



High Resolution Characterization of Pharmaceutical Polymorphs Using Power Compensation DSC



DSC 8500 with 96-position Autosampler.

Introduction

Many pharmaceutical materials exhibit polymorphism, which means that, depending upon the given processing conditions, the crystalline form may exist in two or more states. The crystalline states or forms exhibit different levels of thermodynamic stabilities and an unstable form can melt at a temperature significantly less than the melting point of the thermodynamically stable form. Depending upon the conditions used to generate the crystalline form(s), the drug may exhibit one or more unstable, polymorphic crystalline states. In addition, as one state undergoes melting, it may be followed by crystallization and then melting at increasingly higher temperatures, due to the formation of a more stable state. The existence of these polymorphic crystalline states is important for many pharmaceutical materials, as they can have a major effect upon:

- The uptake of the active drug into the bloodstream once ingested
- The shelf life of the drug.

One polymorphic form of a given drug may be more easily dissolvable or ingestible than another form and the time release of the material can sometimes be controlled by the given type and level of a particular polymorphic form. Additionally, one crystalline form may exhibit a longer shelf life than another form. It is also possible that an easily dissolvable crystalline form can convert, over time, to a less dissolvable form thus changing the pharmaceutically active properties of the drug formulation.

In addition, there are financial considerations tied into the characterization and identification of different polymorphic forms of a given drug, as the different forms are patentable.

For these reasons, it is desirable to have a means of assessing the polymorphic forms exhibited by a pharmaceutical substance. Differential scanning calorimetry (DSC), particularly power compensated DSC, has proven to be an extremely valuable technique for the characterization of polymorphism in pharmaceutical materials.

Power Compensation DSC

DSC measures heat flow into or from a sample under heating, cooling or isothermal conditions. The most advanced DSC on the market is the DSC 8500 from PerkinElmer. The DSC 8500 is designed using the unique power compensation approach, which yields true heat flow measurements. Because of the very low mass (<1 g) and independent furnace design of the power compensation approach, the DSC 8500 provides both the required very high sensitivity and unsurpassed resolution necessary for the measurement of polymorphism exhibited by pharmaceuticals.

The DSC 8500 offer the following key features:

- Very high sensitivity for the detection of weak transitions or small polymorphic forms
- Outstanding and unsurpassed resolution for better separation of polymorphic melting peaks
- The fastest heating and cooling (up to 750 °C/min) to better study kinetic or time dependent effects
- Use of platinum resistance thermometer (PRT) for the measurement of sample temperature which provides better accuracy and reproducibility than thermocouples
- Very stable baseline performance
- *StepScan* DSC for straightforward separation of reversible and irreversible thermal processes or transitions
- Most extensive compliance with 21 CFR, Section 11

In this study, the thermal properties of a pharmaceutical material thought to exhibit polymorphic behavior were characterized using the DSC 8500.

Experimental

The following table provides the experimental conditions used to characterize the pharmaceutical sample.

Experimental Procedure	
Instrument	Power Compensation DSC
Heating rates	10 °C/min 3 °C/min
Sample mass	3 mg
Sample pan	Standard crimped aluminum pan
Purge gas	nitrogen
Temperature range	90 to 170 °C

Results

Displayed in Figure 1 are the DSC results generated on the pharmaceutical material at the typical heating rate of 10 °C/min. The sample appears to yield a single melting endothermic peak with an onset temperature of 107.4 °C. There is no apparent indication of polymorphic behavior.

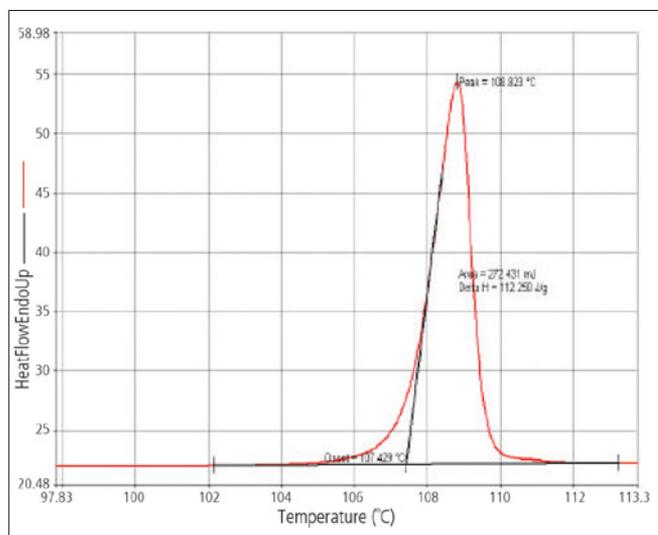


Figure 1. DSC results obtained on pharmaceutical material at a heating rate of 10 °C/min.

