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Letter to the Editor

Estimating the Critical Molecular Mobility Temperature (T_K) of Amorphous Pharmaceuticals

To the Editor:

An important parameter for the classification and characterization of amorphous pharmaceutical materials is the temperature at which the thermodynamic properties (e.g., entropy, enthalpy) of the crystalline and the supercooled liquid states converge (Fig. 1) (1,2). This theoretical temperature range is commonly referred to as the Kauzmann temperature (T_K), after the author who first reported the paradox of amorphous materials potentially having lower enthalpies and entropies than their crystalline counterparts (3). By definition T_K is below both the melting point of the crystalline material (T_m) and the calorimetric glass transition temperature of the amorphous material (T_g). It has been suggested that T_K (or its equivalent) represents the temperature region below which the translational molecular motions responsible for the majority of unwanted physical and chemical changes in pharmaceutical products can be considered to be negligible over the normal product lifetime (1,4,5). Thus, it is possible that T_K represents a conservative maximum storage temperature for amorphous pharmaceutical formulations, and it may be considered to be a critical molecular mobility region for such systems.

Direct experimental determination of T_K is not usually possible because kinetic restrictions render it inaccessible on ordinary experimental timescales. However, it may be estimated by the extrapolation or curve fitting of certain physical properties (e.g., specific volume) which have been determined over a wide range of temperatures above the glass transition temperature (e.g., 6). It is also feasible to roughly estimate T_K from simple "rules of thumb" which represent generalized relationships with key physical properties of the amorphous and crystalline states (e.g., $T_g - 50$ K (1). In this letter we propose some possible alternative methods of *estimating* T_K from the results of relatively simple calorimetry experiments.

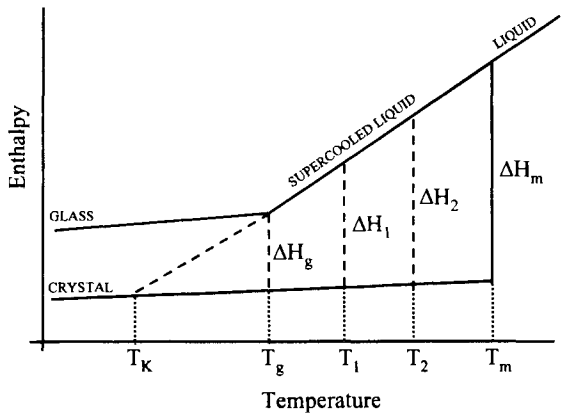

Fig. 1. Schematic of the idealized enthalpy-temperature relationship for amorphous and crystalline pharmaceutical materials.

From a consideration of Fig. 1, and by assuming that the enthalpy increases linearly with temperature for both the crystalline and supercooled liquid states and that this change is small for the crystalline material (7), it is possible to write:

$$[\Delta H_2/(T_2 - T_K)] \approx [\Delta H_1/(T_1 - T_K)]$$

and by a series of rearrangements:

$$[\Delta H_2 \cdot (T_1 - T_K)] \approx [\Delta H_1 \cdot (T_2 - T_K)]$$

$$[(\Delta H_2 \cdot T_1) - (\Delta H_2 \cdot T_K)] \approx [(\Delta H_1 \cdot T_2) - (\Delta H_1 \cdot T_K)]$$

$$[(\Delta H_1 \cdot T_K) - (\Delta H_2 \cdot T_K)] \approx [(\Delta H_1 \cdot T_2) - (\Delta H_2 \cdot T_1)]$$

$$[T_K \cdot (\Delta H_1 - \Delta H_2)] \approx [(\Delta H_1 \cdot T_2) - (\Delta H_2 \cdot T_1)]$$

$$T_K \approx [(\Delta H_1 \cdot T_2) - (\Delta H_2 \cdot T_1)]/(\Delta H_1 - \Delta H_2) \quad (1)$$

where the symbols have the meaning shown in Fig. 1. This series of equations may be derived from first principles using conventional thermodynamic approaches, or by simple trigonometric consideration of Fig. 1. The approach described is based on that outlined by Hoffman (7), and which has been used for inter-converting enthalpies of crystallization and melting measured at different experimental temperatures (8,9,10). For such an application equation 1 should be expanded and rearranged as:

$$\Delta H_x \approx \{[\Delta H_2 \cdot (T_x - T_1)] + [\Delta H_1 \cdot (T_2 - T_x)]\}/(T_2 - T_1) \quad (2)$$

where ΔH_x is the unknown enthalpy change at temperature T_x, the other symbols are as defined previously, and temperatures 1 and 2 are selected from the glass transition, crystallization and melting points. The parameters ΔH_1, ΔH_2, T_1 and T_2 may be experimentally determined by careful application of conventional solution calorimetry and differential scanning calorimetry (DSC) techniques (e.g., 11,12), and then used for the calculation of ΔH_x.

