Pharmaceutical Research, Vol. 22, No. 7, July 2005 (© 2005)
DOI: 10.1007/s11095-005-5363-8

Research Paper

A Quantitative Model to Evaluate Solubility Relationship of Polymorphs from Their Thermal Properties

Chen Mao,[1] Rodolfo Pinal,[1,2] and Kenneth R. Morris[1]

Received February 16, 2005; accepted April 15, 2005

Purpose. The objective of the study is to develop a model to estimate the solubility ratio of two polymorphic forms based on the calculation of the free energy difference of two forms at any temperature. This model can be used for compounds with low solubility (a few mole percent) in which infinite dilution can be approximated.

Methods. The model is derived using the melting temperature and heat of fusion for apparent monotropic systems, and the solid–solid transition temperature and heat of transition for apparent enantiotropic systems. A rigorous derivation also requires heat capacity (C_p) measurement of liquid and two solid forms. This model is validated by collecting thermal properties of polymorphs for several drugs using conventional or modulated differential scanning calorimetry. From these properties the solubility ratio of two polymorphs is evaluated using the model and compared with the experimental value at different temperatures.

Results. The predicted values using the full model agree well with the experimental ones. For the purpose of easy measurement, working equations without C_p terms are also applied. Ignoring C_p may result in an error of 10% or less, suggesting that the working equation is applicable in practice. Additional error may be generated for the apparent enantiotropic systems due to the inconsistency between the observed solid–solid transition temperature and the true thermodynamic transition temperature. This inconsistency allows the predicted solubility ratios (low melt/high melt) to be smaller. Therefore, a correction factor of 1.1 is recommended to reduce the error when the working equation is used to estimate the solubility ratio of an enantiotropic system.

Conclusions. The study of the free energy changes of two crystalline forms of a drug allows for the development of a model that successfully predicts the solubility ratio at any temperature from their thermal properties. This model provides a thermodynamic foundation as to how the free energy difference of two polymorphs is reflected by their equilibrium solubilities. It also provides a quick and practical way of evaluating the relative solubility of two polymorphs from single differential scanning calorimetry runs.

KEY WORDS: flufenamic acid; model; polymorphs; solubility; thermal properties.

INTRODUCTION

Organic compounds can exist in different crystal modifications (1). In fact, crystal polymorphism is a rather common occurrence for organic compounds. Because different polymorphs correspond to crystal arrangements with different free energies, their equilibrium solubilities are necessarily different. In pharmaceutical industry, a crystalline form with greater solubility is typically a more favorable candidate because it, based on the Noyes–Whitney equation (2), implies a possibly higher dissolution rate and, hence, bioavailability. As solubility measurement requires relatively large sample size and sometimes the true solubility value is masked by solvent-mediated transformation, it is desirable to have an optional approach to evaluating relative solubility of polymorphs from their thermal properties, such as melting temperature and heat of fusion. Such an approach uses less sample and is potentially more accurate because measurements of these thermal properties can typically be performed with differential scanning calorimetry (DSC) and therefore are less likely influenced by kinetic processes, whereas the solubility value, in essence, is a true manifestation of the thermodynamic conditions.

The work presented here focuses on building a thermodynamic model that allows the evaluation of solubility relationship of polymorphs from a routine DSC run. The solubility difference in two polymorphs roots in their different free energy levels ΔG. There have been many studies on correlating thermodynamic stability relationship of polymorphs from solubility measurements (3,4). It is therefore feasible to derive solubility relationship of polymorphs from thermodynamic data using the same sets of thermodynamic equations. Crystal polymorphs can be monotropically or enantiotropically related. Monotropic systems are those in which the stable form at absolute zero remains as the stable

[1] Department of Industrial and Physical Pharmacy, Purdue University, West Lafayette, Indiana 47907, USA
[2] To whom correspondence should be addressed. (e–mail: pinal@pharmacy.purdue.edu)

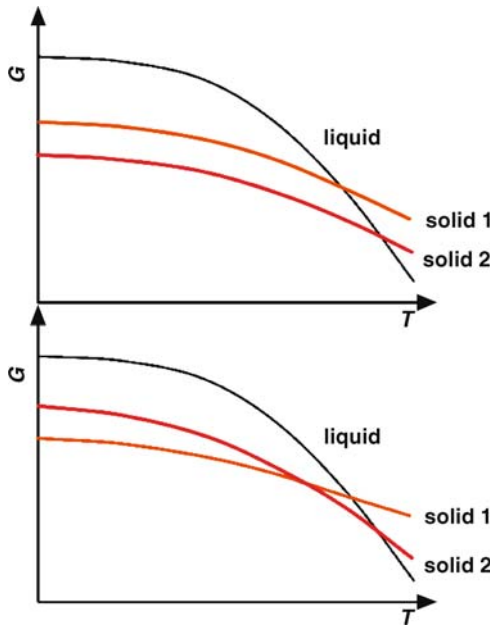

Fig. 1. Gibbs free energy-temperature diagram for monotropic (top) and enantiotropic (bottom) systems.

form up to the melting point. In contrast, enantiotropic systems are those in which there is a solid–solid transition at a temperature below the melting point, such that one form is thermodynamically stable below the transition temperature and the other form is stable at temperatures above the transition point. Figure 1 shows the free energy diagrams of monotropic and enantiotropic systems. It needs to be pointed out that free energy of two solid forms do not necessarily converge with increasing temperature, as is the case in the figure. There are systems where two free energy curves diverge with temperature from absolute zero (5), but this is regarded as a special case in monotropic systems.

