Energetics of Solid State Drugs

Applications of Microcalorimetry

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Introduction

The development and manufacture of drug products requires that numerous studies be carried out to ensure the purity, quality, stability, and safety of the drug product are characterized and well understood. A large percentage of drugs are formulated as solids, which means properties such as crystallinity must be studied. It is well know that a given pharmaceutical chemical entity can often exist in more than one thermodynamically or kinetically stable crystal form. The compound can also exist as a glass (amorphous state). The ability for a compound to exist in these different solid-state forms is known as polymorphism.

Any given pharmaceutical compound may also exist in the form of a solvate. This includes hydrates where water is the solvent included in the solid form. These are generally given the name 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. This is because pharmaceutical properties can be impacted depending on which form or forms exist in the final product. For example, since polymorphs are in different energy states (including metastable forms), the solubility can be affected, which in turn can impact bioavailability. Interconversion from a more soluble, to a less soluble form may occur during manufacturing of the pure drug, during the formulation processes, and after long-term storage, thereby changing the pharmaceutically active properties of the final product.

The chemical stability is different for different polymorphs, with the amorphous phase being particularly unstable compared to a crystalline form. Metastable crystalline (or amorphous) forms may be formed during the manufacturing process, reducing the expected chemical stability (shelf life) of the active pharmaceutical ingredient. Other properties can also be affected, including final particle size, formation of unwanted solvates during dying, flow characteristics, compressibility, etc.

Thermal analysis has long been recognized as a powerful tool for characterizing solid state pharmaceutical systems[1,2,3,4]. Thermal techniques such as DSC, TGA, thermomicroscopy, and microcalorimetry have all been used extensively to quantify the thermodynamic and kinetic properties of polymorphic systems. In this note example applications of microcalorimetry to study polymorphs will be given. Space does not permit discussion of all the possible applications, but those included should give the reader the background information necessary to understand the basic principles involved.

Crystalline Polymorphs

For a given compound, depending on how it was manufactured, one or several crystalline polymorphic forms may coexist, and determining the thermodynamic relationship between the forms is an important requirement for characterization of solid active drug. Although the goal is generally to have a single form present it the final formulated product, it is not always the most stable that is desired. For example, a higher energy form may be more desirable in some cases to enhance solubility. However, if chemical stability is the overriding issue, using the lowest energy form 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 heated the energy of the transition is endothermic. When the phase transition is irreversible, the two forms are monotrops and the transition in monotropic. In this case the transition is exothermic.

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

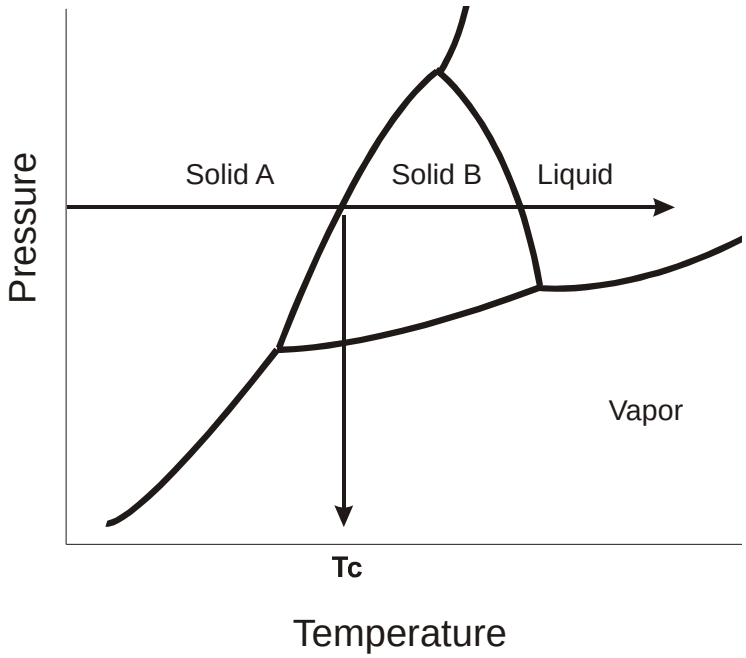

Figure 1. Example phase diagram for enatiotropic polymorphs.

