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Research paper

Thermodynamic behavior of glassy state of structurally related compounds

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Abstract

Thermodynamic properties of amorphous pharmaceutical forms are responsible for enhanced solubility as well as poor physical stability. The present study was designed to investigate the differences in thermodynamic parameters arising out of disparate molecular structures and associations for four structurally related pharmaceutical compounds – celecoxib, valdecoxib, rofecoxib, and etoricoxib. Conventional and modulated temperature differential scanning calorimetry were employed to study glass forming ability and thermodynamic behavior of the glassy state of model compounds. Glass transition temperature of four glassy compounds was in a close range of 327.6–331.8 K, however, other thermodynamic parameters varied considerably. Kauzmann temperature, strength parameter and fragility parameter showed rofecoxib glass to be most fragile of the four compounds. Glass forming ability of the compounds fared similar in the critical cooling rate experiments, suggesting that different factors were determining the glass forming ability and subsequent behavior of the compounds in glassy state. A comprehensive understanding of such thermodynamic facets of amorphous form would help in rationalizing the approaches towards development of stable glassy pharmaceuticals.

Keywords: Differential scanning calorimetry; Amorphous; Glass transition temperature; Fragility; Heat capacity

1. Introduction

From a pharmaceutical perspective, the interest in the amorphous state stems from its higher apparent solubility and dissolution rate as compared to crystalline counterparts [1]. However, the excess properties [2] of enthalpy, entropy and free energy, that endow the desirable property of high solubility, are also responsible for the devitrification tendency of the amorphous systems. Despite numerous studies on amorphous systems, the reach of these systems to the market has been abysmal. This failure can at least in part be attributed to the incomplete understanding of these systems and lack of confidence in their behavior. Thereby, a fundamental understanding of the physicochemical properties of the amorphous state is necessary to develop products with consistent performance.

An investigation of the molecular and thermodynamic factors responsible for the differential behavior of the pharmaceutical amorphous systems is of paramount importance. This is not only likely to lead to a better understanding of the amorphous phase but may also provide leads for rational stabilization strategies for amorphous systems. A number of studies have reported a comparative assessment of the thermodynamic properties of amorphous phases of diverse compounds [3–7]. Zhou et al. related the physical stability of the compounds to configurational thermodynamic quantities and molecular mobility [7]. Shamblin et al. reported the effect of aging and the method of amorphous phase preparation on the thermodynamic properties of sorbitol, sucrose, trehalose, and indomethacin. These studies underscored the

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importance of inherent thermodynamic differences in determining the macroscopic behavior of the investigated compounds. However, most of these studies compared molecules differing to a relatively large extent in their molecular weight, and chemistry. Consequently, these compounds differed with respect to the 'start up' property of glass transition temperature (T_g). Since T_g is the foremost property of amorphous solids, compounds with diverse T_g's will more likely than not present different thermodynamic behavior. Hence, there exists a need to systematically examine the thermal behavior of amorphous phase of structurally similar compounds with comparable T_gs.

The present study was designed to address this issue by taking up a series of structurally related compounds for investigation of their thermodynamic properties. The objective was to investigate the differences in thermodynamic parameters arising out of disparate molecular structures and associations. Four structurally related compounds providing both a sufficient degree of similarity and diversity in their structure – celecoxib, valdecoxib, rofecoxib, and etoricoxib – were chosen as model compounds for the study.

2. Materials and methods

2.1. Materials

Celecoxib (Unichem Laboratories, Mumbai, India), valdecoxib (Aarti Drugs, Mumbai, India), rofecoxib (Ranbaxy Research Laboratories, Gurgaon, India), and etoricoxib (Aarti Drugs, Mumbai, India) were each of >99.9% assay value and were used as received. Calibration standards – gallium (Sigma–Aldrich Co., St. Louis, MO, USA), tin (Sigma–Aldrich Co., St. Louis, MO, USA), indium (Mettler Toledo, Schwerzenbach, Switzerland), and sapphire (Mettler Toledo, Schwerzenbach, Switzerland) were used to calibrate the differential scanning calorimeter (DSC) for enthalpy and temperature.

2.2. Preparation of amorphous forms

Amorphous forms were prepared by heating crystalline drug (3–5 mg) in DSC in a pin-holed aluminum pan to a temperature of about 20 K above the respective melting points, holding for 1 min, and then immediately cooling to 298 K at 20 K/min. The high-performance liquid chromatography assay of the amorphous samples established that no degradation occurred during the preparation of amorphous forms.

2.3. Differential scanning calorimetry

Conventional and modulated temperature (MT) DSC experiments were performed on Mettler Toledo DSC 821^e (Mettler Toledo, Switzerland) instrument, operating with STAR^e software version 5.1, and equipped with an intracooler. The samples (3–5 mg) were analyzed under dry nitrogen purge (80 ml/min) in crimped and pin-holed aluminum pans. Crystalline and amorphous samples were scanned at a rate of 20 K/min over a temperature range of 298 K to well above the respective melting points. The DSC instrument was calibrated for temperature and heat flow using high-purity standards of gallium, indium, and tin. The heat capacity constant was calibrated using a sapphire disc. All DSC measurements were done in triplicate.

