

## THERMODYNAMICS AND RELATIVE SOLUBILITY PREDICTION OF POLYMORPHIC SYSTEMS

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### 25.1 INTRODUCTION

Polymorphism of the crystalline state of pharmaceutical compounds is quite a common phenomenon, which has been the subject of intense investigation for more than 40 years [1]. Polymorphs may significantly differ from each other in variety of physical properties such as melting point, enthalpy and entropy of fusion, heat capacity, density, dissolution rate, and intrinsic solubility. These differences are dictated by the differences in the free energies of the forms, which in turn determine their relative stability at specific temperatures. Two polymorphs are monotropically related to each other if their relative stability remains the same up to their melting points. Otherwise, the forms are related to each other enantiotropically and may display a solid–solid transition at a temperature below the melting point. In practice, monotropic and enantiotropic behavior are usually differentiated by several simple rules based on the experimental heats of fusion, entropies of fusion, heat of solid–solid transition, heat capacities, and densities [2, 3].

In the pharmaceutical industry, drug polymorphism can be a critical problem, and is the subject of various regulatory considerations [4, 5]. One of the principal concerns is based on an effect that polymorphism may have on a drug's bioavailability due to change of its solubility and dissolution rate [6]. A famous example of a polymorphism-induced impact is the anti-HIV drug Norvir (also known as

Ritonavir) [7]. Abbot Laboratories had to stop sales of the drug in 1998 due to a failure in a dissolution test, which was caused by the precipitation of a more stable form II [8]. As a result, Abbot lost an estimated \$250 million in the sales of Norvir in 1998 [9, 10].

A large number of studies have been focused on the polymorphism effect on solubility, many of which were summarized by Pudipeddi and Serajuddin [11]. Several-fold solubility decrease was observed for many polymorphic systems. Therefore, in pharmaceutical industry, it is quite crucial to get comprehensive experimental information on the available drug polymorphs and their relative stability and solubility. Beyond that, it is important to be able to perform an estimation of the potential impact of an unknown, more stable form on a drug's solubility. Knowledge of such an impact should be considered in a risk assessment of the API solid form nomination for commercial development.

There have been a number of studies considering the quantitative models to estimate the solubility ratio of two polymorphs based on the thermal properties of both forms [11–15]. One of the major objective of this work is to determine the potential impact of an unknown more stable form on the drug solubility. This is accomplished by reevaluating those models and paying a special attention to errors, which may be introduced by the most common assumptions with the hope of producing a new more accurate model. Such model should satisfy the following two conditions. It should

require a smaller number of input parameters, predominately relying on the thermal properties of only one (the known) form. When applied to a pair of observed polymorphs, the accuracy of the solubility ratio prediction by this equation should be at least as accurate as any currently known model.

## 25.2 METHODS

Methods used in this work are based on a combination of purely theoretical considerations and statistical analysis of available experimental data. A theoretical analysis of all popular approaches for prediction of absolute and relative solubilities of crystalline forms was performed. Special attention was paid to errors that are introduced by each of the approximations. Literature reports were carefully reviewed for solubility and thermal data of the organic crystals, with focus on drug-like molecules. In order to increase the statistical significance of the analysis, a comprehensive compilation was made of available polymorph solubility ratio data. However, only low solubility data (dilute solutions) for nonsolvated polymorphs was considered.

## 25.3 RESULTS AND DISCUSSION

### 25.3.1 Solubility of a Crystalline Form

The solubility,  $X_i$ , of a crystal form  $i$  in a solution can be presented as

$$\ln X_i = \ln\left(\frac{X_i^{id}}{\gamma_i}\right) = -\frac{\Delta G_i}{RT} - \ln \gamma_i \quad (25.1)$$

where  $X_i^{id}$  is an ideal solubility;  $\gamma_i$  is an activity coefficient, which accounts for deviations from the ideal behavior in a mixture of liquid solute and solvent;  $\Delta G_i$  is a free energy difference between the liquid and solid solute at the temperature of interest,  $T$ , and  $R$  is the universal gas constant. In case no additional phase transition takes place in the temperature range between the temperature of interest,  $T$ , and the melting point,  $T_m$ , the  $\Delta G_i$  can be presented as

$$\Delta G_i = \Delta H_{fus} \left(1 - \frac{T}{T_m}\right) + \int_{T_m}^T \Delta C_p dT - T \int_{T_m}^T \frac{\Delta C_p}{T} dT \quad (25.2)$$

Here,  $\Delta H_{fus}$  is the heat of fusion of the polymorph  $i$  at its melting point,  $T_m$ ;  $\Delta C_p$  is a difference between the heat capacities of the liquid and solid states of the form  $i$ , which is always positive. For practical reasons, it is usually assumed that  $\Delta C_p$  is constant and equal to one estimated at the  $T_m$ ,  $\Delta C_{pm}$ . In that case the free energy difference,  $\Delta G_i$ , can be presented as

$$\Delta G_i = \Delta H_{fus} \left(1 - \frac{T}{T_m}\right) - \Delta C_{pm}(T_m - T) + \Delta C_{pm} T \ln \frac{T_m}{T} \quad (25.3)$$

However, as a rule, the  $\Delta C_{pm}$  property is not available and further approximations should be taken. The most popular assumptions which are used in the literature are  $\Delta C_{pm} = 0$  (Assumption A) and  $\Delta C_{pm} = \Delta S_{fus}$  (Assumption B), where  $\Delta S_{fus}$  is entropy of fusion at the melting point,  $\Delta S_{fus} = \Delta H_{fus}/T_m$ . Equation 25.3 is simplified upon these assumptions to equations 25.4 and 25.5, respectively.

$$\Delta G_i = \Delta H_{fus} \left(1 - \frac{T}{T_m}\right) \quad (25.4)$$

$$\Delta G_i = \Delta H_{fus} \frac{T}{T_m} \ln \frac{T_m}{T} = \Delta S_{fus} T \ln \frac{T_m}{T} \quad (25.5)$$

While the first Assumption A is usually justified by negligibly low value of the  $\Delta C_{pm}$  (which is not always true), the latter one (B) is based on the observation by Hildebrand and Scott that  $\ln X_i^{id}$  is linearly related to  $\ln T$  [16].

In order to understand the errors introduced by both assumptions, they were mathematically derived below from equation 25.3 based on a first-order Taylor expansion of  $\ln(T_m/T) \approx ((T_m/T) - 1)$ , which is correct only in case of  $T_m/T$  close to 1 (Table 25.1).

#### Assumption A

Transformation of  $\ln(T_m/T)$  to  $((T_m/T) - 1)$  in the last term of the equation 25.3, results in the complete cancellation of the last two terms of the equation

$$\begin{aligned} \Delta G_i &\approx \Delta H_{fus}(1 - (T/T_m)) - \Delta C_{pm}(T_m - T) \\ &+ \Delta C_{pm}T((T_m/T) - 1) = \Delta H_{fus}(1 - (T/T_m)) \end{aligned}$$

Thus, the applied transformation is equivalent to neglecting the  $\Delta C_{pm}$  term ( $\Delta C_{pm} = 0$ , equation 25.4). Since at  $T < T_m$ ,  $((T_m/T) - 1)$  is always larger than  $\ln(T_m/T)$  (Table 25.1) and  $\Delta C_{pm}$  is always positive, Assumption A leads to the systematic overestimation of the  $\Delta G_i$  resulting into underestimation of the solubility relative to the predictions based on the equation 25.3. The  $\Delta G_i$  error introduced by the Assumption A relative to equation 25.3 is related to the error of the first-order Taylor series expansion and can be presented as

$$\Delta G_{i,error}^A = \Delta C_{pm}T \left\{ \left( \frac{T_m}{T} - 1 \right) - \ln \frac{T_m}{T} \right\} \quad (25.6)$$

This error is proportional to the  $\Delta C_{pm}$  property, and increases with  $T_m/T$  due to an increasing inaccuracy in the first-order Taylor expansion (Table 25.1).