At constant pressure as form A is heated it undergoes a transition at Tc from form A to form B. This is followed by a second transition from solid form B to the melt phase (liquid). The transitions are both reversible, so if the liquid is cooled form B will form followed by form A as the temperature continues to fall. Since the transition from A to B

or B to A is a solid state transition, the rate of temperature change can impact data obtained during, for example, a scan in a DSC. For example, if the sample is heated rapidly the transition to form B may be kinetically hindered and in fact 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, interpretation of the DSC data can often be complicated, especially if 3 or more forms exist in the sample.

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

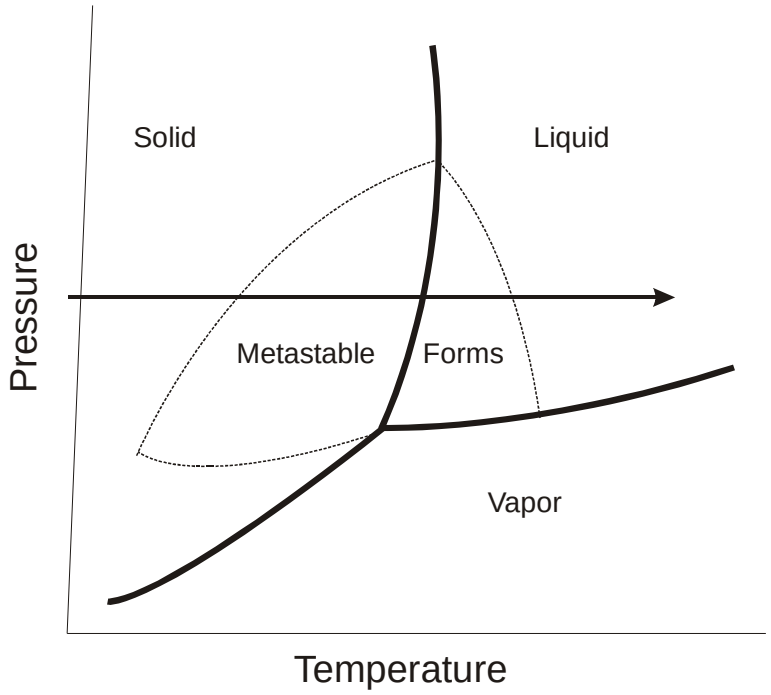

Figure 2. Example phase diagram for monotropic polymorphs.

In this case, there is only one thermodynamically stable solid form 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 processes such as milling. Upon heating the metastable forms will convert to the more stable form and will appear as peaks in a DSC scan if slow enough scanning rates are used. However, upon slow cooling only the thermodynamically stable form will form, 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, by using the correct procedures the phase diagrams can generally be determined, and the Burger Rule can be sued to determine if the forms are enantiotrops or monotrops.

The fundamentals of the Burger Rule are summarized in Table 1. For more information please refer to references 1 and 2.

Form	T_m	ΔH_f	
A	100	5	$A^{\ddagger} \rightarrow B$
B	120	10	**Monotropic** **Exothermic, irreversible**
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A	100	10	$A \leftrightarrow B$
B	120	5	**Enantiotropic** **Endothermic, reversible**

Table 1. The Burger Rule

As the table shows, if melting temperatures and heats of fusion data are generated on pure form A and pure form B it is possible to determine if the polymorphic forms are enatiotropic or monotropic. For monotropic systems, the transition from metastable form 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 melting at a higher temperature than A.

When using DSC in combination with the Burger rule problems can arise if sublimation takes place. Generally Tm can still be determined, but an accurate value for the heat of fusion may not be obtainable. If the melting points of the two forms are close, then there may be significant overlap of the melting peaks, again making it difficult or impossible to obtain accurate heats of fusion.

For these cases, solution microcalorimetry can be of great assistance to the analyst. By using the differences in heats of solution of the forms, in a common solvent, and knowing the heat of fusion accurately for at least one form, it is possible to calculate the heat of fusion of the other form or forms[5]. This is illustrated in figure 3.