2.4. Heat capacity measurements

Modulated temperature DSC (MTDSC) is one of the most acceptable techniques for the measurement of heat capacity at constant pressure (C_p) of crystalline and amorphous pharmaceuticals. However, numerous experimental conditions such as – modulation parameters, purge gas, sample geometry, pan type, and calibration status should be optimized to avoid erroneous results. Helium gas is usually preferred due to its superior thermal conductivity and thereby its ability to afford aggressive modulation. However, due to this very property of helium, it is likely to cause errors because of high sensitivity caused by even subtle changes in gas flow. In the absence of requirement for aggressive modulation and availability of conventional gas flow control valves, nitrogen gas at a flow rate of 80 ml/min was found to be adequate for heat capacity measurements by MTDSC. The modulation parameters for heat capacity measurements were – modulation period of 60 s, amplitude of ±0.3 K, and an underlying heating rate of 0.9 K/min. Samples weighing about 3–5 mg were compressed into discs and encapsulated in standard aluminum pans, crimped, and pin holed. Sample preparation and encapsulation was done to ensure a good sample to pan contact facilitating heat transfer during modulation. Loose powders, especially micronized powders, contain a lot of air, which leads to an underestimation of heat capacity. Therefore, flat discs that ensure good contact at the bottom of the crucible were utilized for MTDSC. Moreover, to match the sample geometry of the amorphous sample (that was formed as a glassy disc upon cooling of the melt), the crystalline sample was compacted. Amorphous samples were prepared from the same crystalline sample *in situ*, and MTDSC of the glassy sample was carried out in a subsequent run. The sample and reference pans weights were matched to within 20 mcg to minimize background heat capacities. As per the manufacturer's recommendation, the DSC cell was 'burned in' (heated to a temperature of 500 °C for 10 min) to maximize sensitivity. MTDSC measurement involved the running of 'blank', 'calibration', and 'sample' runs. Measurement was done over a range of 313–343 K, encompassing the glass transition range for the four compounds. Heat capacity was calculated by deconvolution, using commercial software 'ADSC C_p'. Heat capacity jump at T_g was measured for amorphous samples. Each heat capacity measurement was repeated thrice and arithmetic mean was used for calculations. Relative standard deviation was typically less than 3%.

3. Results and discussion

3.1. Selection of model compounds

The four compounds selected for the study, celecoxib, valdecoxib, rofecoxib, and etoricoxib belong to the pharmacological class of COX-2 inhibitors, and exhibit considerable similarity in molecular structure (Fig. 1). All four molecules possess a three ring chemical structure, while differing in the type and number of substituents. A comparison of the molecular properties of the four model compounds is presented in Table 1. It can be seen that all four have a comparable molecular weight, while two of them, valdecoxib and rofecoxib have exactly the same molecular weight. Celecoxib and valdecoxib possess two NH groups, while rofecoxib and etoricoxib have no such groups, which suggest the potential of the former molecules for H-bonding. Celecoxib has four rotatable bonds as against three each in the other three molecules. The rotatable bonds afford an enhanced degree of conformational freedom to the molecule and can have implication on crystallization from the melt and the amorphous state. The set of these four molecules were deemed appropriate for studying the influence of their structure, on the thermal behavior of crystalline and amorphous phases of these molecules.

3.2. Thermal response of crystalline and amorphous samples

The crystalline forms of celecoxib, valdecoxib, rofecoxib, and etoricoxib showed a single sharp endotherm corresponding to the melting of the crystalline form. The onset point was taken to represent the melting point (T_m), as it is least affected by sample parameters such as sample weight. The T_m of the compounds varied from 409.7 K for etoricoxib to 482.5 K for rofecoxib. The enthalpy of fusion (ΔH_m) values were obtained from the integration of endothermic fusion peak. Enthalpy, and entropy of fusion ($\Delta S_m = \Delta H_m/T_m$) are essential parameters to calculate the configurational enthalpy, entropy, and free energy of the respective amorphous systems. The value of $\Delta S_m/R$ (R being the gas constant) for the studied compounds was larger than 4, suggesting that the crystal growth rate anisotropy is large [8]. This is in concordance with previous reports on melts of low molecular weight organic compounds where directional crystal growth is anticipated [9]. The amorphous samples for all four drugs prepared *in situ* in DSC by melt quenching exhibited a glass transition event consisting of both a step shift in the baseline and an accompanying recovery endotherm. T_g reported as onset was determined as the intersection point of the tangent of baseline before transition and the inflection tangent. No crystallization or melting event was evident for any of the amorphous samples. A summary of thermodynamic quantities observed during DSC scans of crystalline and amorphous samples of the model compounds is shown in Table 2.

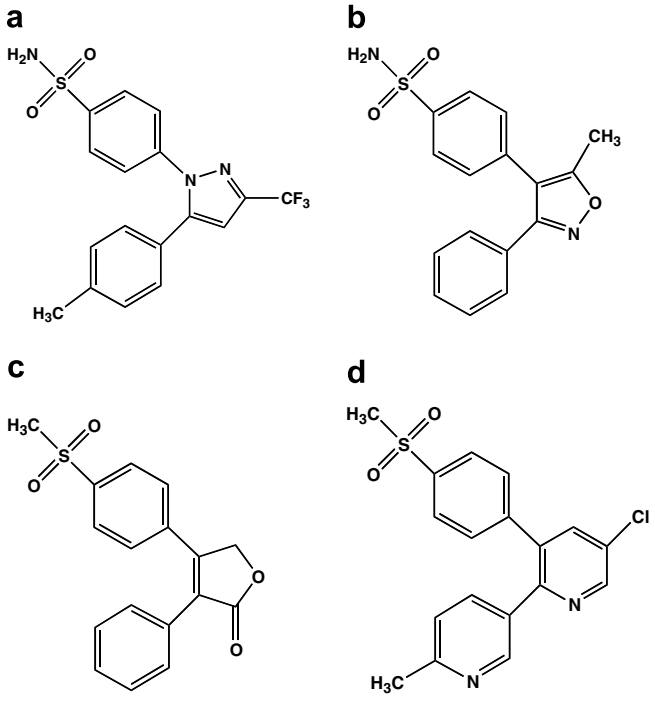

Fig. 1. Structure of the four model compounds selected for study – celecoxib (a), valdecoxib (b), rofecoxib (c), and etoricoxib (d).

