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A High-Sensitivity, High-Speed DSC Technique: Measurement of Amorphous Lactose

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The study of the amorphous content of pharmaceutical materials has been of great interest for many years. However, it has often been difficult to quantify very low levels of amorphous content using differential scanning calorimetry (DSC) because of the small energy changes associated with the measurement of the glass transition (Tg) at these low levels. As a consequence, other techniques have been preferred for this measurement, such as moisture sorption and solution calorimetry. The disadvantage of these techniques is their time-consuming nature.[1]

Recently, a DSC technique has been shown to give greatly increased sensitivity of DSC measurement. HyperDSC™ (**PerkinElmer**, Shelton, CT) allows the clear characterization of weak transitions such as the Tg of the type found in materials of low amorphous content. Examples of this type of analysis on glass transitions can be found in the work of Pijpers and Mathot.[2] In addition, because of the very fast scan rates used in HyperDSC, analyses are made in very short time periods, often less than 30 sec. The ability to measure these difficult transitions in a very short time gives significant benefits to the pharmaceutical and polymer industries.

The following study shows one of the capabilities of the technique brought about by the increase in sensitivity. Other applications include the study of polymorphism and recrystallization processes.[3]

Method description

The technique of DSC has been in use for many years for the characterization of materials properties. In a conventional DSC experiment, the amount of energy (heat) absorbed or released by a sample is measured as it is heated, cooled, or held at a constant temperature. DSC also performs precise temperature measurements.

The HyperDSC method for materials characterization provides the ability to make measurements of the thermal properties of a sample at very fast scanning rates. The fast heating and cooling rates associated with the method, from 200 °C/min to as fast as 500 °C/min, lead to a much increased heat flow signal and therefore dramatically increased sensitivity. The increased sensitivity is derived from the basic principle of the DSC measurement: DSC output is measured in mW (J/sec). As a DSC experiment is accelerated in the HyperDSC method, the same heat flow occurs over a shorter time frame and therefore the thermal event becomes larger. This allows extremely low-energy transitions to be identified and measured with ease.

With the technique, sample changes that can occur during slow heating when using conventional DSC scan rates can be eliminated or reduced. These events include recrystallization during melting, decomposition after melting, or possible structural changes. An identification of the sample in the "as received" state is possible using the method. In the time frame of the scan, the sample does not have the time to undergo any structural changes, and the material analyzed is therefore in the form in which it was presented to the instrument. Examples of this type of analysis on thermoplastics can be found in the work of Pijpers and Mathot.[2]

There are several other important benefits that are realized when using the technique. Its greater sensitivity allows the measurement of much smaller samples, down

to a few micrograms. This is beneficial when only a small quantity of sample is available, as during new product development or production ramp-up. The fast measuring rates allow users to increase sample throughput from the handful of samples often analyzed by traditional DSC to 100 or more runs per day using automated DSC systems that can apply the HyperDSC methods.

Instrumentation/methodology and technique practicalities

To achieve the fast scanning rates used in the method, ultralow-mass furnaces and small dimensions (*Figure 1*) are required to ensure the system is under control when making measurements at rates in the range of 200–500 °C/min. A power compensation DSC, such as the Diamond DSC (**PerkinElmer**), is the only system able to provide all of these features and to demonstrate this technique in practice.

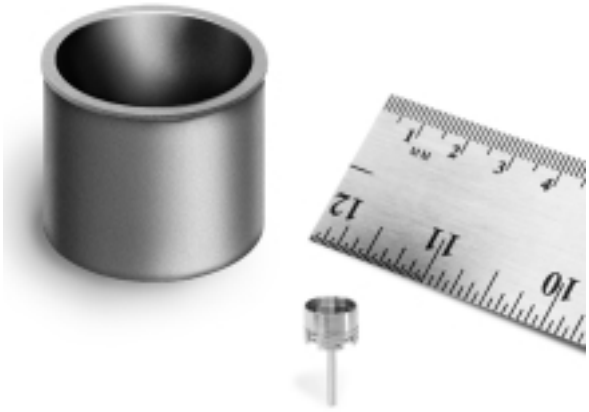

Figure 1 Small-power-compensation furnace compared to the larger heat-flux furnace behind it.

To obtain the most data from HyperDSC, the analyzer should have the ability to collect and measure data very quickly at the beginning of the scan by having small thermal transients, preferably of 12 sec or less. This means that it will quickly collect meaningful data without having to start at very low temperatures.

Because of the large heat flows of transitions that are associated with fast scan rates, it is vital that a large dynamic range is available during the measurements. It is possible that unless the instrument chosen allows a wide dynamic range, the analyzer signal may be swamped by the size of the transitions, which may be over 150 mW in size.