It is obviously observed from the diagram (Fig. 1) that the relative solubility of two polymorphs is temperature dependent because ΔG changes with temperature. To determine the solubility at all temperatures, one needs to find critical points at which ΔG between two phases is zero. This implies that monotropic and enantiotropic systems will have two different sets of equations because the solid–solid transition can be conveniently used for enantiotropic systems but not for monotropic systems.

The present work will also discuss the role that heat capacity (C_p) plays in the model. Heat capacity [related to the second derivative of the $G(T)$ diagram], incidentally, contributes to the temperature dependence of the solubility relationship of polymorphs. In this work a set of working equations devoid of C_p terms will be provided and compared with the full models to verify the effect of C_p on solubility determination.

THEORETICAL SECTION

The solubility of organic nonelectrolytes is given by the following expression:

$$\log X = \log X^{(i)} - \log \gamma \tag{1}$$

where X is the observed mole-fraction solubility, $X^{(i)}$ is the ideal solubility, and γ is the activity coefficient. The ideal solubility is a property of the solute alone and is the same for all solvents. The expression for the ideal solubility (6) is given by:

$$\ln X^{(i)} = -\frac{\Delta S_m (T_m - T)}{RT} + \frac{1}{RT}\int_T^{T_m} \Delta C_p dT - \frac{1}{R}\int_T^{T_m} \frac{\Delta C_p}{T} dT \tag{2}$$

where ΔH_m, ΔS_m, and T_m are the solute's enthalpy, entropy, and temperature of melting, respectively, T is the temperature, R is the gas constant, and ΔC_p is the difference in heat capacity between the solute's liquid and solid phases ($C_{p[liquid]} - C_{p[solid]}$). For many practical applications, the ideal solubility is calculated from Eq. (2) without the heat capacity terms. The heat capacity terms are typically regarded as being small in comparison to the first two terms on the right-hand side of the expression. In addition, these two ΔC_p terms, having opposite signs, tend to cancel each other.

In this report, the theoretical treatment is presented using the full expressions with practical simplifications applied at the end. For purposes of simplicity in the following discussion, Eq. (2) will be expressed in the following alternative form:

$$\ln X^{(i)} = -\frac{\Delta H_m}{RT} + \frac{\Delta S_m}{R} + \frac{1}{RT}\int_T^{T_m} \Delta C_p \, dT - \frac{1}{R}\int_T^{T_m} \frac{\Delta C_p}{T} dT \tag{2'}$$

with this slight change in notation, all solubility expressions used in the following discussion have the same form.

The activity coefficient γ accounts for the deviations from ideal solution behavior of the solute in the particular solvent and is dependent on the solute and solvent combination. For low solubility values, the observed solubility in mass/volume units, S, can be approximated by the following expression:

$$\log S = \log X^{(i)} - \log \gamma + C \tag{3}$$

where C is a constant whose value depends on the solvent (1.7 for water). Equation (3) is a good approximation in cases in which the mole fraction concentration of the solute is small compared with that of the solvent (a few mole percent).

The activity coefficient varies with the solute's concentration. However, for low concentrations, as is the case when the solubility is low, the activity coefficient can be considered constant and equal to its infinite-dilution limiting value. The treatment presented here is therefore applicable to those cases in which the solute exhibits rather low solubility. In a strict sense, the condition necessary for the last two terms in Eq. (3) to be treated as constants is that the volume occupied by the solute in the solution be negligibly small compared with the volume occupied by the solvent. Such a situation, nevertheless, covers a vast number of cases.

In this report we explore the relationship in solubility between crystal forms from their thermodynamic relationship. In the case of two polymorphic forms, 1 and 2, their

solubilities are related in the following fashion, provided the infinite dilution assumption holds:

$$\log\frac{S_1}{S_2} = \log X_1^{(i)} - \log\gamma + C - \left(\log X_2^{(i)} - \log\gamma + C\right) = \log\frac{X_1^{(i)}}{X_2^{(i)}} \quad (4)$$

This means that the difference in solubility between polymorphs is a direct result of their different ideal solubility values. In other words, the difference in solubility between crystal polymorphs is entirely a function of their solid-state properties. This also means that predictions of relative solubilities for crystal polymorphs should be possible from their solid-state properties alone. We should clarify that the assumption of low solubility is simply used to meaningfully separate the terms C and γ in the above expression. In fact, the equivalence between the far left- and far right-hand sides of Eq. (4) will persist even if the values of S_1 and S_2 are high, as long as that the two values are close to each other (the equivalence is exact when $S_1 = S_2$ for any magnitude of solubility, but the solubilities of polymorphs must be different). We should also clarify that because solubility calculations are given as the *logarithm* of the solubility value, throughout the present discussion, whenever discussing differences in solubility, the reference is being made to the difference of the logarithms of the solubility values in question, which, of course, corresponds to the ratio of the experimentally determined values.

In the following section, the equations relating the solubilities between crystal polymorphs are presented for both the monotropic and enantiotropic cases. However, it is pertinent at this early stage to make a very important point: depending on the temperature of interest, for purposes of solubility predictions, enantiotropic systems sometimes require the same treatment as that derived for the monotropic case. This important point will be addressed in more detail later.

Consider a compound that exists in two different crystal forms, 1 and 2. In the present discussion, the notation 1 and 2 will refer to the lower and higher melting polymorph, respectively, whether the polymorphs are monotropically or enantiotropically related.

