APPLICATION NOTE

Differential Scanning Calorimetry

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Practical Applications of HyperDSC in a Pharmaceutical Laboratory

HyperDSC™ (or High Speed DSC), a thermal technique that complements conventional calorimetry, has found applications in the fields of pharmaceutical, polymers and compounds.

This technique features measurements taken at high heating (or cooling) rates, from 100 to 500 °C/min. It is an approach that makes it easier to detect such events as glass transition or the melting of a compound when they are concealed by kinetic phenomena like, for example, water vaporization, crystallization or chemical degradation.

Furthermore, HyperDSC offers greatly enhanced analysis sensitivity due to the concentration of the energy phenomena measured into a very brief space of time. Calorimetric analyses on samples of very low mass (below 10 µg) are thus made possible. The detection limits permitted by this technique can be lowered considerably as compared with conventional DSC, down to values < 1% when quantifying physical forms (amorphous or crystalline). HyperDSC analyses can be carried out on the power compensation DSC 8500 from PerkinElmer shown in Figure 1.

Figure 1. DSC 8500.

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Presentation and relevance of HyperDSC

First, a quick review of the differences between power compensation DSC and heat-flux DSC is presented. Its design and working principle makes power compensation DSC the best technique for analysis at high heating and cooling rates.

The small low-mass furnace (Figure 2) of the power compensation DSC 8500 is highly responsive with respect to the chosen temperature programs. Power compensation provides a direct measurement of the heat flow given off or absorbed by the sample, as well as constant temperature readings up to rates of 500 °C/min.

Figure 2. Sample furnace of a power-compensation DSC.

A very short startup transient

As is shown in Figure 3, it takes the DSC 8500 less than 10 seconds to reach a selected temperature setting, even at a rate as high as 750 °C/min. Thus, for an experiment beginning at -65 °C and carried out at 200 °C/min, the apparatus reaches equilibrium at about –30 °C, the temperature from which any transition can be measured. By comparison, a classical heat-flux DSC can take 30 to 60 seconds and is not ready for the detection of a transition before +35 °C or more likely +135 °C, which therefore makes it necessary to start the analysis at a much lower temperature.

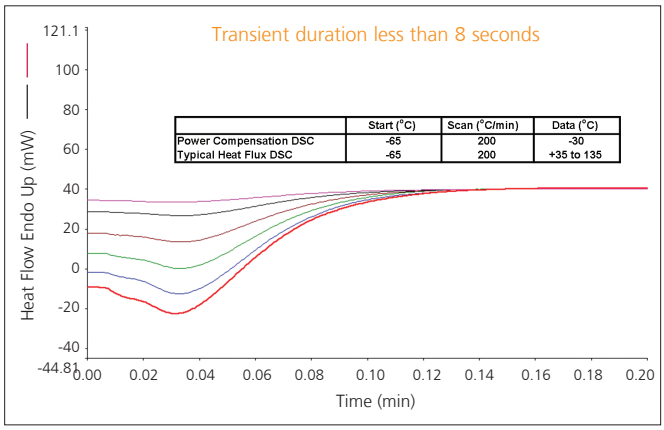

Figure 3. Illustration of the equilibration time for the DSC 8500 furnaces at different heating rates.

A direct, reliable measurement of heat flux up to 750 °C/min.

The melting peak of an Indium standard has reliable onset and enthalpy values at any chosen heating speed, even at 500 °C/min as shown in Figure 4 and the inset Table.

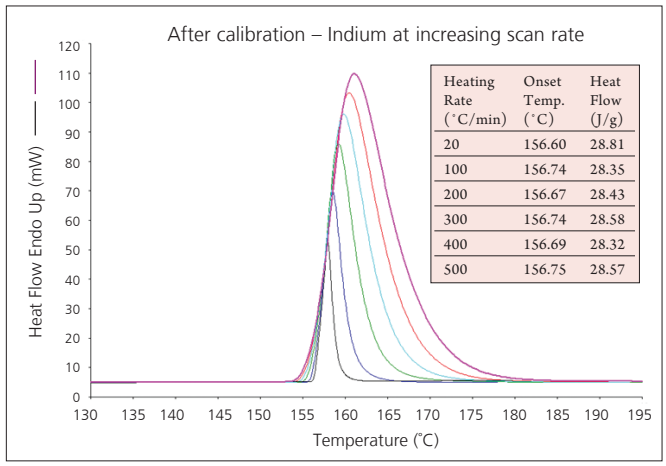

Figure 4. Melting peaks of an Indium standard at different heating rates.

