Applications of Differential Scanning Calorimetry (DSC): Solubility Profiles for Polymorphic Drug Analysis

1. Background

Organic compounds frequently exist in multiple types of crystalline structures, or **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 (ΔH_f), melting point (T_m), and heat capacity change (ΔC_p):[1]

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

By applying this equation to two anhydrous polymorphs of **carbamazepine** (molecular structure shown in Figure 1) 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]

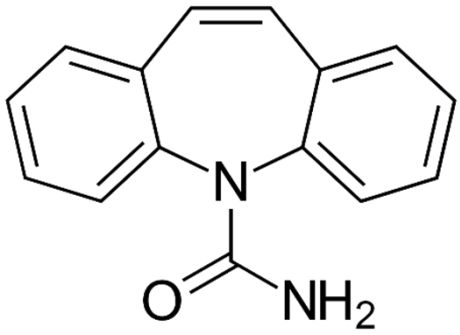

Figure 1: Chemical structure of carbamazepine

2. Experiment

Forms I and III of carbamazepine have different chemical and physical properties, including a melting point difference of 15°C:

- ✓ Form I: Metastable, melts at 189°C with ΔH_f = +26 kJ/mol
- ✓ Form III: Thermodynamically stable, melts at 174°C with ΔH_f = +29 kJ/mol

These values were used to calculate the solubility ratio profile, as shown in Figure 2 (closed circles, ΔH_f = 3.0 kJ/mol). Theoretical curves in the same figure demonstrate the impact of varying the ΔH_f difference (4.5, 6.0, 7.5, and 9.0 kJ/mol) between the two forms.

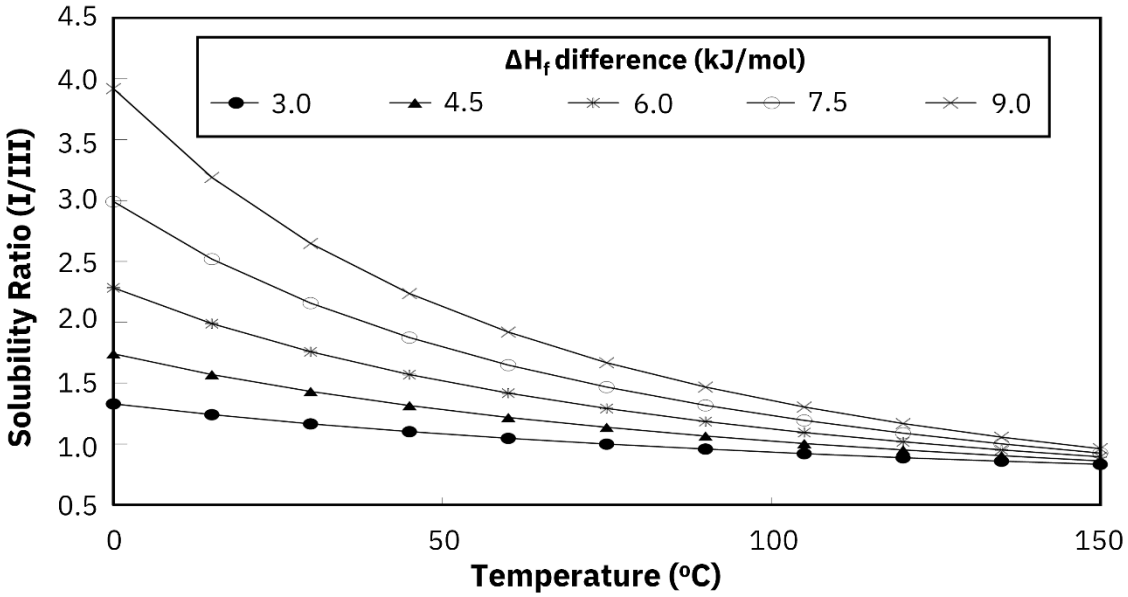

Figure 2: Theoretical solubility ratio profile for Forms I and III of carbamazepine at increasing temperatures (up to 150 °C) and increasing theoretical ΔH_f differences (3.0 – 9.0 kJ/mol).

3. Results

The simulations in Figure 2 show that even if the ΔH_f difference was 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.
To further evaluate the influence of melting point, the actual ΔH_f 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 3, 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.

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.