Monotropic Case. In this type of system, polymorph 2 is the thermodynamically stable form at all temperatures in which a solid phase exists. The solubility expression for the two crystal forms are as follows:

$$\ln X_1^{(i)} = -\frac{\Delta H_{m1}}{RT} + \frac{\Delta S_{m1}}{R} + \frac{1}{RT}\int_T^{T_{m1}} \Delta C_{p1}\,dT - \frac{1}{R}\int_T^{T_{m1}} \frac{\Delta C_{p1}}{T}\,dT \quad (5a)$$

and

$$\ln X_2^{(i)} = -\frac{\Delta H_{m2}}{RT} + \frac{\Delta S_{m2}}{R} + \frac{1}{RT}\int_T^{T_{m2}} \Delta C_{p2}\,dT - \frac{1}{R}\int_T^{T_{m2}} \frac{\Delta C_{p2}}{T}\,dT \quad (5b)$$

where the subscripts 1 and 2 denote polymorph 1 (metastable, lower melting) and polymorph 2 (stable, higher melting), respectively. Equation (4) indicates that the difference in solubility between the two polymorphs, in any solvent, is the same as the difference in their ideal solubilities. Thus, subtracting Eq. (5b) from Eq. (5a), after some rearrangement, gives

$$\ln\frac{S_1}{S_2} = \frac{\Delta H_{m2} - \Delta H_{m1}}{RT} + \frac{\Delta S_{m1} - \Delta S_{m2}}{R} + \frac{1}{RT}\left[\int_T^{T_{m1}} \left(C_{p2}^s - C_{p1}^s\right)dT - \int_{T_{m1}}^{T_{m2}} \Delta C_{p2}\,dT\right] + \frac{1}{R}\left[\int_{T_{m1}}^{T_{m2}} \frac{\Delta C_{p2}}{T}\,dT - \int_T^{T_{m1}} \frac{C_{p2}^s - C_{p1}^s}{T}\,dT\right] \quad (6)$$

where ΔH_m and ΔS_m denote enthalpy and entropy of melting, respectively, with subscripts 1 and 2 the same as above, and the superscript s stands for solid phase.

Enantiotropic Case. In this case there is a transition temperature, T_t, below which the low-melting polymorph 1 is the thermodynamically stable form, and consequently, form 2 is metastable. At temperatures above T_t, the high-melting polymorph 2 becomes the thermodynamically stable form. For enantiotropic systems, the transition is necessarily from low-melting form to high-melting form, i.e., $1 \rightarrow 2$.

Calculation of the ideal solubility corresponds in reality to the calculation of the free energy change necessary for the hypothetical melting of the solute at the temperature of interest, T, instead of at its normal melting temperature, T_m. To calculate ideal solubility for enantiotropic systems, it is critical to take into account if the temperature of interest (i.e., the temperature at which one is going to measure the solubility) is above or below the transition temperature. In enantiotropic systems, the solid–solid transition temperature is necessarily lower than the melting point of the lower melting polymorph ($T_t < T_{m1}$). If the solid transition occurs, the melting of the low-melting polymorph (polymorph 1) will not be observed. Therefore, the expression for the ideal solubility of the low-melting polymorph should include the free energy effects of such a transition, giving the following expression:

$$\ln X_1^{(i)} = -\frac{\Delta H_{m2} + \Delta H_t}{RT} + \frac{\Delta S_{m2} + \Delta S_t}{R} + \frac{1}{RT}\left[\int_T^{T_{m2}} \Delta C_{p2}\,dT + \int_T^{T_t} \left(C_{p2}^s - C_{p1}^s\right)dT\right] - \frac{1}{R}\left[\int_T^{T_{m2}} \frac{\Delta C_{p2}}{T}\,dT + \int_T^{T_t} \frac{\left(C_{p2}^s - C_{p1}^s\right)}{T}\,dT\right] \quad (7)$$

where ΔH_t and ΔS_t are the enthalpy and entropy of the solid–solid transition, respectively. Equation (7) gives the ideal solubility for the low-melting polymorph (species 1) of an enantiotropic system. It is worth noticing that except for a small correction in the heat capacity terms, the expression above does not include parameters bearing subscript 1 on its right-hand side. Because the two polymorphs exist in equilibrium at T_t, it is possible to express the melting pa-

rameters of one polymorph by a combination of the parameters of the solid–solid transition and of the melting of the other form. This fact, as will be discussed later, is of great practical value.

For the high-melting polymorph, the ideal solubility expression is the same as in the monotropic case, i.e., Eq. (5b):

$$\ln X_2^{(i)} = -\frac{\Delta H_{m2}}{RT} + \frac{\Delta S_{m2}}{R} + \frac{1}{RT}\int_T^{T_{m2}} \Delta C_{p2} dT - \frac{1}{R}\int_T^{T_{m2}} \frac{\Delta C_{p2}}{T} dT \quad (5b)$$

The ideal solubility of the high-melting form is the same for both monotropic and enantiotropic systems because the thermodynamic relationship of the high-melting form with the liquid phase is totally unaffected by the existence of a solid–solid transition at T_t. As discussed for monotropic systems, the solubilities of two polymorphs in any solvent are the same as the difference in their ideal solubilities. Thus, we have that for the enantiotropic case, the difference in solubilities for the two forms, by subtracting Eq. (5b) from (7), is:

$$\ln \frac{S_1}{S_2} = -\frac{\Delta H_t}{RT} + \frac{\Delta S_t}{R} + \frac{1}{RT}\int_T^{T_t} \left(C_{p2}^s - Cp_1^s\right) dT - \frac{1}{R}\int_T^{T_t} \frac{\left(C_{p2}^s - C_{p1}^s\right)}{T} dT \quad (8)$$

It is worth to mention that the equation above is identical in form to the ideal solubility expression (Eqs. 5a and 5b). Equation (8) shows that the difference in solubility between enantiotropically related polymorphs is equal to a hypothetical ideal solubility quantity such that the solid–solid transition temperature replaces the melting point and the solid phase 2 replaces the liquid phase.

