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Purity Measurements of Pharmaceuticals and Organics by DSC

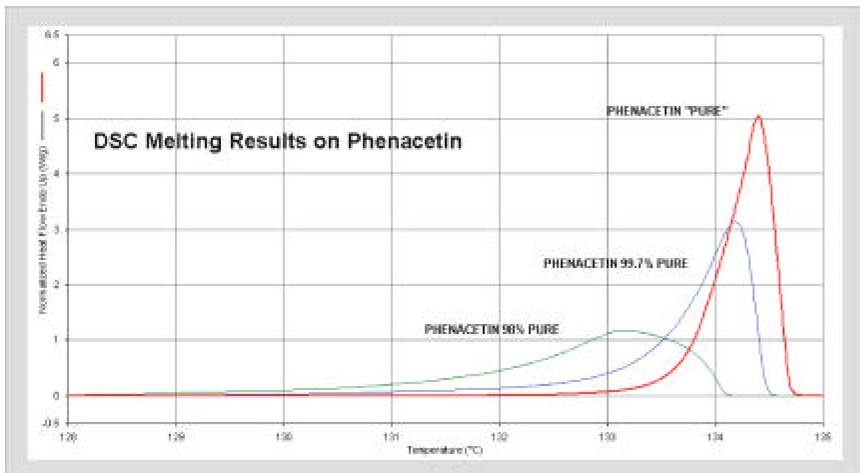
W.J. Sichina, National Marketing Manager

One of the most important tests that can be performed for pharmaceutical and organic materials is the assessment of its purity by differential scanning calorimetry (DSC). The determination of absolute purity of pharmaceuticals and organic materials by DSC has been an accepted technique since the development of commercial DSC instruments in the early 1960s. DSC has proven to be a rapid, accurate, precise and easy-to-use approach for the assessment of the purity of many different types of materials.

PerkinElmer offers a number of DSC instruments for the characterization of a wide range of materials and applications. For purity analysis, the power compensated DSC, available only from PerkinElmer, provides a number of important features and benefits for the assessment of the purity of organic materials:

- Very low mass furnaces (1 g) for sample side and reference side providing rapid response times critical for the accurate measurement of purities
- Measurement of true heat flow rather than temperature differential for more accurate calorimetric determinations
- Use of PRT or platinum resistance thermometers, rather than thermocouples, for the most accurate and precise measurement of sample temperature
- Outstanding resolution providing more theoretically correct melting responses (i.e., narrow peak half-width and greater peak intensity)
- Very high sensitivity

Figure 1. DSC melting results on phenacetin samples with different levels of impurities.



In contrast, many heat flux DSC instruments use a large mass furnace (silver block with mass of 200 g), which provides a relatively slow response time. In addition, the heat flux type DSC instruments utilize thermocouples, which provide a less accurate response as compared to the PRT temperature measurement system. For accurate purity analyses, the DSC cell response time and the performance of the temperature measurement devices become critical. The PerkinElmer power compensated DSC offers the highest possible performance for the measurement of purity of organic materials.

The determination of the purity of an organic substance by DSC is based upon the well-known fact that the presence of even minute amounts of an impurity in a material lowers the melting point and broadens its overall melting range. An example of the effects of an impurity on the melting behavior of an organic substance may be seen in Figure 1, which shows the DSC results on three phenacetin samples of different purity levels.

