# Characterization of Solid State Drugs by Calorimetry

Christin T. Choma
TA Instruments, 109 Lukens Drive, New Castle, DE 19720, USA

Drug product development and manufacture requires numerous studies to ensure that the purity, quality, stability and safety of the product are characterized and well understood. A large percentage of drugs are formulated as solids. Since a given pharmaceutical chemical entity can often exist in more than one thermodynamically or kinetically stable crystal form, and often can also exist as a glass (amorphous state), it is important to characterize the properties of the crystalline and amorphous states and the factors affecting their interconversion. The ability of a compound to exist in these different solid state forms is known as polymorphism.

A pharmaceutical compound may also exist in the form of a solvate such as a hydrate, in which water is incorporated into the solid form. These forms are generally called pseudo-polymorphs. Depending on how a drug is manufactured and/or formulated, one or a mixture of polymorph and pseudo-polymorph forms can be present in the final product.

The study of polymorphism and pseudo-polymorphism is a critical part of the drug development process because pharmaceutical properties can be impacted depending on which forms exist in the final product. For example, since polymorphs are in different energy states (including metastable forms), solubility can be affected, which in turn can impact bioavailability. Interconversion from a more soluble to a less soluble form may occur during manufacture of the pure drug, during formulation processes, and after long-term storage, thereby changing the pharmaceutically-active properties of the final product.

Different polymorphs have different chemical stabilities, with the amorphous phase being particularly unstable compared to the crystalline forms. Metastable crystalline or amorphous forms can reduce the expected chemical stability (shelf life) of the active pharmaceutical ingredient, and affect final particle size, formation of unwanted solvates during drying, flow characteristics, compressibility, etc.

Calorimetry and thermal analysis are powerful tools for characterizing solid state pharmaceutical systems (Giron, 1995; Giron, 1999; Phipps and Mackin, 2000; Gainsford and Buckton, 2001). Thermo-gravimetric analysis (TGA), thermomicroscopy, differential scanning calorimetry (DSC) and isothermal calorimetry have all been used extensively to quantify the thermodynamic and kinetic properties of polymorphic systems. Example applications of calorimetry for studying polymorphs are described in this note, and serve to illustrate the principles involved in applying this technique to the characterization of pharmaceutical solid formulations.

## CRYSTALLINE POLYMORPHS

Depending on how a given compound was manufactured, one or several crystalline polymorphic states may coexist, so determining the thermodynamic relationship between the forms is important for characterizing the solid active drug. Although the goal is general-

ly to have a single form present in the final formulated product, it is not always the most stable state that is desired. For example, a higher energy form may be more desirable if enhanced solubility is required. However, if chemical stability is the overriding issue, using the lowest energy form of the compound may be the best alternative.

Two major types of transitions are possible between crystalline polymorphs. When the transition between two polymorphic forms is reversible, the two polymorphs are enantiotrops and the transition is enantiotropic. When this sample is heated, the energy of the transition is endothermic. However, when the phase transition is irreversible, the two forms are monotrops and the transition is monotropic and exothermic.

Figure 1 shows an example phase diagram associated with two enantiotropic polymorphs. The solid curved lines represent equilibrium boundaries between phases.