Simplified Equations. Equations (4) through (8) are general expressions with applicability to any set of polymorphs, monotropically or enantiotropically related, in any solvent. For the practical application of solubility estimations, it is necessary to get simplified, working expressions. The assumptions made in obtaining the practical working expressions are listed below:

1. The solubility of the drug can be either high or low, given the following:
   (a) Neither of the two polymorphs is highly soluble, so that saturated solutions are dilute and the relationship between X_1 and S_1 and between X_2 and S_2 is the same proportionality constant, or
   (b) if the polymorphs are highly soluble, then the two forms have similar solubility.
2. The solid solute remains pure when in equilibrium with its saturated solution, i.e., the solute and solvent do not combine to form a new solid phase such as a hydrate or a solvate.
3. The quality of the crystalline materials used when applying the methodology described is such that it permits DSC measurements of typical quality. Namely, it is possible to conduct melting experiments and determine the corresponding temperature and heat of the event.
4. The contribution of the heat capacity terms to solubility estimations can be neglected for purposes of solubility estimation.

The expressions for solubility in the preceding section are presented without simplifying assumptions. Because the quality of any prediction is only as good as the applicability of the simplifying assumptions of the procedure, it is best to use the general expressions given above as starting point to make solubility predictions. In this section, simplifying assumptions will be made to the theoretical (general) expressions of the preceding section to obtain "working equations" for solubility predictions of polymorphic systems. This approach has, in our opinion, several advantages. It allows for the use of simpler working equations without a working disconnection from their theoretical origin and meaning. In addition, comparison of predicted and observed solubility values allows for a quantitative assessment of the cost in accuracy that the chosen simplifications bring about.

Equations (5) through (8) all include heat capacity terms. Although experimentally measurable, these terms undoubtedly complicate the use of the expressions. Yalkowsky and Banerjee (6) have argued that the effect of the heat capacity terms (ΔC_{p1} and ΔC_{p2}) in the ideal solubility expression (Eqs. 5a and 5b) can be considered negligibly small compared to the first two terms on the right-hand side of each one of the expressions. The heat capacity terms are small compared with the first two terms of the equation. Using this assumption, the following working expressions are obtained for the ideal solubility of polymorphs 1 and 2:

Monotropic Case

$$\ln X_1^{(i)} \approx -\frac{\Delta H_{m1}}{RT} + \frac{\Delta S_{m1}}{R} \quad (5a')$$

$$\ln X_2^{(i)} \approx -\frac{\Delta H_{m2}}{RT} + \frac{\Delta S_{m2}}{R} \quad (5b')$$

and the difference in solubility between two polymorphs that are monotropically related becomes:

$$\ln \frac{S_1}{S_2} \approx \frac{\Delta H_{m2} - \Delta H_{m1}}{RT} + \frac{\Delta S_{m1} - \Delta S_{m2}}{R} \quad (6')$$

For the enantiotropic case, we make the additional assumption that the heat capacities of the two solid phases are very similar so that the term $C_{p2}^s - C_{p1}^s$ is also negligibly small. This additional assumption should bring little error to the calculation of solubility because it is even better suited than the first assumption, i.e., the difference in heat capacity between two solid phases is smaller than that between a liquid and a solid phase. Using this additional assumption, we get the following.

Enantiotropic Case

$$\ln X_1^{(i)} \approx -\frac{\Delta H_{m2} + \Delta H_t}{RT} + \frac{\Delta S_{m2} + \Delta S_t}{R} \quad (7')$$

Equation (7′) is the working expression for the ideal solubility of the low-melting form. As discussed in the

preceding section, the solubility expression for the high-melting form of an enantiotropic system is the same as in the monotropic case. Thus, for the high-melting form:

$$\ln X_2^{(i)} \approx -\frac{\Delta H_{m2}}{RT} + \frac{\Delta S_{m2}}{R} \qquad (5b')$$

and the difference in solubility between the two forms is given by the working expression:

$$\ln\frac{S_1}{S_2} \approx -\frac{\Delta H_t}{RT} + \frac{\Delta S_t}{R} \qquad (8')$$

MATERIALS AND METHODS

Materials. Flufenamic acid (FFA) was chosen as the model compound for the studies. FFA was purchased from Aldrich (Milwaukee, WI, USA). Pure FFA form III was obtained by dissolving an appropriate amount of FFA as received in toluene at about 80°C and crash-cooling to 0°C with vigorous stirring. FFA form I crystals were acquired by storing the dry form of FFA III crystals in an oven at 115°C overnight and then slowly cooling to room temperature. The polymorphic purity of form I was greater than 97% and that of form III was greater than 99% as determined by powder X-ray diffractometry (PXRD).

Thermal Measurements. The transition temperature, heat of transition, and heat capacity data of two forms of FFA were obtained from a TA Instruments (Newcastle, DE, USA) differential scanning calorimeter with temperature modulation and equipped with a refrigerated cooling system. A crimpled pan configuration was used. Modulated DSC data were obtained using a modulation amplitude of ±0.16°C and a 60-s period with an underlying heating rate of 1°C/min from 75°C to 150°C. The temperature and the heat capacity were calibrated using indium metal and sapphire as the calibration standards, respectively.

Solubility Measurements. The solubility of the two forms of FFA was measured over several temperatures in diacetone alcohol/water (40:60 w/w) mixed solvent. Batch experiments were performed in a tightly sealed 50-mL jacketed glass vessel shielded from light. Excess solid was added to about 20 mL of solvent, and a magnetic stirrer was used to provide agitation. A circulating water bath was used to control the temperature of the solution within ±1°C. After equilibrating overnight, the agitation was halted and an aliquot of solution was filtered and diluted to a concentration between 10 and 20 μg/g. The absorbance at 339 nm was determined with UV spectrometry. The solubility was calculated from a standard curve prepared over the concentration range of 0–25 μg/g.

