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molecular pharmaceutics

Physical Stability and Solubility Advantage from Amorphous Celecoxib: The Role of Thermodynamic Quantities and Molecular Mobility

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Received May 19, 2004

Abstract: Glassy pharmaceuticals, characterized by excess thermodynamic properties, are theoretically more soluble than their crystalline counterparts. The practical solubility advantage of the amorphous form of celecoxib (CEL) is lost due to its proclivity to lose energy and undergo solvent-mediated devitrification. Theoretical assessment of solubility advantage using differences in isobaric heat capacities (C_p) revealed a 7−21-fold enhancement in the solubility of the amorphous form over that of the crystalline state of CEL. The present study attempts to unveil these differences between experimental and theoretical solubility using thermodynamic parameters such as free energy, enthalpy, and entropy. Amorphous CEL exhibited 1.3−1.5 times enhancement in C_p over that for the crystalline form. The zero and critical molecular mobility regions, represented by Kauzmann temperature (T_K) and glass transition temperature (T_g), were found to lie near 246 and 323 K, respectively, for amorphous CEL. The fictive temperature (T_f), an indicator of the configurational entropy of glass, was determined for glassy CEL, signifying the retention of considerable molecular mobility in the glassy phase that may favor nucleation even below T_g. Further, the estimation of various thermodynamic quantities and strength/fragility parameters ($D = 11.5$ and $m = 67.0$) postulated the classification of glassy CEL into moderately fragile liquid, as per Angell's classification. A comprehensive understanding of such thermodynamic facets of amorphous form would help in rationalizing the approaches toward development of stable glassy pharmaceuticals with adequate solubility advantage.

Keywords: Amorphous; thermodynamics; heat capacity; fragility; solubility; celecoxib

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Introduction

The solubility of a molecule contributes critically toward its "drugability", by influencing the dissolution and bioavailability (BA), especially in the case of biopharmaceutics classification system (BCS) class II and IV drugs. The solid state (crystalline or amorphous) of a drug molecule can significantly affect its dissolution rate, claiming solid-state manipulation as a viable avenue for dissolution rate enhancement.[1] The disorderliness in molecular arrangement bestows glassy systems with excess thermodynamic properties relative to the crystalline state, like enthalpy, entropy, and free energy that contribute to higher solubility.[2]

Apart from solubility gain, the excess properties invoke the nonequilibrium glassy phase to reestablish energetic equilibrium with its surroundings. The Kauzmann temperature denotes the point of zero molecular mobility, while fictive temperature is an indicator of considerable configu-

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10.1021/mp049938f CCC: $27.50

rational entropy (S_{conf}) and molecular mobility of nonequilibrium systems below the glass transition temperature (T_g). When the temperature approaches the glass transition region, the average molecular relaxation time (τ) typically follows a non-Arrhenius temperature dependence that may allow a large increase in molecular mobility, with a little rise in temperature in the region just above T_g.[3] Contrary to structural relaxation in the solid phase, higher crystallization kinetics in the presence of a dissolution medium favors rapid devitrification of these high-energy disordered glassy systems into lower energy ordered crystalline states. This solvent-induced rearrangement of molecular order is a major cause of disparity between theoretically possible and experimentally achievable solubility gains for amorphous solids.[4]

The present study attempts to evaluate these thermodynamic differences between the stable crystalline and the metastable amorphous phase of celecoxib (CEL), a BCS class II drug[5] (low solubility and high permeability). The amorphous form of CEL is known to provide initial enhancement in solubility,[6,7] but its rapid solvent-mediated reversion to the crystalline form results in loss of solubility advantage. Using thermodynamic tools, it is possible to predict the solubility gain of the amorphous form over the crystalline state. The investigation of the temperature dependence of structural flexibility for amorphous CEL, in terms of isobaric heat capacity (C_p), enthalpy (H), entropy (S), and Gibb's free energy (G), is one of the major aims of this study. Categorization of glassy CEL into strong/fragile classification using thermodynamic data is likely to provide further explanations to its abridged stability and solubility advantage.

Experimental Section

Materials. The crystalline form of CEL was purchased from Unichem Laboratories Ltd., Raigad, India.