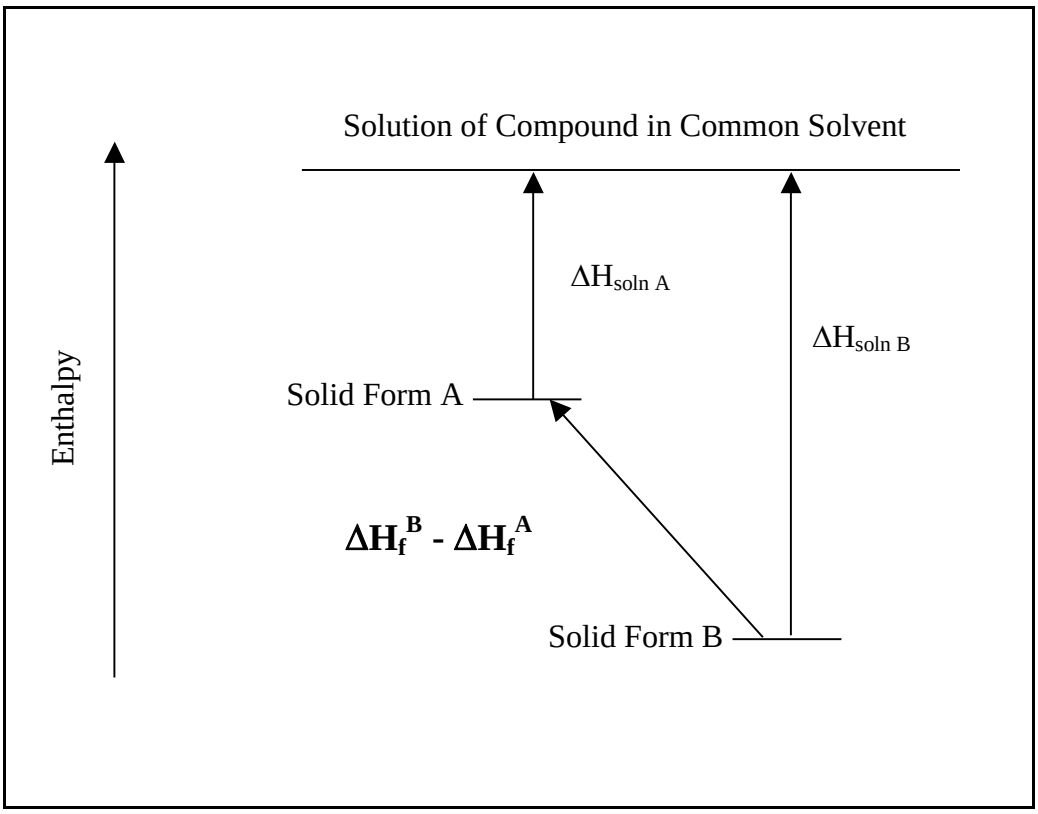

Figure 3. Measuring differences in heat of fusion with solution microcalorimetry.

THT offers a microcalorimetry system well suited for measuring heats of solution. The uRC, shown in figure 4 measures the heat change associated with the dissolution process. Solid samples of about 20mg up to 100mg are held in a small reusable ampoule suspended below the surface of the solvent (see figure 5). Upon mixing the solid with the solvent the resulting enthalpy change is compared to an electronic calibration to obtain the heat of solution.

Figure 4. The THT uRC isothermal solution calorimeter

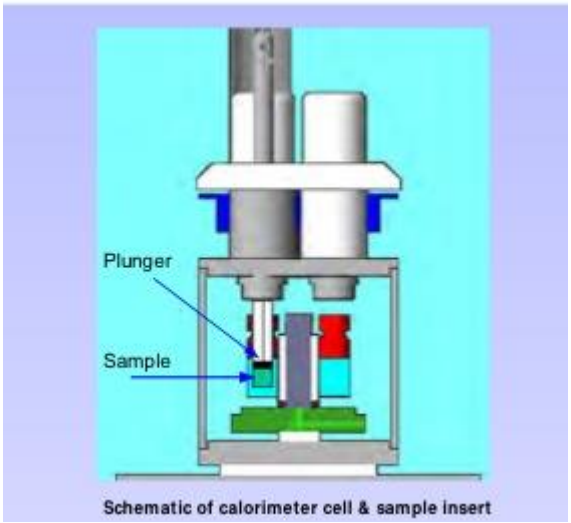

Figure 5. uRC solid/liquid mixing vessel.