HyperDSC's enhanced sensitivity

Fast Scan DSC provides increased sensitivity with decreasing experiment time because the output of a DSC is mW or J/sec. Figure 5 depicts the increase in heat flow signal at higher heating rates.

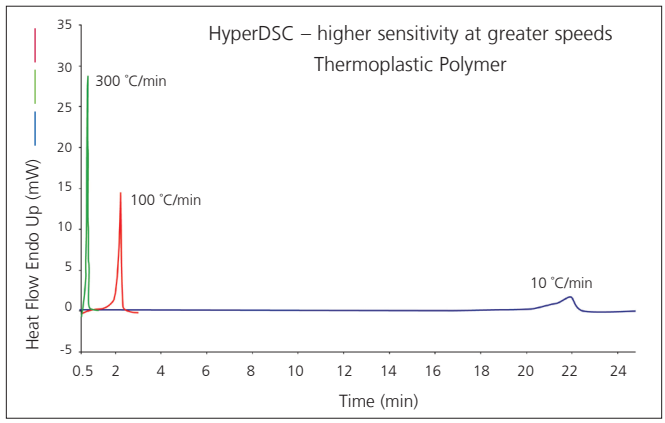

Figure 5. Increased sensitivity at higher scanning rates.

The enthalpy measured remains the same independent on the scanning rate; only the intensity of the signal is reinforced because of the concentration of energy absorbed or released in a very short time frame.

Analysis of a polymorph mixture

The first sample shown is a mixture of Carbamezipine stable Form I and metastable Form III. Figure 6 shows an experiment carried out at 500 °C/min in which a very weak endotherm was detected for the melting of Carbamazepine Form III, a polymorph making up only 1% of the sample content.

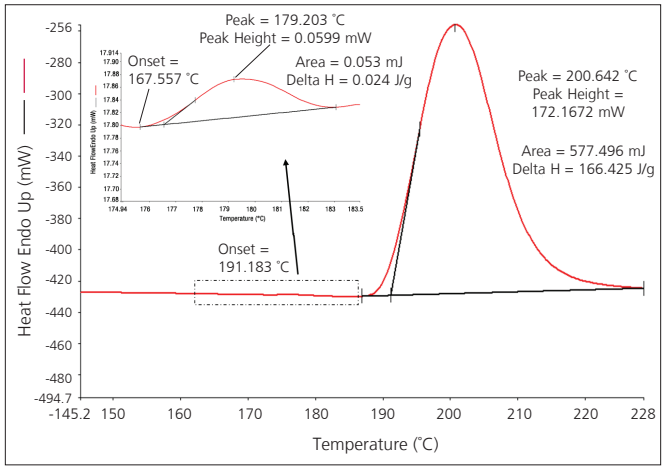

Figure 6. Detection of 1% Carbamezipine Form III using HyperDSC.

Analysis of a weak glass transition (Tg)

The detection of a glass transition in an amorphous material is also improved by HyperDSC (Figure 7). With HyperDSC detection limits < 1% (w/w) can be reached in order to quantify the amorphous material in pharmaceutical compounds.[1]

At such heating rates, thermal gradients within the sample can have an impact, widening the signals detected and superimposing thermal phenomena inside the material. One way to limit this thermal gradient is to perform analyses on samples of very small mass, less than a milligram.[2]