#### Assumption B

In an attempt to counterbalance the error introduced by the direct Taylor expansion transformation used in the

**TABLE 25.1** Relative Errors of the First-Order  $\ln(T_m/T)$  Expansions for Different  $T_m/T$  Values

| $T_m/T^a$     | $\ln(T_m/T)$ | $(T_m/T)-1^b$ | Relative Error (%) <sup>b</sup> | $2((T_m/T)-1)/((T_m/T)+1)^c$ | Relative Error (%) <sup>c</sup> |
|---------------|--------------|---------------|---------------------------------|------------------------------|---------------------------------|
| 1.1 (330/300) | 0.095        | 0.1           | 4.9                             | 0.095                        | -0.1                            |
| 1.2 (360/300) | 0.182        | 0.2           | 9.7                             | 0.182                        | -0.3                            |
| 1.3 (390/300) | 0.262        | 0.3           | 14.3                            | 0.261                        | -0.6                            |
| 1.4 (420/300) | 0.337        | 0.4           | 18.9                            | 0.333                        | -0.9                            |
| 1.5 (450/300) | 0.406        | 0.5           | 23.3                            | 0.400                        | -1.3                            |
| 1.6 (480/300) | 0.470        | 0.6           | 27.7                            | 0.462                        | -1.8                            |

<sup>a</sup> Examples of  $T_m$  and  $T$  values in  $K$  are presented in the parenthesis.  $T$  is chosen to be close to the room temperature.

<sup>b</sup> First-order Taylor series expansion:  $\ln(T_m/T) \approx ((T_m/T)-1)$ .

<sup>c</sup> First-order expansion adopted by Hoffman [22]  $\ln(T_m/T) \approx 2((T_m/T)-1)/((T_m/T)+1)$ . This expansion is significantly more accurate than the first-order Taylor expansion.

Assumption A, one may apply a reverse transformation,  $((T_m/T)-1) \approx \ln(T_m/T)$ , to equation 25.4

$$\begin{aligned}\Delta G_i &= \Delta H_{\text{fus}}(1-(T/T_m)) = \Delta H_{\text{fus}}(T/T_m)((T_m/T)-1) \\ &\approx \Delta H_{\text{fus}}(T/T_m)\ln(T_m/T) = \Delta S_{\text{fus}}T \ln(T_m/T)\end{aligned}$$

The result is equivalent to equation 25.5, which was derived under assumption of  $\Delta C_{pm} = \Delta S_{\text{fus}}$ . Since  $\Delta H_{\text{fus}}$  (and  $\Delta S_{\text{fus}}$ ) is always positive and the error introduced by the reverse transformation is opposite to the one introduced by the direct transformation (Assumption A), a cancellation of errors should take place. The resulting  $\Delta G_i$  error introduced by the Assumption B relative to equation 25.3 is equal to

$$\begin{aligned}\Delta G_{i,\text{error}}^{\text{B}} &= \Delta G_{i,\text{error}}^{\text{A}} + \Delta S_{\text{fus}}T \left\{ \ln \frac{T_m}{T} - \left( \frac{T_m}{T} - 1 \right) \right\} \\ &= (\Delta C_{pm} - \Delta S_{\text{fus}})T \left\{ \left( \frac{T_m}{T} - 1 \right) - \ln \frac{T_m}{T} \right\}\end{aligned}\quad (25.7)$$

It is apparent from this equation that the error will change sign in case of  $\Delta S_{\text{fus}} > \Delta C_{pm}$ , resulting in underestimation of the  $\Delta G_i$  and overestimation of solubility relative to the predictions based on the equation 25.3. In the case where  $\Delta S_{\text{fus}}$  is more than twice as large as  $\Delta C_{pm}$ , an absolute error introduced by Assumption B will exceed the error introduced by Assumption A. This phenomenon may have resulted in contradicting results of the relative accuracy of Assumptions A and B in the literature [17–20]. It was shown recently [21] that a relation between  $\Delta S_{\text{fus}}$  and  $\Delta C_{pm}$  properties is dependent on a chemical class of organic compounds. A ratio of the absolute  $\Delta G_i$  errors introduced by Assumptions B (equation 25.7) and A (equation 25.6),  $\Delta G_{i,\text{error}}^{\text{B}}/\Delta G_{i,\text{error}}^{\text{A}} = (|\Delta C_{pm} - \Delta S_{\text{fus}}|/\Delta C_{pm})$ , is presented for 68 organic compounds in Figure 25.1. Only 12 nondrug-like compounds out of total 68 displayed a relative error of more than 1, indicating that Assumption B introduces a higher absolute error than Assumption A. A majority of these compounds can be characterized by the low value of their differential heat capacities,  $\Delta C_{pm} < 40 \text{ J}/(\text{mol K})$  (Figure 25.1). All of these considerations provide justifica-

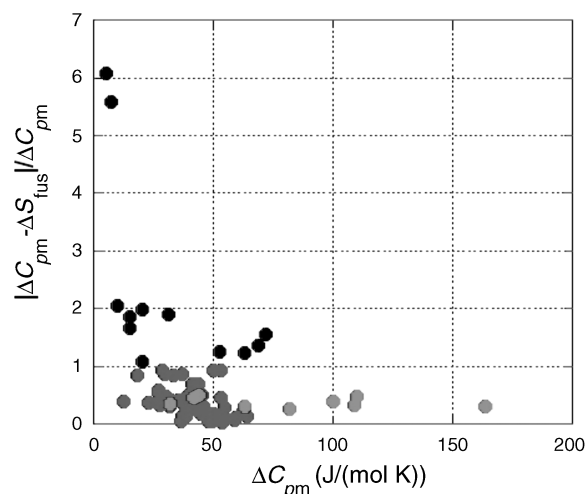
tion for the application of Assumption B over Assumption A for drug-like compounds.

### Assumption C

Another valuable approximation of equation 25.2, was proposed by Hoffman [22] based on a significantly more accurate series expansion of  $\ln(T_m/T)$  than the first-order Taylor expansion applied above (Table 25.1)

$$\Delta G_i = \Delta H_{\text{fus}}(T_m - T) \frac{T}{T_m^2} \quad (25.8)$$

The differential heat capacity,  $\Delta C_p$ , is assumed to be both not negligible and independent of temperature. The lack of significant errors introduced by the  $\ln(T_m/T)$  expansion,



**FIGURE 25.1** A ratio of the absolute  $\Delta G_i$  errors introduced by the Assumptions B and A relative to equation 25.3,  $|\Delta C_{pm} - \Delta S_{\text{fus}}|/\Delta C_{pm}$ , versus differential heat capacity values  $\Delta C_{pm}$  for 68 organic compounds. The closer this ratio is to zero, the lower is the error introduced by the Assumption B relative to equation 25.3. The compounds for which the Assumption B introduces higher absolute error than the Assumption A are highlighted in black. The drug compounds (Paracetamol [20], Anisic acid [20], Diethylstilbestrol [20], Mannitol [20], Naproxen [20], Caffeine I [25], Carbamazepine I [25], Progesterone I [25], Acetamide [27]) are highlighted in light gray. All other data are taken from Pappa et al. [21]

**TABLE 25.2 Absolute Errors of the  $\Delta G_i$  Predictions at the Room Temperature According to the Equation 25.3 and Assumptions A (Equation 25.4), B (Equation 25.5), and C (Equation 25.8) Relative to the Results Obtained Utilizing Temperature-Dependent  $\Delta C_p$  Values (Equation 25.9)<sup>a</sup>**

| Name                      | $T_m$<br>(K) | $\Delta H_{fus}$<br>(kJ/mol) | $\Delta C_{pm}$<br>(J/(mol K)) | $\Delta C_p$ ( $T = 298.2$ K)<br>(J/(mol K)) | Error Relative to Equation<br>25.9 (kJ/mol) |               |               |               |
|---------------------------|--------------|------------------------------|--------------------------------|--|---|---------------|---------------|---------------|
|                           |              |                              |                                |  | Equation 25.3                               | Equation 25.4 | Equation 25.5 | Equation 25.8 |
| Carbamazepine I [25]      | 463.7        | 26.3                         | 109.8                          | 164.6  | 0.7   | 4.4           | 2.5           | 1.0           |
| Carbamazepine III [25]    | 452.4        | 27.2                         | 111.3                          | 184.3  | 1.0   | 4.3           | 2.5           | 1.1           |
| Paracetamol [24]          | 442.2        | 28.1                         | 99.6                           | 165.8  | 0.6   | 3.3           | 1.6           | 0.3           |
| Anisic acid [20]          | 455.4        | 27.8                         | 81.4                           | 150.6  | 0.8   | 3.3           | 1.4           | 0.0           |
| Diethylstilbestrol [20]   | 441.8        | 28.8                         | 43.8                           | 262.3  | 2.0   | 3.2           | 1.5           | 0.2           |
| Mannitol [20]             | 438.7        | 50.6                         | 163.8                          | 290.3  | 1.1   | 5.3           | 2.4           | 0.1           |
| Naproxen [20]             | 428.5        | 31.5                         | 108.6                          | 220.3  | 0.9   | 3.3           | 1.7           | 0.4           |
| MAE <sup>b</sup> (kJ/mol) |              |                              |                                |  | 1.0   | 3.9           | 1.9           | 0.4           |

<sup>a</sup> The  $\Delta A_2$  term (equation 25.9) is different from zero only in the case of carbamazepine.

