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DSC AND TG/DTA AS PROBLEM-SOLVING TOOLS: CHARACTERIZATION OF PHARMACEUTICAL COMPOUNDS

Problem

A scientist working for a major pharmaceutical R&D center is having difficulties in interpreting the DSC results obtained on an excipient material. The results obtained on the compound are displayed in Figure 1 and the scientist is uncertain as to the assignment of the observed transitions.

Solution

To order to enhance the characterization of pharmaceutical materials, as well as many other types of samples, cyclic DSC and simultaneous TG/DTA provide two very powerful approaches.

Differential scanning calorimetry (DSC) measures heat flow into or out of a sample as the material is either heated, cooled or held isothermally, or a combination of these. Cyclic DSC is performed by heating a sample, cooling it back to the desired starting temperature, and then reheating. A direct comparison can be made between the data obtained during the first and second heating segments to establish the nature of the transitions taking place within a sample as it is heated. Using cyclic DSC, events can be better identified as to whether they are reversible, such as Tg, or irreversible, such as the loss of water or crystallization.

Cyclic DSC experiments can be performed relatively quickly, by heating at 20°C/min, cooling back at 40°C/min, and then reheating at 20°C/min. Advantages offered by cyclic DSC over temperature modulated DSC (TMDSC) are the time savings and ease of use. The maximum heating rate that can be used with TMDSC is 5°C/min. If a sample is heated from -40 to 250°C, the total time of the TMDSC experiment would be 58 minutes, at 5°C/min. Using cyclic DSC, as described above, the total time would only be 45 minutes.

The Seiko EXSTAR DSC6000 offers the following major advantages for the study of pharmaceutical compounds:

- High sensitivity (the Seiko EXSTAR DSC6100 offers the highest sensitivity of any DSC instrument on the market)
- Very stable baseline performance for highly reproducible results
- Exceptional subambient performance for the study of Tg's near or below 0°C
- State-of-the-art add-on robotic accessory for unattended operation

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- 20 point temperature calibration for unsurpassed accuracy
- 10 point enthalpic calibration for highly accurate heat capacities and heats of transition

Thermogravimetric analysis (TGA) measures weight loss (or gain) as a sample is either heated or held under isothermal conditions. The data obtained via a TGA instrument can be further enhanced through the ability to simultaneously measure both the TGA weight loss and the heat flow response. The Seiko TG/DTA provides this powerful ability which greatly aids in the characterization of the properties of a sample.

The Seiko EXSTAR TG/DTA6000 offers the following advantages:

- Simultaneous measurement of TGA and DTA signals
- Direct temperature calibration since thermocouple is in direct contact with sample pan
- True horizontal purging for optimal performance with coupled techniques such as TGA-FTIR or TGA-MS
- Ability to perform measurements in auto stepwise isothermal mode for unsurpassed resolution of severely overlapping weight loss events
- High sensitivity
- Stable baseline performance
- 20 point temperature calibration for the greatest accuracy across the entire temperature range (up to 1500°C)
- Direct conversion of DTA signal to DSC units (mW) via 10 point DSC enthalpic calibration

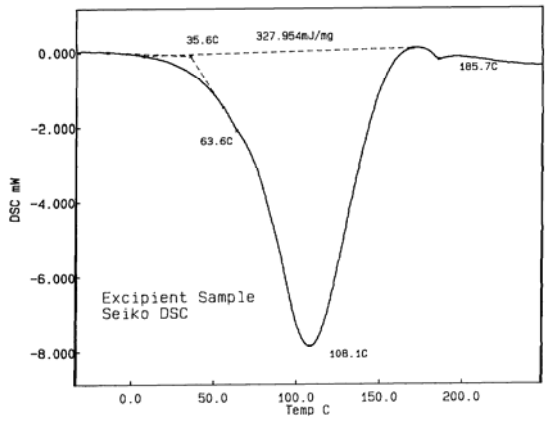

Figure 1

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Displayed in Figure 1 are the DSC results obtained on a pharmaceutical compound. Without further information about the sample, it is difficult to interpret the results. What is the cause of the large endothermic peak at 108°C? What is the nature of the small event at 180°C? Both cyclic DSC and TG/DTA can help in the assignments of the transitions and make data interpretation much easier.

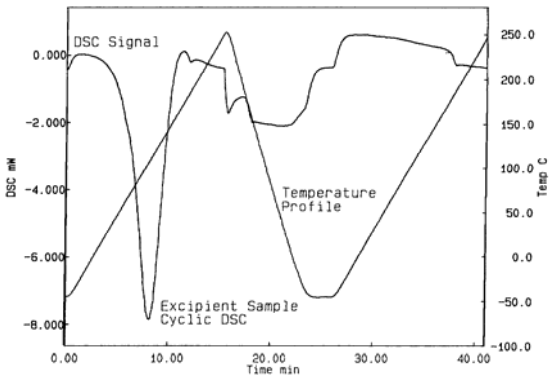

Figure 2

Displayed in Figure 2 are the complete cyclic DSC results obtained for the pharmaceutical compound. The plot shows the DSC heat flow and sample temperature as a function of time. In the two heating ramps, the sample is heated at a rate of 20°C/min while, during the cooling segment, the sample is cooled at a rate of 40°C/min. The temperature-time profile demonstrates the outstanding temperature control offered by the Seiko DSC using 22 bit, ultra high resolution A/D converter technology (US Patent 4734678).

