



Methodology for Thermal Analysis of Excipients

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ABSTRACT

Excipients are the components of a pharmaceutical formulation other than the active ingredient. Their purity, stability and other physical characteristics must be qualified along with those of the active component. Drug analysis methodology is often reported for excipients since these materials are universally available, and publication does not present an appearance of revealing trade secrets. Thermal analysis methods of drug analysis are reviewed and it is shown how DSC Tzero™ Technology improves the results. Detecting and characterizing polymorphs and pseudo-polymorphs and the characterization of amorphous formulations are described.

INTRODUCTION

The physical characteristics of the "inactive" components in a drug formulation are important to the effectiveness of the final product. In a solid dosage formulation, these components "bulk up" the active components to make an easy-to-administer pill, provide the proper consistency, and stabilize the active ingredient. Excipients, like most active drug substances exhibit polymorphism. That is, they can exist in an amorphous phase and/or one or more crystalline phases. These phases have different physical characteristics such as stability, shelf life, rate of dissolution and bioavailability. In the manufacture of the drug formulation the amount of the different polymorphs may vary depending upon processing conditions. There may be a gradual change in the distribution of polymorphs as less stable forms convert to more stable forms during storage. Therefore drug manufacturers investigate the phase diagrams of prospective drug substances and excipients, and check final formulations for the presence of unintended polymorphs.

Since different polymorphic forms have different melting points, DSC may distinguish the polymorphs. If one physical form changes to another, the energy associated with the transition is measured. DSC is useful in assessing stability and establishing phase diagrams due to its ability to measure heats and temperatures of transition.

Similar issues surround the presence of *hydrated* forms of materials. These are referred to as pseudo-polymorphs. The presence of a hydrated form can easily be detected by thermogravimetry (TGA) detecting a weight loss when the hydrate is heated through its decomposition temperature.

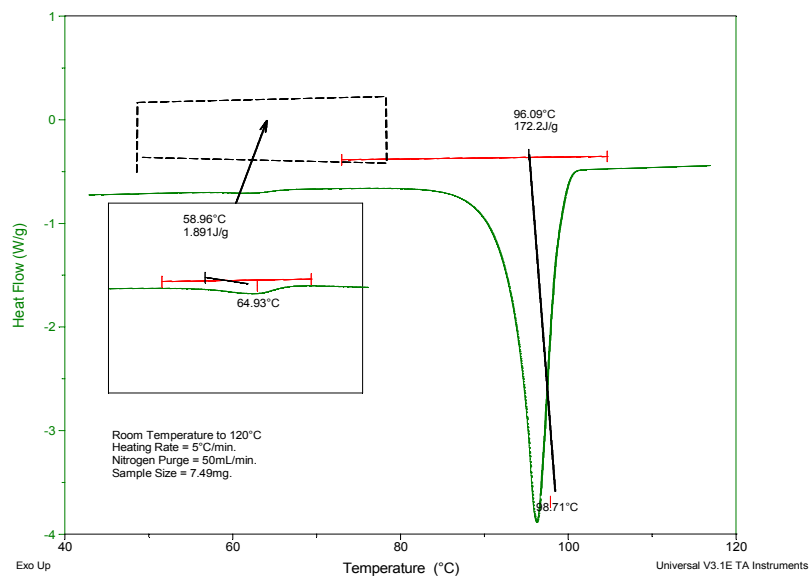


Figure 1 – Detection of Trace Amounts of α -Sorbitol in γ -Sorbitol

The amorphous phase is another example of polymorphism. Incomplete crystallization from the melt leads to the presence of amorphous components, the physical characteristics for which are very different from the crystalline forms. Grinding may produce small amounts of the amorphous phase. For other formulations the excipient and active component are both in the amorphous phase to promote dissolution, and hence, bioavailability. DSC detects an amorphous phase by its glass transition observed as a change in specific heat capacity.

Where both excipient and drug substance are in the same amorphous phase the processing of the formulation is through freeze-drying the aqueous mixture. This is a slow and energy-intensive process that involves slowly heating the amorphous mixture under vacuum from deep subambient to above ambient temperatures as the water concentration is decreased. Modulated DSC® (MDSC®) has been shown to be a valuable tool for determining the optimum temperature for freeze-drying based on the concentration-dependent glass transition temperature (T_g) of the water-drug-excipient mixture (1).

EXPERIMENTAL

A Q1000 DSC is used in this study. Samples were obtained from several sources and run without further purification or treatment. Sample specimen encapsulation was either crimped, or hermetically sealed, standard aluminum capsules.

RESULTS AND DISCUSSION

Crystalline Polymorphism

Because of its compression characteristics, its sweetness, and compatibility with active ingredients, sorbitol is commonly used as an excipient.

Figure 1 shows the detection of trace amounts of α -Sorbitol in γ -Sorbitol when heated at 5 °C/min.