<sup>b</sup> Mean absolute error is calculated as an arithmetic average of the absolute errors of the predictions performed by the corresponding approach.

and perhaps a more justified approximation for the  $\Delta C_p$ , make Assumption C a generally more thermodynamically sound model than Assumptions A and B. Additionally, equation 25.8 can be seen as equivalent to equation 25.4 (Assumption A) scaled down by a factor of  $T/T_m$ . This effectively introduces a correction for the overestimation of the  $\Delta G_i$  by Assumption A.

### 25.3.2 Comparison of the Assumptions

A rigorous comparison of Assumptions A, B, and C is complicated by the fact that the differential heat capacity in equation 25.2 is temperature dependent, and for the general case increases as temperatures decrease [18, 20, 23]. Even for the cases when the  $\Delta C_p$  at the melting point is known, equation 25.3 might not produce a reliable reference for comparison. An accurate temperature dependence of the heat capacities of both solid and liquid states in a polynomial form,  $C_p = A_0 + A_1T + A_2T^2$ , has limited data available in the literature [20, 24, 25]. Applicability of such a model depends on the reliability of an extrapolation of the observed temperature behavior of the heat capacities above (liquid state) and below (solid state, supercooled liquid)  $T_m$  at the temperature of interest. The difference between the coefficients ( $A_i$ ) of the liquid and solid forms reflects a temperature dependence of the differential heat capacity. In such a case, the free energy difference between the liquid and solid solutes can be presented as

$$\Delta G_i = \Delta H_{fus} \left(1 - \frac{T}{T_m}\right) - \Delta A_0(T_m - T) + \Delta A_0 T \ln \frac{T_m}{T} - \Delta A_1 \frac{(T_m - T)^2}{2} - \Delta A_2 \frac{2T_m^3 + T^3 - 3TT_m^2}{6} \quad (25.9)$$

where  $\Delta A_i = A_i$  (liquid)  $- A_i$  (solid). In Table 25.2,  $\Delta G_i$  predictions at room temperature using equation 25.3 and Assumptions A, B, and C are compared with the results based on equation 25.9. The differential heat capacities of all the compounds increase significantly at room temperature relative to the values at their melting points (Table 25.2). The temperature dependence of the  $\Delta C_p$  leads to a decrease of the predicted  $\Delta G_i$  values at the room temperature relative to the predictions based on the differential heat capacities at  $T_m$  (equation 25.3). A resulting mean absolute error (MAE) of equation 25.3 predictions is 1.0 kJ/mol (Table 25.2). This  $\Delta G_i$  error corresponds to an average underestimation of the ideal solubilities at room temperature by 33%. The MAE values of the  $\Delta G_i$  predictions based on Assumptions A, B, and C for the same compounds relative to results obtained by the equation 25.9 are 3.9, 1.9, and 0.4 kJ/mol, respectively. The corresponding errors of the ideal solubility predictions at the room temperature are 79%, 54%, and 15%, respectively. Thus, the presented results demonstrate that the Hoffman approximation significantly outperforms Assumptions A and B. The largest error of ideal solubility prediction at ambient temperature is made using Assumption A which introduces a large  $\Delta G_i$  error.

### 25.3.3 Application to Polymorphs Solubility Ratio

The solubility ratio of polymorphs can be presented by equation 25.10, and seems to be an optimal test for validation of the different  $\Delta G_i$  models considered in the Section 25.3.1.

$$\frac{X_i}{X_j} = \frac{X_i^{id} \gamma_j}{X_j^{id} \gamma_i} = \frac{\gamma_j}{\gamma_i} \exp\left(-\frac{\Delta G_i - \Delta G_j}{RT}\right) \equiv \frac{\gamma_j}{\gamma_i} \exp\left(-\frac{\Delta \Delta G_{ij}}{RT}\right) \quad (25.10)$$

Recently, evaluations of different models for polymorph solubility ratio prediction based on thermal properties of the polymorphs were reported [11, 12]. Pudipeddi and Serajuddin have found that for 10 polymorphic pairs, predictions based on Assumption C were “slightly closer” to the experimental data than the results obtained by Assumption A [11]. Mao et al. have considered calculations based on the Assumption A [12]. A validation of this approach on nine polymorphic systems led to the conclusion that the utilization of Assumption A typically leads to an error of only 10% or less. An obvious drawback of these two studies is that the very limited datasets of the polymorph pairs were adopted for the testing of only selected assumptions. Therefore, to increase statistical significance of the results, further side-by-side verification of all three assumptions using larger experimental data sets could prove to be very important.

Two different data sets were selected for the models validation in this study, which contains 10 monotropically related (Table 25.3) and 18 enantiotropically related (Table 25.4) pairs of nonsolvated polymorphs. Each data point in these sets contains information on experimental properties such as solubility,  $X_i$ , melting point,  $T_m$ , and heats of fusion,  $\Delta H_{\text{fus}}$ . The following considerations were taken into account during the data selection. There is quite a common misperception that the polymorph solubility ratio is solvent independent. However, according to equation 25.10, this is only true when the activity coefficients for the two polymorphs are identical to each other in any solvent [12, 26]. This takes place in the case of an infinite solubility limit (dilute solution). In such a case, each polymorph in the liquid state is not a significant part of the solvent system in which the actual solubility is measured. Thus, whenever possible, solubility data was chosen for polymorphs approximately tens of milligram per milliliter or less. Moreover, at these low concentrations, there is no need to convert milligram per milliliter or microgram per milliliter units to mol fractions, in which equation 25.10 is presented. One drawback of the selection of very low solubility data is a higher standard deviation of the experimental polymorph solubility ratios (Appendix 25.A).

**25.3.3.1 Monotropic Case** The initial validation of the solubility ratio models was performed using monotropically related polymorphs. In the following discussions, notations 1 and 2 will refer to the higher and lower soluble polymorphs. Equations used for the solubility ratio predictions in this section are explicitly listed in Appendix 25.B. Given that low solubility experimental data was selected for the test, it seems reasonable to expect that cancellation will not only take place between the activity coefficients of both polymorphs in the solution, but also between the errors introduced by the  $\Delta G_i$  assumptions. Results of the relative solubility predictions utilizing Assumptions A, B, and C (Appendix 25.B) for each polymorph are presented in Table 25.3. The corresponding