The following study was carried out using a Diamond DSC fitted with an Intracooler IIp (**PerkinElmer**) cooling system. The analyzer used a helium purge gas with a rate of flow of 30 mL/min, and 50-µL aluminum pans with pin holes were used for the entire study. The DSC was calibrated for temperature and heat flow at individual scan rates used in the study with reference materials having transitions in the range of interest. This is exactly the same procedure that would be used for conventional slow DSC scan rates.

Study of the Tg exhibited by mixtures of spray-dried lactose

There has been great interest over the years in the study of the Tg of amorphous lactose. Lactose is a very important excipient for pharmaceuticals and is used widely as a diluent in the formulation of tablets as well as being used as a carrier in dry powder inhalation (DPI) products.[4,5] It is because of its wide use as an excipient that information about the form in which it is manufactured is critical. Changes in its structural form can lead to changes in the characteristics and performance of a formulation, e.g., agglomeration within the powder of a DPI. This is an example of a case in which the recrystallization from small domains of amorphous material can cause a major effect on the performance of a pharmacuetical. There are many examples in the literature where instability in the physical structure of the active pharmaceutical ingredient leads to changes in bioavailability.[1]

HyperDSC was selected as the tool to determine the amorphous content because of the speed and sensitivity of the technique. Two samples of lactose were used for the study. The first sample was a spray-dried lactose that approached 100% amorphous content as determined by solution calorimetry, DSC, and thermogravimetric analysis (TGA),[6] and the second was a fully crystalline sample of the α-lactose monohydrate.

Figure 2 shows the effect of analyzing the spray-dried sample of lactose by conventional and HyperDSC methods.

Conventional DSC is represented by the data collected with scan rates of 20 °C/min and 100 °C/min, and the HyperDSC data are collected at scan rates of 250, 400, and 500 °C/min. All of the scans were performed on the same analyzer.

The Tg of lactose is normally seen in the temperature range of 100–120 °C and is difficult to identify using conventional DSC scan rates. However, the increased sensitivity that comes from using HyperDSC allows the identification and quantification of the Tg event. After examining the data, it was seen that the Tg of the lactose was in the temperature range of 80–100 °C. This lower Tg temperature was believed to be caused by the plasticization of the lactose by water, which is not lost during the fast scan. After the glass transition, an exotherm associated with recrystallization is observed, and this is followed by two melting events. The two peaks are associated with the two forms of lactose that recrystallize from the post-Tg material. The first peak is the melting of anhydrous α lactose, and the second peak is associated with β lactose.

It is also worth noting that recrystallization of the sample still occurs even at 500 °C/min and there is no loss of resolution of the melting of the two forms of crystalline lactose. The melting profiles of the two forms of lactose show a relationship between the recrystalline kinetics and the heating rate. Taking note of the differences in the melting enthalpies, it appears that the relative amount of the lower melting form, anhydrous α lactose, increases when the heating rate is raised. Consequently, the relative amount of the higher melting form, β lactose, that recrystallizes post-Tg is reduced at the higher scan rates.

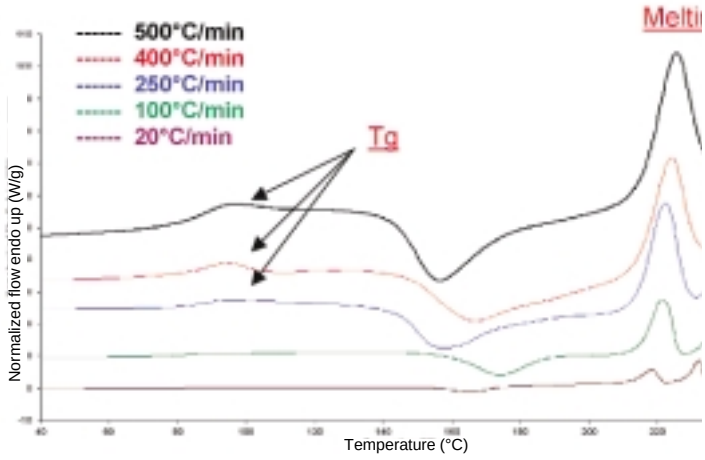

Figure 2 Thermogram showing the analysis of spray-dried lactose at a variety of heating rates.