Figure 6 illustrates data obtained for two polymorphic forms of a pharmaceutical compound. Note the excellent repeatability on duplicate runs.

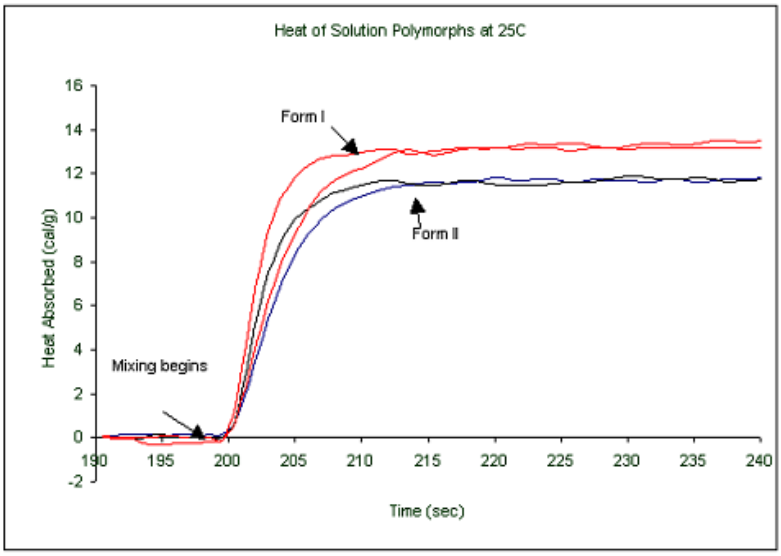

Figure 6. Heats of solution for polymorphic materials.

The difference in measured heats of solution between the polymorphic forms was 0.67kcal/mole.

It was mentioned earlier that the rapid scanning rates used with DSC instruments can result in not detecting kinetically hindered solid state transitions between polymorphs. The THT uRC is capable of scanning at rates as low as 0.2 C/min, which is ideally suited for studying near equilibrium solid-state conversions between polymorphs.

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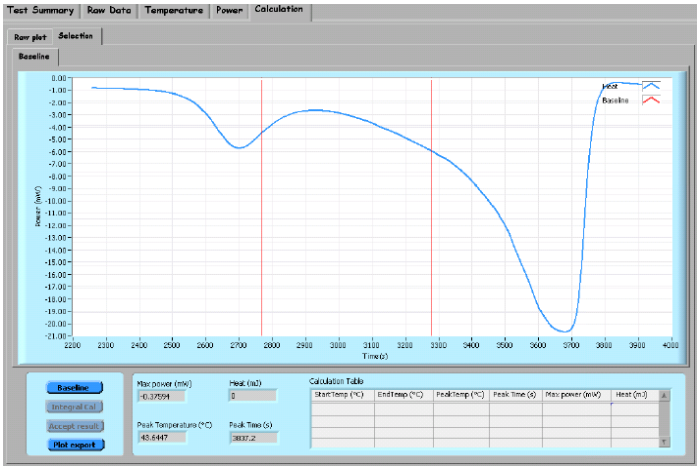

Figure 7. The uRC in scanning (DSC) mode.

The very large sample size (up to 1g of solid) results in significantly better sensitivity at very slow scanning rates when compared to traditional DSC, where typically a few milligrams of sample are studied. Also, since the uRC can be operated isothermally, the

energetics and kinetics of one form converting into another can be determined, in real-time, even if the process requires days to complete.

Figure 8 shows an example of real-time conversion of an enatiotropic form A to form B. The sample size was approximately 500 mg, about 100x the sample size typically studied in a DSC. Isotherms were run for 1.5 hours at 60, 70, and 80C. 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 came to completion in about 10 hours.