MAE values relative to the experimental  $X_1/X_2$  observations are 1.01, 0.50, and 0.32, respectively. These observations disagree with previous reports that Assumption A results in an error of only 10% or less [12], and that Assumption C is just slightly closer to the experimental data than the results obtained by Assumption A [11]. The obtained MAE values demonstrate that a complete cancellation of errors does not take place, and, as a result, Assumption C remains significantly more accurate than the others. According to the error analysis presented in the Section 25.3.1 (equations 25.6 and 25.7), the lack of error cancellation in the  $\Delta\Delta G_{12}$  prediction can be accounted for by nonnegligible differences of the  $\Delta C_{pm}$  ( $(\Delta C_{pm} - \Delta S_{\text{fus}})$  in case of the Assumption B) and/or  $T_m$  properties between the two polymorphs. For example, in case of Assumption A, the error of the  $\Delta\Delta G_{12}$  prediction relative to the one based on equation 25.3 can be presented as a difference of  $\Delta G_{i,\text{error}}^A$  errors (equation 25.6) between two polymorphs

$$\Delta\Delta G_{\text{error}} = T \left\{ \Delta C_{pm1} \left[ \left( \frac{T_{m1}}{T} - 1 \right) - \ln \frac{T_{m1}}{T} \right] - \Delta C_{pm2} \left[ \left( \frac{T_{m2}}{T} - 1 \right) - \ln \frac{T_{m2}}{T} \right] \right\} \quad (25.11)$$

The following two limiting cases can be derived from equation 25.11. In the case of relatively insignificant variations of the  $\Delta C_{pm}$  terms, the  $\Delta\Delta G_{\text{error}}$  is proportional to  $T \{ [((T_{m1}/T) - 1) - \ln(T_{m1}/T)] - [((T_{m2}/T) - 1) - \ln(T_{m2}/T)] \}$ . In the case where variations of  $\Delta C_{pm}$  are noticeably more significant than the variations of  $T_m$ , the  $\Delta\Delta G_{\text{error}}$  is proportional to  $(\Delta C_{pm1} - \Delta C_{pm2})$ . The  $\Delta C_{pm}$  values should be replaced by the  $(\Delta C_{pm} - \Delta S_{\text{fus}})$  differences for the error estimation of the  $\Delta\Delta G_{12}$  prediction based on the Assumption B.

It is easy to show from equation 25.10 that for dilute solutions, the difference between the natural logarithms of polymorph solubility ratios as predicted by Assumptions A or B, and equation 25.3, should be proportional to the  $\Delta\Delta G_{\text{error}}$

$$\ln \left( \frac{X_1}{X_2} \right)_{A,B} - \ln \left( \frac{X_1}{X_2} \right)_{\text{equation 25.3}} = - \frac{\Delta\Delta G_{\text{error}}}{RT} \quad (25.12)$$

According to equation 25.11 in case of the Assumption A this difference will be equal to  $\{ \Delta C_{pm2} [((T_{m2}/T) - 1) - \ln(T_{m2}/T)] - \Delta C_{pm1} [((T_{m1}/T) - 1) - \ln(T_{m1}/T)] \} / R$ . It is reasonable to propose that the difference between natural logarithms of polymorph solubility ratios as predicted by Assumptions A or B, and those observed experimentally, may be described by the similar factors as presented in equations 25.11 and 25.12. In the absence of the  $\Delta C_{pm}$  values, a correlation was tested between the  $\ln(X_1/X_2)$

TABLE 25.3 Comparison of the Experimental and Predicted Solubility Ratios for Monotropically Related Polymorphic Pairs

| Compound                                   | $T_{m1}$ (K) | $\Delta H_{fus1}$ (kJ/mol) | $T_{m2}$ (K) | $\Delta H_{fus2}$ (kJ/mol) | $T$ (K) | $S_1/S_{2,exp}$   | Assumption A | Assumption B | Assumption C | Equation 25.13 | Equation 25.14 | Equation 25.15 | Equation 25.16 |
|--|--------------|----------------------------|--------------|----------------------------|---------|-------------------|--------------|--------------|--------------|----------------|----------------|----------------|----------------|
| Chloramphenicol palmitate (A/B) [27, 28]   | 362          | 41.9                       | 368          | 64.1                       | 303     | 4.2               | 5.95         | 4.93         | 4.19         | 5.14           | 4.74           | 4.10           | 3.60           |
| Tolbutamide (I/III) [27, 29]               | 379          | 18.5                       | 400          | 24.5                       | 303     | 1.22              | 2.42         | 2.08         | 1.84         | 1.29           | 1.78           | 1.65           | 1.55           |
| Ritonavir (I/II) [9]                       | 395.2        | 56.4                       | 398.2        | 63.3                       | 298     | 2.39 <sup>a</sup> | 2.29         | 2.01         | 1.80         | 2.17           | 2.02           | 1.83           | 1.69           |
| MK571 (II/I) [30]                          | 425.2        | 49.0                       | 437.2        | 54.0                       | 309     | 1.64              | 2.59         | 2.08         | 1.77         | 1.56           | 1.77           | 1.61           | 1.50           |
| Cyclopenthiiazide (II/I) [31] <sup>b</sup> | 496.2        | 98.42                      | 512.5        | 105.5                      | 310     | 1.78              | 6.32         | 3.40         | 2.30         | 1.72           | 2.96           | 2.31           | 1.93           |
| E2101 (II/I) [32]                          | 413.0        | 35.2                       | 421.3        | 38.2                       | 298     | 1.25              | 1.74         | 1.54         | 1.40         | 1.32           | 1.43           | 1.35           | 1.28           |
| Indomethacine ( $\alpha/\gamma$ ) [15]     | 429.2        | 36.14                      | 435.2        | 36.49                      | 318     | 1.1               | 1.19         | 1.14         | 1.10         | 1.11           | 1.04           | 1.03           | 1.03           |
| Acemetacin (II/I) [3]                      | 423.2        | 48.4                       | 423.7        | 50.7                       | 293     | 1.67              | 1.36         | 1.29         | 1.23         | 1.52           | 1.34           | 1.27           | 1.22           |
| Torasetamide (II/I) [33]                   | 430.2        | 29                         | 434.7        | 37.2                       | 293     | 2.74              | 3.26         | 2.58         | 2.16         | 2.51           | 3.00           | 2.45           | 2.10           |
| Cimetidine (A/B) [34, 35]                  | 413.5        | 44.03                      | 413.7        | 44.08                      | 298     | 1.15              | 1.01         | 1.01         | 1.01         | 1.21           | 1.01           | 1.00           | 1.00           |
| MAE  |              |                            |              |                            |         |                   | 1.01         | 0.50         | 0.32         | 0.19           | 0.38           | 0.27           | 0.33           |

Results of application of the equations 25.14–25.16 adopting  $T_m = T_{m2}$  are presented. The explicit equations for solubility ratio predictions are presented in Appendix 25.B.

<sup>a</sup> Polymorph solubility data in ethyl acetate:heptanes (2:1) mixture is adopted for solubility ratio estimation.

<sup>b</sup> An enantiotropic relationship between forms I and II with a very low transition temperature was proposed in the literature [14].

$-\ln(X_1/X_2)_{\text{exp}}$  predictions based on the different assumptions and  $\{[(T_{m2}/T)-1]-\ln(T_{m2}/T)]-[(T_{m1}/T)-1]-\ln(T_{m1}/T)]\}$  property (Figure 25.2). High linear correlation coefficients,  $R^2$ , of 0.92 and 0.91 were found for the predictions based on Assumptions A and B, respectively (Figure 25.2a and b). This observation suggests a higher and a more systematic contribution to the  $\Delta\Delta G_{\text{error}}$  by the differences in the  $T_m$  values, rather than by the differences in the  $\Delta C_{pm}$  or  $(\Delta C_{pm} - \Delta S_{\text{fus}})$  properties. A noticeably weaker correlation (having an  $R^2$  of 0.72, Figure 25.2c) was observed for the predictions based on Assumption C.