Preparation of Amorphous CEL. Amorphous CEL was prepared by melting the crystalline drug in a stainless steel beaker over a hot plate (~448 K) and quench cooling over crushed ice. For determination of C_p, amorphous CEL was prepared within the differential scanning calorimeter (DSC) instrument. A weighed amount of crystalline CEL, sealed in a pinholed aluminum pan, was heated to 448 K at a heating rate of 20 K/min, held for 2 min at 448 K, and then immediately cooled to 298 K at −20 K/min. This cooling rate was found to provide amorphous CEL with highest T_g value compared to that obtained at lower cooling rates. The chemical stability of quench-cooled product was assessed by HPLC analysis, wherein the peak purity was above 99.99%.

DSC Analysis. The DSC analyses were performed using a 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 a dry nitrogen purge (80 mL/min) in sealed pinholed aluminum pans at a heating rate of 5 K/min, unless otherwise specified. The instrument was calibrated for temperature and heat flow using high-purity standards of indium and zinc.

Measurement of C_p Using Modulated DSC (MDSC). The C_p for the crystalline and amorphous CEL were determined using a modulated temperature program in the DSC instrument, employing a period of 60 s, a temperature amplitude of ±0.5 K, and an underlying heating rate of 1 K/min. Samples weighing about 3−5 mg were sealed in pinholed aluminum pans and analyzed under a dry nitrogen purge (80 mL/min). The C_p values of the samples were then obtained by deconvoluting the total heat flow curve into nonreversing and reversing signals, using commercial software (Mettler Toledo STAR^e Software, Mettler Toledo, Switzerland). The instrument was calibrated for C_p using alumina. The C_p values of the crystalline and amorphous CEL were measured over a temperature range from 15 K below T_g to 25 K above T_g. The mean results of triplicate determinations are reported.

Solubility Determination. The temperature dependence of aqueous solubility of amorphous CEL was studied at 308, 318, 328, 338, and 348 K. An excess quantity of freshly prepared, powdered and sieved (BSS No. 60, mesh size 250 μm) sample was placed in 15 mL screw-capped glass vials containing 5 mL of distilled water, preequilibrated to the desired temperature. The vials were mechanically shaken in a shaker water bath (Julabo SW 23, Seelbach, Germany) at 200 rpm. At specified time intervals, samples ($n = 3$) were withdrawn, filtered, and analyzed for drug content at 252 nm spectrophotometrically (Perkin-Elmer, Lambda 20), after appropriate dilution.

Results and Discussion

Thermal Response of Crystalline and Amorphous CEL. As reported earlier,[6] DSC analysis of crystalline CEL showed a single sharp fusion endotherm in the temperature range 434−438 K. On the other hand, quench-cooled amorphous CEL exhibited a glass transition event (onset $T_g = 324$ K) followed by a recrystallization exotherm in the temperature range 372−378 K and a broad fusion endotherm in the temperature range 434−441 K. The quench-cooled product was found to be chemically stable. The transition of a glassy sample into the supercooled liquid state at T_g signifies the gain of molecular mobility leading to crystallization, which depends on the energetics of molecules to form an ordered lattice. The crystallization tendency of the amorphous CEL was assessed in terms of the reduced crystallization temper-

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Table 1. Thermodynamic Parameters for a Range of Structurally Diverse Pharmaceutical Glass-Formers

drug	MW[a]	T_m (K)	T_g (K)	T_m/T_g	T_c (K)	$(T_c - T_g)/(T_m - T_g)$	$\Delta C_p^{T_g}$ (J/g·K)	T_K (K)	$T_g - T_K$ (K)	D	m
acetaminophen[b]	151.16	442	296	1.49	343	0.32	0.64	236	60	9.3	79.5
celecoxib[c]	381.38	435	323	1.35	363	0.36	0.26	246	77	11.5	67.0
diazepam[d]	284.74	398	315	1.26	na[e]	na	0.46	249	66	10.0	78.1
felodipine[f]	384.26	416	317	1.31	na	na	0.40	247	70	10.0	69.5
fenofibrate[b]	360.84	353	253	1.40	313	0.60	0.45	204	49	8.8	83.4
flopropione[g]	182.17	452	335	1.35	389	0.46	0.70	269	66	9.0	80.5
glibenclamide[h]	494.00	450	331	1.36	na	na	0.45	261	70	10.0	76.7
griseofulvin[h]	352.77	494	364	1.36	406[i]	0.32	0.36	272	92	12.0	61.2
hydrochlorthiazide[h]	297.73	547	385	1.42	na	na	0.31	292	93	12.0	67.9
indomethacin	357.80	435[j]	323[k]	1.35	370[k]	0.42	0.37[l]	240[l]	83	8.9[m]	43.3
nifedipine[g]	346.34	445	322	1.38	391	0.56	0.27	228	94	15.0	54.3
phenobarbital[g]	232.24	448	319	1.40	430	0.86	0.46	246	73	11.0	70.2
polythiazide[h]	439.87	493	346	1.42	na	na	0.34	270	76	10.0	70.2
probucol[n]	516.84	399	295	1.35	na	na	0.27	222	73	12	58.0
ritonavir[b]	720.96	395	323	1.22	*o*	*o*	0.55	275	48	6.4	107.3
temazepam[d]	300.74	392	339	1.16	na	na	0.42	239	100	15.0	52.8