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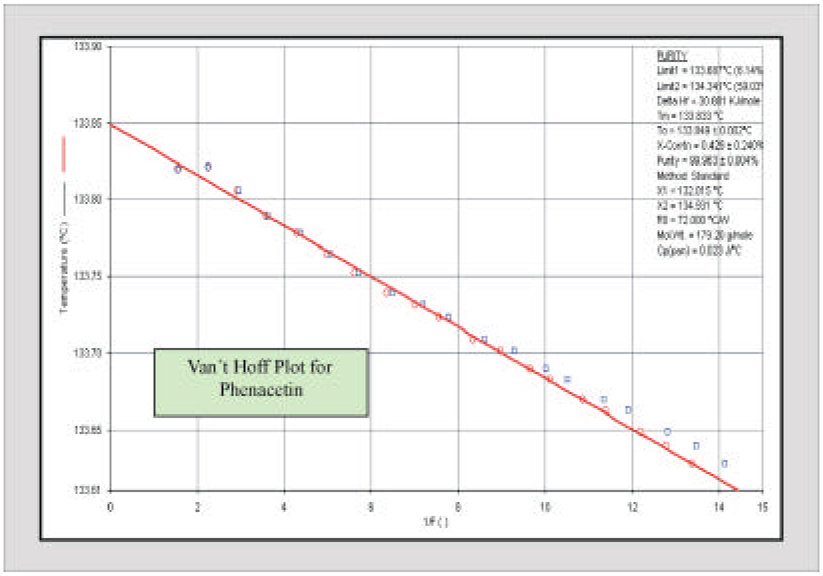
Figure 2. Van't Hoff plot for phenacetin sample generated using purity option in Pyris software.



The DSC results show that the melting point of the 'pure' phenacetin becomes depressed and broader with increasing levels of impurities. This phenomenon can be used to assess the quantitative purity level of the material.

The purity of an organic substance can be estimated by DSC based on the shape and the temperature of the DSC melting endotherm, as is shown in Figure 1. This procedure utilizes the van't Hoff equation, which is given as:

$$1/Fs = [\Delta H/R] \bullet [To - Ts] / To^2 \bullet [1/X_2]$$

where Ts is the instantaneous sample temperature and the melting temperature (°K) and To is the melting temperature of the pure substance, ΔH is the heat of melting of the pure material (J/g), X_2 is the mole fraction of impurity in the sample, R is a constant (8.314 J/mole°), and Fs is the fraction of sample melting at temperature Ts. The fraction Fs is given as As/At where As is the area of the melting endotherm up to temperature Ts and At is the total area of melting endotherm.

The van't Hoff equation predicts that a linear response should be obtained if the sample temperature, Ts, is plotted against the reciprocal of the fraction of the sample melted at that temperature. What is done with the DSC purity approach is to divide the melting endotherm into partial melting areas to give the fraction melted, Fs, at a temperature Ts. The slope of the line yields the melting point depression, $RTo^2X_2/\Delta H$, and a Y-intercept value of the melting temperature of the 100% pure substance, To.

Because the PerkinElmer power compensated DSC provides the highest possible resolution as compared to heat flux DSC instrument, under identical experimental conditions, the power compensated DSC is able to yield more well-defined and more accurate partial areas of melting. The partial areas are not 'smeared' over a narrow temperature interval, as would be the case with the lesser resolved heat flux DSC. The high resolution afforded by the power compensated DSC yields inherently better partial melting areas; and, therefore, better purity analysis.

This is shown in Figure 2 for the most pure phenacetin sample. The results were obtained using the purity analysis option in the PerkinElmer Pyris software.

In practice, when analyzing samples for purity using DSC, best (most accurate) results are obtained using the following conditions:

- Slow scanning rates (1 to 2 C/min)
- Small sample mass (approximately 1 to 2 mg)
- Proper sample encapsulation
- Correction for thermal resistance
- Heat capacity contribution of the sample pan and sample
- Proper temperature selection for the analyses
- Van't Hoff linearization

With regards to sample encapsulation, the volatile aluminum sample pan is recommended for most samples. It is important to ensure that the bottom of the pan is flattened after crimping to obtain the best results.