Table 1
Molecular properties of the four model compounds

	MW	*n*O/N[a]	*n*OH/NH[a]	*n*rotb[a]
Celecoxib	381.38	5	2	4
Valdecoxib	314.36	5	2	3
Rofecoxib	314.36	4	0	3
Etoricoxib	358.84	4	0	3

*n*O/N, number of oxygen and nitrogen; *n*OH/NH, number of OH and NH; *n*rotb, number of rotatable bonds.
[a] Calculated with a web-based molecular descriptor calculator (http://www.molinspiration.com) using chemical structure inputs.

3.3. Glass forming ability

The glass forming ability describes the relative ability of compounds to form a glassy state upon supercooling of the melt. Good glass formers are ones for which the probability of germinating a crystal rather than forming a glassy solid during cooling at normal rates is so small that crystallization does not take place [10]. They have very low nucleation probabilities at all temperatures (especially between T_m and T_g). On the contrary, poor glass formers require exceeding of a critical cooling rate for successful formation of glass. The glass forming ability is dictated by both thermodynamic and kinetic factors [11]. Thermodynamically, the glass forming ability originates from a crystalline state that is not substantially more stable than the amorphous state. The critical cooling rate, q_c, necessary for vitrification rather than crystallization is defined as [12]

$$q_c = (T_m - T_n)/\tau_{1n} \quad (1)$$

Table 2
Thermodynamic quantities obtained from crystalline and amorphous forms of the four model compounds

	T_m (K)	ΔH_m (kJ/mol)	ΔS_m (J/mol/K)	$\Delta S_m/R$	T_g (K)	T_m/T_g
Celecoxib	435.3	37.6	86.3	10.4	331.4	1.31
Valdecoxib	442.0	32.7	74.0	8.9	329.5	1.34
Rofecoxib	482.5	37.0	76.7	9.2	327.6	1.47
Etoricoxib	409.7	27.0	66.0	7.9	331.8	1.23

where T_m is the melting point, T_n is the temperature under consideration, and τ_{1n} is the induction time for nucleation. The glass forming ability of melts can be ranked based upon the glass formation or failure under similar inert environmental conditions. In order to evaluate the glass forming ability of the melts of the four drugs, the melts were cooled from above their respective T_m to a temperature of 298 K. Cooling rates employed were 20, 15, 10, 5, 2, 1, and 0.3 K/min. A successful glass formation for all the four compounds (as confirmed by lack of any crystallization/melting peaks in reheating scan) was achieved at all the studied cooling rates, suggesting that the critical cooling rate for all the four drugs lies below 0.3 K/min, which is difficult to quantify due to very long experimental times. Although the normal melt-quench program has been reported to prepare amorphous form of a large number of drugs, specific requirement of higher cooling rates have also been reported; for example, for anti-viral drug UC-781 [13] (critical cooling rate 90 K/min) and for paracetamol [7] (requires immediate quenching in liquid nitrogen). Therefore, on a relative basis, all the four compounds in the study were 'good' glass formers and behaved similarly in their glass forming ability.

3.4. Specific heat capacity

In order to separate the two concomitantly occurring thermodynamic events of glass transition and enthalpy relaxation, and to get a true estimate of heat capacity, MTDSC analyses of crystalline and amorphous forms of the drugs were performed. A reheating scan was utilized after the heat capacity determination in order to ensure that crystallization had not set in during the heat capacity determination. The variation in heat capacity was gradual for all of the crystalline forms throughout the temperature scale studied, which was in sharp contrast to the amorphous forms that showed a characteristic step-change at T_g (shown in Fig. 2a for celecoxib, results for the other three compounds were similar to celecoxib). These results are indicative of a sharp increase in molecular specific volume around T_g, a thermodynamic necessity. Specific heat capacity is an important parameter for the characterization of amorphous state because it is one of the few thermodynamic quantities that are experimentally accessible. The higher C_p of the liquid above T_g requires that a new contribution to the enthalpy and entropy of substance must begin at T_g. This is the main source of entropy of fusion, because the latter is largely accounted for by the ΔS added

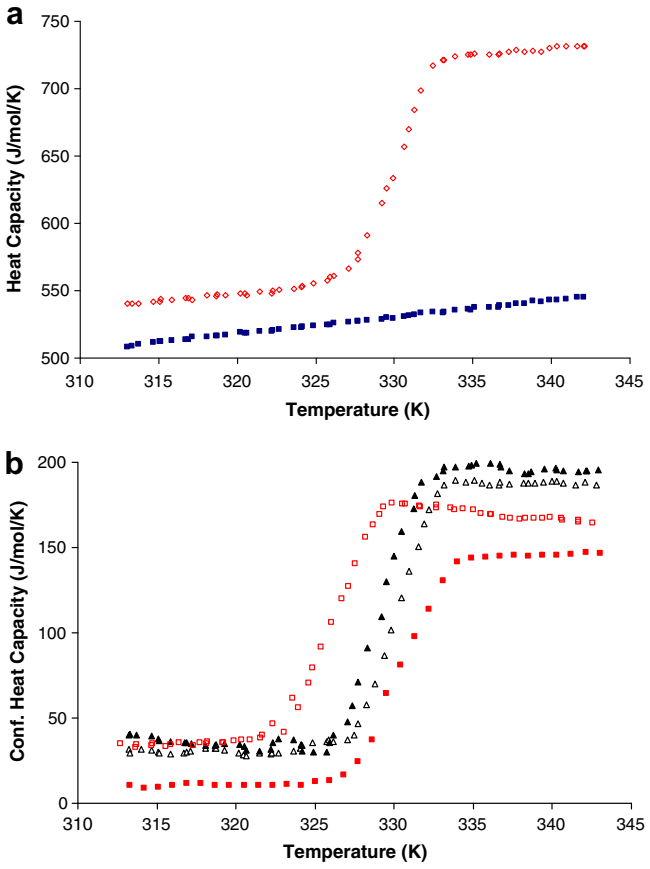

Fig. 2. Heat capacity as a function of temperature for crystalline celecoxib (■) and amorphous celecoxib (◇) across the temperature range of glass transition (a); and configurational heat capacity of celecoxib (△), valdecoxib (▲), rofecoxib (□), and etoricoxib (■) (b). Relative standard deviation in heat capacity was less than 3%.

