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Practical Estimation of Amorphous Solubility Enhancement Using Thermoanalytical Data: Determination of the Amorphous/Crystalline Solubility Ratio for Pure Indomethacin and Felodipine

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ABSTRACT

Use of amorphous phases can mitigate the low *in vivo* exposures of poorly soluble, crystalline active pharmaceutical ingredients. However, it remains challenging to accurately predict the solubility enhancement offered even by a pure amorphous phase relative to the crystalline form. In this work, a methodology is presented that allows estimation of the amorphous:crystalline solubility ratio, α, using only measured thermodynamic quantities for each of the pure phases. With this approach, α values of 7.6 and 4.7 were calculated for indomethacin and felodipine, respectively, correlating more closely than previous predictions with the experimentally measured values of 4.9 and 4.7 reported in the literature. There are 3 key benefits to this approach. First, it uses simple mathematical functions to more precisely relate the temperature variations in the heat capacity (C_p) to allow a more accurate estimation of the configurational energy difference between the 2 phases, whereas traditional models typically assume that C_p of both phases are constant(s). Second, the Hoffman equation is leveraged in translating the free energy of crystal lattice formation to the actual temperature of interest (selected to be 25°C/298K in this work), again, for better accuracy. Finally, as only 2 modulated differential scanning calorimetry scans are required (one for each phase), it is attractive from an experimental simplicity standpoint.

Introduction

The use of amorphous and other noncrystalline physical forms of active pharmaceutical ingredients (APIs) provides a mechanism for enhancing the solubility and, hence, the oral bioavailability of compounds that are poorly soluble in their native crystalline state. Noncrystalline phases, such as those present in stabilized melts and amorphous dispersions,[1-8] lack lattice energy and exhibit higher configurational energies than their crystalline counterparts, resulting in enhanced relative solubility that comes as a direct result of their lower thermodynamic stability.[9] Oftentimes, the solubility enhancement gives rise to faster dissolution rates that can also contribute to greater *in vivo* exposure of a given drug; however, kinetic factors are not considered in this work. Regardless, as a direct consequence of their inherent instability, it can be difficult to measure the thermodynamic solubility of pure amorphous phases because they are prone to crystallization.[10,11] This can lead to measurements of transient or apparent solubility, rather than the true thermodynamic phase solubility. Therefore, the accurate prediction of solubility enhancement (of pure API phases), in lieu of direct measurement, can be of significant benefit in guiding formulation development activities. The goal of this work is to put forth a new methodology for doing such, using minimal thermoanalytic data as the input.

In recent years, various approaches for predicting amorphous solubility enhancement have been put forth.[12-16] Unfortunately, the methods currently available in the literature typically overestimate the solubility ratio, α, for most pharmaceutical compounds. Indeed, it has been written that "in some cases, the predicted solubility of the amorphous drug is as much as 1600 times that of its crystalline form."[13] Although a recently proposed method[14] showed early promise in predicting α values that are in better agreement with solubility measurements (in comparison to the "configurational thermodynamic"[17] methodologies[12,13] preceding it—see in the following section), for certain compounds, its physical basis might warrant further clarification.

Although the physical interpretation of the traditional equations comprising the configurational thermodynamic approach are well

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understood, the estimations of α using it have remained quite poor despite improvements in thermoanalytic instrumentation (e.g., the advent of modulated differential scanning calorimetry [MDSC]) that have allowed for more accurate determinations of the relevant input physical parameters. The authors' perspective is that the fundamental equations used in that approach are too simplistic for 2 main reasons. First, they assume that the thermodynamic quantities of interest are constants, whereas, for example, the amorphous phase heat capacity (C_p) in the vicinity of the glass transition[18] temperature (T_g) varies markedly with small changes in temperature (T). Second, they typically rely on values of the enthalpy and entropy of fusion determined at the melting point, without back-extrapolation to lower temperatures more relevant to solubility determinations ($T = 298$ K was selected in this work for ease of bridging to published solubility data, per Table 1, although 310 K is of more potential interest from a biorelevant perspective).

In this work, a physically intuitive methodology is presented to enable the practical estimation of α for pure API phases that do not contain significant levels of impurities. As with previous, related works on this topic, the effects of stabilizing polymers and other excipients on α are considered to be out of scope. Moreover, the proposed methodology assumes that, although it is typically more hygroscopic than its crystalline counterpart(s),[14] the amorphous phase is adequately protected from moisture via appropriate handling before measurement and by a continuous dry nitrogen sweep during the measurement, so that water content correction is unnecessary. Using these assumptions, the true thermodynamic solubilities corresponding to each of the 2 pure phases can be compared directly. In addition, they allow for only 2 MDSC scans, one for each pure phase, to be acquired for α prediction. Note that MDSC is required to accurately measure the heat capacity change during the glass transition because, unlike the melts of crystalline phases, they are second-order phase transitions (per the Ehrenfest classification).