RESULTS AND DISCUSSION

General Agreement. The predicted and experimental solubility ratios of two polymorphs of FFA at different temperatures are compared in Table I. The predicted and experimental solubility ratios of other drugs, calculated from literature data, are also presented. Whenever the heat capacity values of two polymorphs are available, evaluations from the general equations (containing C_p terms) and the working equations (not containing C_p terms) are both listed to test the assumption that heat capacity terms make only negligibly small contributions.

Of all the compounds tested, the predicted and experimental solubility ratios are similar. The error of prediction in most cases is less than 10%. This could partially result from the experimental errors during temperature and heat measurements. The results show that, in general, the proposed model can be used to predict the relative solubility of two polymorphs from their thermal properties for both monotropic and enantiotropic systems. It is, however, important to point out that due to the logarithm relation in these models, a

Table I. Estimation of Solubility Ratios for Different Polymorphic Systems

Compounds, polymorphs	Predicted solubility ratio		Experimental solubility ratio	Solvent and temperature
	No C_p terms	With C_p terms		
Apparent enantiotropic systems				
Flufenamic acid form III/I	0.87	0.80	0.96	Diacetone alcohol/water mixture; 30°C
	0.83	0.70	0.92	Diacetone alcohol/water mixture; 10°C
Carbamazepine form III/I (9,10)	0.67	0.78	0.82	2-Propanol; 17°C
	0.73	0.80	0.88	2-Propanol; 40°C
Sulfamerazine form II/I (5,11)	0.85	0.94	0.90	Water; 30°C
Sulfathiazole form α/β (18)	0.46	–	0.54	Water; 30°C
	0.54	–	0.64	Water; 45°C
Mefenamic acid form I/II (16,17)	0.72	–	0.78	Ethyl acetate; 25°C
	0.72	–	0.74	Water; 25°C
Lifibrol form II/I (15)	0.27	–	0.44	Buffer solution; 12°C
Apparent monotropic systems				
Carbamazepine form III/I (10)	0.80	0.72	0.82	2-Propanol; 17°C
	0.87	0.78	0.88	2-Propanol; 40°C
Indomethacin form α/γ (12,13)	1.19	–	1.1–1.2	Water; 45°C
MK571 form II/I (14)	2.61	–	1.9	MEK; 35°C
	2.45	–	2.1	MEK; 45°C

small variation in experimental values might lead to a relatively larger error in the resulting solubility ratio.

For an enantiotropic system, the solid–solid transition may or may not be observed during a routine DSC run. The heating rate can alter the kinetics of these transitions such that they may be inhibited. In such cases the enantiotropic system becomes an "apparent monotropic system." The relative solubility of its polymorphs, therefore, needs to be estimated using the equations derived for monotropic systems. An interesting case is that of carbamazepine, for example (Table I). Depending on the experimental conditions, such as the heating rate chosen for the DSC analysis of the material, the solid–solid transition of carbamazepine can be kinetically inhibited, such that it may or may not be observed. Table I shows the two sets of solubility ratios for carbamazepine calculated using both the monotropic and enantiotropic case equations. The results show that both models can predict the solubility ratio within reasonable margin of error. One may also notice that the enantiotropic systems, in most cases, exhibit smaller estimate solubility ratios than the experimental values. The reason for this trend is discussed in detail in the next sections.

Discussion on Enantiotropic Equations. Unlike solid–liquid transition that always occurs at thermodynamic melting temperature, the solid–solid transition among organic polymorphs is more susceptible to kinetic processes and frequently observed at a temperature higher than the thermodynamic transition temperature. Consider the case where during a DSC run, the solid–solid transition is observed at the temperature T_t' that is greater than the thermodynamic temperature T_t, i.e., $T_t' > T_t$. The solubility ratio of two polymorphs, based on Eq. (8), would be

$$\ln\frac{S_1}{S_2}\bigg|_{T_t'} = -\frac{\Delta H_t'}{RT} + \frac{\Delta S_t'}{R} + \frac{1}{RT}\int_T^{T_t'} (C_{p2}^s - C_{p1}^s)\mathrm{d}T - \frac{1}{R}\int_T^{T_t'} \frac{(C_{p2}^s - C_{p2}^s)}{T}\mathrm{d}T \quad (8^*)$$

The enthalpy and entropy of transition at this temperature, $\Delta H_t'$ and $\Delta S_t'$, are related to their corresponding values at the thermodynamic transition temperature, ΔH_t and ΔS_t, with the following relations:

$$\Delta H_t' = \Delta H_t + \int_{T_t}^{T_t'} \left(C_{p2} - C_{p1}\right)\mathrm{d}T \quad (9)$$

$$\Delta S_t = \Delta S_t + \int_{T_t}^{T_t'} \frac{\left(C_{p2} - C_{p1}\right)}{T}\mathrm{d}T \quad (10)$$

By combining Eqs. (9) and (10) with Eq. (8*), we have

$$\ln\frac{S_1}{S_2}\bigg|_{T_t'} = -\frac{\Delta H_t}{RT} + \frac{\Delta S_t}{R} + \frac{1}{RT}\int_T^{T_t} \left(C_{p2}^s - C_{p2}^s\right)\mathrm{d}T - \frac{1}{R}\int_T^{T_t} \frac{\left(C_{p2}^s - C_{p1}^s\right)}{T}\mathrm{d}T = \ln\frac{S_1}{S_2}\bigg|_{T_t} \quad (11)$$

Equation (11) shows that the model derived for the enantiotropic systems Eq. (8) holds true regardless of the temperature at which the solid–solid transition is observed. However, this expression, when applied at $T_t' > T_t$, becomes practically less applicable. When the polymorphic transition is observed at a temperature higher than the true thermodynamic transition, the true value of entropy of transition, ΔS_t, is not directly measurable by DSC. In these cases, the relationship between the *observed* temperature and heat of transition and the true entropy of transition, is as follows:

$$\Delta S_t > \Delta S_t' = \frac{\Delta H_t'}{T_t'} \quad (12)$$

where the prime-superscripted quantities correspond to the values *observed* from the DSC measurements.

