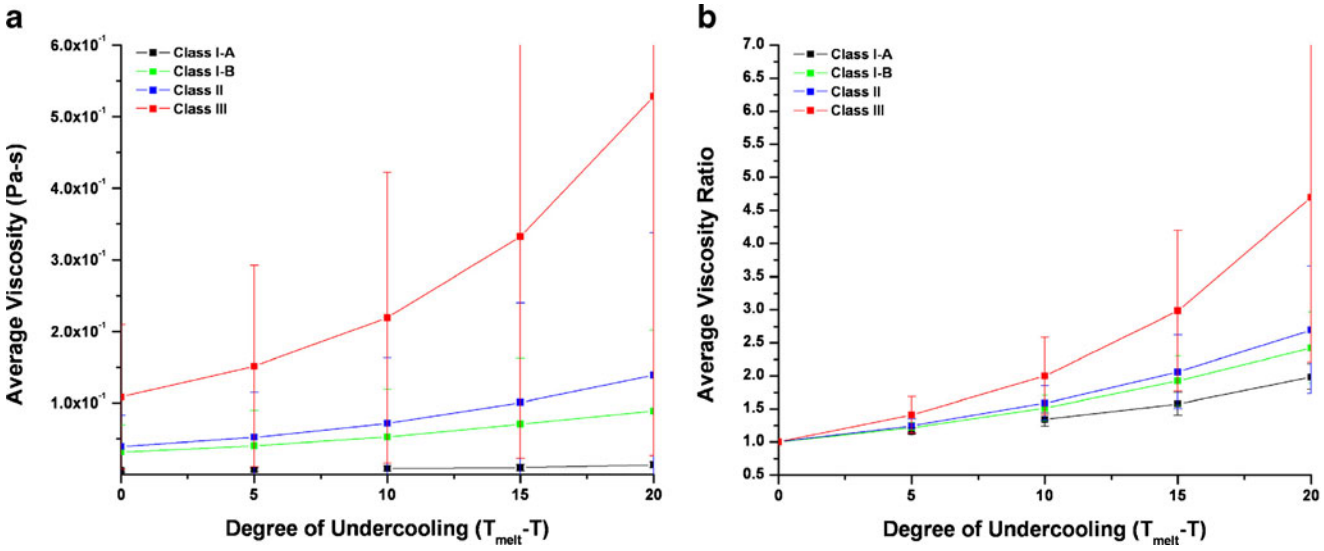

Fig. 3 Comparison of the average viscosity (**a**) and average viscosity ratio (**b**) between the different classes of compounds (class (I-A), class (I-B), class (II), class (III)) as a function of temperature through the undercooled melt regime.

generally as the friction between neighboring molecules (15); however, viscosity is a complex phenomenon interdependent on molecular properties (structure, intermolecular interactions) as well as external forces (temperature, pressure) (14). The viscosity of a compound at its melting point is considered important in determining the glass forming ability of a liquid (16), whereby only liquids with a certain viscosity at the melting point and/or a rapidly rising viscosity on cooling are amenable to glass formation at easily attainable cooling rates. The viscosity at the melting point is also related to the $T_b/T_m > 2$ empirical rule for glass forming liquids; it has been observed that molecular compounds for which the ratio of the boiling temperature (T_b) to the melting temperature is 2 or greater will more easily form glasses under achievable cooling conditions (16–20). Wang and Angell (21) point out that this "rule" defines a group of compounds for which the viscosity is sufficiently large at the melting point that crystallization will be retarded. For these compounds, the melting point is low relative to the boiling point; hence, the viscosity should be proportionally higher. In a recent publication, Angell discusses this issue further (22). By surveying a number of liquids which crystallize sufficiently slowly from the undercooled state such that the viscosity can be measured in the undercooled region, he concludes that a compound generally needs to have a viscosity at the melting point no lower than 0.01–1 Pa-s to be a good glass former. The question is then posed: What determines if a crystal will melt to give a viscosity at or above this critical range? Since the melting point is determined by the point at which the free energy of the liquid is equal to the free energy of the solid, it is apparent that compounds with lower melting points are characterized either by poor packing in the crystal structure or a high cohesive energy in the liquid relative to the crystal lattice energy. The critical viscosity values discussed by Angell thus appear to be good predictors of the glass-forming ability of the compounds investigated in our studies. All class (I-A) compounds have melt viscosities that are indeed lower than 0.01 Pa-s, while all class (II) (with the exception of tolazamide) and class (III) compounds, both of which have high glass-forming abilities, have melt viscosities higher than this value. The majority of class (I-B) compounds also have melt viscosities above the critical range, although there are a couple of exceptions. Summarizing, out of the 31 compounds studied, 22 have melt viscosities above 0.01 Pa-s and can form glasses, while out of the 9 compounds with melt viscosities less than 0.01 Pa-s, only 3 of the compounds can be quenched as glasses.

