Differential Scanning Calorimetry Data and Solubility Profiles

Background

Organic compounds frequently exist in multiple **polymorphic forms**, each exhibiting distinct physical properties such as solubility, melting point, or heat of fusion. Polymorphism plays a significant role in pharmaceutical development, particularly for poorly soluble drugs.

The following well-known thermodynamic equation relates **solubility (X)** to **heat of fusion (ΔHf)**, **melting point (Tm)**, and **heat capacity change (ΔCp)** [1]:

$$\log X = -\frac{\Delta H_f}{2.303R}\left(\frac{1}{T} - \frac{1}{T_m}\right) + \frac{\Delta C_p}{2.303R}\left[\left(1 - \frac{T_m}{T}\right) - \ln\left(\frac{T_m}{T}\right)\right]$$

By applying this equation to two **anhydrous polymorphs of carbamazepine (Forms I and III)**, and solving the equations simultaneously, one can derive the **ratio of their solubilities**. This theoretical approach, when combined with experimental **calorimetric data**, yields a calculated **transition temperature** that agrees closely—within 2°C—with the value estimated from **experimental solubility data** [2].

Experimental Thermodynamic Parameters

Forms I and III of carbamazepine show a melting point difference of 15°C:

- **Form I**: Melts at 189°C with ΔHf = 26 kJ/mol
- **Form III**: Melts at 174°C with ΔHf = 29 kJ/mol

These values were used to calculate the **solubility ratio profile**, as shown in **Figure 1 (closed circles)**. Theoretical curves in the same figure demonstrate the impact of varying the ΔHf difference (4.5, 6.0, 7.5, and 9.0 kJ/mol) between the two forms.

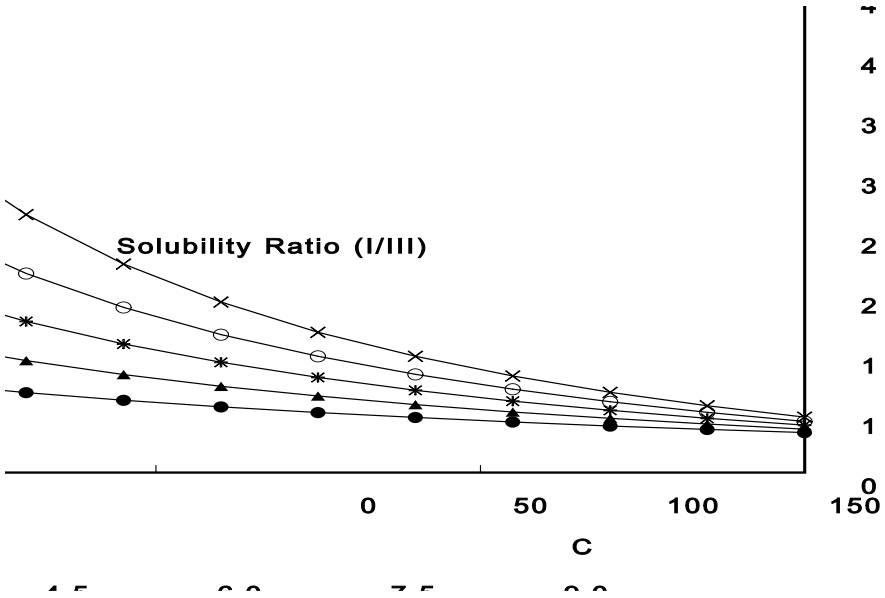

Figure 1

These simulations show that **even if the ΔHf difference had been as high as 9.0 kJ/mol**, Form I would have been only about **three times more soluble** than Form III at room temperature—demonstrating the **modest influence of heat of fusion differences** on solubility ratio.

Effect of Melting Point Differences on Solubility

To further evaluate the influence of melting point, the **actual ΔHf values** of the two polymorphs were held constant, while the **melting point difference** was varied across a broad range—up to 37.5°C.

As shown in **Figure 2**, these simulations again indicate a **modest effect**: even with large melting point differences, Form I would have been **less than twice as soluble** as Form III.

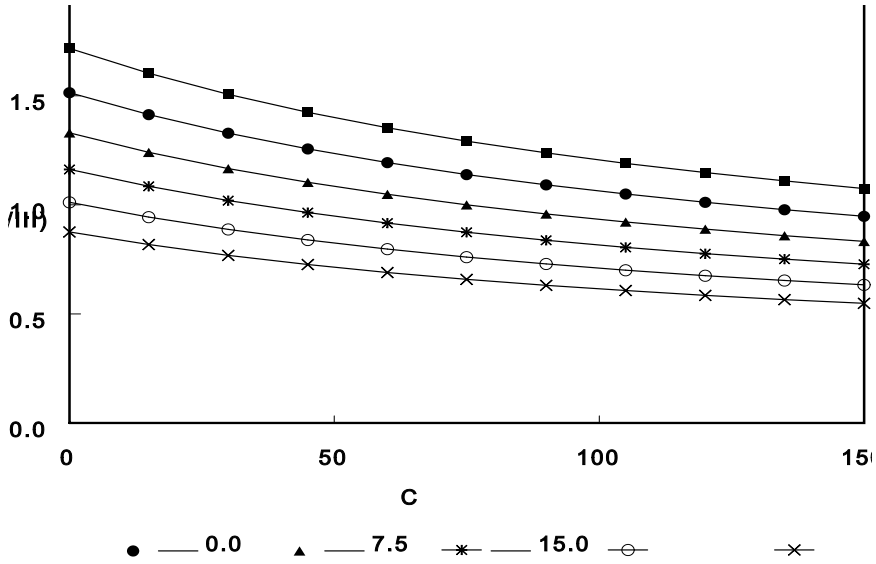

Figure 2

Discussion and Implications

The theoretical treatment supports a key observation from previous experimental studies: **polymorphs rarely show dramatically different solubilities** [2]. This finding has practical consequences for **pharmaceutical formulation**:

- For **highly soluble polymorphs**, minor solubility differences may not impact product performance.
- However, for **poorly soluble drugs**, even small solubility variations can affect **bioavailability**, absorption, or dosage form performance.
- Additionally, **non-solubility properties** such as **density, compressibility, or crystal shape** may affect manufacturability and necessitate strict **polymorphic control** during formulation development.

Accurate detection of melting points and heats of fusion is critical to these analyses. The **DSC 600 by AMI** offers high-resolution thermal detection, exceptional baseline stability, and precise integration tools for quantifying enthalpic transitions—making it ideal for evaluating polymorphic behavior and supporting solubility modeling in early formulation work.

References

[1] David J. W. Grant and Takeru Higuchi in *Techniques of Chemistry*, Volume XXI, *Solubility Behavior of Organic Compounds*; J. Wiley & Sons: New York, 1990.

[2] Behme, R. J.; Brooke, D. *J. Pharm. Sci.* **1991**, *80*, 986–990.