[a] Molecular weight. [b] Reference 8. [c] Current work. [d] Reference 9. [e] Data not available. [f] Reference 10. [g] Reference 11. [h] Reference 4. [i] Reference 12. [j] Reference 13. [k] Reference 14. [l] Reference 15. [m] Reference 16. [n] Reference 17. [o] No crystallization.

ature, $(T_c - T_g)/(T_m - T_g)$[8] (where T_c and T_m stand for peak crystallization and melting temperatures, respectively), which represents a normalized measure of departure of compound from T_g for spontaneous crystallization. This value was found to be 0.36 for amorphous CEL, signifying its moderate tendency toward spontaneous crystallization. A comparison of different thermodynamic measures was attempted with various structurally diverse pharmaceutical glass-formers (Table 1) reported in the literature.

The reduced crystallization temperature facilitated the comparison of ease of crystallization for compounds with different T_gs. Out of the 16 drugs compared, acetaminophen and griseofulvin were found to have the fastest crystallization tendencies and phenobarbital was found to have the slowest, with ritonavir exhibiting no crystallization. These results clearly depict the significant role of departures of T_c and T_m from T_g in the crystallization of amorphous compounds. On the other hand, a greater entropic barrier to crystallization has been postulated as the major cause for physical stability of the amorphous form of ritonavir.[8]

***C_p* of Crystalline and Amorphous CEL.** For C_p determination, amorphous CEL was prepared in situ in the DSC instrument, as detailed above. The thermal response of this sample during heating rescan at 20 K/min exhibited a single glass transition event overlapping with an enthalpy recovery event. The differences in the thermal response of quench-cooled and in situ prepared amorphous CEL can be attributed to partially crystalline nature of the former due to relatively inferior cooling of the melt and exposure to atmospheric humidity conditions, leading to crystallization during DSC analysis.

In order to separate the two concomitantly occurring thermodynamic events (glass transition and enthalpy relaxation) and to get a true estimate of C_p, MDSC analyses of crystalline and amorphous forms of CEL were performed. The values of C_p for both the samples varied with increase in temperature (Figure 1), with higher values for amorphous form. The variation was gradual for the crystalline form throughout the temperature scale studied, which was in sharp

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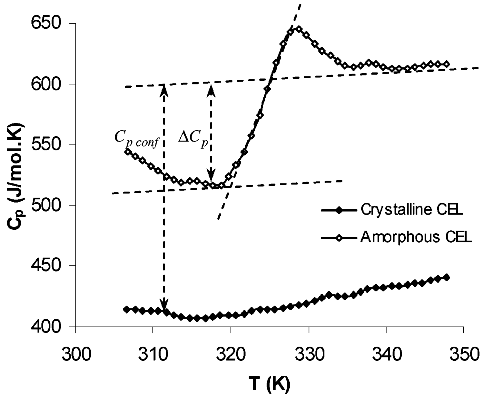

Figure 1. Plot of heat capacity vs temperature for crystalline and amorphous CEL. The broken lines have been drawn to guide the measurement of C_{p_conf} and ΔC_p.