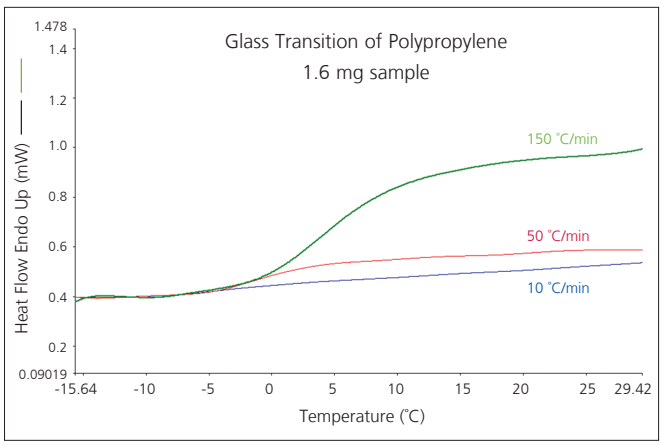

Figure 7. Detection of a Tg at different heating rates.

Application of HyperDSC to several Sanofi-Aventis samples

Polymorphism

This active ingredient comprises a mixture of physical forms (phases α + β).

A DSC measurement under standard conditions at 10 °C/min causes form α to transform into form β, which prevents the two crystalline forms from being quantified by comparing melting enthalpies.

In this case, HyperDSC inhibits phase transformation, and the melting endotherms of the two forms can thus be used to quantify the mixture. Figure 8 shows an experiment at 100 °C/min, carried out on a reconstituted mixture of form α / form β at 95 / 5%.

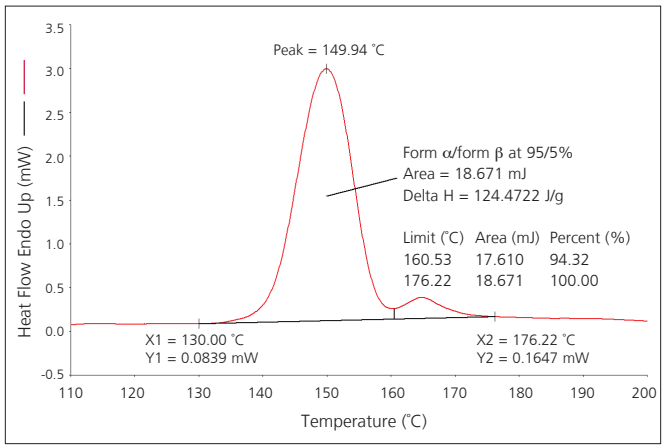

Figure 8. Detection of 5% active ingredient from β by HyperDSC.

Transition separation by HyperDSC

Glass transition and evaporation

This amorphous active ingredient has a high water content (about 10%) whose evaporation conceals glass transition during a DSC analysis under conventional conditions (5 °C/min). An experiment at 300 °C/min pushes water evaporation up to high temperatures, making it possible to detect glass transition, as is shown in Figure 9. The decomposition of the compound is clearly identified after evaporation.

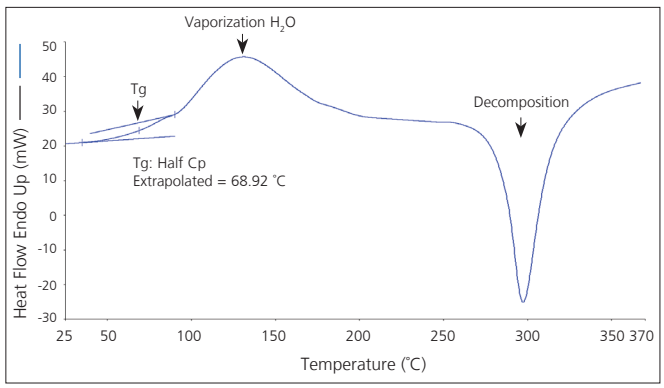

Figure 9. Separation of events by HyperDSC.

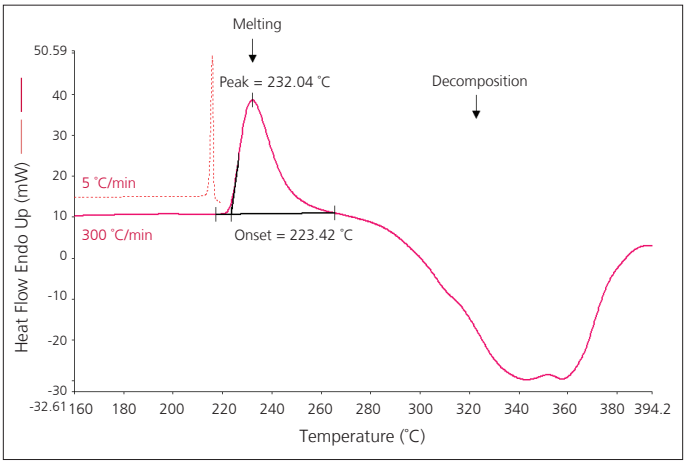

Figure 10. HyperDSC detection of the melting endotherm before decomposition of the active ingredient.