Found simple linear regressions (Figure 25.2) can be used for estimations of likely errors in the solubility ratio predictions of monotropically related polymorphs based on the different assumptions. The MAE values of the prediction (0.24, 0.22, and 0.19, respectively) are based on Assumptions A, C, and B after the errors are corrected by using simple functions of the melting points. The latter result corresponds to the best agreement with the experimental observations using the approaches presented in Table 25.3. This suggests that the polymorph solubility ratio of the monotropically related polymorphs can be best predicted through the following relationship

$$\ln \frac{X_1}{X_2} = \ln \left( \frac{X_1}{X_2} \right)_B + 0.188 - 43.096 \left\{ \left[ \left( \frac{T_{m2}}{T} - 1 \right) - \ln \frac{T_{m2}}{T} \right] - \left[ \left( \frac{T_{m1}}{T} - 1 \right) - \ln \frac{T_{m1}}{T} \right] \right\} \quad (25.13)$$

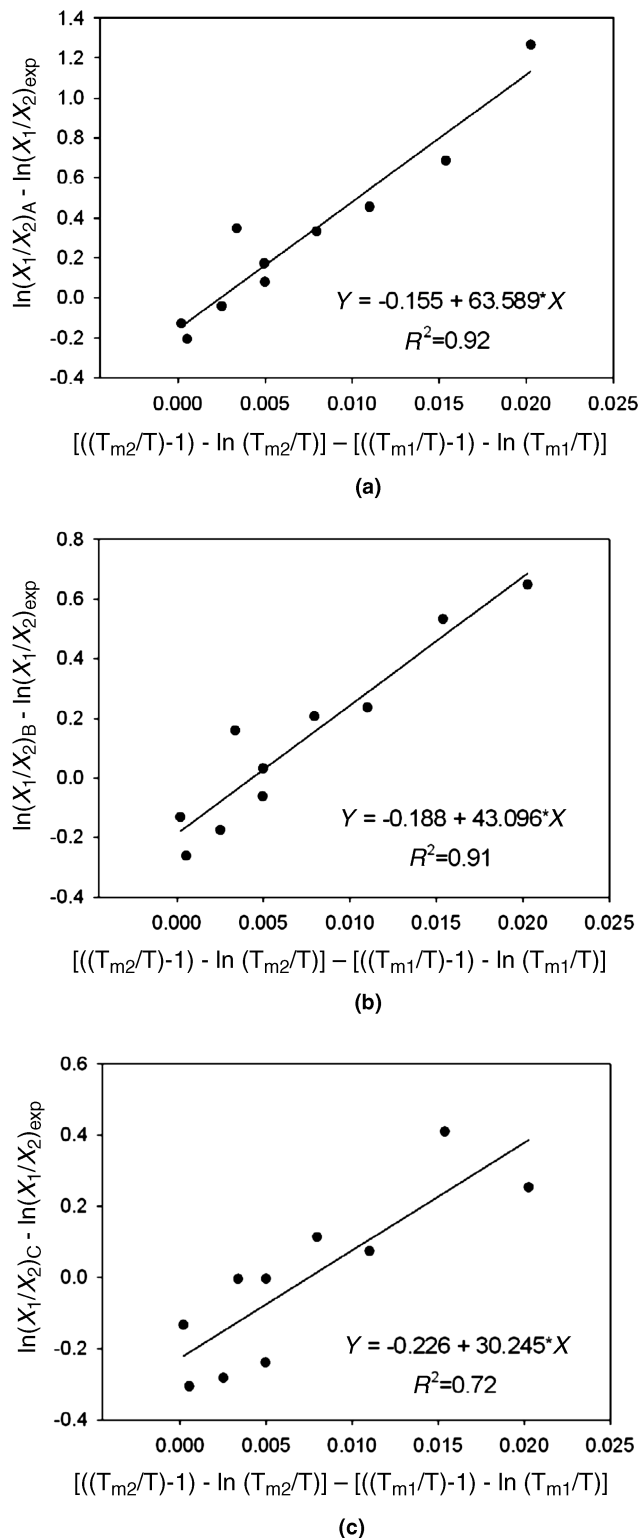
Based on the above observation of the high contribution to the  $\Delta\Delta G_{\text{error}}$  by the differences in the  $T_m$  values, an alternative approach can be suggested. In order to better counterbalance the prediction errors, it was proposed to adopt a single  $T_m$  value for both polymorphs used in the solubility ratio predictions. In this case, an improvement of the predictions should take place through the increase of  $\Delta G_1$  ( $T_m = T_{m2}$ ), or the decrease of  $\Delta G_2$  ( $T_m = T_{m1}$ ). The following simplifications of the  $\Delta\Delta G_{12}$  calculation based on Assumptions A, B, and C are proposed

$$\Delta\Delta G_{12} = (\Delta H_{\text{fus1}} - \Delta H_{\text{fus2}}) \left( 1 - \frac{T}{T_m} \right) \quad (25.14)$$

$$\Delta\Delta G_{12} = (\Delta H_{\text{fus1}} - \Delta H_{\text{fus2}}) \frac{T}{T_m} \ln \frac{T_m}{T} \quad (25.15)$$

$$\Delta\Delta G_{12} = (\Delta H_{\text{fus1}} - \Delta H_{\text{fus2}}) (T_m - T) \frac{T}{T_m^2} \quad (25.16)$$

Besides a possible improvement of the polymorph solubility prediction, the proposed equations more importantly depend on only two input parameters:  $T_m$  of one of the forms,



**FIGURE 25.2** A correlation between the  $\ln(X_1/X_2)_{\text{exp}}$  values based on the Assumptions A (a), B (b), and C (c) and the  $\{[(T_{m2}/T)-1]-\ln(T_{m2}/T)]-[(T_{m1}/T)-1]-\ln(T_{m1}/T)]\}$  property.

and a difference between the enthalpies of fusion of the two polymorphs. This fact makes these equations useful for solving one of the major objective of the current study—the development of a working equation for the estimation of the potential impact of an unknown more stable form on drug solubility.

The application of equations 25.14–25.16 in predicting the solubility ratio of monotropically related polymorphs adopting  $T_m = T_{m2}$  is presented in Table 25.3. Equations 25.14 and 25.15 dramatically improve agreement with the experimental data. The MAE drops from 1.01 to 0.38 for Assumption A using equation 25.14. In the case of Assumption B, the MAE changes from 0.50 to 0.27 using equation 25.15. No improvement was found for Assumption C, in which the MAE value practically does not change when adopting equation 25.16 with a single  $T_m$  value of  $T_{m2}$ . When  $T_m = T_{m1}$ , the MAE values for equations 25.14–25.16 are 0.28, 0.29, and 0.35, respectively. This demonstrates behavior of the  $X_1/X_2$  predictions similar to those found with  $T_m = T_{m2}$ .

**25.3.3.2 Enantiotropic Case** A thermodynamic expression of the solubility ratio of enantiotropically related polymorphs requires knowledge of the temperature and enthalpy of the solid–solid transition [12], which is often difficult to measure accurately. For this reason, only enantiotropic systems with available melting properties for both polymorphs were included in this study. Results of the application of Assumptions A, B, C to the predictions of the solubility ratio of the enantiotropically related polymorphs are presented in the Table 25.4. An overall accuracy of the predictions is noticeably better than it was found for the monotropic system (Table 25.3). As in the monotropic case, the agreement with the experimental data is worse for the calculations based on Assumption A (MAE value is 0.34), relative to those based on Assumptions B and C (MAE values are 0.28 and 0.25, respectively).

No strong correlation was found between the  $\ln(X_1/X_2) - \ln(X_1/X_2)_{\text{exp}}$  values and the  $\{[(T_{m2}/T) - 1] - \ln(T_{m2}/T)\} - [(T_{m1}/T) - 1] - \ln(T_{m1}/T)$  property in case of enantiotropic system based on the different assumptions. Thus, error correction similar to that proposed by equation 25.13 is not applicable to the enantiotropic case. However, an improvement of the predictions based on Assumptions A, B, and C is possible by the application of equations 25.14, 25.15 and 25.16, respectively (Table 25.4). The best performance was found for equations 25.16 and 25.15, both resulting in MAE values of respectively 0.22 and 0.24 (where  $T_m = T_{m2}$  or  $T_{m1}$ ).

It should be noted that equations cannot describe the change of the relative stability of the enantiotropically related polymorphs with temperature. To do so would result in the  $\Delta\Delta G_{12}$  property having the wrong sign above the solid–solid transition,  $T_s$ , ( $\Delta\Delta G_{12}(T_s) = 0$ ). Thus, the application of these

equations to enantiotropic polymorphs is limited to systems with temperatures below  $T_s$ .