In terms of the new calculations presented in this approach, approximate C_p functions are put forth to more accurately reflect the real-world T-dependence of the heat capacity change of each phase—specifically, in the region around the T_g where the biggest change in C_p is observed for the amorphous phase. Doing so allows for a more accurate estimation of the configurational energy difference between the 2 phases than obtained by standard approaches that assume C_p is constant. In addition, the Hoffman equation[23] is leveraged as a means of translating the Gibbs free energy of crystal lattice formation to the selected (a single, common) reference temperature. Care is taken to ensure that all thermodynamic quantities, for both phases, are referenced to the same temperature (in this case, "T_2", which is defined later) before they enter into the calculation of α, so as to improve the accuracy of the prediction.

To demonstrate the utility of the proposed approach, α values are calculated for indomethacin and felodipine using physical quantities available from the literature. Those compounds were selected solely on the basis that there was sufficient published thermoanalytical data on them to perform the calculations described herein, as well as to compare the predicted α values to experimentally measured ones (also taken from the literature). However, the methodology presented in this work is sufficiently general so as to allow the determination of α at any T, for any given amorphous:crystalline pair of a pure compound.

Results and Discussion

The solubility ratio, α, of a given compound (API) is defined as follows:

$$\alpha = \frac{a_a}{a_x} \tag{1}$$

where the numerator, a_a, represents the activity of a saturated solution of the amorphous phase and the denominator, a_x, is the corresponding activity of the dissolved crystalline phase, both at standard temperature and pressure. The previously mentioned solubility ratio is related to a Gibbs free energy difference between the 2 solid phases, $\Delta G_{a\text{-}x}$, at each T, as described by the equation:

$$\Delta G_{a-x} = -RTln\left(\frac{a_a}{a_x}\right) = -RTln(\alpha) \tag{2}$$

where R is the universal gas constant. Because the solubility ratio at standard temperature and pressure is of interest in this work, $T = 298$ K is used in Equation 2 (however, physiological and other temperatures can also be used).

In the absence of comparative solubility measurements, $\Delta G_{a\text{-}x}$ can be estimated from thermal data that is often more easily and rapidly collected. To show how that can be done in a physically rigorous manner, one can start by examining the generic phase diagrams depicted in Figure 1. That figure shows both the origin of the T_g of the amorphous phase and the melting point (fusion temperature), T_f, of the crystalline form. More importantly, it highlights the relative physical instability of the amorphous form that, in turn, leads to the solubility enhancement.

Figure 2 illustrates that as T is increased, the C_p of the crystalline phase exhibits very different behavior compared to that of the amorphous phase.[24] As the amorphous phase transforms from a glass to a supercooled, metastable liquid at T_g, there is a distinct change in C_p. On the other hand, the corresponding increase in C_p for the crystalline form is more subtle over the same temperature range, as it is largely attributable to simply an increase in vibrational motion—there is no phase transformation until T_f is reached (not shown). The difference in heat capacities between the 2 phases, $\Delta C_{p,a\text{-}x}$, relates the configurational energy difference between the amorphous and crystalline phases (at any given T), which

Table 1
Tabulated Thermodynamic Parameters, Taken From the Literature, Used in the Determination of the Amorphous:Crystalline Solubility Ratio, α, for the 2 APIs Investigated in This Work

API	MW	ΔH_f	$C_{p,a,T1}$	$C_{p,a,T2}$	$C_{p,x,T1}$	$C_{p,x,T2}$	T_1	T_2	T_g	T_f	$\Delta G_{a,T2\text{-}T1}$	$\Delta G_{x,T2\text{-}T1}$	$\Delta G_{c,T2}$	α_{298}	Literature α
Indomethacin	357.8[a]	36.5[a]	422[c]	583[c]	404[c]	440[c]	295[c]	355[c]	315[d]	435[a]	−2.83	−2.38	−5.48	**7.6**	4.9[c]
Felodipine	384.3	30.8[b]	503[b]	753[b]	473[b]	588[b]	273[b]	373[b]	320[b]	415[b]	−9.36	−8.35	−2.80	**4.7**	4.7[e]

Information regarding purity of the respective phases can be inferred from, for example, Murdande et al.[15] and Marsac et al.[19]
Units: MW = g/mol; T = K; ΔH, ΔG = kJ/mol; C_p = $JK^{-1}mol^{-1}$.
The "literature α" values are measured solubility ratios that are compared to the predicted values at 298 K, "α_{298}," shown in bold, using the proposed Equation 9.
[a] Murdande et al.[15]
[b] Marsac et al.[19]
[c] Murdande et al.[14]
[d] Kearns et al.[20] and Crowley and Zografi.[21]
[e] Bhole and Patil.[22]