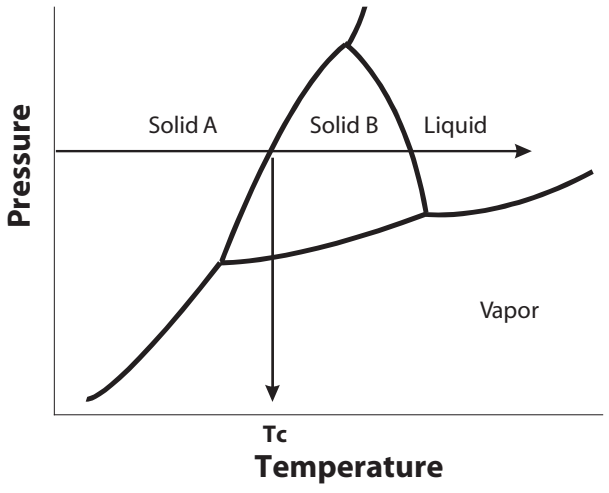


*Figure 1. Example phase diagram for enantiotropic polymorphs.*

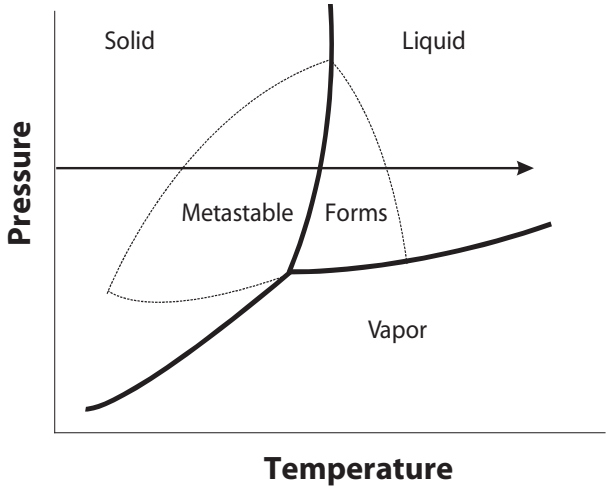


*Figure 2. Example phase diagram for monotropic polymorphs.*

As form A is heated at constant pressure, it undergoes a transition at $T_c$ to state B. This is followed by a second transition from solid B to the melt phase (liquid). The transitions are both reversible, so if the liquid is cooled it will transition into B, followed by A as the temperature continues to decrease. Since the transition from A to B or B to A is a solid state transition, the rate of temperature change can impact the data obtained during a DSC scan. For example, if the sample is heated rapidly, the transition to form B may be kinetically hindered and a single peak may be observed associated with the melting of pure form A. Intermediate heating rates can result in partial conversion of A to B (an endothermic peak) followed by melting of A and B. Therefore, care must be taken in the interpretation of DSC data, especially if three or more forms exist in the sample.

Figure 2 shows an example phase diagram for a monotropic system, where dotted lines represent boundaries between metastable forms.

In this case, there is only one thermodynamically stable state that transforms directly to the melt when heated. However, the diagram points to the existence of potential metastable solid forms which can result from rapid cooling from the melt or from processes such as milling. Upon heating, these metastable states will convert to the more stable form and will

appear as peaks in a DSC scan if sufficiently slow scan rates are used. However, upon slow cooling only the thermodynamically stable form will result, and upon reheating a single endothermic transition (melting) will be observed.

Interpretation of DSC thermograms can be complicated, especially when several polymorphic forms are present in the same sample. However, the phase diagram can generally be determined if the experiment is designed properly.

| Form | $T_m$ | $\Delta H_f$ | |
|---|---|---|---|
| A | 100 | 5 | $A^{\ddagger} \rightarrow B$ |
| B | 120 | 10 | Monotropic<br>Exothermic, irreversible |
| ---------- | ---------- | ---- | |
| A | 100 | 10 | $A \leftrightarrow B$ |
| B | 120 | 5 | Enantiotropic<br>Endothermic, reversible |

*Table 1. The Burger Rule*

DSC and the Burger Rule can be used to determine if the forms observed in a phase diagram are enantiotrops or monotrops. The fundamentals of the Burger Rule are summarized in Table 1, and are explained in detail in Giron (1995) and Giron (1999).

As the table shows, if the melting temperatures and heats of fusion are measured for pure A and pure B, it is possible to determine if the polymorphic forms are enantiotropic or monotropic. For monotropic systems, the transition from metastable A to B will be exothermic, and the melting point of B will be greater than that of A. For enantiotropic systems the transition from A to B will be endothermic, with B again melting at a higher temperature than A.

When using traditional DSC instruments (which generally scan quickly and tend to have rather low sensitivity) in combination with the Burger rule, problems can arise if sublimation takes place. Generally the $T_m$ can still be determined, but it may not be possible to obtain an accurate value for the heat of fusion. In addition, if the melting points of the two forms are close, there may be significant overlap of the melting peaks, again making it difficult to obtain accurate heats of fusion. This problem can be overcome by using DSC instruments designed specifically for pharmaceutical research (high sensitivity and large sample volumes), or by using an isothermal solution calorimeter. In the latter case, differences in the heats of solution of the various states in a common solvent, together with accurate knowledge of the heat of fusion for at least one form, allow calculation of the heat of fusion of the other forms (Gu and Grant, 2001) as illustrated in Figure 3.