Three separate data files can be obtained from the cyclic DSC experiment: the 'as-received' or 1st heat results; the 2nd heat data, which reflects the reversible aspects of the sample; and the subtracted file obtained by simply subtracting the 2nd heat data from the 1st heat results. The subtracted file represents the irreversible characteristics of the sample.

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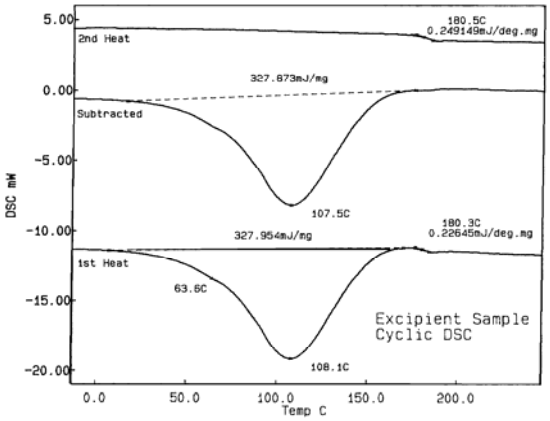

Figure 3

Displayed in Figure 3 are the three separate data sets for the pharmaceutical compound obtained using cyclic DSC. The lower most curve represents the DSC results for the 'as received' sample. The upper most trace is that of the 2nd heating segment and this represents the reversible aspects. The center curve is the subtracted data set and reflects the irreversible aspects of the material.

The cyclic DSC results reveal that the endothermic event at 108°C is irreversible in nature and is most likely due to the evolution of moisture from the sample. This can be easily confirmed using TGA. The 2nd heat results show that the small transition observed near 180°C is actually a glass transition event. A classic stepwise change in heat flow is clearly observed in the 2nd heat data set confirming that the transition at 180.5°C is a Tg with

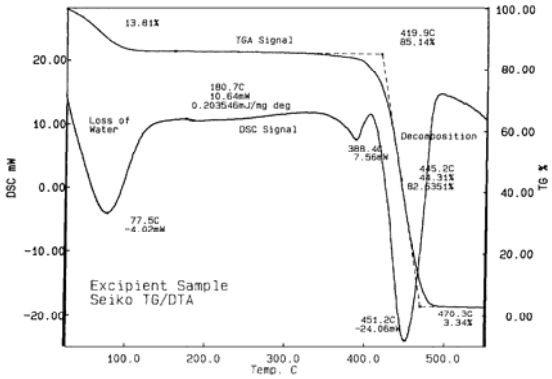

Figure 4

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a change in heat capacity, ☐Cp, of 0.249 mJ/mg deg.

The conclusions made using cyclic DSC were tested for accuracy using the Seiko TG/DTA and these results are displayed in Figure 4. This figure shows the TGA weight loss (%) and the simultaneous DTA data which was automatically converted to DSC heat flow units (mW).

The TGA/DSC results confirm that the DSC endothermic event observed in the vicinity of 108°C is indeed due to the loss of volatiles, most likely water given the temperature. The amount of water is found to be 13.8%, based on the TGA weight loss data. The simultaneous TGA/DSC results show that the TGA weight loss corresponds exactly to the DSC endothermic peak.

The main decomposition of the pharmaceutical compound is observed as a large mass loss event in the TGA signal with an onset temperature of 419.8°C. The total mass loss is 82.6% due to the thermal degradation of the sample.

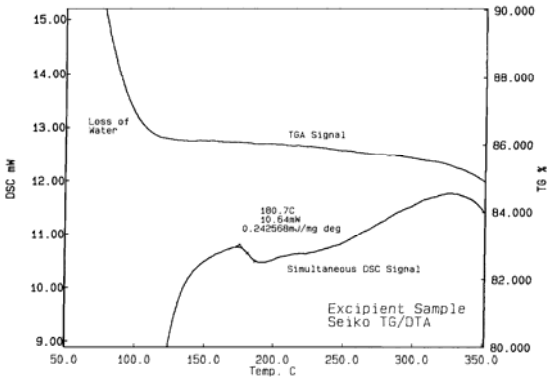

Figure 5

The simultaneous DTA-DSC signal associated with the Seiko TG/DTA has enough sensitivity to detect the small glass transition event associated with the pharmaceutical compound. Displayed in Figure 5 is an enlarged view of the DSC and TGA signals in the region near Tg. Since the sample does not lose mass in this region, the TGA data is flat while the simultaneous DSC signal does exhibit the small change in heat flow associated with the sample's glass transition event. The Tg as obtained using the Seiko TG/DTA agrees very well with that obtained via the dedicated Seiko DSC instrument (180.7°C from TG/DTA and 180.5°C from DSC).

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Summary

Cyclic DSC experiments can be performed on materials to better aid in the identification of transitions observed while heating. Cyclic DSC experiments can be conducted relatively quickly and three data sets are obtained: 1st heat or the 'as received' results; the 2nd heat data, reflecting reversible aspects and making it easier to see glass transition events; and the subtracted data set which reflects irreversible aspects of the sample. TG/DTA further aids in the analysis of a material by helping in the assignment of irreversible events, such as the loss of volatiles. The simultaneous measurement of TGA and DTA signals makes the assignment of the transitions much less ambiguous. The data is further enhanced using the automatic conversion of the DTA signal to user friendly DSC units.

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