However, a closer examination of the data reveals the presence of a small shoulder on the higher temperature end of the melting peak. This may be seen in Figure 2, which presents an enlarged view of the melting transition.

These results now show the definite presence of a shoulder at 111 °C associated with the pharmaceutical sample. This is a strong indicator of polymorphic behavior. The identification of a possible polymorph can be examined by taking advantage of the time dependent nature of the polymorphic transitions. Altering the DSC heating rate, which contains time dependency or velocity, can be used to help identify a possible polymorphic state.

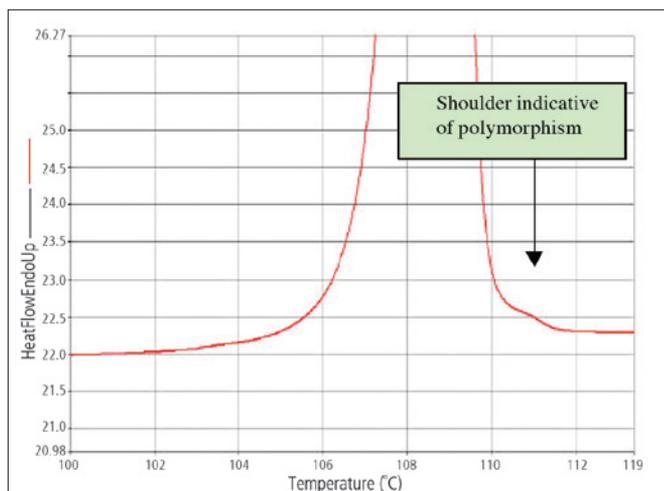


Figure 2. Enlarged view of melting peak showing shoulder at 111 °C.

This particular sample was analyzed using a slower heating rate of 3 °C/min. The DSC results obtained at the slower heating rate are displayed in Figure 3. At a rate of 3 °C/min, the pharmaceutical sample now yields unmistakable evidence of polymorphism. The material undergoes a melting transformation at 107.2 °C immediately followed by a crystallization event, as reflected by the exothermic peak at 109 °C. A DSC instrument with extraordinarily high resolution is required to be able to detect and resolve the crystallization peak, which occurs so closely to the polymorphic melting transition.

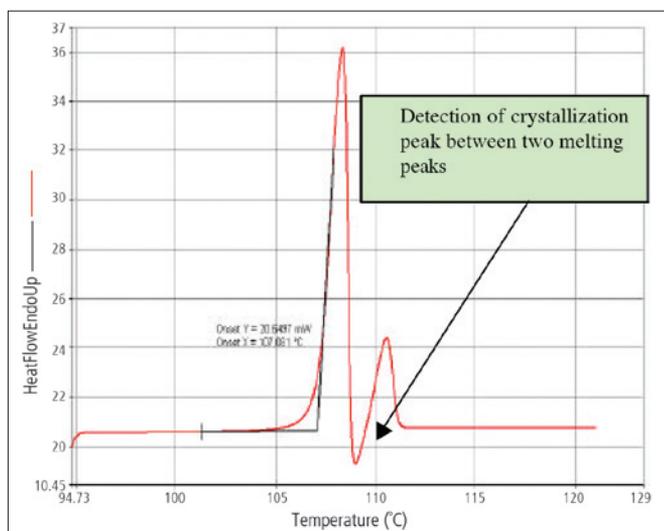


Figure 3. DSC results on pharmaceutical material at heating rate of 3 °C/min.

This particular pharmaceutical polymorphic sample was also analyzed on a high performance, competitive, heat flux DSC instrument (which features heat flow correction equations). The heat flux DSC was unable to detect the presence of the three transitions (unstable melt, crystallization and stable melt) even at slower heating rates. The heat flux DSC devices have a very high furnace mass (150 g), which yields much slower response times as compared to the Power Compensation DSC. As the results in this study show, a DSC instrument with extremely high resolution is necessary for the successful and complete detection of polymorphism associated with many pharmaceutical materials.

Summary

The PerkinElmer Power Compensation DSC provides high sensitivity and unsurpassed resolution necessary to detect polymorphism exhibited by many pharmaceutical materials. The observation of the polymorphic forms is important for the pharmaceutical and drug discovery industries as polymorphism can have a major effect on the release of the active drug into the bloodstream and on its shelf lifetime. The low mass furnace design of the Power Compensation DSC provides extremely fast response times to ensure that thermal transitions are detected and well resolved. In this study, the Power Compensation DSC was able to pull out the polymorphic nature of a particular pharmaceutical substance. A high performance, competitive heat flux DSC instrument was unable to detect the poly-morphism (crystallization) of this particular sample.