between T_g and T_m. As glass is not in thermal equilibrium, the measured C_p does not represent a true thermodynamic property, and thus should be regarded as an 'apparent' or 'effective' C_p only. ΔC_p values were material dependent with valdecoxib showing the largest and rofecoxib showing the least jump at T_g.

In addition to the heat capacity jump at T_g for amorphous compounds, the configurational heat capacity (C_p^{conf}) is of special interest, since it is determined by the temperature dependence of configurational entropy, and is thus a measure of the temperature dependence of non-vibrational molecular mobility. The configurational heat capacity is the difference between the heat capacities of crystalline and amorphous phases ($C_p^a - C_p^x$). Fig. 2b shows the configurational heat capacities as a function

Table 3
Heat capacity jump (ΔC_p), configurational heat capacity (C_p^{conf}), γC_p, and K values obtained by MTDSC of crystalline and amorphous forms of celecoxib, valdecoxib, rofecoxib, and etoricoxib over temperature range of 313–343 K

	ΔC_p (J/mol/K)	C_p^{conf} (J/mol/K)	γC_p	K (kJ/mol)
Celecoxib	168.6	192.6	0.875	60.03
Valdecoxib	176.0	198.0	0.889	56.62
Rofecoxib	141.5	160.3	0.882	58.31
Etoricoxib	147.1	168.7	0.872	43.96

of temperature for the four compounds. The change in C_p^{conf} values at T_g of the four compounds showed the similar order as that for ΔC_p, with valdecoxib showing the largest, and rofecoxib the smallest change at T_g. The small configurational heat capacity below T_g shows that the heat capacities in the glassy state were close but not equal to that of the crystalline state. The values of ΔC_p and C_p^{conf} obtained for the four compounds by MTDSC are summarized in Table 3.

3.5. Configurational thermodynamic properties

The configurational quantities are a means to express the thermodynamics of the glassy state with respect to the crystalline state. Since the amorphous form has an inherent tendency to devitrify to the crystalline form, it is intuitive that the difference in the thermodynamic quantities of the amorphous and crystalline states would dictate the relative tendency for crystallization. The configurational enthalpy (H_{conf}) and configurational entropy (S_{conf}) were calculated from the configurational heat capacity, and enthalpy and entropy of fusion.

$$H_{conf} = \Delta H_m - \int_T^{T_m} C_p^{conf}\, dT \quad (2)$$

$$S_{conf} = \Delta S_m - \int_T^{T_m} \frac{C_p^{conf}}{T}\, dT \quad (3)$$

The two were then used to arrive at configurational free energy (G_{conf})

$$G_{conf} = H_{conf} - (TS_{conf}) \quad (4)$$

The changes in the above three configurational thermodynamic properties are shown as a function of temperature across the glass transition range for the four compounds (Fig. 3).

The crystallization from the amorphous state has been demonstrated at both above and below T_g [14]. However, from a practical perspective, the temperature of interest lies in the glassy region, since, this is the temperature range that is most likely to be encountered during the product shelf life. In the glassy region, the configurational enthalpy curves representing the enthalpic driving force for crystallization, and were in the order – celecoxib > etoricoxib > valdecoxib > rofecoxib, with an approximate range of 8 kJ/mol (Fig. 3a). The configurational entropy curves