While the value of the viscosity at the melt clearly appears to be important, the rate of increase of the viscosity on cooling can also be considered key. At the melting point, the free energy difference between the crystal and liquid is zero; hence, there is no thermodynamic driving force for crystallization. As the melt is cooled, the nucleation rate is dictated by three parameters, the free energy difference between the liquid and the crystal, the value of the interfacial free energy between the crystal nuclei and the liquid, and the fluidity (or viscosity) of the liquid, as outlined by Eq. 1 and 2. Hence, a more rapid increase in viscosity will decrease the nucleation rate, all other factors being equal. Therefore, we might predict that compounds with a steeper increase in viscosity upon cooling might be more resistant to crystallization, if the melt viscosities and the height of the nucleation barrier is similar. For example, we can compare the viscosity ratios of chlorpropamide, a class (I-B) compound which crystallized during the viscosity measurements, to probucol, a class (III)

Table 1 Physical and Molecular Properties of Class (I-A) Molecules Evaluated

Molecule	MW (g/mol)	T_m (°C)	T_g (°C)	T_m-T_g (°C)	ΔH_{fus} (J/cm^3)	ΔS_{fus} (J/cm^3-K)	ΔG_v (J/cm^3)	$\eta_{melt} \times 10^{-3}$ (Pa-s)	# Rotatable Bonds
4-biphenylmethanol	184.2	99	−22	122	170	0.46	−27.3	5.01	2
Benzamide	121.1	127	−10	137	211	0.53	−40.1	2.86	1
Benzocaine	165.2	89	−31	120	165	0.46	−24.0	4.60	3
Haloperidol	375.9	152	33	119	189	0.44	−39.6	8.62	6
Lidocaine	234.3	68	−39	107	78	0.23	−8.6	7.64	5
Phenacetin	179.2	136	2	134	216	0.53	−42.7	4.18	3

Estimated T_g values taken from reference (8)

ΔG_v values measured using the Hoffman equation at temperature (T) = 298 K

Rotatable bonds calculated from PubChem

compound in which crystallization was not observed. Chlorpropamide had a melt viscosity ($\eta_{melt} = 9.33 \times 10^{-2}$ Pa-s) similar to that of probucol ($\eta_{melt} = 8.03 \times 10^{-2}$ Pa-s), yet at a degree of undercooling equal to 40°C, probucol exhibited a much higher viscosity ratio (≈ 82) compared to chlorpropamide (≈ 10), which crystallized. The higher rate of increase in viscosity for probucol as the temperature was depressed thus hindered the diffusion of molecules together to form nuclei, contributing to a much lower crystallization tendency. Similar trends can be observed between other class (I-B) and class (III) compounds with similar melt viscosities, whereby class (III) compounds exhibited much higher rates of change in viscosity with temperature and were resistant to crystallization. Although an exact correlation between viscosity and crystallization tendency is not to be expected in all cases, since the thermodynamic parameters contributing to crystallization tendency will vary between compounds, the results obtained in this study clearly indicate that it is a very important parameter contributing to crystallization tendency, as expected from theoretical considerations.