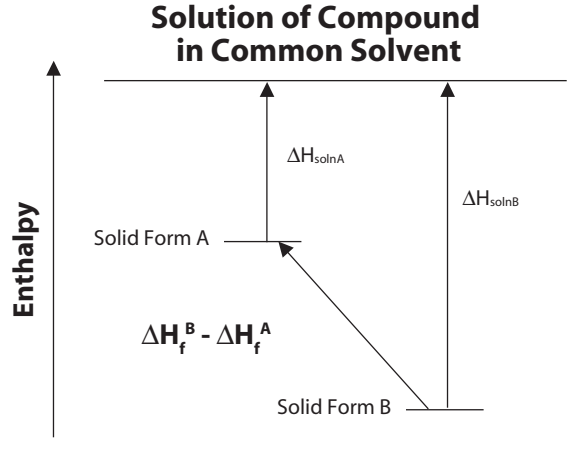


*Figure 3. Measuring differences in heat of fusion with solution microcalorimetry.*

**Instrumentation:**

As previously mentioned, rapid DSC scanning rates cannot detect kinetically hindered solid state transitions between polymorphs, and large samples are often required to obtain accurate heat measure-

ments. The MC-DSC is a slow scanning, large sample size (up to 1 g), high sensitivity DSC ideally suited for studying the energetics and kinetics controlling solid state conversions between polymorphs. In addition, the ability to run three samples against a common reference results in higher throughput. The MC-DSC can also be operated as an isothermal or step-scan instrument.

**Practical examples:**

Figure 4 presents data obtained on a TAM solution calorimeter for two polymorphic forms of a pharmaceutical compound. Note the excellent repeatability on duplicate runs. The difference in measured heats of solution between the polymorphic forms was 0.67 kcal/mole.

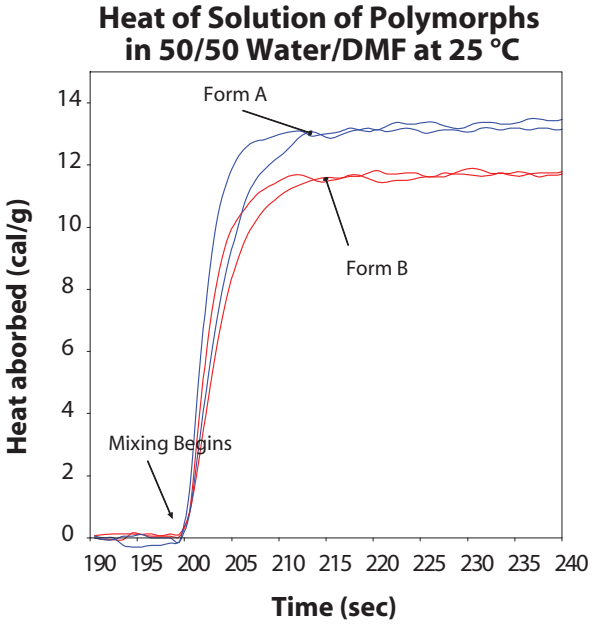


*Figure 4. Heats of solution for polymorphic materials obtained on a TAM solution calorimeter.*

Figure 5 shows an example of enantiotropic form A being converted in real-time to form B using the MC-DSC. The sample size was approximately 500 mg. Isotherms were collected for 1.5 hours at 60°, 70° and 80 °C; at 90 °C, the expected endothermic transition spontaneously occurred, with excellent agreement between duplicate runs. The curve shape suggests an autocatalytic mechanism, consistent with nucleation and growth, which went to completion in about 10 hours.