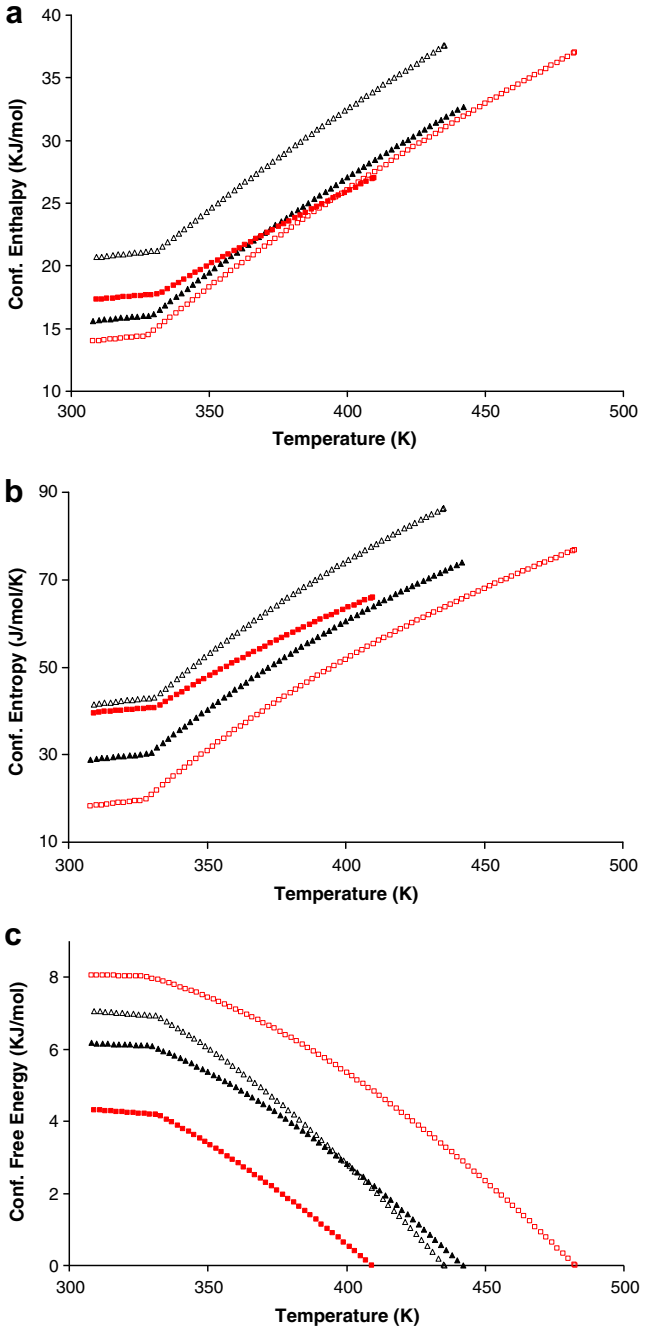

Fig. 3. Configurational thermodynamic properties – configurational enthalpy (a); configurational entropy (b); and configurational free energy (c), representing the thermodynamic drive, barrier, and overall force for crystallization, respectively, for celecoxib (△), valdecoxib (▲), rofecoxib (□), and etoricoxib (■).

signify the entropic barrier to crystallization [7], and this barrier was highest for celecoxib (Fig. 3b). The distinctly higher entropic barrier for celecoxib may be attributed to its ability to exist in larger number of molecular conformations [15]. Celecoxib molecule has four rotatable bonds as against three each for the other three molecules. The configurational free energy curves denote the overall thermodynamic force for crystallization and this is a balance of

the enthalpy and entropy curves. The contribution of entropy, however, is magnified because entropy term gets multiplied by temperature. It can be seen that the order for configurational free energy – rofecoxib > celecoxib > valdecoxib > etoricoxib reflects the dominant role of entropy in determining the overall force for crystallization (Fig. 3c). Although celecoxib had the greatest drive towards crystallization, because it also had the greatest barrier to crystallization, it culminated in its having a lesser overall force as compared to rofecoxib that had lower values of configurational enthalpy and entropy. Similar observations may be made for the supercooled liquid region of the four compounds. Celecoxib presented the highest enthalpic force for crystallization, while having a higher (although almost the same as etoricoxib) entropic barrier as well. This led to celecoxib having a lesser overall thermodynamic force than rofecoxib.

3.6. Kauzmann temperature

Kauzmann temperature (T_K) represents the temperature region below which the translational molecular motions responsible for the majority of physical and chemical changes in the pharmaceutical products can be considered negligible even over long experimental time scales [16,17], and thus represents the conservative maximum storage temperature for amorphous formulations (Fig. 4). Since a direct experimental determination of T_K is not possible, mathematical methods are used for the estimation of this thermodynamically important parameter.

One of the ways to approximate T_K is $T_g - 50$ K. This is based on the fact that molecular motions continue to decrease with temperature below T_g, and are assumed to reach a minimum value at T_K. Another rough estimate of T_K is given by [18]

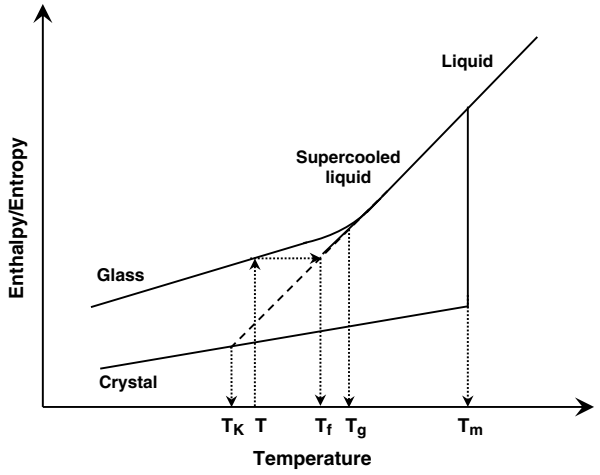

Fig. 4. A schematic representation of enthalpy/entropy versus temperature differences for a liquid capable of both crystallizing and forming glass. T_K represents the Kauzmann temperature, where the entropy of extrapolated supercooled liquid equals that of the crystal. T_f is the fictive temperature corresponding to glass at temperature T.

$$T_K \cong \frac{(T_g)^2}{T_m} \tag{5}$$

For substances that exist in both crystalline and amorphous states, like the four compounds in this study, T_K can be estimated from enthalpy or entropy of fusion in combination with the heat capacity data for crystalline and supercooled liquid states [5,18]

$$T_K = T_m - \left(\frac{\Delta H_m}{C_p^{conf}}\right) \tag{6}$$

Other more precise methods of T_K estimation can either be entropy-based T_{KS} or enthalpy-based T_{KH}, with the enthalpy based T_{KH} occurring at a lower temperature [2,19]. Since the configurational entropy directly determines mobility, T_{KS} has been proposed to be the better measure of T_K [5]. T_{KS} was used for all subsequent calculations and was taken to be the temperature to represent the point where molecular mobility reaches a minimal, limiting value

$$\frac{1}{T_{KS}} = \frac{1}{T_m}\left\{1 + \left(\frac{\Delta H_m}{K}\right)\right\} \tag{7}$$

$$\frac{1}{T_{KH}} = \frac{1}{T_m}\left\{\exp\left(\frac{\Delta H_m}{K}\right)\right\} \tag{8}$$