A value for T_K can be estimated using equation 1 from a knowledge of the temperatures and enthalpy changes associated with melting, crystallization and/or the glass transition. For example, equation 1 can be written as:

$$T_K \approx [(\Delta H_g \cdot T_m) - (\Delta H_m \cdot T_g)]/(\Delta H_g - \Delta H_m) \quad (3)$$

where T_m and ΔH_m are the melting temperature and heat of fusion of the crystalline material, and T_g and ΔH_g are the glass

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transition temperature and the enthalpy difference between the amorphous and crystalline states respectively (Fig. 1). Solution calorimetry may be used to determine ΔH_g (e.g., 11), and T_g, T_m, and ΔH_m can be measured by differential scanning calorimetry (12), and thus T_K estimated. Equation 1 can also be written as:

$$T_K \approx [(\Delta H_c \cdot T_m) - (\Delta H_m \cdot T_c)]/(\Delta H_c - \Delta H_m) \quad (4)$$

where T_c and ΔH_c are the temperature and enthalpy of crystallization for an amorphous sample, and T_m and ΔH_m are the temperature and heat of fusion of the crystalline form (Fig. 1). Each of these parameters could be determined by the careful application of differential scanning calorimetry (12), and then used to estimate T_K.

To illustrate the use of the proposed approach for estimating T_K for amorphous pharmaceuticals we can utilize DSC data reported for an amorphous drug (indomethacin (13)). For this material the temperature at which translational molecular motions become negligible has been estimated using two independent methods (4,6), and this temperature can be considered to be approximately equivalent to T_K (14,15). For the system of the higher melting polymorph and the amorphous form of indomethacin it is reported that T_m = 161°C (434 K), ΔH_m = 110 J/g, $T_c \approx$ 100°C (373 K) and $\Delta H_c \approx$ 70 J/g (13). Substituting these values into equation 4 results in an estimate of T_K of ≈ -7°C (266 K), which compares favorably with the critical molecular mobility temperature of this material estimated from the results of enthalpy relaxation measurements (−6°C (267 K) (4)) and viscosity determinations (−17°C (256 K) (6)). The estimated T_K value is also very consistent with the sub-zero temperature at which the amorphous indomethacin needed to be stored in order to prevent spontaneous crystallization over a period of several months (1,13).

The estimation of T_K values from enthalpy and temperature data as described above relies upon the extrapolation and convergence of straight lines drawn through just two pairs of enthalpy-temperature coordinates. The approach is thus very sensitive to the accuracy of each of the experimental data points used. To minimize such problems Equation 1 may be re-derived in terms of the slopes of the enthalpy *vs.* temperature plots in Fig. 1, that is, using the heat capacities of the liquid and crystalline states (C_{pl} and C_{pc}):

$$T_K = T_m - (\Delta H_m/(C_{pl} - C_{pc})) \quad (5)$$

With this modification the accuracy of the estimate of T_K is likely to be considerably improved since mean heat capacity values can be determined from data collected over a wide range of temperatures. Equation 5 may be simplified if it is assumed that the heat capacities of the glassy and crystalline states are approximately equal (Fig. 1), and this provides another means of estimating T_K from the results of simple calorimetric measurements:

$$T_K = T_m - (\Delta H_m/\Delta C_p) \quad (6)$$

where ΔC_p is the heat capacity change at the glass transition temperature. This equation is a specific case of the Kirchhoff equation which is usually used for estimating melting enthalpy values of crystalline materials at different experimental temperatures (16).

It is important to note that there are many instances when the approaches described in this letter may not provide a usable estimate of T_K. These situations include systems with multiple inter-converting crystal forms (e.g., hydrates, polymorphs), materials which degrade upon melting (e.g., sucrose, lactose), materials where incomplete crystallization occurs, systems which are not at a pseudo-equilibrium state (e.g., rapidly relaxing glasses), and impure materials where T_g and T_m may be significantly depressed. It should also be remembered that the accuracy with which T_K can be estimated using these approaches is strongly dependent upon the quality of the thermodynamic data used for the calculations, which frequently depends upon the experimental conditions used for their determination (e.g., experimental scanning rate). Bearing in mind these practical limitations, the theory of the described approaches is sound and with the careful selection of the appropriate form of equation 1 it should provide several alternate means of estimating a very important property of amorphous pharmaceutical materials which is usually experimentally inaccessible.

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