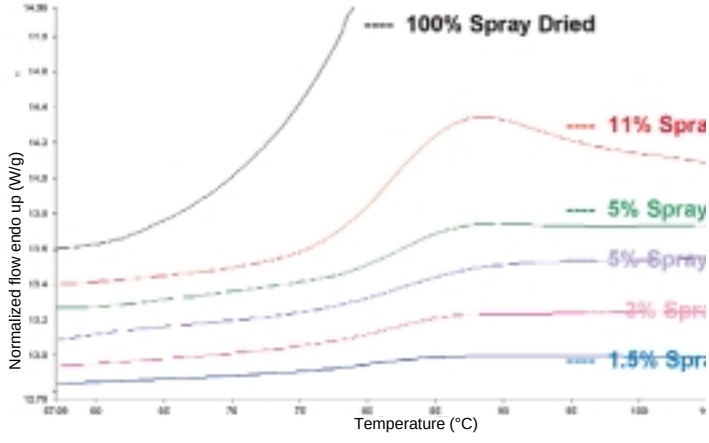

Figure 3 Thermogram showing the analysis of the Tg of mixtures of spray-dried lactose.

Examination of mixture of spray-dried lactose and α-lactose monohydrate

In order to test the sensitivity of HyperDSC for low amorphous content, a series of samples were prepared by mixing a known percentage of spray-dried lactose into a sample of α-lactose monohydrate. A range of percentages were chosen from 100% spray-dried lactose down to 1.5% spray-dried lactose mixed into α-lactose monohydrate.

Separately, a sample of 1% amorphous content lactose was obtained from **PharMaterials** (London, U.K.). This independent sample had been found to contain 1% amorphous content by a solution calorimetry method, and is typical of the samples received for analysis in the industry.

In order to be able to analyze the Tg of the very low percentages of spray-dried lactose, a HyperDSC rate of 500 °C/min was chosen. This rate was found to show the largest Tg on the spray-dried lactose and was therefore used in these analyses. *Figure 3* shows the Tg region for the samples prepared.

The step height change of the Tg was measured from the onset to the maximum height for the sample, giving an

indication of the change of the specific heat of transition for the Tg.

This procedure was carried out for all of the samples. It was found that there is a linear relationship between Tg height and percentage amorphous content, as shown in *Figure 4*. The data in Figure 4 show the potential for the development of a methodology for quantitatively measuring very low amorphous content using HyperDSC, and for the case of lactose this has been shown for levels lower than 1.5%. The sample of 1% amorphous content analyzed under the same conditions showed a clear Tg and verified the sensitivity of the technique.

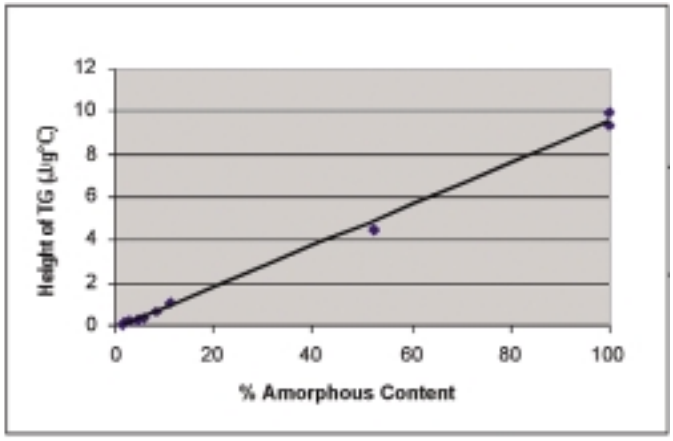

Figure 4 Step height of the lactose Tg as a function of the amorphous content.

Conclusion

This study demonstrates the ability of HyperDSC to measure very low amorphous content in this system down to levels better than 1.5%, a lower level of detection than was previously possible using conventional scan rate DSC methods. In addition to providing the high sensitivity required to make these measurements, the technique also provides a major time savings over other methods, with average sample analysis on the order of 30 sec.

HyperDSC has many benefits for pharmaceutical and polymer research laboratories because it can offer the ability to rapidly screen samples with minimal sample preparation while measuring very low levels of amorphous material.

References

1. *Yu L. Amorphous pharmaceutical solids, preparation, characterisation and stabilisation. Adv Drug Deliv Rev 2001; 48:27–42.*
2. *Pijpers TFJ, Mathot VBF, Goderis B, et al. High-speed calorimetry for the study of the kinetics of (re)vitrification, crystallization, and melting of macromolecules. Macromolecules 2002; 35:3601–13.*
3. *Ford JL, Mann TE. High speed differential scanning calorimetry of polymorphic transitions in nifedipine. J Pharm Pharmacol 2002; 54:S1.*
4. *Hogan SE, Buckton G. The quantification of small degrees of disorder in lactose using solution calorimetry. Int J Pharmaceutics 2000; 207(1-2):57–64.*
5. *Chidavaenzi OC, Buckton G, Koosha F. The effect of co-spray drying with polyethylene glycol 4000 on the crystallinity and physical form of lactose. Int J Pharmaceutics 2001; 216(1-2):43–9.*
6. *Shergill S. Determination of amorphous content using differential scanning calorimetry (DSC). MPharm Thesis. Kings College, University of London.*

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