The estimation of T_{KS} and T_{KH} requires knowledge of the temperature dependence of C_p^{conf}. The temperature dependence of C_p^{conf} above T_g is material specific, it may increase or decrease linearly, or follow a hyperbolic relation in supercooled liquid state of small organic molecules. It can be derived as follows

$$C_p^{conf} = \frac{K}{T}, \tag{9}$$

where K is a constant. The ability of Eq. (9) to describe C_p^{conf} of the amorphous materials in this study was investigated by plotting the product, $K = C_p^{conf} \cdot T$ as a function of temperature (data not shown), which showed a nearly zero slope value. The value of K was taken as the y-intercept of the lines of best fit through the data (Table 3). Though the T_g values of the four compounds were in a range of less than 3 K, the T_K values differed significantly over a range of ~40 K. Values of T_K were used to calculate parameters related to the fragility of the molecules (discussed later). Table 4 presents the T_K values calculated for the four compounds using the above formulae.

3.7. Fictive temperature

Although T_K represents the lower limit in temperature where mobility ceases in hypothetical supercooled liquid, real amorphous systems (glasses) are not in equilibrium in this temperature regime. In practice, glass formation results in excess configurational entropy that gets 'kinetically trapped' as the system fall out of equilibrium. The fictive temperature of a glass represents the temperature at which the equilibrium supercooled liquid has the same

Table 4
Calculated Kauzmann temperatures (T_K) based on different calculations; $T_g - T_K$; T_K/T_g; strength parameter (D); fragility parameter (m); and fictive temperature (T_f) at 298 K for celecoxib, valdecoxib, rofecoxib, and etoricoxib

	T_K[a] (K)	T_K[b] (K)	T_{KS}[c] (K)	T_{KH}[d] (K)	T_K[e] (K)	T_g–T_K (K)	T_K/T_g	D	m	T_f[f] (K)
Celecoxib	281.4	252.3	267.7	232.8	240.2	63.7	0.81	8.8	83.3	326.8
Valdecoxib	279.5	245.6	280.2	248.1	276.9	49.3	0.85	6.5	107.1	325.6
Rofecoxib	277.6	222.4	295.2	255.8	251.7	32.4	0.90	4.0	162.0	323.8
Etoricoxib	281.8	268.8	253.7	221.5	249.5	78.1	0.76	11.3	68.0	327.1

[a] Determined from T_g-50 rule.
[b] Determined from T_g and T_m.
[c] Based on configurational entropy.
[d] Based on configurational enthalpy.
[e] Based on configurational heat capacity.
[f] At 298 K.

thermodynamic properties as the real non-equilibrium glass (Fig. 4) [20]. T_f is not a single temperature and indeed there is a fictive temperature corresponding to glass at different temperatures. T_f is mathematically bound by the limits $T_K < T_f < T_g$, and for a freshly prepared glass, it is given by [5]

$$\frac{1}{T_f} = \left(\frac{\gamma C_p}{T_g}\right) + \left\{\frac{(1-\gamma C_p)}{T}\right\}, \tag{10}$$

where

$$\gamma C_p = \frac{(C_p^l - C_p^g)}{(C_p^l - C_p^x)}, \tag{11}$$

where l, g and x denote the equilibrium supercooled liquid, glass and crystalline states, respectively. γC_p shows the relative differences in the heat capacities of the crystal, real glass and equilibrium supercooled liquid. The temperature dependence of T_f is in turn bound by the values of γC_p which is bound by $0 < \gamma C_p < 1$. The T_f values of glassy drugs were calculated for the range of temperatures bounded by $T_K < T_f < T_g$ (Fig. 5). At a temperature of 298 K, the fictive temperatures of the four glasses were – celecoxib 326.8 K, valdecoxib 325.6 K, rofecoxib 323.8 K, and etoricoxib 327.1 K (Table 4). It is perceptible that below T_g, T_f is always greater than T, representing the captured molecular mobility of a glass that may have a role to play in physical and chemical instability of glass. The practical utility of characterizing a glass in terms of its T_f is that it allows the molecular mobility to be estimated from excess enthalpy or entropy present in a glass [17]. The unique property of the fictive temperature is that it is independent of the DSC heating rate used to measure it. It has therefore been proposed as a reliable quality control tool for amorphous pharmaceuticals [21].

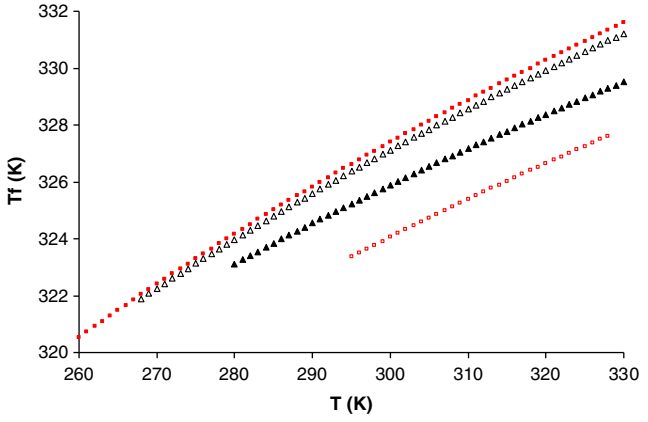

Fig. 5. Predicted fictive temperatures as a function of temperature for the range T_K to T_g for celecoxib (△), valdecoxib (▲), rofecoxib (□), and etoricoxib (■).