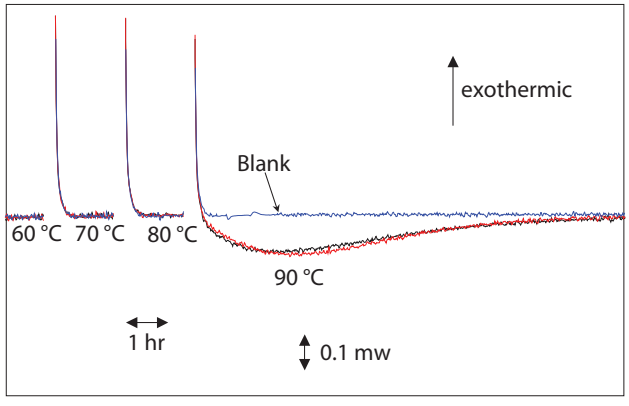


*Figure 5. Monitoring isothermal polymorph conversions on a MC-DSC.*

Figure 6 illustrates real-time monitoring of the kinetics of solid state polymorph conversions with a MC-DSC. The black trace resulted from adding a small amount of form B as an impurity. Notice that the conversion began at a lower temperature (80 °C), and at 90 °C the time required for full conversion was reduced significantly. Both these results are consistent with "seeding" the conversion via a nucleation and growth mechanism.

## THE AMORPHOUS PHASE

Amorphous material is generally produced during drying, milling, crystallization, freeze-drying or rapid cooling from the melt. Amorphous materials have greater solubility

than crystalline forms, resulting in better bioavailability. However they are generally hygroscopic, and have reduced chemical stability. Amorphous materials are also subject to physical instability; thus, especially in the presence of moisture, they can convert to lower energy, less soluble crystalline forms.

DSC and/or powder X-ray diffraction are normally used to characterize amorphous material in pharmaceutical systems. However, when less than about 10–20% amorphous material is present in a mixed polymorphic system, quantitative detection becomes difficult. Isothermal microcalorimetry and scanning microcalorimetry are both powerful tools for detecting low levels of amorphous material in the pure drug and in formulations, even when the levels are as low as 1%.

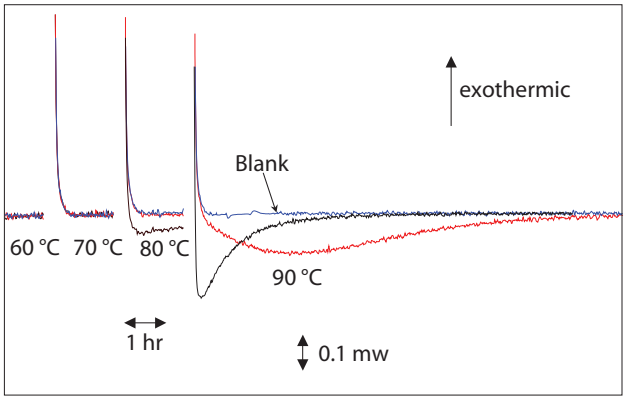


*Figure 6. Impact of a small amount of form B on polymorphic conversion of form A measured on a MC-DSC.*

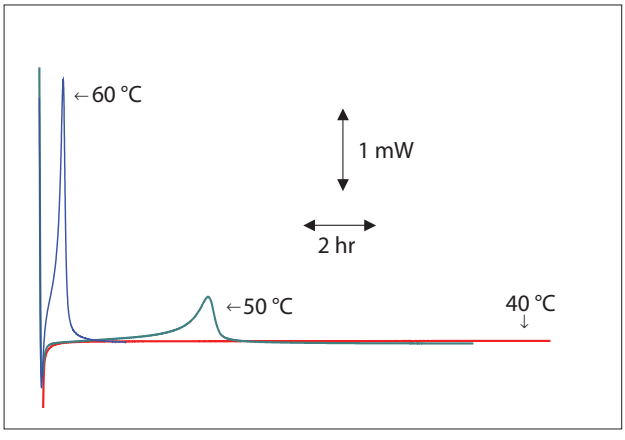


*Figure 7. Conversion of the amorphous to crystalline phase, monitored with a MC-DSC.*

When the glass transition temperature of the amorphous drug is fairly low (*e.g.*, in the range 30–70 °C), holding the sample isothermally at a temperature slightly above the glass transition permits crystallization of the drug to be monitored. An example is given in Figure 7, where the glass transition temperature for the partially amorphous sample (about 1%) was approximately 45 °C. Below the glass transition no conversion from amorphous to crystalline phase was detected. When the temperature was raised to slightly above the glass transition temperature (50 °C), the expected conversion was detected, peaking after about 4.5 hours. At 60 °C the conversion took place much faster, peaking in less than 1 hour. The area under the curves can be compared to the heat generated for crystallization of the pure amorphous phase in order to quantify the fraction of amorphous material in the samples. Running the isotherms at various temperatures also results in a better understanding of the kinetics, and therefore the physical stability of the amorphous phase.

