Pharmaceutical Polymorphism by Rapid Heat-Cool DSC

INTRODUCTION

As a technique, interest has been growing in performing differential scanning calorimetry (DSC) at higher than typical (10 °C/min) temperature-scanning rates. This is because a variety of material characterization challenges exist that can benefit dramatically from rapid heating or cooling rate experiments. For example, the investigation of metastable states and time-dependent transitions would profit greatly from fast scanning rates. In general, higher scanning rates will also increase the heat flow sensitivity for subtle transitions although this benefit is usually tempered by the small mass requirement of the rapid scanning rates.

A DSC has been designed specifically for operation at high scanning rates – up to 2000 °C/min in heating with similarly high cooling rates. Key technologies introduced by TA Instruments are essential to, and have been incorporated into the instrument known as Project RHC. For example, Tzero technology improves the resolution and the sensitivity of the measured sample heat flow rates, especially for very weak effects, and improves the instrument baseline. Also, infrared heating, introduced in the Q5000IR TGA, provides a “massless” infrared heat source. Readers interested in further details on the instrument design should refer to reference 1.

This applications note reports on the study and accurate determination of pharmaceutical polymorphism by rapid heat-cool (RHC) DSC.

RESULTS and DISCUSSION

Crystalline pharmaceutical drugs often exist in polymorphic forms that have the same chemical composition but differ in crystalline structure and physical properties such as solubility, bioavailability and storage stability. Also, the most stable form may not be the one desired for a particular application. For these reasons, plus others associated with the development and manufacture of efficient and effective drug delivery systems, it is important to know if a specific compound can exist in different polymorphic forms.

DSC is the most widely used analytical technique for studying and measuring crystalline polymorphs. However, inexperienced users often misinterpret results if they fail to realize the metastable nature of the material, i.e. the sample may be changing as it is heated due to inherent kinetic processes. These include crystallization of amorphous material and conversion of less stable polymorphic forms into more stable versions that melt at higher temperatures.

Crystalline conversions can potentially be suppressed if the scan rate of the DSC is high enough. This would allow the investigation of the morphological structure that exists in the as-received sample and how that structure might change on heating. Figure 1 contains an overlay of four scans at different ramp rates on the pharmaceutical crystal tolbutamide that displays polymorphism. Tolbutamide is known to have at least three polymorphs. Results are plotted in heat capacity units for comparison. At the slowest ramp rate (50 °C/min), the data include a glass transition, followed by two crystallization exotherms and two melting endotherms. The first crystallization exotherm is a cold crystallization of the amorphous material. The crystal structure formed during the cold
crystallization subsequently melts and is immediately followed by a second crystallization exotherm, a polymorphic transition into a more thermodynamically favorable crystal structure. This structure melts near 150 °C. Upon increasing the scan rate, the crystallization exotherms are suppressed, but not completely eliminated. At a scan rate of 750 °C/min, all crystallization activity is completely suppressed and only the glass transition is still detected. The rapid scan data thus indicate that this pharmaceutical material is in a 100% amorphous state initially. This study demonstrates the utility of the RHC in analysis of metastable structure in pharmaceutical polymorphs. Only at elevated heating rates are the kinetic processes sufficiently suppressed, so that the original amorphous structure can be accurately measured.

Figure 1 – Tolbutamide scanned at increasing ramp rates.

REFERENCES


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