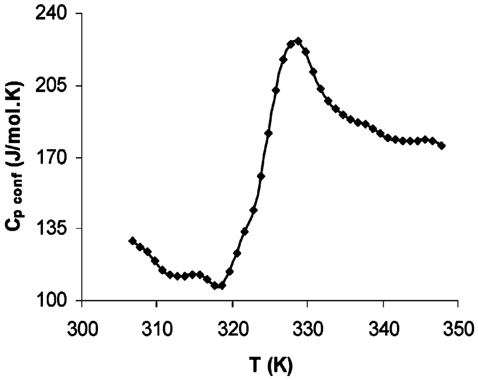

Figure 2. Configurational heat capacity of CEL as a function of temperature.

contrast to the amorphous form showing a characteristic step-change around a temperature of 320 K, with thermal overshoot in the temperature range 325−335 K. The height of this thermal overshoot response is directly proportional to the heat capacity change at T_g ($\Delta C_p^{T_\text{g}}$)[18] and, in turn, the fragility (discussed later) of an amorphous substance. The T_g of amorphous CEL was estimated to be 323 K, the temperature at half-height of the stepwise change in C_p.

Amorphous CEL showed nearly 1.3−1.5 times enhancement in C_p values within temperature range of 320−329 K, indicating its fragile nature.[19] High fragility of amorphous solids is usually associated with greater metastability, free energy, thermodynamic activity, and corresponding solubility. The high C_p values of the amorphous form are a contribution of marked changes in molecular mobility due to additional degrees of freedom, which results in nondirectional, noncovalent interactions in the sample when in the supercooled liquid region above T_g.[20] The $\Delta C_p^{T_\text{g}}$ provides a relative measure of number of accessible molecular conformations at T_g and, therefore, may be helpful in predicting the ease of crystallization. A comparison with other pharmaceutical glass-formers (Table 1) showed flopropione with the highest (0.70) and CEL with the lowest (0.26) $\Delta C_p^{T_\text{g}}$ value. This increase in $\Delta C_p^{T_\text{g}}$ will lead to more stable glass with both reduced enthalpy and entropy that contribute to free energy in opposite directions. The contribution of enthalpy outweighs entropy, which might not result in a tangible solubility advantage for amorphous CEL.

Configurational heat capacity (C_{p_conf}), a thermodynamic measure of temperature-induced structural changes, is given by

$$C_{p_\text{conf}} = C_p^\text{a} - C_p^\text{c} \tag{1}$$

where C_p^a and C_p^c are the measured heat capacities of the amorphous and crystalline forms, respectively. The C_{p_conf} for CEL followed minimal variation in the glassy region, until T_g, when a sharp increase was observed over the glass transition region, followed again by a plateau in the supercooled liquid region (Figure 2). These results are indicative of a sharp increase in molecular specific volume around T_g, a thermodynamic necessity. As an experimentally accessible thermodynamic quantity, C_p is an important parameter for characterization of the amorphous state.[21] Of particular interest is C_{p_conf}, which is governed by the temperature dependence of S_conf and, thus, nonvibrational molecular mobility. As glass is not in thermal equilibrium, the measured C_p does not represent a true thermodynamic property and, thus, is regarded as an "apparent" or "effective" C_p only.[15]

Thermodynamics in the Quasi-Equilibrium Glassy State. According to the well-established thermodynamic relationship between amorphous and crystalline phases, the entropy of a liquid decreases more rapidly than that of a crystal, with the decrease in temperature. Therefore, S_conf of extrapolated quasi-equilibrium glass vanishes at a finite temperature. Extrapolation to temperatures below this point would lead to an unfeasible result of disordered supercooled liquids having lower entropy than the ordered crystals. This temperature of "entropy crisis" is termed the Kauzmann temperature (T_K).[22] In reality, the entropy crisis is avoided by the ergodicity-breaking at T_g. At T_K and below, rotational and diffusive motions are improbable, even over extremely long time scales.

A rough estimate of T_K is given by

$$T_\text{K} \cong \frac{T_\text{g}^{\,2}}{T_\text{m}} \tag{2}$$

This gives a value of T_K near 240 K for amorphous CEL.