Interestingly, *within* the same class, compounds with the higher rates of increase of viscosity on cooling tended to have a lower temperature range for the undercooled melt regime (T_m-T_g). The reduced glass transition temperature (T_g/T_m), first described by Kauzmann (23) and later by Turnbull (24), is perhaps the most common metric used to assess the glass-forming ability (GFA) of organic molecules. Thus, one might predict that compounds with lower (T_m-T_g) values and hence higher T_g/T_m values would be more resistant to crystallization. However, there are multiple examples in this study where compounds with similar (T_m-T_g) values exhibited very different crystallization tendencies, indicating T_g/T_m is actually not a good predictor of GFA for organic molecules. This is due to the fact that compounds with similar melt viscosities and (T_m-T_g) values may exhibit different rates of change of viscosity with temperature. One example is provided by chlorpropamide and ketoconzazole, which have similar melt viscosities and (T_m-T_g) values; however, ketoconazole has a much higher rate of change of viscosity than chlorpropamide and is much more resistant to crystallization.

Fragility

Another commonly used metric to describe the crystallization tendency or GFA of a material is the "kinetic fragility" of the undercooled liquid state (25,26). Liquid fragility is defined as

Table 2 Physical and Molecular Properties of Class (I-B) Molecules Evaluated

Molecule	MW (g/mol)	T_m (°C)	T_g (°C)	T_m-T_g (°C)	ΔH_{fus} (J/cm^3)	ΔS_{fus} (J/cm^3-K)	ΔG_v (J/cm^3)	$\eta_{melt} \times 10^{-3}$ (Pa-s)	# Rotatable Bonds
4-biphenylcarboxaldehyde	182.2	59	−50[a]	109	143	0.43	−13.2	5.05	2
Antipyrin	188.2	111	−22	133	169	0.44	−29.3	4.18	1
Chlorpropamide	276.7	124	16	108	141	0.35	−26.4	93.26	4
Flufenamic acid	281.2	135	17	118	143	0.35	−28.1	13.86	3
Tolbutamide	270.3	129	4	125	121	0.30	−23.3	41.01	5

Estimated (denoted [a]) and measured T_g values taken from reference (8)

ΔG_v values measured using the Hoffman equation at temperature (T) = 298 K

Rotatable bonds calculated from PubChem

Table 3 Physical and Molecular Properties of Class (II) Molecules Evaluated

Molecule	MW (g/mol)	T_m (°C)	T_g (°C)	T_m-T_g (°C)	ΔH_{fus} (J/cm^3)	ΔS_{fus} (J/cm^3-K)	ΔG_v (J/cm^3)	$\eta_{melt} \times 10^{-3}$ (Pa-s)	# Rotatable Bonds
Acetaminophen	151.2	170	24	146	249	0.56	−54.7	13.64	1
Bifonazole	310.4	151	17	134	156	0.37	−32.5	10.07	4
Celecoxib	381.4	163	58	105	149	0.34	−32.3	51.30	3
Cinnarizine	368.5	121	7	114	130	0.33	−23.9	25.80	6
Dibucaine	234.3	68	−39	100	100	0.30	−10.5	130.50	10
Nifedipine	346.3	173	45	128	152	0.34	−33.7	36.20	5
Tolazamide	311.4	172	18	154	170	0.38	−37.6	6.61	3

T_g values taken from reference (8)

ΔG_v values measured using the Hoffman equation at temperature (T) = 298 K

Rotatable bonds calculated from PubChem

the sensitivity of an undercooled liquid's "structure" to rearrange to a more energetically favorable arrangement under temperature perturbations (27). Angell (28) established a classification (strong/fragile) system to characterize the kinetic fragility of undercooled liquids based on the temperature dependence of their viscosity (or relaxation), cooling below T_m towards T_g. According to this classification scheme, liquids exhibiting an Arrhenius temperature dependence with viscosity (or relaxation), described as strong liquids, tend to not undergo structural changes as a function of temperature and are good glass formers. In contrast, fragile liquids show a non-Arrhenius temperature dependence with viscosity (relaxation) and tend to undergo structural reorganization with temperature changes and have higher crystallization tendencies. The temperature-dependent nature of viscosity (or relaxation) can be modeled using the Vogel-Tamman-Fulcher (VTF) equation:

$$\eta = \eta_0 \exp\left(\frac{DT_0}{T - T_0}\right) \tag{4}$$

where η is the viscosity of the material at temperature T, η_0 is the viscosity for the unrestricted material, D is the strength