The validity of the relation $\Delta S_t = \Delta H_t'/T_t'$ would dictate a thermodynamically reversible process by which the transition free energy, ΔG_t, is zero. This assumption holds true only if $T_t' = T_t$. When $T_t' > T_t$, $\Delta G_t'$ becomes negative and ΔS_t has to be expressed using the following relation:

$$\Delta S_t = \frac{\Delta H_t' - \Delta G_t'}{T_t'} \quad (13)$$

It is important to clarify at this point that the ratio of solubilities between two enantiotropically related polymorphs is completely unaffected by the temperature at which the solid–solid transition is observed by DSC, even if such transition is not observed at all. The only thing that changes by having $T_t' \neq T_t$ is the error involved in DSC-based solubility *estimates*.

The irreversible transition free energy $\Delta G_t'$ cannot be readily measured from DSC experiments. The best possible estimate, therefore, can only be made by combining Eqs. (8*) and (12), i.e., by assuming a reversible transition. This small conundrum is the direct result from the assumptions regarding the role of heat capacity terms in the estimations of solubility. In short, using the nonequilibrium (i.e., as measured by DSC) heat and temperature of the solid transition to estimate the entropy of the transition involves an error. The correction for this error can be made, exactly, by including the heat capacity terms, but it is well established that for the overall estimation of solubility, the heat capacity terms can be neglected. The question is then how much error is brought about by knowingly applying the experimentally determined (by DSC) heat and temperature of transition into the solubility estimations.

The solubility ratio resulting from this approximation would necessarily be smaller than the true value due to the following relation derived from Eqs. (8*), (12), and (13):

$$\ln\frac{S_1}{S_2}\bigg|_{\mathrm{Est}} = \ln\frac{S_1}{S_2}\bigg|_{\mathrm{True}} + \frac{\Delta G_t'}{RT_t'} \quad (14)$$

where $\ln\frac{S_1}{S_2}|_{\mathrm{Est}}$ and $\ln\frac{S_1}{S_2}|_{\mathrm{True}}$ are the estimated and true solubility ratio of enantiotropic systems, respectively, and the irreversible transition free energy $\Delta G_t'$ is necessarily a negative value. This relation, indeed, agrees with the experimental results. The estimated solubility ratios for enantiotropic systems (Table I), in most cases, are smaller than the experimental values. The magnitude of the difference depends on the degree of deviation of T_t' from T_t and the change of $(S_2 - S_1)$ with temperature. From the experimental result,

it seems that this difference is less than 15% in most cases. The error of this magnitude, for sparingly soluble materials available for this model, will not significantly affect the decision making.

Effect of C_p. Because the accurate measurement of C_p requires additional experimental work, the general assumption is that the effect of C_p is negligibly small and tends to be discarded without generating significant error (6). The same assumption, supported by the fact that the effect of ΔC_p integrals (which appear as pairs with opposite signs), of magnitude significantly smaller than ΔH, was applied in estimating the thermodynamic relationship of the polymorphs (4,5). The experiments show that the estimates, without considering ΔC_p terms, led to a variation of the final solubility ratio by approximately 10%. This suggests that in most cases, the contribution of ΔC_p terms is small enough to be neglected in determining the relative solubility of polymorphs with low solubility.

For enantiotropic systems that do not show the solid–solid transition at the true equilibrium temperature (a very common occurrence), the absolute value of the first ΔC_p term, $\frac{1}{RT}\int_T^{T_t'} (C_{p2}^s - C_{p1}^s)dT$, is necessarily greater than the second ΔC_p term, $\frac{1}{R}\int_T^{T_t'} \frac{(C_{p2}^s - C_{p1}^s)}{T}dT$ Eq. (8*). Burger and Ramberger (7) argued that based on a statistical thermodynamics model, for polymorphs A and B, with A being more stable at 0 K, $(C_{pB} - C_{pA})$ is always positive. In enantiotropic systems, polymorph A is the low-melting form and polymorph B is the high-melting form, so $(C_{p2}^s - C_{p1}^s)$ is in theory always a positive number for enantiotropic systems. Furthermore, for most practical cases, the temperature at which the solubility is estimated, T, is lower than the observed transition temperature, T_t'. Therefore, the estimate of solubility ratios of enantiotropic systems with the full equation Eq. (8) should result in a greater number than the estimate with only the working equation without ΔC_p Eq. (8′). It is, however, important to remember that there are exceptions to the heat capacity rule, as in the case of flufenamic acid or paracetamol (8). The above conclusion applies for most, but not all, enantiotropically related polymorphic forms. Based on these studies, it is recommended that one may correct the solubility ratio of enantiotropic systems estimated from Eq. (8′) by a factor of ~1.1 to reduce the error resulting from the discrepancy between T_t and T_t' and the negligence of ΔC_p terms.