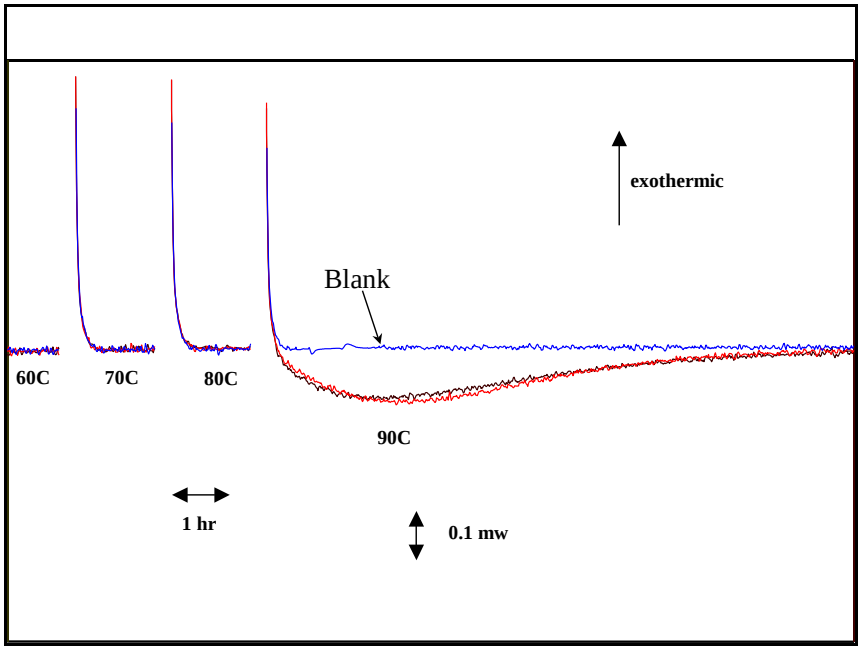

Figure 8. Monitoring isothermal polymorph conversions on a microcalorimeter.

Figure 9 illustrates the ability of microcalorimetry to monitor and compare, in real-time, the kinetics of solid-state polymorph conversions. The black line resulted from adding a small amount of form B as an impurity. Notice that the conversion began at a lower temperature (80C), and at 90C the time required for full conversion was reduced significantly. Both these results are consistent with "seeding" the conversion via a nucleation and growth mechanism

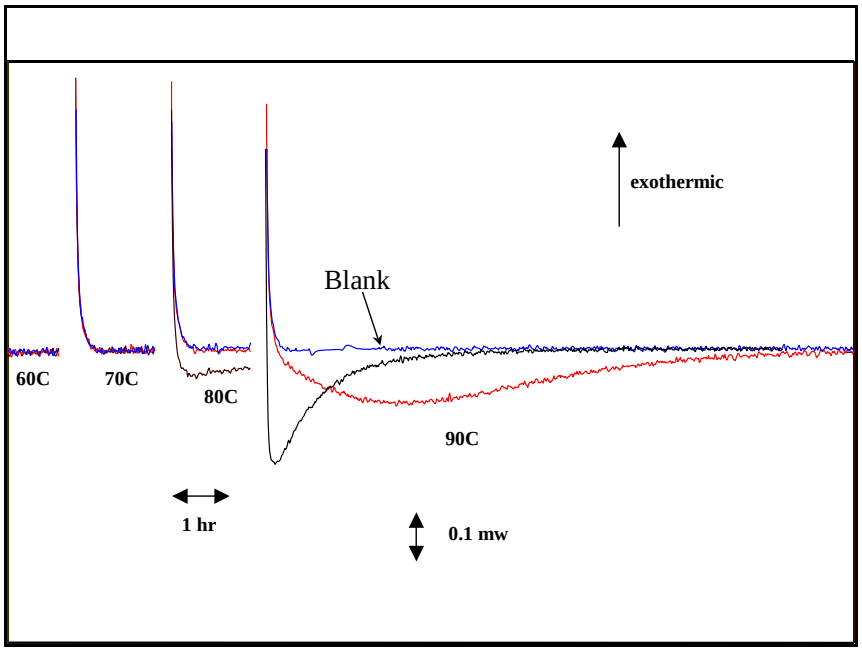

Figure 9. Impact of a small amount of impurity of form B.