Table 4 Physical and Molecular Properties of Class (III) Molecules Evaluated

Molecule	MW (g/mol)	T_m (°C)	T_g (°C)	T_m-T_g (°C)	ΔH_{fus} (J/cm^3)	ΔS_{fus} (J/cm^3-K)	ΔG_v (J/cm^3)	$\eta_{melt} \times 10^{-3}$ (Pa-s)	# Rotatable Bonds
Aceclofenac	354.2	153	10	143	201	0.47	−42.3	14.30	7
Clotrimazole	344.8	145	30	115	128	0.31	−26.2	107.0	4
Felodipine	384.3	147	45	100	117	0.28	−24.1	154.0	6
Fenofibrate	360.8	81	−19	102	118	0.33	−15.7	27.00	7
Ibuprofen	206.3	77	−45	122	152	0.43	−19.2	13.34	4
Indomethacin	357.8	162	45	116	148	0.34	−31.9	70.32	4
Itraconazole	705.6	168	58	110	111	0.25	−24.3	365.0	11
Ketoconazole	531.4	150	45	105	139	0.33	−29.0	234.0	7
Ketoprofen	254.3	95	−3	98	142	0.39	−21.9	108.0	4
Loratadine	382.9	136	37	99	93	0.23	−18.5	191.0	2
Miconazole	416.6	86	1	85	117	0.33	−16.5	182.0	6
Nilutamide	317.2	155	33	122	156	0.36	−32.9	30.35	1
Nimesulide	308.3	150	21	129	160	0.38	−33.4	15.50	4
Probucol	516.8	127	27	100	69	0.17	−13.2	80.30	8
Procaine	236.3	62	−39	101	130	0.39	−12.7	32.00	7
Ritonavir	720.9	126	49	77	113	0.28	−37.6	1990	18

T_g values taken from reference (8)

ΔG_v values measured using the Hoffman equation at temperature (T) = 298 K

Rotatable bonds calculated from PubChem

parameter, and T_0 is the zero mobility temperature which for some systems coincides with the thermodynamically derived Kauzmann temperature (29). T_0 can be related to the strength parameter (D) by the following equation:

$$\frac{T_g}{T_0} = 1 + \frac{D}{2.303\log(\eta_g/\eta_0)} \quad (5)$$

where $\log(\eta_g/\eta_0) \approx 17$ (19,30). The strength parameter (D) describes the kinetic fragility of the liquid and, depending on its value (strong liquids have D values >30, fragile liquids have D values <10), has been used to describe the crystallization tendency or glass-forming ability (GFA) of the material (31–33).

There has been some debate about the appropriate temperature range for fitting of viscosity data to the VTF equation (19,34,35), with some systems showing more than one VTF regime and/or a cross-over to an Arrhenius dependence. Stickel *et al.* (35) observed that for simple organic glass formers, the VTF equation (Eq. (4)) was valid from the melting temperature down to approximately $0.4T_g$ (assuming $T_g=0$ and $T_m=1$), at which point the temperature dependence of viscosity (or relaxation) changed and a modified VTF equation was needed to accurately model the data. For our compound set, viscosity measurements for three class (II) compounds (bifonazole, cinnarizine, tolazamide) and all the class (III) compounds except clotrimazole and ritonavir extend beyond this threshold; thus, for fitting purposes the data was truncated at this point. Table 5 shows the VTF parameters obtained by fitting the measured viscosity data for class (I-B), (II), and (III) compounds to the VTF equation by simultaneously varying both the strength parameter and the zero mobility temperature (T_0) until the best fit was achieved. Proper fitting of the data to the VTF equation could not be achieved for class (I-A) compounds due to the small number of measurable data points recorded. The calculated strength

Table 5 Calculated Zero Mobility Temperatures (T_0) and Strength Parameters (D) for Class (I-B), Class (II), and Class (III) Compounds