From the above considerations which are based on the analysis of the largest reported experimental data set of both monotropic and enantiotropic systems, an application of the original (equation 25.8, Appendix 25.B) and modified (equation 25.16) Hoffman approaches as well as of equation 25.15 are recommended for an accurate solubility ratio prediction for both monotropic and enantiotropic polymorphic systems. Since the latter two approaches utilize the melting temperature measurements of only one form,  $T_{m2}$  or  $T_{m1}$ , they can be used in combination with the statistical analysis of the differences of the heat of fusions of polymorphs, for an estimation of the potential impact of an unknown more stable form on drug solubilities (see Section 25.4 for more details).

#### EXAMPLE 25.1 PREDICTION OF IDEAL SOLUBILITY RATIO BETWEEN FORMS II AND I OF ACETMETACIN AT 293 K BASED ON THE ASSUMPTIONS A, B, AND C AND REGRESSION EQUATION 25.13

The thermal data for both forms of Acemetacin are presented in Table 25.3. Initially  $\Delta G_{II}$  and  $\Delta G_I$  properties should be calculated for each form adopting equations corresponding to Assumptions A (equation 25.4), B (equation 25.5), and C (equation 25.8). The resulting values at 293K are listed in Table 25.5. At the next step, differences between  $\Delta G_{II}$  and  $\Delta G_I$  properties should be calculated to obtain  $\Delta\Delta G$  values. In order to calculate  $\ln(X_{II}^{id}/X_I^{id})$  values, the negative of the  $\Delta\Delta G$  predictions should be divided by  $RT$  factor.  $RT$  at 293K is equal to  $8.314 \times 10^{-3}$  (kJ/(mol K))  $\times$  293 (K) = 2.436 kJ/mol. All the above steps are combined in the explicit equations presented in Table 25.B1 in Appendix 25.B. The  $\ln(X_{II}^{id}/X_I^{id})$  value calculated based on the Assumption B is used in combination with  $\{[(T_{m2}/T) - 1] - \ln(T_{m2}/T)\} - [(T_{m1}/T) - 1] - \ln(T_{m1}/T)$  property for  $\ln(X_{II}^{id}/X_I^{id})$  prediction based on the regression equation 25.13. Results of all the intermediate calculations are summarized in Table 25.5. Finally, exponent of  $\ln(X_{II}^{id}/X_I^{id})$  results gives the polymorphs solubility ratio predictions based on all four methods. For this particular example, the best and the worst agreement with the experimental value of 1.67 is obtained by the equation 25.13 and Assumption C, respectively.

#### 25.4 APPLICATION TO AN ESTIMATION OF LIKELY IMPACT ON DRUG SOLUBILITY BY UNKNOWN MORE STABLE FORM

Below we present two approaches to predict a likely change of drug solubility due to form change. The first thermal data approach is based on a combination of



**TABLE 25.4 Comparison of the Experimental and Predicted Solubility Ratios for Enantiotropically Related Polymorphs**

| Compound                              | $T_{m1}$ (K) | $\Delta H_{fus1}$ (kJ/mol) | $T_{m2}$ (K) | $\Delta H_{fus2}$ (kJ/mol) | $T$ (K) | $S_1/S_{2,exp}$ | Assumption A | Assumption B | Assumption C | Equation 25.14 | Equation 25.15 | Equation 25.16 |
|---------------------------------------|--------------|----------------------------|--------------|----------------------------|---------|-----------------|--------------|--------------|--------------|----------------|----------------|----------------|
| Axinitib (IV/VI) [36–38]              | 491.90       | 47.15                      | 484.80       | 51.79                      | 310     | 1.25            | 1.62         | 1.53         | 1.45         | 1.91           | 1.67           | 1.51           |
| Axinitib (IV/XXV) [36–38]             | 491.90       | 47.15                      | 490.40       | 50.43                      | 310     | 1.25            | 1.54         | 1.42         | 1.33         | 1.60           | 1.45           | 1.34           |
| Paracetamol (II/I) [27, 39]           | 429          | 26.9                       | 442          | 28.1                       | 303     | 1.3             | 1.45         | 1.30         | 1.21         | 1.16           | 1.13           | 1.11           |
| Buspiron-HCl (II/I) [40]              | 476.8        | 42.24                      | 463.0        | 47.45                      | 303     | 1.7             | 1.49         | 1.49         | 1.46         | 2.04           | 1.78           | 1.60           |
| Carbamazepine (I/III) [41]            | 462          | 26.4                       | 448          | 29.3                       | 299     | 1.20            | 1.19         | 1.21         | 1.21         | 1.47           | 1.37           | 1.30           |
| F2692 [27]                            | 453          | 27.17                      | 445          | 29.32                      | 303     | 1.8             | 1.15         | 1.16         | 1.15         | 1.31           | 1.25           | 1.20           |
| Gepirone hydrochloride (II/I) [42]    | 485          | 41.6                       | 453          | 47.1                       | 303     | 2.01            | 0.99         | 1.19         | 1.31         | 2.06           | 1.80           | 1.62           |
| Indiplon [43]                         | 465.51       | 41.63                      | 463.08       | 45.89                      | 298     | 1.1             | 1.74         | 1.58         | 1.46         | 1.85           | 1.63           | 1.48           |
| Nimodipine (I/II) [3]                 | 397.2        | 39                         | 389.2        | 46                         | 298     | 2               | 1.52         | 1.49         | 1.46         | 1.94           | 1.78           | 1.66           |
| Phenylbutazone (II/III) [27]          | 370          | 21.9                       | 368          | 24.4                       | 303     | 1.1             | 1.15         | 1.14         | 1.13         | 1.19           | 1.17           | 1.16           |
| Piroxicam (I/II) [44]                 | 475.8        | 36.54                      | 472.9        | 37.43                      | 310     | 0.99            | 1.06         | 1.07         | 1.06         | 1.13           | 1.10           | 1.08           |
| Propranolol hydrochloride (I/II) [45] | 436.2        | 31.35                      | 435.0        | 36.62                      | 293     | 1.34            | 1.98         | 1.75         | 1.60         | 2.03           | 1.78           | 1.61           |
| Retinoic acid (II/I) [46]             | 456.3        | 36.8                       | 456.9        | 37.1                       | 310     | 1.32            | 1.05         | 1.04         | 1.03         | 1.04           | 1.03           | 1.03           |
| RG12525 (II/I) [47]                   | 431.0        | 43.10                      | 427.8        | 46.86                      | 304     | 1.26            | 1.41         | 1.35         | 1.31         | 1.54           | 1.43           | 1.36           |
| Sulfathiazole (I/III) [27]            | 474.2        | 27.75                      | 446.8        | 29.47                      | 303     | 1.68            | 0.81         | 0.93         | 1.01         | 1.25           | 1.20           | 1.16           |
| WIN63843 (I/III) [48]                 | 337.7        | 28.87                      | 334.4        | 31.88                      | 296     | 1.04            | 1.04         | 1.04         | 1.05         | 1.15           | 1.14           | 1.13           |
| Cimetidine (C/B) [34, 35]             | 417.5        | 43.13                      | 413.7        | 44.08                      | 298     | 1.23            | 0.99         | 1.01         | 1.03         | 1.11           | 1.09           | 1.08           |
| Cimetidine (C/A) [34, 35]             | 417.5        | 43.13                      | 413.5        | 44.03                      | 298     | 1.07            | 0.98         | 1.01         | 1.02         | 1.11           | 1.09           | 1.08           |
| MAE                                   |              |                            |              |                            |         |                 | 0.34         | 0.28         | 0.25         | 0.29           | 0.24           | 0.22           |

 Results of application of the equations 25.14–25.16 adopting  $T_m = T_{m2}$  are presented. The explicit equations for solubility ratio predictions are presented in Appendix 25.B.

