APPLICATION NOTE

Thermal Analysis

Authors

Paul Gabbott

PerkinElmer, Inc.
Shelton, CT USA

Confirming Polymorphic Purity with HyperDSC

Polymorphism

Many materials have complex molecular structures that are able to exist in more than one crystalline form, a phenomenon termed polymorphism. Different forms may have different properties and for pharmaceutical use it is important to be able to produce a pure and stable crystalline form of any material to be offered for use as a drug.

Using a Differential Scanning Calorimeter (DSC) different forms of such materials may be identified from their melting profiles and differing melting points. Sometimes melting points are so close together that a high resolution analyzer such as the PerkinElmer® Diamond DSC is needed to distinguish them, though on other occasions they may be more distinct. An example is shown (Figure 1) where one form has melted and then recrystallized into a second form, which has then melted at a higher temperature, a classic picture of polymorphism.

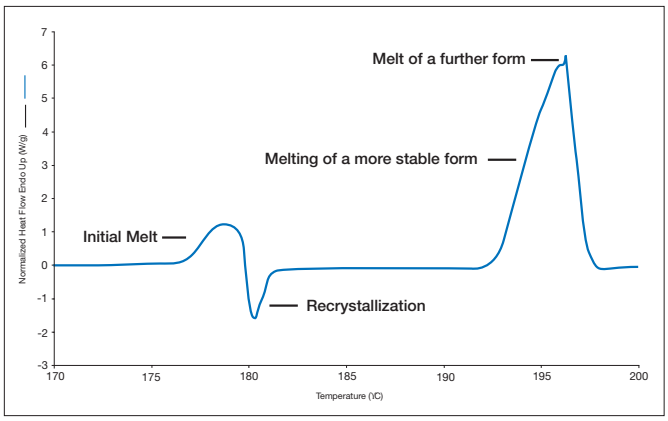

Figure 1. Classic polymorphic behavior as observed by DSC at slow rates from Carbamazepine Form III scanned at 10 °C/min. The sample melts at approximately 175 °C and then recrystallizes very quickly, to produce a second more stable form that melts at approximately 193 °C. This melting peak shows an apparent spike which is due to the melting of a further form.

However, from a slow scan of Carbamazepine, it is impossible to tell whether just one pure form existed to begin with or not. We can see that the sample is recrystallizing, yet we do not know whether all of the higher melting forms resulted from this recrystallization or not, and consequently, whether there was any high melting impurity present in the initial sample.

PerkinElmer®
For the Better

By scanning very quickly, HyperDSC™ offers the potential to prevent this recrystallization, enabling us to measure the sample as received, so that the polymorphic purity can be confirmed.

HyperDSC

HyperDSC is a technique where valid DSC measurements are made while scanning at rates of up to 500 °C/min. Power-Compensation DSCs, such as the Diamond DSC, are unique in their performance allowing high scan rates to be obtained and rapid measurements to be made at these rates, giving valid measurement of the heat flows occurring in the sample. Two main advantages of this technique are:

- ability to analyze the sample without changing it
- significant increase in sensitivity.

While the increase in sensitivity is significant for many measurements, (1, 2) and is evident in the traces below (Figures 2-4), it is the ability to analyze the Carbamazepine without changing it that offers the most potential here. Can we find a rate which is fast enough to prevent recrystallization and so enable us to determine how many forms were present initially? Samples of Carbamazepine were heated at increasing scan rates to find out.

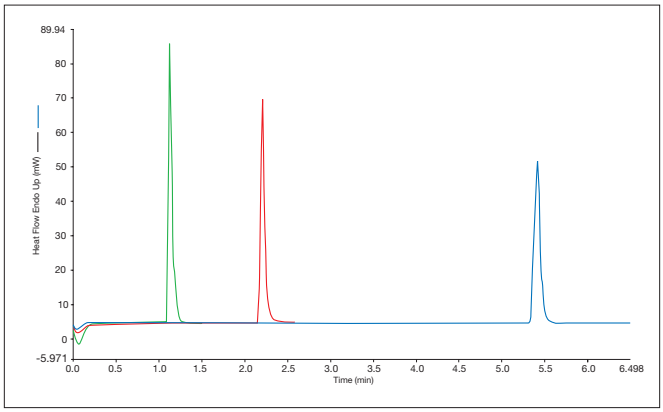

Figure 2. Why Increasing Sensitivity? Indium shown on a time axis after scanning at 100, 50, and 20 °C/min. At higher rates the heat flow produces a narrower, taller peak resulting in higher sensitivity.