Molecule	T_0 (°C)	T_g (°C)	$\lvert T_0\text{-}T_g \rvert$ (°C)	Strength Parameter (D)
4-biphenylcarboxaldehyde	−105	−50*	55	6.0
Antipyrin	−60	−22	38	4.5
Chlorpropamide	−54	16	70	7.3
Flufenamic acid	−26	17	43	4.7
Tolbutamide	−40	4	44	5.9
Acetaminophen	−33	24	57	6.0
Bifonazole	−20	17	37	4.4
Celecoxib	10	58	48	4.7
Cinnarizine	−24	7	31	4.4
Dibucaine	−95	−39	56	8.7
Nifedipine	−3	45	48	5.3
Tolazamide	−63	18	81	6.7
Aceclofenac	−31	10	41	4.8
Clotrimazole	11	30	19	4.5
Felodipine	11	45	34	4.6
Fenofibrate	−46	−19	27	4.4
Ibuprofen	−83	−45	38	5.7
Indomethacin	6	45	39	4.7
Itraconazole	−3	58	59	6.3
Ketoconazole	−1	45	46	5.4
Ketoprofen	−38	−3	35	5.3
Loratadine	7	37	30	4.6
Miconazole	−32	1	33	4.8
Nilutamide	3	33	30	4.4
Nimesulide	−4	21	25	4.3
Probucol	−6	27	33	4.5
Procaine	−76	−39	37	5.8
Ritonavir	0	49	49	5.6

T_g values taken from reference (8)

T_0 and strength parameters calculated by simultaneously fitting measured viscosity data to the VTF equation (Eq. 4)

parameters (Table 5) were all less than 10, indicating the compounds evaluated are kinetically fragile liquids. Angell and others (19,28,36) observed that the non-Arrhenius temperature dependence of viscosity (or relaxation) is a hallmark of organic glass-forming liquids. For these types of systems, neighboring molecules are held together by non-covalent (H-bonding) or non-Coloumb dispersive interactions, which are much weaker than the three-dimensional network structures formed through covalent bonds observed in strong liquids such as SiO_2 (37). Although interesting, this trend has been observed previously for pharmaceutical systems from relaxation experiments (38–43).

As discussed above, strong liquids exhibit an Arrhenius dependence, while fragile liquids exhibit a non-Arrhenius dependence in terms of the change in viscosity with temperature. Figure 4 shows a schematic of an Angell plot where the viscosities are plotted as a function of the measurement temperature scaled to the calorimetric glass transition temperature and illustrates how strong/fragile behavior of an undercooled liquid varies with the strength parameter (D). From this figure, one can see that an undercooled liquid with a high strength parameter ($D \geq 50$) exhibits an Arrhenius dependence of viscosity with T_g-scaled temperature, and as the strength parameter decreases below 20, the non-Arrhenius temperature dependence of viscosity becomes more pronounced. Figure 5 illustrates the extremes of behavior, showing the temperature dependence of the viscosity for a strong liquid ($D = 100$) and a fragile liquid ($D = 5$), whereby the viscosity data collected in this study has been superimposed on the plot. It is apparent that the compounds investigated in this study show viscosity temperature dependencies characteristic of fragile liquids. Perhaps more surprising, the log viscosity *vs.* T_g-scaled temperature plots for the compounds are all very similar and non-Arrhenius in nature, at least when compared to the extreme patterns of behavior which the strong-fragile classification system cover, with essentially no observable difference between the different classes of compounds. This is interesting because there are clear differences in the absolute measured viscosities between the compounds, as discussed above. Although these differences on an absolute scale can be significant, upon taking the logarithm of the data these differences become minimal. Hence, when plotted as log viscosity *vs.* T_g/T plots, all the compounds fall onto one region of the plot, as observed in Fig. 5. Thus, these results show that both good glass-formers and poor glass-formers exhibit the same non-Arrhenius temperature dependence on viscosity, and hence "Angell" plots as seen in Fig. 5 give minimal information regarding the crystallization tendency or GFA of organic compounds. This should not be surprising, as crystallization is a complex process dependent not only on viscosity, but also on thermodynamic properties of the material as well as other potential factors.