**TABLE 25.5 Prediction of Ideal Solubility Ratio Between Forms II and I of Acemetacin at 293K Based on the Assumptions A, B, C and the Regression Equation 25.13**

| Approach       | $\Delta G_{II}$<br>(kJ/mol) | $\Delta G_I$<br>(kJ/mol) | $\Delta\Delta G$<br>(kJ/mol) | $\frac{\{[(T_{mI}/T)-1]-\ln(T_{mI}/T)\}}{-\{[(T_{mII}/T)-1]-\ln(T_{mII}/T)\}}$ | $\ln(X_{II}^{id}/X_I^{id})$ | $X_{II}^{id}/X_I^{id}$ |
|----------------|-----------------------------|--------------------------|------------------------------|--|-----------------------------|------------------------|
| Assumption A   | 14.891                      | 15.640                   | -0.749                       |  | 0.308                       | 1.36                   |
| Assumption B   | 12.321                      | 12.932                   | -0.612                       |  | 0.251                       | 1.29                   |
| Assumption C   | 10.309                      | 10.815                   | -0.506                       |  | 0.208                       | 1.23                   |
| Equation 25.13 |                             |                          |                              | 5.257E-04  | 0.416                       | 1.52                   |

statistical analysis of the experimental heat of fusion differences between polymorphic pairs and the one proposed in the current work equation 25.16 for the ideal solubility ratio prediction. The second, solubility ratio approach is based on statistical results from experimental solubility ratio observations.

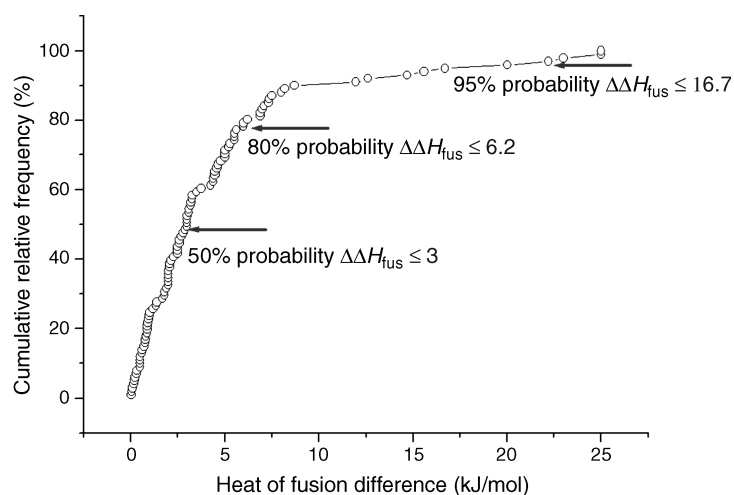
#### 25.4.1 Thermal Data Approach

This approach is based on application of the modified Hoffman equation 25.16 coupled with statistical analysis of experimentally determined heat of fusion differences between polymorphs. The ideal solubility ratio predictions can be carried out for a known form with available melting temperature and likely changes in heat of fusion,  $\Delta\Delta H_{fus}$ . In order to do that, a survey of thermal data for 101 polymorphic pairs was carried out, where most of the data were found in one literature source [27] and the rest were taken from the Tables 25.3 and 25.4 of the current study. Trends in heat of fusion changes between polymorphs were presented in the form of the cumulative relative frequency distribution in Figure 25.3. The cumulative relative frequency distribution is particularly useful for describing the likelihood that a

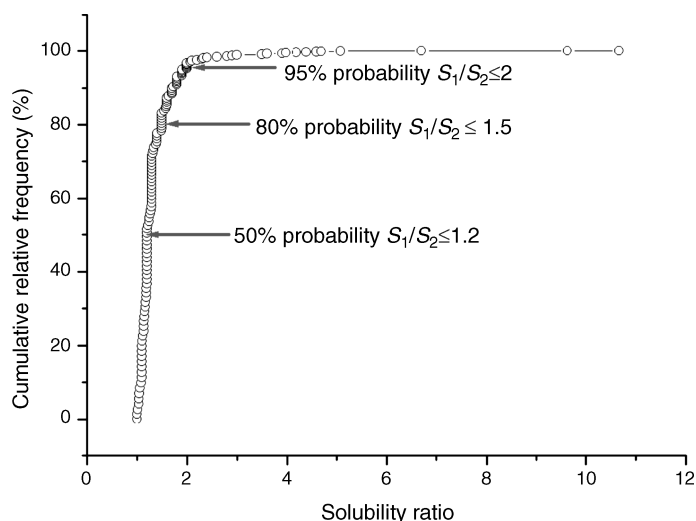
variable (heat of fusion difference) will not exceed a certain value. It was found that there is a 50% probability that the change in heat of fusion for a polymorphic pair is less or equal to 3.0 kJ/mol (Figure 25.3). The probability of heat of fusion difference between a pair of polymorphs not exceeding values of 6.2 kJ/mol and 16.7 kJ/mol is respectively 80% and 95%. Combining these  $\Delta\Delta H_{fus}$  values with equation 25.16 allows estimation at the different probability levels of maximum impact on ideal solubility by a new more stable polymorph. Although the thermal data approach relies on the statistical analysis (of  $\Delta\Delta H_{fus}$ ), it introduces some degree of dependence on the thermal properties ( $T_m$ ) of the reference form through equation 25.16. Therefore, predictions based on this method are form-specific.

#### 25.4.2 Solubility Ratio Approach

An alternative approach is based on the statistical analysis of the polymorph solubility ratio observations. A survey of solubility changes for 153 polymorphic pairs was carried out, where most of data were found in open literature sources [11], and some were extracted from in-house Pfizer data or provided by company associated institutions. A



**FIGURE 25.3** Cumulative relative frequency distribution of experimental differences of heats of fusion,  $\Delta\Delta H_{fus}$ , for 101 polymorphic pairs. Data points corresponding to 50%, 80%, and 95% probabilities of  $\Delta\Delta H_{fus}$  is not exceeding a certain threshold are indicated by arrows.



**FIGURE 25.4** Cumulative relative frequency distribution of experimental solubility ratios,  $X_1/X_2$ , for 153 polymorphic pairs. Data points corresponding to 50%, 80%, and 95% probabilities of solubility ratio is not exceeding a certain threshold are indicated by arrows.

statistical analysis of the experimental data was performed on the basis of cumulative relative frequency distribution, presented in Figure 25.4. It was found that there is a 50% probability that the change in solubility is less than 1.2-fold for a polymorphic switch (Figure 25.3). The probability of the solubility ratio between a pair of polymorphs not exceeding value of 1.5 is 80%. It was also shown that only in 5% of the studied cases the change in solubility for polymorphic pairs would be more than twofold (Figure 25.4).

The presented trend of probabilities of the relative solubility changes is purely statistical and does not provide any direct dependence on thermal data of the current form. Therefore, this approach may be considered as form non-specific one. In addition, majority of the solubility ratio measurements are performed at different temperatures in the range of 20–40°C [11], rather than at the room temperature, which may introduce some level of noise in the predictions based on this method.

### EXAMPLE 25.2 ESTIMATION OF A LIKELY IMPACT ON SOLUBILITY BY A NEW FORM OF RITONAVIR

Analysis of a possible impact on solubility by a new form should be defined by a selected probability limit of the  $X_1/X_2$  (the solubility ratio approach) and  $\Delta\Delta H_{\text{fus}}$  (the thermal data approach) changes. In this example, the 80% probability was selected to provide a reasonably high level of confidence of predictions by both methods. In case more than one polymorphic form exists, a probability of further increase of the polymorphs solubility ratio as well as of the  $\Delta\Delta H_{\text{fus}}$  should be estimated relative to the least stable form. In case of Rito-

navir, the most unstable and soluble form is I. The 80% probability of heat of fusion increase according to the thermal data approach is not exceeding 6.2 kJ/mol (Figure 25.3). This  $\Delta\Delta H_{\text{fus}}$  value together with the melting point of form I,  $T_{\text{mI}} = 395.2\text{K}$  (Table 25.3), are used to predict a likely change of solubility of form I at the room temperature by equation 25.16. The estimated impact is not exceeding 1.59-fold. The 80% probability of the change in solubility between two polymorphs according to the solubility ratio approach is less or equal to 1.5-fold. The two methods provide similar estimated change of the ideal solubility with respect to the least stable form for a probability level of 80%. It is known that a more stable form II was discovered later for Ritonavir. The observed heat of fusion difference and solubility ratio between forms II and I are respectively 6.9 kJ/mol and 2.39 (Table 25.3). These values correspond to respectively 82% and 98% probability limits of the  $\Delta\Delta H_{\text{fus}}$  and  $X_1/X_2$  changes, and exceed the thresholds predicted within the probability limit of 80%. Therefore, both approaches suggest a quite low probability of further impact on solubility by a hypothetical new stable form.