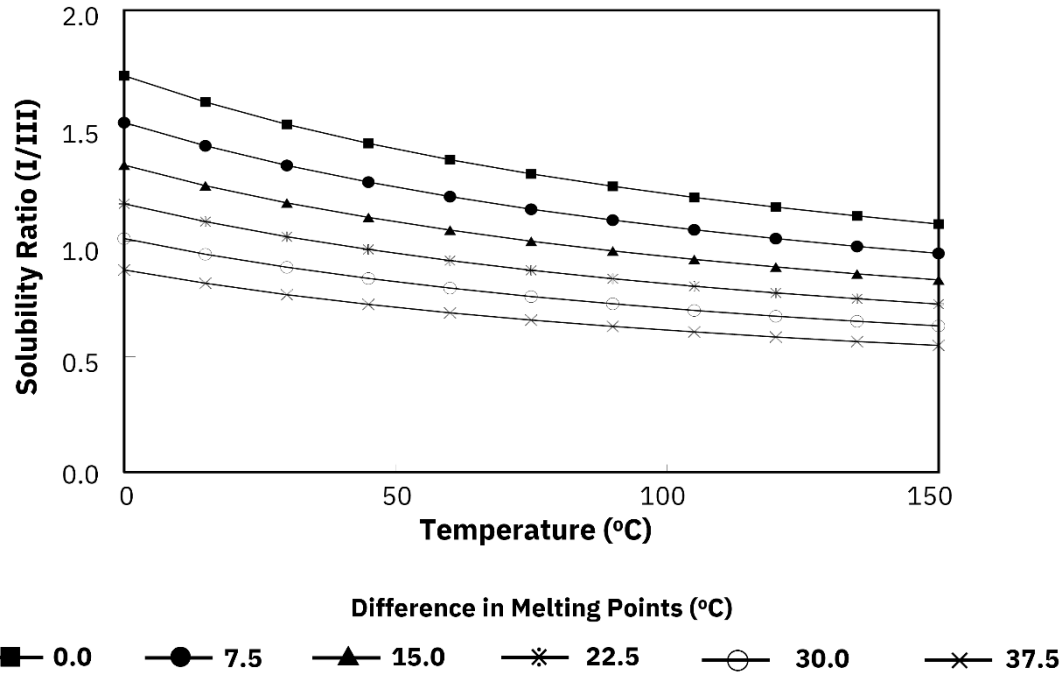

Figure 3: Theoretical solubility ratio profile for Forms I and III of carbamazepine at increasing temperatures (up to 150 °C) and increasing differences in melting points (0.0 – 37.5).

4. Conclusions

Accurate detection of melting point and heat of fusion is critical to these analyses, and **differential scanning calorimetry (DSC)** provides highly sensitive analysis of crystalline phase transitions. DSC experiments can identify unique melting points and enthalpy changes in drug compounds, helping with purity analysis, solubility control, and other pharmaceutical applications.

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.

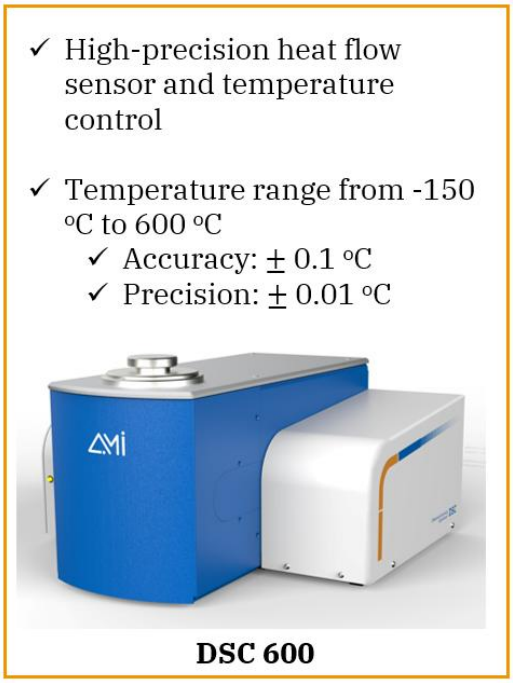

*Figure 4: Highlighted features of **DSC 600***

5. References

(1) Grant, D. J. W.; Higuchi, T. *Solubility behavior of organic compounds*. Techniques of Chemistry, Vol. 21; Wiley, 1990.
(2) Behme, R. J.; Brooke, D. Heat of fusion measurement of a low melting polymorph of carbamazepine that undergoes multiple-phase changes during differential scanning calorimetry analysis. *J. Pharm. Sci.* **1991**, *80*, 986–990.