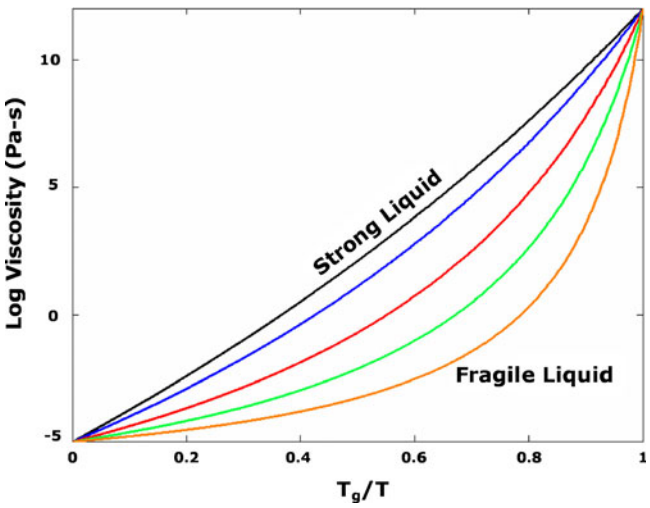

Fig. 4 Schematic illustration depicting the non-Arrhenius dependence of viscosity as a function of T_g-scaled temperature using the VTF equation (Eq. 4) for a hypothetical material with different strength parameters (D). T_g for the material was assumed to be = 273 K (0°C), and the relationship between T_0 and T_g is given by Eq. 5. D = 100 (black), D = 50 (blue), D = 20 (red), D = 10 (green), D = 5 (orange).

CONCLUSIONS

Viscosities measured in the undercooled melt regime showed a link between both the viscosity at the melting temperature (η_{melt}) as well as the rate of change of viscosity with temperature (viscosity ratio) and the crystallization tendency of that compound from the undercooled melt state. Compounds with very high crystallization tendency exhibited much lower melt viscosities compared to compound with very low crystallization tendency, with an

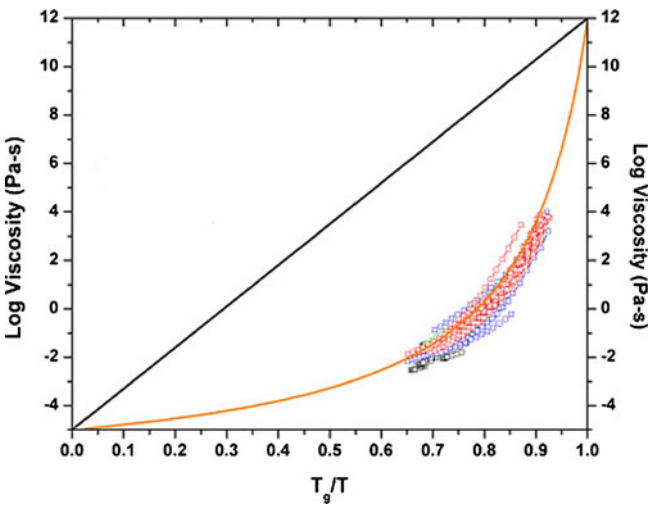

Fig. 5 T_g-scaled plots of viscosity for the different classes of compounds. Class (I-A)—*black squares*, class (I-B)—*green squares*, class (II)—*blue squares*, and class (III)—*red squares*. *Solid black* (strong liquid, $D = 100$) and orange (fragile liquid, $D = 5$) lines from Fig. 4 are overlaid to help illustrate the kinetic fragility of the compounds evaluated.

observed melt viscosity of 10^{-2} Pa-s appearing as a threshold separating good glass formers from non-glass formers. In addition, rapidly crystallizing compounds showed a much lower temperature dependence of viscosity compared to good glass formers, whose viscosities increased dramatically with decreasing temperature, hindering diffusion of molecules to form nuclei or crystal growth during cooling through the undercooled melt regime. Interestingly, some compounds with similar T_g/T_m values exhibited vastly different temperature dependencies of viscosity as well as different crystallization tendencies, indicating T_g/T_m should not be considered a reliable predictor of crystallization tendency. Calculated strength parameters (D), obtained from fitting of the VTF equation, revealed that all the compounds investigated were kinetically fragile liquids, irrespective of their observed crystallization tendencies. Thus, this study shows that viscosity is indeed one critical attribute governing the crystallization tendency upon cooling through the undercooled melt regime.