HyperDSC Method

Samples weighing approximately 1 mg of Carbamazepine Form III obtained from Aldrich® Chemical Company were crimped in standard DSC pans and heated at rates of up to 500 °C/min using a PerkinElmer Diamond DSC. To ensure good thermal contact, all pans were inspected to make sure the base of the pans were flat. Helium was used as a purge gas. This is because helium has a higher thermal conductivity than more commonly used purge gases, such as nitrogen or air, resulting in better heat transfer and peak resolution – which is important at high rates. Results are shown in Figures 3 and 4.

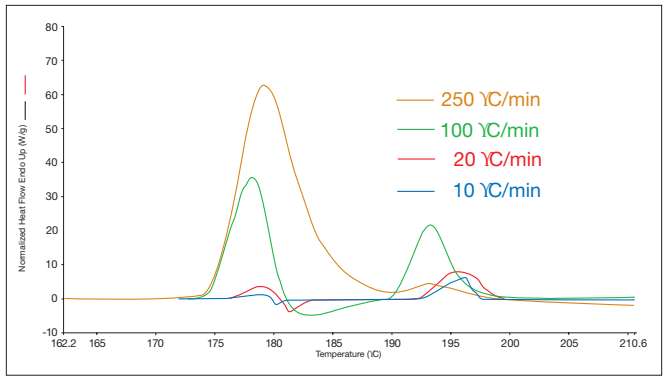

Figure 3. Carbamazepine Form III heated at rates of up to 250 °C/min. The proportion of higher melting forms is reduced, but not eliminated.

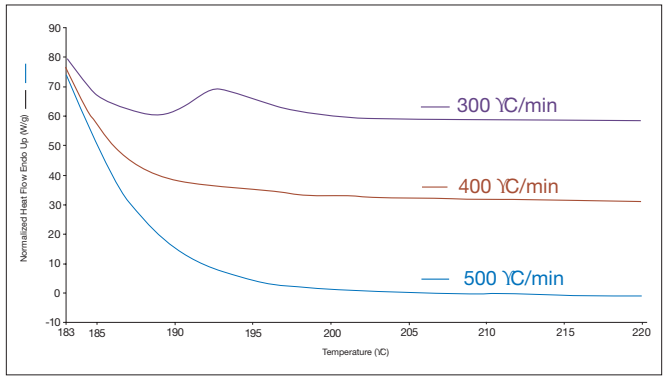

Figure 4. Carbamazepine Form III. Thermograms of the tail of the main melting peak at very high heating rates, showing that at 500 °C/min there is no higher melting form.

Examining this data, it can be seen that even at 250 and 300 °C/min a small amount of higher melting form remains. Even at 400 °C/min traces of higher melt material can be seen, and it is only at 500 °C/min that a clean single melt is observed. This data shows that at increasing scan rates, the recrystallization of the Carbamazepine sample is gradually reduced, and along with this, traces of the higher melting forms produced by this recrystallization. It is only at 500 °C/min, that recrystallization is completely prevented and a pure melt observed. Had evidence of higher melting forms remained, then this would have indicated contamination in the sample to start with. The complete lack of higher melting forms at 500 °C/min indicates that the Carbamazepine Form III sample was of a single polymorphic form to begin with. A similar conclusion has been reached in a study of Carbamazepine Form III using a PerkinElmer Pyris™ 1 DSC where scan rates of up to 250 °C/min were used (3). The use of helium as a purge gas coupled with the higher performance of the Diamond DSC in this study, has produced a clearer definition of the melting profiles of the different crystal forms at high scan rates.

Conclusions

Different materials will exhibit different kinetics, but the principle shown here is that by making measurements using very high scan rates, true sample properties can be measured without giving the sample time to change. In this case, the polymorphic purity of a pharmaceutical material has been confirmed in a manner not possible using slow scan rates.

References

1. Paul Gabbott, Paul Clarke, Tim Mann, Paul Royall, Sukhraj Shergill. *A High Sensitivity, High Speed DSC Technique: Measurement of Amorphous Lactose.* American Laboratory August 2003.

2. Pijpers TFJ, Mathot VBE, Goderis B., et. al. *High – Speed calorimetry for the study of kinetics of (re) vitrification, crystallization and melting of macromolecules.* Macromolecules 2002; 35:3601-13.

3. Caroline McGregor, Mark H. Saunders, Graham Buckton, Robert Saklatvala. *The use of high-speed differential scanning calorimetry (HyperDSC) to study the thermal properties of Carbamazepine polymorphs.* Thermochimica Acta Article in Press, August 2004.

PerkinElmer, Inc.
940 Winter Street
Waltham, MA 02451 USA
P: (800) 762-4000 or
(+1) 203-925-4602
www.perkinelmer.com

PerkinElmer®

007199A_01