Practical Use of the Model. The practical significance of this model lies in its ability to evaluate the relative solubility of two polymorphic forms of an organic compound within a reasonable degree of accuracy. One may choose from the full equations or simplified working equations depending on the time, sample quantity, and equipment availability. Such a solubility ratio can be quickly estimated by conventional DSC runs, or it can be estimated with increased accuracy through C_p measurements using a modulated DSC. The first step toward the practical use of the model is to identify

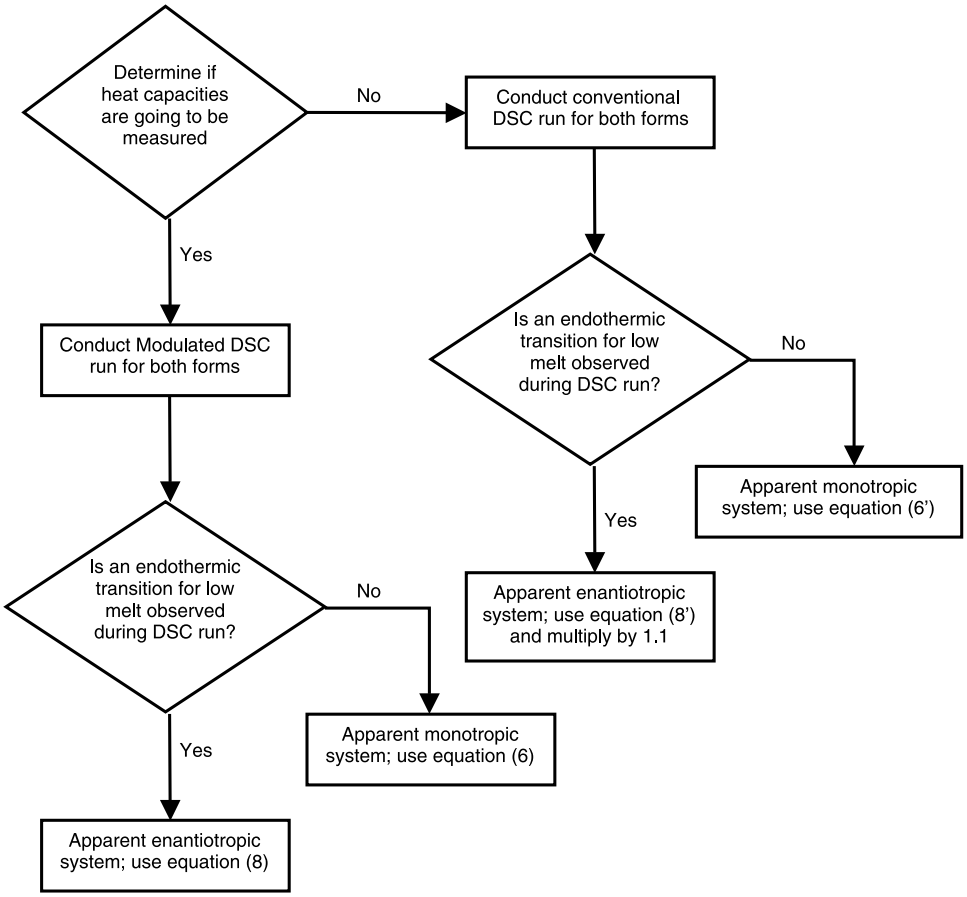

Fig. 2. A decision tree to estimate the solubility ratio of two polymorphic forms using the quantitative model.

Table II. Possible DSC Thermal Observations for Polymorphic Systems and the Corresponding Equations to Apply for Their Solubility Ratio Estimation

Observations				Methodology		
Transition observed?	Melting point	Heat of event[a]	Solubility	Relationship[b]	Transition temperature[a]	Case[b] (use equation)
No	$T_2 > T_1$	$\Delta H_{m2} > \Delta H_{m1}$	$S_1 > S_2$	Monotropic	n.a.	Monotropic [Eq. (6) or (6′)]
Yes	T_1 not seen T_2 seen	$\Delta H_t'$ seen ΔH_{m1} not seen ΔH_{m2} seen	$S_1 > S_2$	Enantiotropic	$T_t \le T_t'$ $T_t < T$	Enantiotropic [Eq. (8) or (8′)]
Yes	T_1 not seen T_2 seen	$\Delta H_t'$ seen ΔH_{m1} not seen ΔH_{m2} seen	$S_2 > S_1$	Enantiotropic	$T_t \le T_t'$ $T < T_t$	Enantiotropic [Eq. (8) or (8′)]
No	$T_2 > T_1$	$\Delta H_{m1} > \Delta H_{m2}$	$S_2 > S_1$	Enantiotropic	$T_t > T$	Monotropic [Eq. (6) or (6′)]
No	$T_2 > T_1$	$\Delta H_{m1} > \Delta H_{m2}$	$S_1 > S_2$	Enantiotropic	$T_t < T$	Monotropic [Eq. (6) or (6′)]

[a] T_t is the true equilibrium transition temperature, whereas T_t' is the temperature at which the solid–solid transition is observed by DSC ($\Delta H_t'$ is the heat of the event observed at T_t').

[b] Relationship above refers to the true thermodynamic relationship between the crystal forms. Case refers to the equations to apply in practice based on the behavior of the materials involved and, consequently, the experimentally available parameters.

whether the systems are apparently monotropic (no solid–solid transition is observed during the DSC run for both forms) or apparently enantiotropic (an endothermic transition is observed for the low-melting form before melting during the DSC run). These two different systems are treated with two different sets of equations for their solubility ratio evaluations. For apparent enantiotropic systems, a correction factor of 1.1 is used if the working equation is chosen for the estimation. The entire process is illustrated in the format of a decision tree as shown in Fig. 2. This factor of 1.1 is by no means universal, but it corresponds to a reasonable correction based on experimental data as well as on published information, which is rather limited. However, one important consideration is that for enantiotropic systems, the amount of heat evolved during the solid–solid transition ($\Delta H_t'$) is not any arbitrary number. The heat evolved is actually fixed, in relation to the true equilibrium value, by the temperature at which the event is observed (T_t').