ACKNOWLEDGMENTS & DISCLOSURES

The authors would like to thank the National Science Foundation Engineering Research Center for Structured Organic Particulate Systems (NSF ERC-SOPS) (EEC-0540855) for financial support. This work was funded in part by a grant from the Lilly Endowment, Inc., to Purdue University College of Pharmacy. The American Foundation for Pharmaceutical Education (AFPE) is acknowledged for a fellowship to JAB. The Purdue Graduate School is acknowledged for the Ross fellowship to JAB.

REFERENCES

1. Lipinski CA. Drug-like properties and the causes of poor solubility and poor permeability. J Pharmacol Toxicol. 2000;44:235–49.
2. Leuner and C, Dressman J. Improving drug solubility for oral delivery using solid dispersions. Eur J Pharm Biopharm. 2000;50:47–60.
3. Six K, Daems T, de Hoon J, Van Hecken A, Depre M, Bouche MP, *et al.* Clinical study of solid dispersions of itraconazole prepared by hot-stage extrusion. Eur J Pharm Sci. 2005;24:179–86.
4. Dong ZD, Chatterji A, Sandhu H, Choi DS, Chokshi H, Shah N. Evaluation of solid state properties of solid dispersions prepared by hot-melt extrusion and solvent co-precipitation. Int J Pharm. 2008;355:141–9.
5. Crowley MM, Zhang F, Repka MA, Thumma S, Upadhye SB, Battu SK, *et al.* Pharmaceutical applications of hot-melt extrusion: part I. Drug Dev Ind Pharm. 2007;33:909–26.
6. Chiou and WL, Riegelman S. Pharmaceutical applications of solid dispersion systems. J Pharm Sci. 1971;60:1281–302.
7. Sinha S, Baboota S, Ali M, Kumar A, Ali J. Solid dispersion: an alternative technique for bioavailability enhancement of poorly soluble drugs. J Disper Sci Technol. 2009;30:1458–73.
8. Baird JA, Van Eerdenbrugh B, Taylor LS. A classification system to assess the crystallization tendency of organic molecules from undercooled melts. J Pharm Sci. 2010;99:3787–806.
9. Andronis and V, Zografi G. Molecular mobility of supercooled amorphous indomethacin, determined by dynamic mechanical analysis. Pharm Res. 1997;14:410–4.
10. Hancock BC, Dupuis Y, Thibert R. Determination of the viscosity of an amorphous drug using thermomechanical analysis (TMA). Pharm Res. 1999;16:672–5.
11. Kestur US, Lee H, Santiago D, Rinaldi C, Won YY, Taylor LS. Effects of the molecular weight and concentration of polymer additives, and temperature on the melt crystallization kinetics of a small drug molecule. Cryst Growth Des. 2010;10:3585–95.
12. Schmelzer JWP, editor. Nucleation theory and applications. Weinheim: Wiley-VCH; 2005.
13. Simmons JH, editor. Nucleation and crystallization in glasses. Ohio: American Chemical Society; 1982.
14. Viswanath DS, Ghosh TK, Prasad DL, Dutt NVK, Rani KY. Viscosity of liquids: theory, estimation, experiment, and data. Dordrecht: Springer; 2007.
15. Wright PG. The variation of viscosity with temperature. Phys Ed. 1977;12:323.
16. Uhlmann DR. A kinetic treatment of glass formation. J Non-Cryst Solids. 1972;7:337–348.
17. Turnbull D, Cohen MH. Concerning reconstructive transformation and formation of glass. J Chem Phys. 1958;29:1049–54.
18. Angell CA, Dworkin A, Figuiere P, Fuchs A, Szwarc H. Strong and fragile plastic crystals. J Chim Phys PCB. 1985;82:773–7.
19. Angell CA. Formation of glasses from liquids and biopolymers. Science. 1995;267:1924–35.
20. Wang and LM, Richert R. Glass transition dynamics and boiling temperatures of molecular liquids and their isomers. J Phys Chem B. 2007;111:3201–7.
21. Wang LM, Angell CA, Richert R. Fragility and thermodynamics in nonpolymeric glass-forming liquids. J Chem Phys. 2006;125:074505-1–074505-8.
22. Angell CA. Glass-formers and viscous liquid slowdown since David Turnbull: enduring puzzles and new twists. MRS Bull. 2008;33:544–55.
23. Kauzmann W. The nature of the glassy state and the behavior of liquids at low temperatures. Chem Rev. 1948;43:219–56.
24. Turnbull D. Under what conditions can a glass be formed. Contemp Phys. 1969;10:473–88.
25. Angell CA. The old problems of glass and the glass-transition, and the many new twists. Proc Natl Acad Sci USA. 1995;92:6675–82.
26. Senkov ON. Correlation between fragility and glass-forming ability of metallic alloys. Phys Rev B. 2007;76:104202-1–6.
27. Green JL, Ito K, Xu K, Angell CA. Fragility in liquids and polymers: new, simple quantifications and interpretations. J Phys Chem B. 1999;103:3991–6.
28. Angell CA. Relaxations in complex systems, National Technical Information Service. Springfield: U.S Department of Commerce; 1985.
29. Tanaka H. Two-order-parameter model of the liquid-glass transition I. Relation between glass transition and crystallization. J Non-Cryst Solids. 2005;351:3371–84.
30. Miller AA. Molecular interpretation of Vogel equation for polymer liquid mobility. Macromolecules. 1978;11:859–62.
31. Lu and Q, Zografi G. Properties of citric acid at the glass transition. J Pharm Sci. 1997;86:1374–8.
32. Gupta P, Chawla G, Bansal AK. Physical stability and solubility advantage from amorphous celecoxib: the role of thermodynamic quantities and molecular mobility. Mol Pharm. 2004;1:406–13.