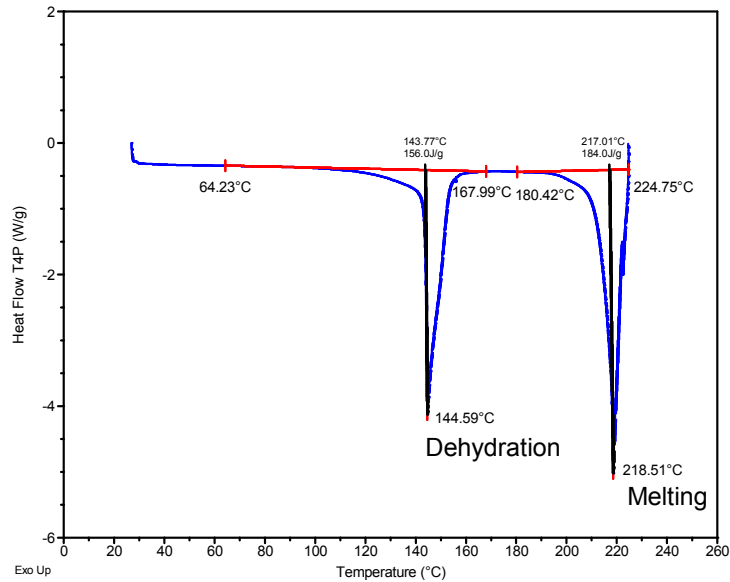


Figure 2 – Decomposition of Lactose Monohydrate

Pseudo-Polymorphism

Perhaps the most used excipient is lactose available in either the anhydrous or monohydrate form. The material in the monohydrate form can be easily detected or determined by heating through the decomposition temperature of the hydrate by either DSC or TGA.

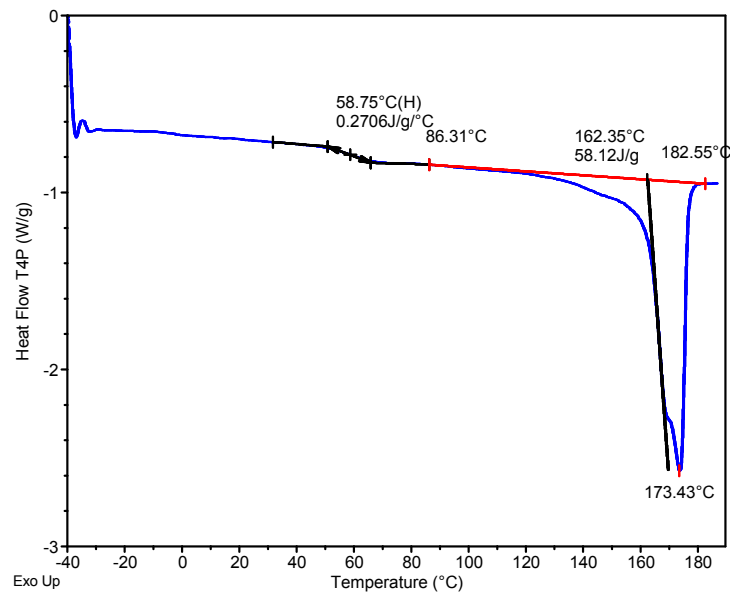


Figure 3 – Polylactide “As Received”

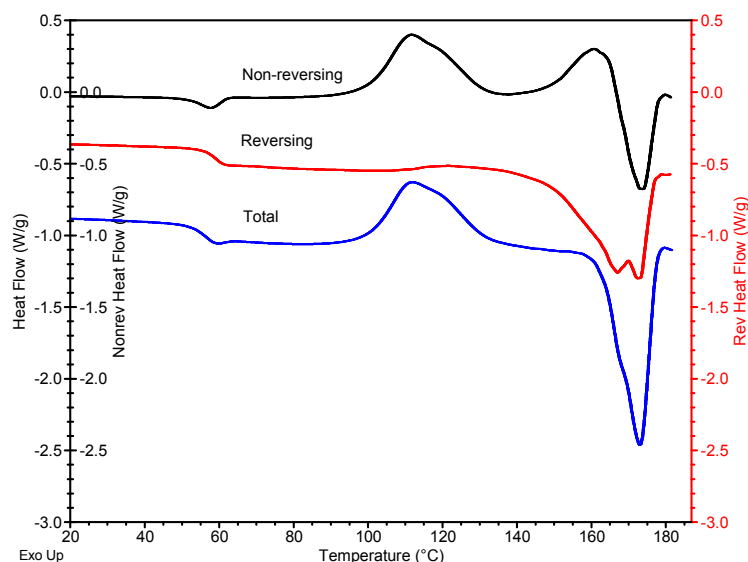


Figure 4 – Fast MDSC® of Amorphous Polylactide

Rapid Analysis Techniques for a Semi-Crystalline Polymeric Excipient

L-Polylactide (PL) is an ingestible, biodegradable semi-crystalline polymer used as an excipient and matrix for microencapsulation. The rate of dissolution, and of diffusion, for the active ingredient is metered by the level of amorphous content, which in turn is controlled by the thermal history of the polymer. Figure 3 shows PL in the form as received. From the glass transition it is clear that there is amorphous content, and from the crystalline melting there is a crystalline phase. Two recently improved methods for investigating such a system are fast DSC and fast MDSC®.