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Direct experimental determination of T_K is hindered by kinetic restrictions, which lead to inaccessibility of an equilibrium supercooled liquid at T_K. It can only be fairly estimated from thermodynamic principles.[21,23,24] Estimation of T_K can be either entropy-based (T_{KS}) or enthalpy-based (T_{KH}), with T_{KS} being the favorably accepted determinant of temperature corresponding to achievement of a minimum, limiting value of molecular mobility.[15]

$$\frac{1}{T_{KS}} = \frac{1}{T_m}\left(1 + \frac{\Delta H_m}{K}\right) \tag{3}$$

Its estimation requires a knowledge of the temperature dependence of $C_{p_{conf}}$, which follows a hyperbolic relation in the supercooled liquid state of small organic molecules.[15]

$$C_{p_{conf}} = \frac{K}{T} \tag{4}$$

The validity of eq 4 for CEL was established by plotting $C_{p_{conf}}T$ vs T (data not shown), which resulted in a nearly zero slope value. The T_{KS} for amorphous CEL was calculated to be 246 K, quite close to an earlier predicted value of 240 K. The value of T_K was 77 K below T_g, indicating a moderately fragile behavior. This is contrary to the generally accepted "$T_g - 50$ K" rule as the predictor of temperature of negligible molecular mobility. The $T_g - T_K$ values for other pharmaceutical glass-formers fall in the range 48−100 K (Table 1), signifying the importance of molecular conformations in the relaxation process of metastable solid-state forms. The T_K stands as a good estimate for how far a liquid can conceivably be supercooled before the glass transition must intervene, because $T_g \gtrsim T_K$. Thus, T_K marks the lower limit to T_g obtainable at different cooling rates for supercooled liquids. Also, T_K represents a conservative maximum storage temperature for amorphous pharmaceutical formulations, and may be considered to be a region of critical molecular mobility for such systems.

Another important parameter useful in understanding the dynamics of glasses is the fictive temperature (T_f), which is the temperature at which an equilibrium system has the same thermodynamic properties as a glassy system at experimental temperature (T):[25]

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

where

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

where l, g, and x denote the equilibrium supercooled liquid, glass, and crystalline states, respectively. The value of C_p in eqs 5 and 6 was calculated at T_g. Values of γC_p can be used to characterize the temperature dependence of relaxation times of real glasses, or "fragility", where $\gamma C_p = 1$ corresponds to a "strong" glass and $\gamma C_p = 0$ corresponds to a "fragile" glass. The value of γC_p for amorphous CEL was found to be 0.46, indicating its moderately fragile behavior.

The value of T_f relates the S_{conf} of equilibrium supercooled liquid to that of a nonequilibrium system having a S_{conf} of equal value at lower temperature. 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.[26] Thus, T_f, being independent of heating rates encountered in DSC, can serve as a reliable quality control tool for amorphous pharmaceuticals.[27] The T_f values of glassy CEL were calculated for the range of temperatures bounded by $T_K < T_f < T_g$ (Figure 3). Below T_g, T_f is always greater than T, representing enough molecular mobility of a glass relative to supercooled liquid that may favor crystallization. In a previous study on physical stability of amorphous CEL at aging temperature (T_a) equivalent to 298 K and 0% RH,[28] increase in relaxed enthalpy was observed with time, signifying sufficient molecular mobility favoring crystallization below T_g. This is due to a lower value of 14 K for $T_g - T_f$ in comparison to the higher value of 29 K for $T_g - T_a$, representing high S_{conf} below T_g. Thus, instead of remoteness from T_g, the magnitude of difference in the value of T_f from T_g should act as a better guide of storage temperature for reducing molecular mobility of glassy pharmaceuticals.

Rating at Fragility Index. An increment in $\Delta C_p^{T_g}$ for amorphous CEL is a reflection of its fragile nature. The fragility concept proposed by Angell[19] classifies liquids as strong or fragile, on the basis of either the differences in temperature dependence of τ or the magnitude of change in $C_{p_{conf}}$ at T_g. Structurally, fragile liquids are so flexible that, with little thermal excitation, they reorganize to structures that fluctuate over a wide variety of molecular arrangements and coordination states. Strong liquids, on the other hand, have a built-in resistance to structural change, and their vibrational spectra and radial distribution functions show little reorganization despite wide variations of temperature. The major significance of substance fragility lies in the deter-

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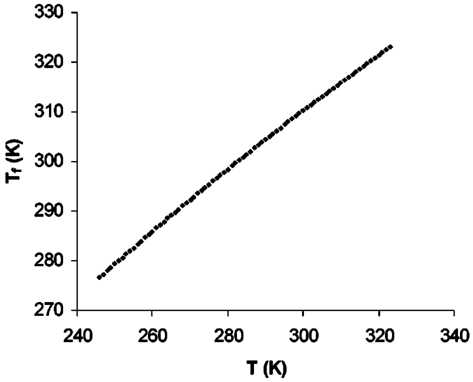

Figure 3. Predicted fictive temperatures for amorphous CEL as a function of temperature.

mination of its chemical, physical, or mechanical stability with changing temperature.