33. Kaushal and AM, Bansal AK. Thermodynamic behavior of glassy state of structurally related compounds. Eur J Pharm Biopharm. 2008;69:1067–76.
34. Stickel F, Kremer F, Fischer EW. The scaling of the dielectric and electric relaxation in 2 low-molecular-weight glass-forming liquids. Physica A. 1993;201:318–21.
35. Stickel F, Fischer EW, Richert R. Dynamics of glass-forming liquids 2. Detailed comparison of dielectric relaxation, dc-conductivity, and viscosity data. J Chem Phys. 1996;104:2043–55.
36. Bohmer R, Ngai KL, Angell CA, Plazek DJ. Nonexponential relaxations in strong and fragile glass formers. J Chem Phys. 1993;99:4201–9.
37. Hodge IM. Strong and fragile liquids—a brief critique. J Non-Cryst Solids. 1996;202:164–72.
38. Kim and SJ, Karis TE. Glass-formation from low-molecular-weight organic melts. J Mater Res. 1995;10:2128–36.
39. Crowley and KJ, Zografi G. The use of thermal methods for predicting glass-former fragility. Thermochim Acta. 2001; 380:79–93.
40. Zhou DL, Zhang GGZ, Law D, Grant DJW, Schmitt EA. Physical stability of amorphous pharmaceuticals: importance of configurational thermodynamic quantities and molecular mobility. J Pharm Sci. 2002;91:1863–72.
41. Zhou DL, Grant DJW, Zhang GGZ, Law D, Schmitt EA. A calorimetric investigation of thermodynamic and molecular mobility contributions to the physical stability of two pharmaceutical glasses. J Pharm Sci. 2007;96:71–83.
42. Graeser KA, Patterson JE, Zeitler JA, Gordon KC, Rades T. Correlating thermodynamic and kinetic parameters with amorphous stability. Eur J Pharm Sci. 2009;37:492–8.
43. Hoppu P, Hietala S, Schantz S, Juppo AM. Rheology and molecular mobility of amorphous blends of citric acid and paracetamol. Eur J Pharm Biopharm. 2009;71:55–63.