Fast MDSC

When a sample is heated in a DSC at conventional heating rates such as 10 or 20 °C/min there is evidence of crystallization as well as melting. To separate these effects, MDSC is used. Figure 4 is a modulated DSC experiment using an underlying heating rate of 10 °C/min and a modulation period of 20 s. The glass transition with its simple sigmoidal shape is seen in the reversing heat flow curve, followed by a decrease in heat capacity attending cold crystallization, followed immediately by the onset of melting. The nonreversing heat flow curve shows a physical aging peak attending the glass transition followed by the heat of cold crystallization, followed by crystallization of crystallite perfection that attends melting. The unresolved sum of the above effects is seen in the total heat flow signal, similar to that observed in traditional DSC at 10 °C/min.

Fast DSC

Another methodology to remove the confusing effects of crystallization during a melt is that of scanning materials at a sufficiently fast heating rate to prevent crystallization. In this way the melting profile better reflects the initial distribution of

crystal and crystallite forms. However, fast heating rates produce temperature gradients within the DSC cell and between the DSC cell and the sample. These gradients result in errors in temperature assignment and peak shape. Fortunately, Advanced Tzero™ Technology specifically addresses these errors, calibrates the DSC to evaluate them, and then compensates for them in its measuring circuitry. This allows scan rates of up to 150 °C/min to be used.

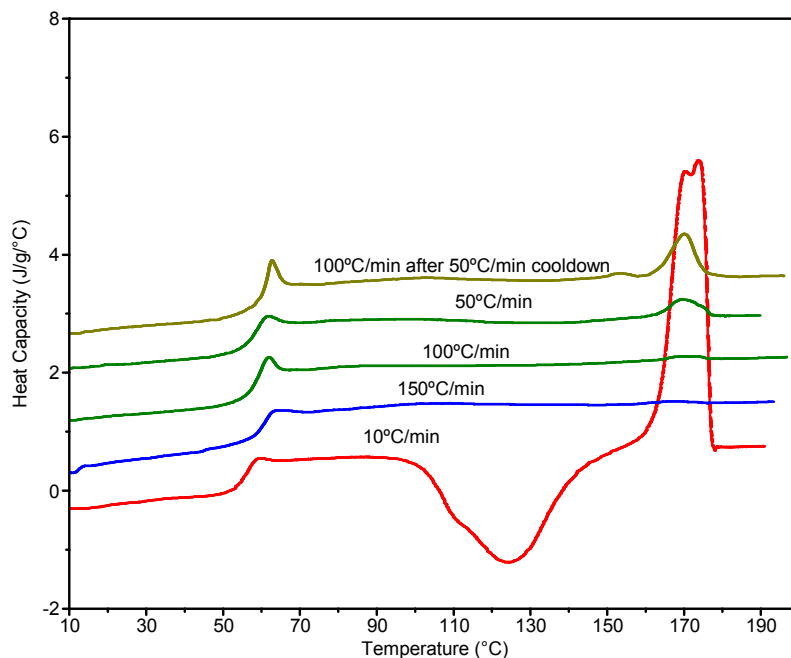


Figure 5 – DSC of Rapidly Cooled Polylactide at Several Heating Rates. (Curves are offset for comparison.)

Figure 5 shows PL that has been cooled rapidly in the DSC, run at several heating rates. Samples run at the fastest rates showed little or no evidence of crystallization. Samples with similar treatment heated at 50 °C/min showed some crystallization, and samples heated at 10 °C/min showed essentially complete crystallization, based on the energies of the melting and crystallization peaks.

CONCLUSIONS

Tzero technology with its improved resolution and baseline stability finds application in the routine characterization of pharmaceutical materials, such as excipients. The use of Advanced Tzero Technology allows the use of faster heating rates up to 150 °C/min, thus enabling the investigation of unstable forms using heating rates that do not allow time for substantial crystallization. And the ability to use shorter MDSC periods with faster underlying rates facilitates the use of MDSC as a practical laboratory technique.

REFERENCES

1. L. C. Thomas, et al, *Today's Chemist at Work*, Jan **2002**, 21-22.

KEYWORDS

differential scanning calorimetry, glass transition, melting, modulated differential scanning calorimetry, pharmaceuticals

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