According to "rule of thumb" for fragility determination, $T_m/T_g > 1.5$ signifies strong, and $T_m/T_g < 1.5$ signifies fragile liquids. 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.[29] The T_m/T_g value of 1.35 calculated for amorphous CEL indicates its moderately fragile nature, which is in concordance with the results obtained from γC_p. Comparison with other pharmaceutical glass-formers showed this ratio to lie in the range 1.16−1.49, postulating the moderately fragile behavior of pharmaceuticals.

The Vogel−Tamman−Fulcher equation in modified form describes the relationship between τ and T in the supercooled region,

$$\tau = \tau_0 \exp\left(\frac{DT_0}{T - T_0}\right) \tag{7}$$

where τ_0, D, and T_0 are constants, τ_0 being the time scale of vibrational motions, D being the strength parameter, and T_0 representing the T at which τ becomes infinite, signifying negligible molecular mobility. Fragility is also a function of T_0/T_g, a determinant of departure of glass from Arrhenius behavior.[30] This ratio lies between 0 (strong) and 1 (fragile) and was estimated to be 0.76 for amorphous CEL, substantiating its moderately fragile nature. A large D value (>30) represents "strong" behavior, and low D value (<10) represents "fragile" behavior.[17] The D value for amorphous CEL, calculated from eq 7 at $T = T_g$ after substituting 10^{-14} s, 100 s, and T_K for τ_0, τ, and T_0, respectively, was found to be 11.5, further assisting in its positioning into the moderately fragile class of liquids.

An alternative fragility parameter m, defined by eq 8, can also be used to predict the dynamic behavior of glassy substances.

$$m = \frac{D(T_0/T_g)}{(\ln 10)[1 - (T_0/T_g)]^2} \tag{8}$$

A larger m value indicates rapidly changing dynamics at T_g equating to "fragile" behavior. To calculate m, a minimum value called $m_{\min}$ must first be defined:

$$m_{\min} = \frac{D(T_0/T_g)}{(\ln 10)[1 - (T_0/T_g)]} \tag{9}$$

For amorphous CEL, m was calculated to be 67.0, with $m_{\min}$ of 16.0. These results further strengthened the moderately fragile behavior of amorphous CEL. As compared in Table 1, the D values of all pharmaceutical glass-formers varied from 6.4 to 15.0, while m values varied from 43.3 to 107.3. Fragility denotes the temperature dependence of S_{conf} of glasses and is a measure of how much excess S_{conf} is present in the glass. In terms of pharmaceutical stability, the knowledge of these strength parameters provides an estimate of degree of undercooling necessary for τ to exceed the expected storage time.

Solubility Prediction. Prediction of relative solubility of amorphous over crystalline CEL was attempted using the method of Parks and co-workers.[31] The Gibbs free energy difference (G_{conf}) between the two phases reflects the ratio of their "escaping tendencies" and is directly proportional to thermodynamic activity (a), which is approximately proportional to solubility (σ), provided laws of dilute solution apply. Therefore,

$$G_{\text{conf}} = RT \ln\left(\frac{\sigma_a}{\sigma_c}\right) \tag{10}$$

Hence, because the stable crystalline form has the lowest G, it also has lowest values of a and σ. The G_{conf} is related to S_{conf} and enthalpy difference (H_{conf}) by

$$G_{\text{conf}} = H_{\text{conf}} - TS_{\text{conf}} \tag{11}$$

The values for H_{conf} and S_{conf} are calculated from T_m, enthalpy of melting (ΔH_m), entropy of melting (ΔS_m), and C_p as follows:

$$H_{\text{conf}} = \Delta H_m - \int_T^{T_m} C_p \, dT \tag{12}$$

$$S_{\text{conf}} = \Delta S_m - \int_T^{T_m} \frac{C_p}{T} \, dT \tag{13}$$

$$\Delta S_m = \frac{\Delta H_m}{T_m} \tag{14}$$

The changes in H_{conf}, S_{conf}, and G_{conf} with T for CEL are depicted in Figure 4. The H_{conf}/T curve represents the

