APPLICATION NOTE

Thermal Analysis

Confirming Polymorphic Purity with HyperDSC

Introduction

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 used as a drug component. Using a Differential Scanning Calorimeter (DSC), different forms of such materials may be identified from their melting profiles and differing melting points. 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. This is a classic picture of polymorphism. However, from a slow scan of carbamazepine, it is impossible to tell whether a single pure form existed to begin with or not. We can see that the sample is recrystallizing, yet we do not know whether or not all of the higher melting forms resulted from this recrystallization, and, consequently, whether there was any high melting impurity present in the initial sample. 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.

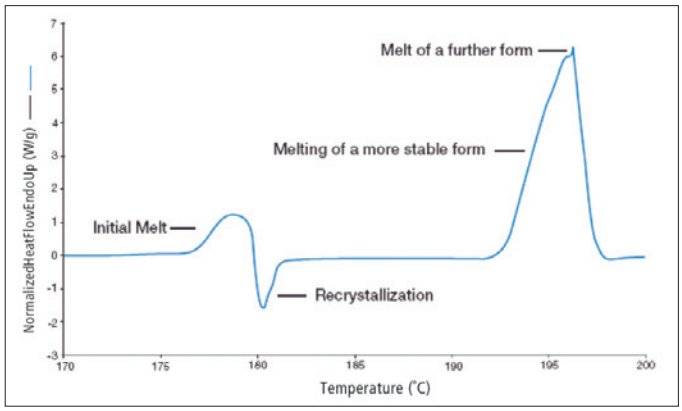

Figure 1. Classic polymorphic behavior as observed by DSC at slow rates from carbamazepine Form III scanned at 10 °C/min. The sample melts at approximately 175 °C and then recrystallizes very quickly to produce a second more stable form that melts at approximately 193 °C.

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HyperDSC

HyperDSC is a technique by which valid DSC measurements are made while scanning at rates of 300 to 750 ˚C/min. Double-furnace DSCs, such as the PerkinElmer® DSC 8500, are unique in their performance, allowing high scan rates and rapid measurements to be made at one time, 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 shown (Figures 2-4), it is the ability to analyze the carbamazepine without changing it that offers the most potential. To discover a fast enough rate that prevents recrystallization and enables us to determine how many forms were initially present, samples of carbamazepine were heated at increasing scan rates.

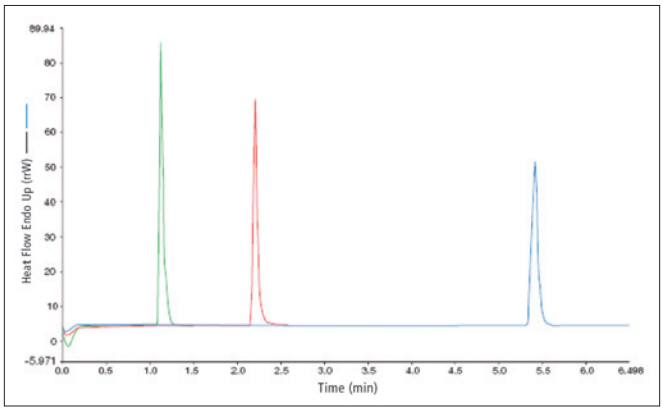

Figure 2. Why Increasing Sensitivity? Indium shown on a time axis after scanning at 100, 50, and 20 ˚C/min. At higher rates the heat flow produces a taller peak resulting in higher sensitivity.

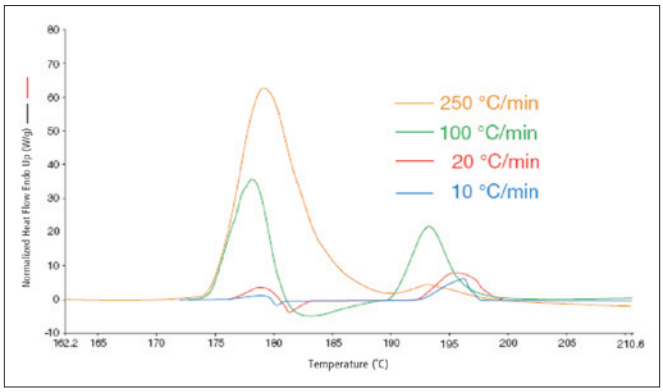

Figure 3. Carbamazepine Form III heated at rates of up to 250 ˚C/min. The proportion of higher melting forms is reduced, but not eliminated.

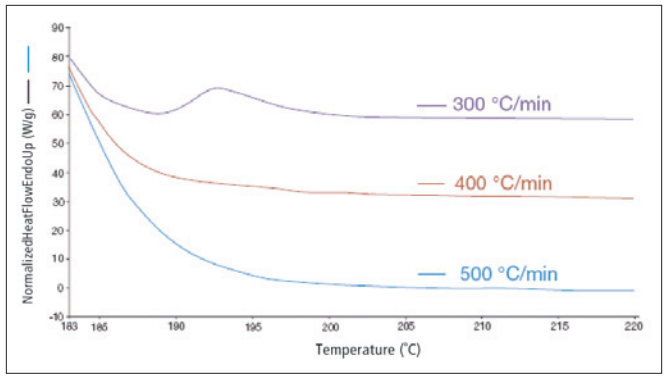

Figure 4. Carbamazepine Form III. Thermograms of the tail of the main melting peak at very high heating rates, showing that at 500 ˚C/min there is no higher melting form.

Result

Examining the data in Figures 3 and 4, 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. The use of helium as a purge gas coupled with the higher performance of the DSC 8000 in this study has produced 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 T.F.J., Mathot V.B.E., Goderis B., et. al. *High-Speed calorimetry for the study of kinetics of (re) vitrification, crystallization and melting of macro-molecules.* Macromolecules 2002; 35:3601-13.

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