3.8. Fragility

The concept of fragility proposed by Angell classifies liquids as 'strong' or 'fragile', based on the differences in temperature dependence of mean molecular relaxation time (τ) or on magnitude of change in C_p^{conf} at T_g [22]. Strong liquids show an Arrhenius type of relationship, with activation energy independent of temperature. Fragile liquids conversely show a non-linear dependence of viscosity upon temperature with a deviation from Arrhenius behavior characterized by temperature dependent activation energy.

The ratio T_m/T_g has been proposed as an indicator of the fragility of liquid [23]. The melting points of the four drugs vary substantially, but the glass transition temperature of all the four drugs was in a close range of ~3 K. Consequently, T_m/T_g of the compounds varied from 1.47 for rofecoxib to 1.23 for etoricoxib. According to the "rule of thumb" for fragility determination, a $T_m/T_g < 1.5$ signifies fragile behavior, while $T_m/T_g > 1.5$ indicates strong glass characteristics. All the four amorphous samples exhibited a $T_m/T_g < 1.5$, signifying their fragile behavior (Table 2). This is in accord with the generally accepted notion that amorphous pharmaceuticals fall under the category of fragile liquids [3]. Within the homologous series of glass-formers, the values of T_m/T_g are sensitive to subtle functional group substitutions that affect intermolecular interactions. These changes though need not necessarily have an effect on the fragility of glass formers [24]. Important structural information can be derived by considering T_m/T_g values, however, the same may not be indicative of differences in fragility. Strictly considering, this rule of

thumb is applicable to molecules in homologous series, and as will be shown by means of other more authoritative parameters, T_m/T_g is not a real indicator, at least for the studied compounds.

Another way of describing fragility is in terms of the heat capacity jump seen at T_g. Generally, fragile liquids are characterized by huge jumps in C_p at T_g, while strong glasses have a negligible jump, sometimes making the detection of T_g a challenging task [10]. The 'strong' liquids due to their self-reinforcing tetrahedron network structures manifest their resistance to structural degradation by small changes in heat capacity at T_g ($C_p^l/C_p^{conf} \approx 1.1$). By contrast, the 'fragile' cases, which always have large increases in heat capacity (60–80%) at T_g, are usually liquids without directional bonds and often with ionic or aromatic character. The high ΔC_p values of amorphous form are a contribution of marked changes in molecular mobility due to additional degrees of freedom, which results in non-directional, non-covalent interactions in the sample when in supercooled liquid region above T_g. A comparison of the compounds in terms of C_p jump at T_g showed rofecoxib to have the smallest jump (141.5 J/mol K) of all, suggesting rofecoxib to be the least fragile among the compounds studied. However, the results of C_p jump at T_g cannot be viewed in isolation. Exceptions to the correlation between increase in C_p^{conf} at T_g and fragility has been observed in the case of H-bonding liquids [22]. Some peculiarities associated with H-bonding liquids need to be considered separately. The high C_p jumps for not so fragile H-bonding liquids can be understood if the rearrangement of the molecules in stress relaxing process involves the disruption of some type of bond [25]. The exceptional behavior of H-bonding molecules is probably due to the fact that rearrangement of molecules will involve, not only the work of locally expanding the liquid to give it a favorable configuration, but also the energy to rupture one or more hydrogen bonds between the molecular units. From the structural point of view, all the four compounds come under the class of small organic molecules and are expected to exhibit a fragile behavior. They are also likely to exhibit weak directional forces in between the molecules, mainly due to aromatic non-directional interactions. The difference, however, may lie in the stronger intermolecular interactions, such as H-bonding. As opposed to rofecoxib and etoricoxib; celecoxib and valdecoxib possess H-bonding ability (due to the presence of sulfonamide moiety) and this could be contributing to a higher ΔC_p jump at T_g. Rofecoxib and etoricoxib are relatively 'non-bonding' molecules, and exhibit lower C_p jump at T_g (Table 3). In addition to the H-bonding capabilities, factors such as the presence of impurities and crystal packing efficiency may also influence the outcome of thermodynamic parameters including fragility. This makes it difficult to speculate the factors that determine the comparative overall behavior for structurally similar compounds.

The heat capacities of crystalline, glassy and supercooled liquid states can be captured in terms of γC_p (Eq. (11)), which has been used as a marker of strong/fragile behavior [5]. The values of γC_p are bound by $0 < \gamma C_p < 1$. At one extreme, the C_p of the glass and crystal are very similar in value, giving $\gamma C_p \cong 1$, indicating Arrhenius behavior and $T_f = T_g$ At the other extreme, the C_p of glass is essentially equivalent to the supercooled liquid giving $\gamma C_p \cong 0$. This condition is one where the heat capacity jump is almost negligible and is indicative of strong behavior of glass. Because the values of γC_p for studied compounds were in a close range of 0.87–0.88, a fragile behavior of the compounds under study can be inferred (Table 3).

Another way of looking at the fragility of the compounds is the positioning of T_K with respect to T_g. Since, the fragility of a liquid dictates the steepness of the viscosity/mean molecular relaxation time (τ) fall near T_g, T_K gets more close to T_g in more fragile liquid and thereby the ratio T_K/T_g and $T_K - T_g$ may be taken as numerical expressions of fragility [26]. T_K/T_g is a determinant of the departure of glass from Arrhenius behavior. This ratio lies between 0 (strong) and 1 (fragile). Rofecoxib with the highest value of 0.90 signified its most fragile nature (Table 4). A value of $T_g - T_K < 50$ indicates a fragile glass former, while $T_g - T_K > 50$ is indicative of strong behavior of the glass. Based on this principle, rofecoxib with a $T_g - T_K$ value of 32.4 is a fragile liquid when compared to celecoxib and etoricoxib. The value for valdecoxib at 49.3 is borderline. These values are in accord with the generally accepted notion of molecular motions ceasing at temperatures $\sim T_g - 50$ K.