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. They are also subject to physical instability, in that over time, 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 useful tools for detecting low levels of amorphous material in the pure drug, and in formulations, when the levels are as low as 1%.

As mentioned earlier, the large sample sizes that can be used in microcalorimeters, versus a DSC, makes it possible to detect much smaller transitions under isothermal conditions. This results in upwards of 100x more sensitivity, which in turns means much lower levels of amorphous material can be detected by inducing the material to crystallize and using the area under the peak to quantify the amount of amorphous drug present.

When the glass transition temperature of the amorphous drug is in the range of about 30 to 70C, simply holding the sample isothermally at a temperature slightly above the glass transition temperature permits monitoring the conversion process to crystalline drug.

An example is given in figure 10 where the glass transition temperature for the partially amorphous sample (about 1%) was approximately 45C.

Notice, that as expected, when below the glass transition no conversion from amorphous to crystalline phase was detected. When slightly above the glass transition temperature (50C) the expected conversion was detected with a peak at about 4.5 hours. At 60C the conversion took place much faster, with a peak at less than 1 hour. The area under the curves can be compared to the heat generated for pure amorphous phase to quantify the amount of amorphous fraction in the samples. Running the isotherms at various temperatures also results in a better understanding of the kinetics, and therefore physical stability of the amorphous phase.

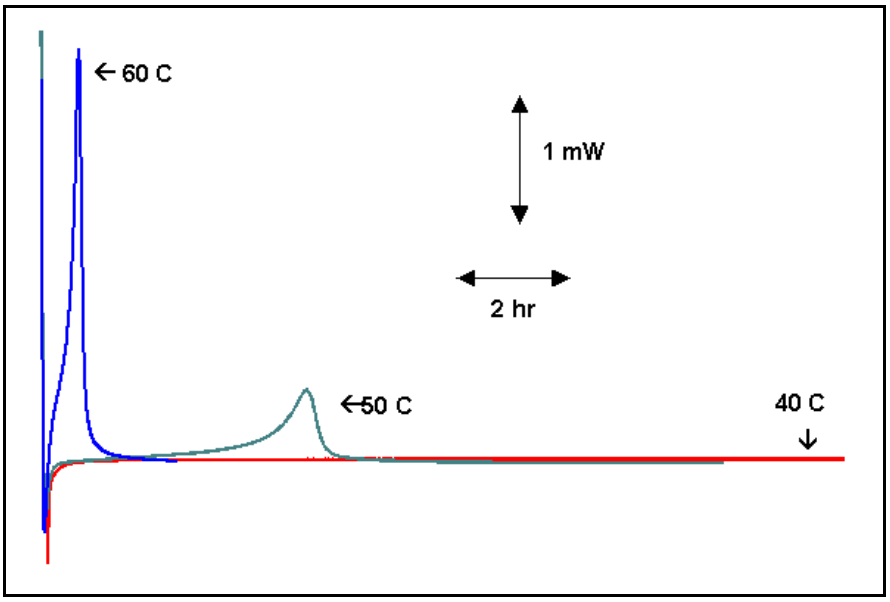

Figure 10. Monitoring conversion of amorphous to crystalline phase.

In some cases the glass transition temperature of the sample of interest may be too high to obtain data easily using an isothermal microcalorimeter. Also, if degradation takes place at the elevated temperatures it can result in errors. In these cases it is typical to expose the sample to an elevated humidity, which reduces the glass transition temperature, to permit detection of the conversion process at more moderate temperatures.

The large sample sizes that can be used with the uRC microcalorimeter permits adding a small vial of sample in the presence of a saturated salt solution into the measurement chambers. Figure 11 shows such an arrangement.