In summary, a system of polymorphs can be monotropic or enantiotropic. This is an immutable property of the system. In practical terms, however, estimating the solubility of polymorphs depends on what solid state parameters are experimentally accessible in the laboratory. When the solid–solid transition of an enantiotropic system is not observed, the equation for the monotropic system can be applied, simply because of the type of experimental parameters available in such a case. However, this does not mean that enantiotropic systems in which the solid transition is not observed will be the same in all observable ways to monotropic systems. Table II lists the different situations that can be encountered while applying the flow chart of Fig. 2. The left-hand side of the table lists the type of experimental situations that a user could face in the laboratory. The right-hand side of the table shows the underlying relationship and the working expression to apply in each case.

CONCLUSIONS

The solubility relationship of two polymorphic forms may be predicted from their thermal properties. For apparent monotropically related polymorphs, the melting temperature and heat of fusion of two forms are needed to make the estimate, whereas for apparent enantiotropically related forms, only the solid–solid transition temperature and heat of transition are needed. A rigorous model requires the measurement of heat capacity of solids and liquid forms. However, one of the objectives of this work is to link theory with practice, leading to the actual application of the equations in the typical preformulation and early development laboratories. Ignoring heat capacity terms typically leads to an error of only 10% or less. For apparent enantiotropic systems, the deviation of the observed transition temperature from the thermodynamic transition temperature may give rise to some additional error of 15% or less. Therefore, a correction factor of 1.1 is recommended to reduce the error of enantiotropic systems when the working equation is used. Because the observed (nonequilibrium) heat and temperature for solid transition in enantiotropic systems do not vary independently from each other, future studies will be able to show how well a general one-value correction factor works in practice.

ACKNOWLEDGMENTS

The authors would like to thank Dr. Hitoshi Hatakeyama and Dr. Stephan Boerrigter for their valuable discussions. The study is financially supported by The Purdue–Wisconsin–Michigan Program on the Chemical and Physical Stability of Pharmaceutical Solids.

REFERENCES

1. S. R. Byrn, R. R. Pfeiffer, and J. G. Stowell. *Solid-State Chemistry of Drugs*, SSCI Inc., West Lafayette, IN, 1999.
2. A. A. Noyes and W. R. Whitney. The rate of solution of solid substances in their own solutions. *J. Am. Chem. Soc.* **19**:930–934 (1897).
3. T. T. Higuchi and D. J. W. Grant. *Solubility Behavior of Organic Compounds*, John Wiley and Sons, New York, 1990.
4. C.-H. Gu and D. J. W. Grant. Estimating the relative stability of polymorphs and hydrates from heats of solution and solubility data. *J. Pharm. Sci.* **90**:1277–1287 (2001).

5. L. Yu. Inferring thermodynamic stability relationship of polymorphs from melting data. *J. Pharm. Sci.* **84**:966–974 (1995).
6. S. H. Yalkowsky and S. Banerjee. *Aqueous Solubility: Methods of Estimation for Organic Compounds*, Marcel Dekker, New York, 1992.
7. A. Burger and R. Ramberger. On the polymorphism of pharmaceuticals and other molecular crystals. I. *Mikrochim. Acta (Wien)* **2**:259–271 (1979).
8. E. V. Boldyreva, V. A. Drebushchak, I. E. Paukov, Y. K. Kovalevskaya, and T. N. Drebushchak. DSC and adiabatic calorimetry study of the polymorphs of paracetamol, an old problem revisited. *J. Therm. Anal. Calorim.* **77**:607–623 (2004).
9. G. Defossemont, S. L. Randzio, and B. Legendre. Contributions of calorimetry for Cp determination and of scanning transitiometry for the study of polymorphism. *Cryst. Growth Des.* **4**:1169–1174 (2004).
10. R. J. Behme and D. Brooke. Heat of fusion measurement of a low melting polymorph of carbamazepine that undergoes multiple-phase changes during differential scanning calorimetry analysis. *J. Pharm. Sci.* **80**:986–990 (1991).
11. M. R. Caira and R. Mohamed. Positive identification of two orthorhombic polymorphs of sulfamerazine ($C_{11}H_{12}N_4O_2S$), their thermal analyses and structural comparison. *Acta Crystallogr.* **B48**:492–498 (1992).
12. B. Legendre and Y. Feutelais. Polymorphic and thermodynamic study of indomethacin. *J. Therm. Anal. Calorim.* **76**:255–264 (2004).
13. B. C. Hancock and M. Parks. What is the true solubility advantage for amorphous pharmaceuticals? *Pharm. Res.* **17**:397–404 (2000).
14. S. Ghodbane and J. A. McCauley. Study of the polymorphism of 3-(((3-(2-(7-chloro-2-quinolinyl)-(*E*)-ethenyl)phenyl) ((3-(dimethylamino-3-oxopropyl) thio) methyl)-thio) propanoic acid (MK571) by DSC, TG, XRPD and solubility measurements. *Int. J. Pharm.* **59**:281–286 (1990).
15. A. Burger and A. Lettenbichler. Polymorphism and preformulation studies of lifibrol. *Eur. J. Pharm. Biopharm.* **49**:65–72 (2000).
16. A. Burger and R. Ramberger. Thermodynamic relationships between polymorphic modifications—flufenamic acid and mefenamic acid. *Mikrochim. Acta.* **1**:17–28 (1980) (in German).
17. S. Romero, B. Escalera, and P. Bustamante. Solubility behavior of polymorphs I and II of mefenamic acid in solvent mixtures. *Int. J. Pharm.* **178**:193–202 (1999).
18. M. Kanke and K. Sekiguchi. Dissolution behavior of solid drugs II. Determination of the transition temperature of sulfathiazole polymorphs by measuring the initial rates. *Chem. Pharm. Bull.* **21**:878–884 (1973).