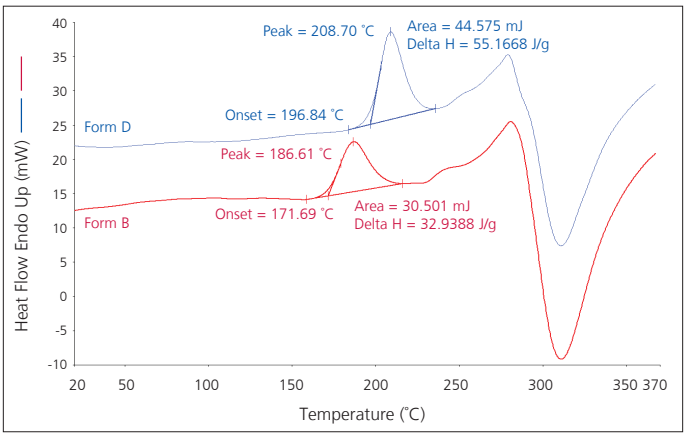

Figure 11. HyperDSC detection of the melting endotherm before decomposition of the active ingredient.

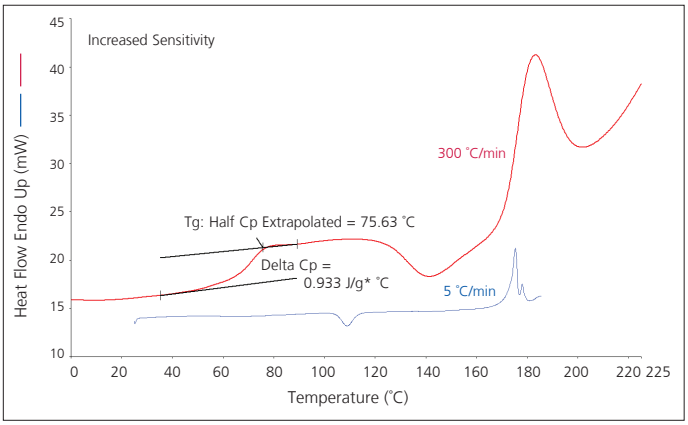

Figure 12. Comparison of different scannig rates on a lyophylisate.

Melting and decomposition

Figure 10 shows the capability of HyperDSC to distinguish melting from the chemical decomposition of the molecule.

Similar for forms B and D, two polymorphs of another component, HyperDSC clearly separates the melting endotherms of each form from the decomposition exotherm of the active ingredient as shown in Figure 11. It should be noted that the melting temperatures and enthalpies for the two polymorphs are different while the decomposition profile is the same at higher temperature.

Enhanced sensitivity for a Lyophilisate

The analyzed lyophilisate is made up half of glycine and half of an active ingredient in amorphous form. Figure 12 shows how HyperDSC contributes to the detection of the glass transition, in comparison with conventional DSC.

Summary

HyperDSC is an excellent tool to enhance material characterization. It provides multiple benefits in the pharmaceutical analysis. As demonstrated – HyperDSC increases the sensitivity of DSC analysis, separates transitions and allows better evaluation of polymorphic materials. The analysis time is very short and permits you to increase your sample throughput or to use this technique as a screening tool for new materials.

References

1. M. Hurtta; I. Pitkänen; Thermochimica Acta 419 (2004) 19-29.

2. Pijpers, Thijs F.J.; Mathot, Vincent B.F.; Goderis, Bart; Scherrenberg, Rolf L.; van der Vegte, Eric W.; Macromolecules 2002, 35, 3601-3613.

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