If the glass transition temperature of the sample is too high to allow easy and accurate data collection with an isothermal microcalorimeter, the sample can be exposed to elevated humidity. This reduces the glass transition temperature and permits detection of the conversion process at more moderate temperatures. A vial of sample is sealed in a second vial containing a saturated salt solution. Since different salt solutions provide different relative humidities, placing samples sealed with saturated salt solutions in, for example,

different sample chambers in the TAM provides a sensitive and rapid (hours) approach for characterizing low (< 1%) polymorphic content in drugs. In addition, a water adsorption cell is available for the TAM that permits rapid and precise control of a wide humidity range in the sample vial. Programmed ramps or steps in humidity can be a very powerful approach for determining the stability of an amorphous drug substance as a function of temperature and moisture.

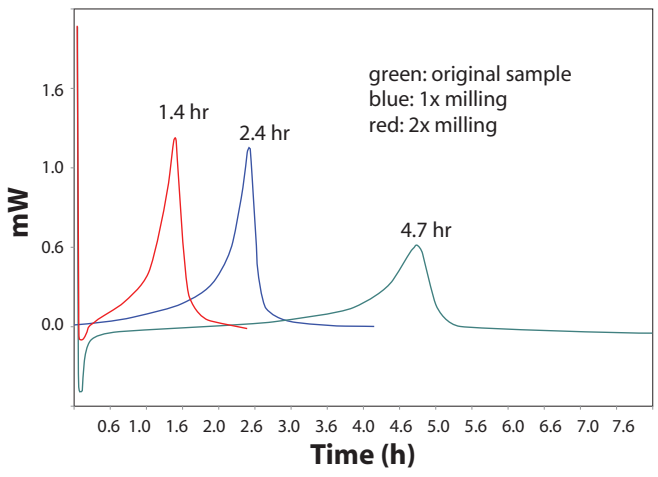


*Figure 8. Monitoring conversion to hydrate in a microcalorimeter.*

## PSEUDO-POLYMORPHS

Solvated systems are often studied by techniques such as moisture sorption, thermogravimetric analysis (TGA) and DSC. The large energy changes associated with solvation or desolvation generally provide adequate signal even from fairly small samples. Isothermal microcalorimetry also plays a critical role in the study of pseudo-polymorphs, especially when unexpected results are obtained from other thermal techniques. For example, TGA was unable to detect formation of a drug hydrate in the presence of lactose monohydrate since there was no net change in mass associated with exchange of water between the drug substance and the lactose excipient. However, as shown in Figure 8, the conversion was easily detected by isothermal microcalorimetry since it is an enthalpy-based measurement. The technique could differentiate different particle sizes on the basis of the time required for the formation of the hydrated drug, with smaller particle sizes converting faster than large particles. In addition, since the area under each curve is the same, isothermal microcalorimetry proved that hydrate formation was occurring uniformly throughout each particle, and was not just a surface reaction.

## SUMMARY

A large percentage of pharmaceutical products are formulated as solids due to their ease of manufacture and packaging, and for the convenience of the patient. However, pharmaceutical compounds can often exist in more than one solid state form, including polymorphs and pseudo-polymorphs. Since the solid state structure has potentially significant impact on the stability and bioavailability of the final product, it is essential that the solid state energetics of the compound be characterized and understood.

DSC permits determination of phase diagrams between polymorphic forms, and isothermal microcalorimetry provides critical thermodynamic and kinetic data for the physical characterization of solid state compounds and final solid dosage formulations. Taken together, these two calorimetric approaches are indispensable for helping ensure the integrity, stability and bioavailability of solid pharmaceutical products.

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