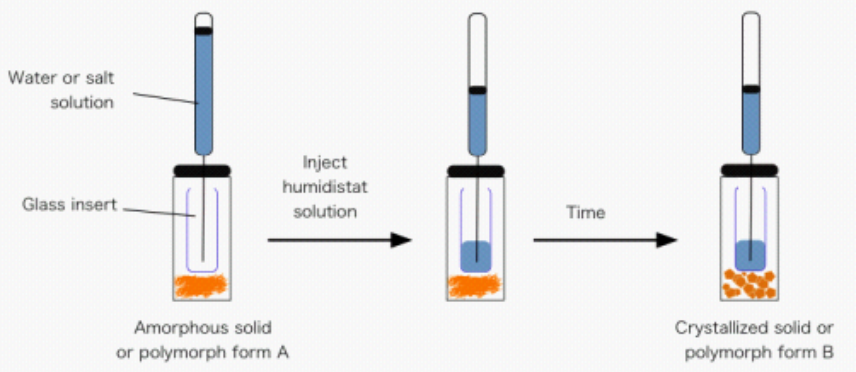

Figure 11. Using saturated salt solutions to induce amorphous crystallization.

Programmed ramps or steps in humidity can be very powerful for determining the stability of an amorphous drug substance as a function of temperature and moisture.

Pseudo-Polymorphs

Solvated systems are generally studied using techniques such as moisture sorption, TGA, and DSC. The large energy changes associated with formation of a solvate, or desolvation as in the case with TGA, generally results in adequate detection limits, even on fairly small samples.

Microcalorimetry can still play a critical role in the study of pseudo-polymorphs, especially when unexpected results are obtained from the other thermal techniques. In the example shown in figure 12, TGA was unable to detect formation of a 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 the data shows, the conversion was detectable using microcalorimetry since it is an enthalpy-based measurement. Notice also, that different particle sizes resulted in different times required for the formation of the hydrated drug, with smaller particle sizes converting sooner than large particles.

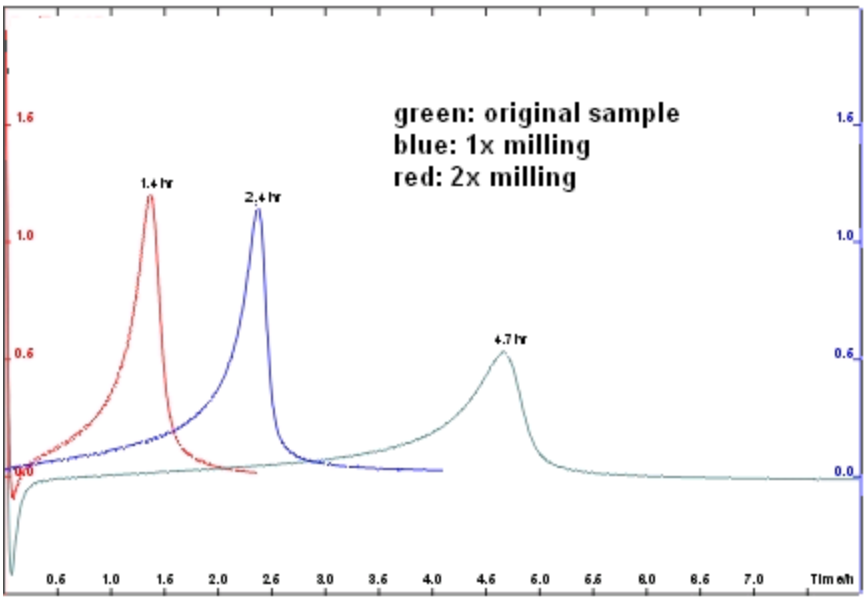

Figure 12. Monitoring conversion to hydrate in a microcalorimeter.

Summary

A large percentage of pharmaceutical products are formulated as solids due to the ease of manufacture and packaging, and the convenience for the patient. However, it has been recognized that 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 be characterized and well understood.

Thermal analysis techniques have for many years been considered critical in the study of solid-state pharmaceutical compounds. Traditional methods such as DSC permit determination of phase diagrams between polymorphic forms, and techniques such as TGA permit determining the thermal behavior of solvates and hydrates. However, in some cases these techniques may not be sufficient alone to fully understand the thermodynamic and kinetic relationships between the solid-state forms.

Examples were given above that show how microcalorimetry should be considered as an essential tool to complement more traditional thermal analysis techniques in any pharmaceutical laboratory. The ability to carry out long-term isothermal studies, with much better detectibility limits than traditional thermal techniques, can often produce critical thermodynamic and kinetic data for the physical characterization of solid-state compounds and final solid dosage formulations.

More info:

References

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