### 25.4.3 Qualification/Quantification of Impact of Likely Form Change on Drug Absorption

A significant solubility difference between two polymorphs can result in difference in oral absorption and may affect bioavailability [49]. Orally administrated immediate-release drug products are categorized in the Biopharmaceutics Classification System (BCS) according to their aqueous solubility and permeability [50]. These properties together with dissolution rate control drug absorption. Absolute bioavailability of a drug is also affected by first-pass intestinal and

hepatic metabolism [51]. It is reasonable to assume that polymorphic forms of a particular compound should display similar permeabilities and first-pass clearances. Therefore, the differences in fraction absorbed and absolute bioavailability between oral products (based on different polymorphs) is controlled by solubility and dissolution rate. This assumes that the polymorphs interaction with excipients is negligible. While the dissolution rate can be generally controlled by changing the particle size, a thermodynamic aqueous solubility is a fundamental property of the polymorphic form which cannot be modified.

The classification of drug form solubility is based on dimensionless dose number  $D_0$ , which is a function of maximum dose strength  $D$  (mg) and solubility,  $S$  (mg/mL)

$$D_0 = \frac{D}{V_0 S}. \quad (25.17)$$

Here,  $V_0$  is volume of water taken with the dose which is generally set to 250 mL. Solid forms of drugs with  $D_0$  equal or less than 1 are considered being highly soluble [52]. According to the BCS system such forms are characterized as Classes I and III. An estimation of a likely change in solubility due to transformation to a new more stable form allows prediction of the potential impact on  $D_0$  that a new form could present. The potential risk associated with the late discovery of a new stable form can be accessed based on a degree of probability of solubility (and  $D_0$ ) change, as discussed above, and projected change of drug absorption. A qualitative analysis of the impact of form change on absorption can be based on the BCS system; here, we classify risk as associated with a potential change of the drug class from I to II or from III to IV. In addition, computational simulations (e.g., GastroPlus, Simulationsplus, Inc., Lancaster, CA) may be adopted for a (semi) quantitative analysis of sensitivity of drug absorption to a potential form change.

## 25.5 CONCLUSION

One of the main purposes of this study is to develop valid methods for the estimation of a potential impact of an unknown more stable form on drug solubility. This information has a crucial practical application in the pharmaceutical industry by supporting the risk assessment of an API solid form selection for commercial development of an oral drug. Two independent approaches to predict a likely change of drug solubility due to the form change were suggested in the current study. One of them is based on the modified Hoffman equation 25.16, which was found through a consistent theoretical consideration of the errors introduced by the different popular assumptions used for absolute and relative polymorph solubility predictions.

In addition, the first side-by-side validation of all three popular assumptions for the relative polymorph solubility

prediction was performed on the largest up-to-date experimental dataset. It was demonstrated that Assumption A ( $\Delta C_{pm} = 0$ ) results in noticeable errors which significantly exceed the previously reported values of 10% or less [12]. Based on the current study, this assumption is not recommended for the polymorph solubility ratio prediction of drug-like molecules, especially in case of the monotropically related systems. The superiority of Assumption C (Hoffman equation) over the other assumptions, and in particular over Assumption A was found to be much stronger than was previously reported [11]. Assumption B ( $\Delta C_{pm} = \Delta S_{fus}$ ) demonstrated an intermediate performance between Assumptions A and C.

Finally, based on the error analysis, a new model, equation 25.13, was proposed for the solubility ratio prediction of the monotropically related polymorphs. This model provided the best agreement with the experimental dataset of 10 polymorphic pairs.

## 25.A APPENDIX

### 25.A.1 Propagation of Errors of the Solubility Ratio Measurements

Assuming independence of the solubility measurements of two polymorphs,  $X_1$  and  $X_2$ , the standard deviation of the solubility ratio,  $k = X_1/X_2$ , can be expressed as [53]

$$\sigma(k) = \left[ \left( \sigma(X_1) \frac{\partial k}{\partial X_1} \right)^2 + \left( \sigma(X_2) \frac{\partial k}{\partial X_2} \right)^2 \right]^{1/2} \quad (25.A.1)$$

In case of  $\sigma(X_1) \approx \sigma(X_2) = \sigma(X)$ , the following resulting equation can be obtained

$$\sigma(k) = \left[ \left( \frac{\sigma(X)}{X_2} \right)^2 + \left( \frac{k\sigma(X)}{X_2} \right)^2 \right]^{1/2} = \frac{\sigma(X)}{X_2} (1 + k^2)^{1/2} \quad (25.A.2)$$

Equation (25.A.2) demonstrates that the error of the solubility ratio measurements increases with increase of the  $k$  value, and with decrease of the polymorph solubility,  $X_2$ . For example, for the solubility  $X_2$  of 0.2  $\mu\text{g/mL}$ ,  $\sigma(X)$  equal to 0.02  $\mu\text{g/mL}$ , and  $k$  value of 2, the  $\sigma(k)$  is equal to 0.22.

## 25.B APPENDIX

### 25.8 ACKNOWLEDGMENTS

The authors would like to thank Mr. Brian Samas, Dr. Neil Feeder, Dr. Paul Meenan, Dr. Robert Docherty, and Dr. Bruno Hancock for the valuable comments and discussions. The authors also wish to thank Mr. Anthony M. Campeta for providing the experimental thermal and solubility data on the

TABLE 25.B1 Explicit Equations Used for Predictions of Polymorphs Solubility Ratio

| Based on       | Equation   | Comments                       |
|----------------|--|--------------------------------|
| Assumption A   | $\ln \frac{X_1}{X_2} = \frac{\Delta H_{\text{fus}2} \left(1 - \frac{T}{T_{m2}}\right) - \Delta H_{\text{fus}1} \left(1 - \frac{T}{T_{m1}}\right)}{RT}$   |                                |
| Assumption B   | $\ln \frac{X_1}{X_2} = \frac{\Delta H_{\text{fus}2} \frac{T}{T_{m2}} \ln \frac{T_{m2}}{T} - \Delta H_{\text{fus}1} \frac{T}{T_{m1}} \ln \frac{T_{m1}}{T}}{RT}$   |                                |
| Assumption C   | $\ln \frac{X_1}{X_2} = \frac{\Delta H_{\text{fus}2} (T_{m2} - T) \frac{T}{T_{m2}^2} - \Delta H_{\text{fus}1} (T_{m1} - T) \frac{T}{T_{m1}^2}}{RT}$   |                                |
| Equation 25.13 | $\ln \frac{X_1}{X_2} = \ln \left( \frac{X_1}{X_2} \right)_B + 0.188 - 43.096 \left\{ \left[ \left( \frac{T_{m2}}{T} - 1 \right) - \ln \frac{T_{m2}}{T} \right] - \left[ \left( \frac{T_{m1}}{T} - 1 \right) - \ln \frac{T_{m1}}{T} \right] \right\}$ | Only for the monotropic system |
| Equation 25.14 | $\ln \frac{X_1}{X_2} = \frac{(\Delta H_{\text{fus}2} - \Delta H_{\text{fus}1}) \left(1 - \frac{T}{T_m}\right)}{RT}$  | $T_m = T_{m2}$ or $T_{m1}$     |
| Equation 25.15 | $\ln \frac{X_1}{X_2} = \frac{(\Delta H_{\text{fus}2} - \Delta H_{\text{fus}1}) \frac{T}{T_m} \ln \frac{T_m}{T}}{RT}$   | $T_m = T_{m2}$ or $T_{m1}$     |
| Equation 25.16 | $\ln \frac{X_1}{X_2} = \frac{(\Delta H_{\text{fus}2} - \Delta H_{\text{fus}1}) (T_m - T) \frac{T}{T_m^2}}{RT}$   | $T_m = T_{m2}$ or $T_{m1}$     |

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