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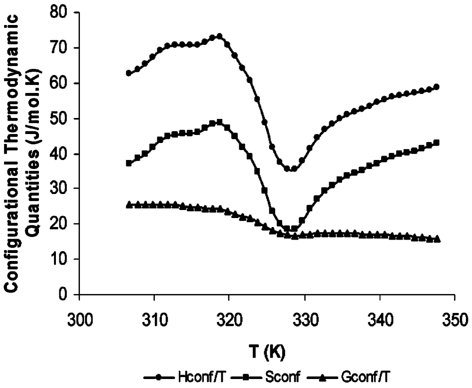

Figure 4. Change in configurational thermodynamic quantities of CEL with temperature.

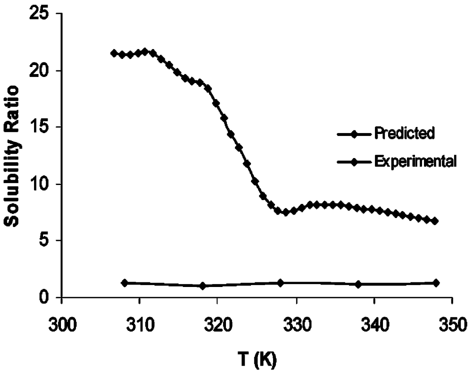

Figure 5. Comparison of predicted and observed solubility ratios of amorphous vs crystalline CEL as a function of temperature.

enthalpic driving force for crystallization, while the entropic barrier is given by S_{conf} curve. The overall thermodynamic driving force that balances the H_{conf} and S_{conf} components is represented by the G_{conf}/T curve. The trends in these curves showed an increase in enthalpic driving force and entropy barrier, and a net decrease in thermodynamic driving force for crystallization in the glassy region (307−319 K), followed by a sharp decrease in these parameters above T_g, signifying the impact of extent of molecular mobility encountered above T_g favoring crystallization. The S_{conf} is inversely related to the probability that molecules will have proper orientation and conformation for crystal nucleation. Molecules with lower S_{conf} require less mobility for spontaneous crystallization. On the other hand, compounds that are flexible and can exist in a number of molecular conformations in the supercooled liquid state are expected to exhibit larger S_{conf} values.

The predicted solubility ratios for amorphous vs crystalline form are shown in Figure 5. A stepwise change in predicted solubility ratios were observed at T_g, characteristic of the C_p change at this temperature. Higher free energy of the glassy state resulted in high solubility ratios, which decreased with increase in temperature above T_g, with a nearly logarithmic dependence. This decrease is a result of decline of G_{conf} at temperatures above T_g, which is an interplay of enthalpy and entropy. The magnitude of predicted solubility ratio for amorphous vs crystalline CEL varied between 7- and 21-fold in the temperature range 348−307 K. These values were comparable to those reported for glassy indomethacin,[4] a drug with nearly similar T_g, T_m, and ΔH_m values.

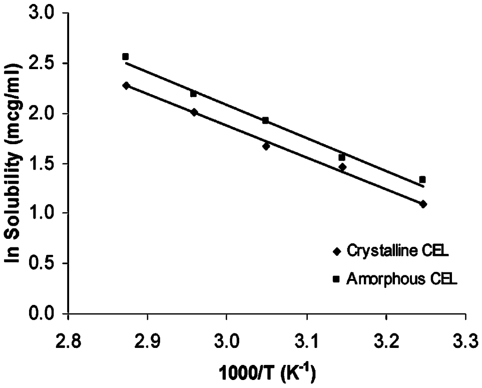

Figure 6. The van't Hoff plots of crystalline and amorphous CEL.