The strength parameter (D) obtained from the Vogel [27] – Tammann [28] – Fulcher [29] equation is commonly employed to describe the fragility

$$\tau = \tau_0 \exp\left\{\frac{DT_0}{(T - T_0)}\right\}, \tag{12}$$

where τ_0, D and T_0 are constants, τ_0 being the time scale of vibrational motions, and T_0 representing the temperature at which τ becomes infinite, signifying negligible molecular mobility. For all practical purposes, T_K is taken to represent T_0. A large D value (>30) represents 'strong' behavior and low D value (<10) represents 'fragile' behavior [3]. The D value for amorphous forms were calculated from Eq. (12) at $T = T_g$ after substituting 10^{-14} s, 100 s, and T_K for τ_0, τ, and T_0, respectively. D value for rofecoxib of 4.0 was not only substantially lower than for the other three compounds, but also one of the lowest ever reported for pharmaceuticals [3] (Table 4).

In addition to strength parameter, 'fragility parameter' m, defined by Eq. (13), can be alternatively used to predict the dynamic behavior of glassy substances [30]

$$m = \frac{D(T_0/T_g)}{(\ln 10)\{1 - (T_0/T_g)\}^2} \tag{13}$$

A larger m value indicates rapidly changing dynamics at T_g, in other words, the fragile behavior. For the four amor-

phous samples, m varied from being 162.0 for rofecoxib to a minimum of 68.0 for etoricoxib (Table 4). Although all the four samples showed m value characteristic of fragile liquids, rofecoxib showed the most fragile pattern of all the studied compounds. In terms of pharmaceutical stability, the knowledge of these strength parameters provides an estimate of the degree of undercooling necessary for τ to exceed the expected storage time.

The plot of log τ as a function of temperature scaled to T_g may be used to visualize the comparative fragilities (Fig. 6). This plot is analogous to the Angell's plot [10], which is a plot of log viscosity instead of log τ. At temperatures $T = T_g$, all amorphous substances are assumed to exhibit a mean molecular relaxation time of 100 s. However, as the temperature is increased above T_g, a sharp fall in the values of τ is encountered and molecular mobility increases dramatically. It was apparent that although all the four compounds exhibited an unambiguous fragile behavior, the decrease in log τ was most pronounced for rofecoxib signifying its most fragile nature.

It may not be appropriate to assign either of the strong or fragile liquids as 'good' or 'bad' behavior. From a pharmaceutical perspective, based on the application, either a strong or fragile behavior might be desired. In cases where a stabilization of the amorphous material by reduction in temperature is desired, a strong dependence exhibited by fragile behavior might be preferred. It was suggested by Hatley [31] that fragile liquids, because they exhibit a rapid plummeting of viscosity and relaxation times, are likely to exhibit a higher value of T_K, the zero molecular mobility temperature. However, on the downside, the fragile system is also prone to widespread changes with only a few degree excursions in storage temperature [17]. Thus, there is a clear trade-off between the desire to be able to influence the product's molecular mobility and the need for its properties to remain unchanged with changes in environmental conditions.

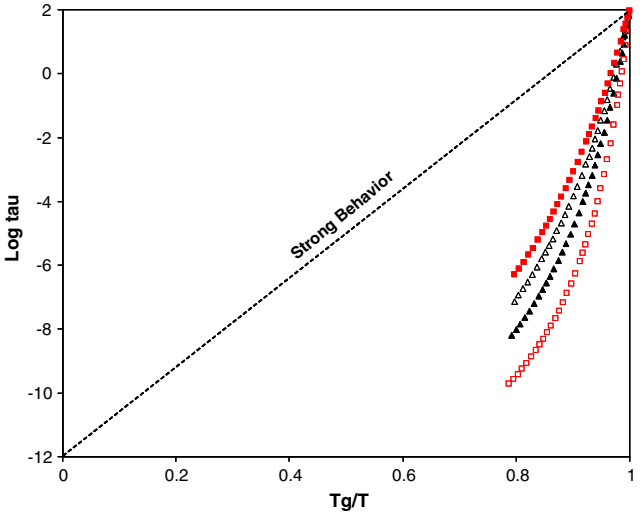

Fig. 6. Plot of log predicted mean molecular relaxation time (τ) vs. temperature scaled to T_g for celecoxib (△), valdecoxib (▲), rofecoxib (□), and etoricoxib (■). The dashed line represents the ideal strong behavior, while deviations from linearity signify fragility.

4. Conclusions

The study investigated the thermodynamic properties of amorphous forms of four structurally related compounds and found appreciable differences in the thermodynamic behaviors. Celecoxib presented both a higher enthalpic driving force as well as higher entropic barrier to crystallization; while rofecoxib presented the highest overall thermodynamic force to crystallization. The T_g of the four compounds were grossly similar, while the T_K varied considerably, thereby highlighting the noticeable differences in the fragility of the four compounds. The strength and fragility parameters calculated from VTF equation showed the order of fragility to be rofecoxib > celecoxib > valdecoxib > etoricoxib. Although the heat capacity jump at T_g showed results contrary to other fragility parameters, they can be attributed to the differential H-bonding ability of the molecules. The glass forming ability studied in terms of the critical cooling rate experiments showed all the four compounds to behave in a similar fashion. However, since the four compounds presented differences in fragilities, it may be speculated that a diverse set of factors are at play in determining glass fragility and glass forming ability. The present work highlights the role of varied thermodynamic parameters in the overall behavior of the amorphous systems. Such an understanding can lead to the design of 'robust' amorphous delivery systems.

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