Solubility Determination. In contrast to the theoretical free energy and entropy values, the experimentally determined solubility values were used to find the thermodynamic explanation for the enhanced aqueous solubility of the amorphous form. The energetics of solubilization was studied by determining the solubility of crystalline and amorphous forms of CEL as a function of temperature (two temperatures below and two above T_g). As reported earlier for amorphous systems[12] and metastable polymorphs,[32] the peak solubilities were taken as the estimates of their solubility. The respective van't Hoff plots are shown in Figure 6. The solubility of both the crystalline and the amorphous form increased linearly with increase in temperature, signifying the endothermic nature of the solubilization process. The heat of solution (ΔH_{sol}), as derived from the slope of resultant van't Hoff plots, was found to be slightly lesser for the amorphous form ($\Delta H_{sol} = 26.55$ kJ/mol) in comparison to the crystalline form ($\Delta H_{sol} = 27.56$ kJ/mol). This is due to the high entropy difference (ΔS = 1.48 J/K·mol) and free energy (ΔG = 569.86 J/mol) available for solution, resulting in ease and spontaneity of the solubilization process, with high solubility values. These differences may be a result of differences in van der Waals interaction, the extent of the total energy associated with H-bonding in different solid-state forms, and their vibrational frequencies. But an infinitesimal heat of transition ($\Delta H_{trans} = 1.01$ kJ/mol) favors rapid devitrification, and loss of solubility advantage experimentally.

The aqueous solubility of amorphous CEL was invariably higher than that of its crystalline counterpart at all the temperatures studied. As compared in Figure 5, experimentally determined solubility ratios were far less than those predicted. A nearly constant value (∼1.3) for these experimentally determined solubility ratios denotes the role of similar activity coefficients of CEL molecules involved in

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solubilization of crystalline and amorphous phases. The predicted values are practically difficult to achieve due to strong driving force for crystallization in the presence of dissolution media, but they can provide an indication of theoretical driving force for initial dissolution of amorphous compound under any given conditions. The solvent-mediated devitrification of CEL was delayed by poly(vinyl pyrrolidone) (PVP), when used at 20% w/w content in a CEL−PVP solid dispersion.[33] Thus, the dynamics of molecular motions favoring rearrangement to gain order are subdued by specific stabilizers, like PVP, which provide enhanced solid-state stability as well as solubility advantage.

Conclusions

The amorphous form of a substance possesses excess thermodynamic properties (enthalpy, entropy, free energy) in comparison to its crystalline form. These properties are useful in estimating the stability as well as the probable solubility advantage of amorphous forms. The amorphous form of CEL, with higher C_p than the crystalline form, showed a sharp increase of nearly 1.3−1.5 times in C_p at T_g. On the basis of various indicators of glass fragility, such as $(T_c - T_g)/(T_m - T_g)$, $\Delta C_p^{T_g}$, $T_g - T_K$, γC_p, T_m/T_g, T_0/T_g, D, and m, amorphous CEL was categorized into moderately fragile glass. A comparison with varying pharmaceutical glass-formers of high structural diversity showed that CEL exhibited a common trend of moderate fragility. Moreover, the $C_{p_{\text{conf}}}$ of CEL indicated a theoretical possibility of achievement of 7−21-fold enhancement in aqueous solubility of the amorphous form over the crystalline form. A rapid solvent-mediated devitrification of amorphous CEL, coupled with moderately fragile behavior, is the cause of these discrepancies in theoretical and experimental solubility ratios. Attempts to stabilize the amorphous CEL, both in the solid phase and in the presence of dissolution medium, will provide the real advantage of this high-energy form. Further, these thermodynamic interpretations shall provide useful insights in designing of physically stable and pharmaceutically exploitable amorphous systems.

Abbreviations Used

C_p, heat capacity; D, strength parameter; $C_{p_{\text{conf}}}$, configurational heat capacity; G, free energy; G_{conf}, configurational free energy; H, enthalpy; H_{conf}, configurational enthalpy; m, fragility parameter; S_{conf}, configurational entropy; T, temperature; T_0, zero molecular mobility temperature; T_a, aging temperature; T_c, crystallization temperature; T_f, fictive temperature; T_g, glass transition temperature; T_K, Kauzmann temperature; T_m, melting temperature; τ, average molecular relaxation time; $\Delta C_p^{T_g}$, heat capacity change at glass transition temperature; ΔH_m, enthalpy of melting; ΔH_{sol}, heat of solution; ΔH_{trans}, heat of transition; ΔS_m, entropy of melting; σ, solubility.

Acknowledgment. It is a pleasure to thank Professor Bruno C. Hancock for explaining the thermodynamic calculations. The help provided by Mr. Mahesh Tripathi, Mettler Toledo, Mumbai, India, and Dr. Markus Schubnell, Mettler Toledo, Switzerland, in MDSC calculations is gratefully acknowledged.

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