All DSC instruments require a correction for thermal resistance, Ro, in order to generate the most accurate purity results. With a DSC, there is a

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PerkinElmer Instruments
761 Main Avenue
Norwalk, CT 06859-0010 USA
Tel: 80O-762-4000 or
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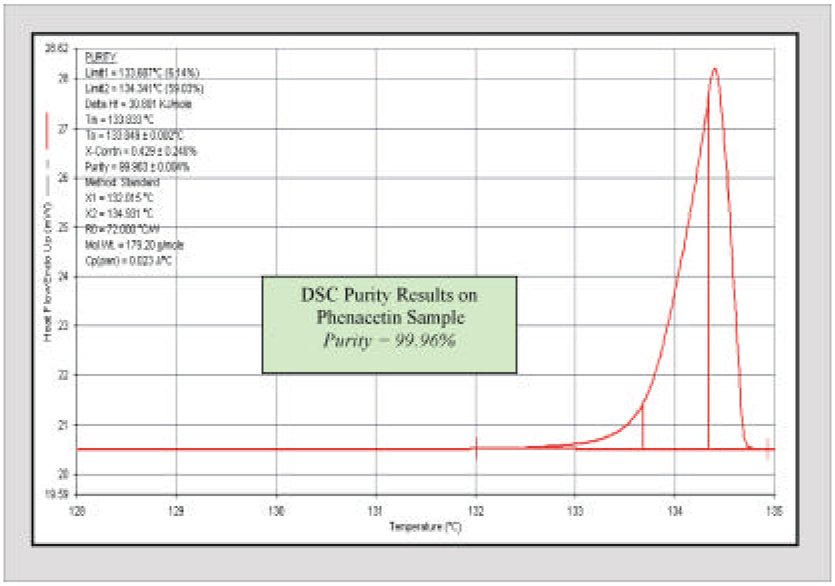
Figure 3. DSC purity results on phenacetin material.



small temperature difference between the true sample temperature and the temperature of the sample holder as a result of this thermal resistance. This temperature difference is proportional to the thermal resistance constant, which is constant for a given DSC and is reproducible from run to run. This thermal resistance involves assessing the slope of the onset of the melting endotherm of a high purity indium metal standard. Using the slope of this onset line, the thermal resistance of the DSC can be calculated using the following equation:

$$Ro = dTs/dt$$

Where Ro is the thermal resistance constant and dTs/dt is the scanning rate. Although the correction is very small, it does significantly affect the purity results. With the power compensated DSC from PerkinElmer, this thermal resistance correction is relatively small compared to more massive heat flux DSC instruments.

The PerkinElmer purity software features a correction for the heat capacity of the sample pan and the sample itself. The heat capacity contributed by the pan and the sample is oftentimes neglected, but it does have a small, but significant, effect on the assessment of the partial melting areas of an organic substance. The PerkinElmer software does take this small heat capacity effect into account thus providing more accurate purity determinations.

The final point regarding the purity analysis concerns the van't Hoff linearization. In many cases, it has been found that the van't Hoff plot obtained from the melting curve is not the straight line as is predicted from the van't Hoff equation. Instead, a curved line is sometimes obtained. In most cases, the curved response results from the underestimation of the amount of melting which has occurred at lower temperatures which is not observable on the DSC melting results. The higher the degree of impurity, the greater the amount of departure from linearity. This underestimation of the amount of initial melting results in larger calculated values of the melting fraction term, 1/F, resulting in the curved response of the van't Hoff plot. Since the amount of peak area which is undetected at the lower temperatures is constant (referred to as x) for a given DSC, the van't Hoff plot can be made linear by adjusting the value of x until a best-fit linear plot is obtained. The PerkinElmer purity software automatically assesses the value of x and corrects the results in the subsequent purity analysis. Figure 2 shows the uncorrected data in blue (slightly curved) and the corrected data points (linearized) in red.

Shown in Figure 3 are the results obtained from the DSC purity analysis on the phenacetin material. The purity information is displayed in the left column in the plot. The purity of the phenacetin substance was found to be 99.96%.

The PerkinElmer Pyris DSC purity analysis software permits the assessment of purities for samples which undergo simultaneous degradation during melting, which frequently occurs with pharmaceutical materials. This is done using a multiple linear regression analysis (MRL) approach and this special treatment of decomposition for purity

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Norwalk, CT 06859-0010 USA
Tel: 800-762-4000 or
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calculations is unique to the PerkinElmer software.

Summary

DSC can be used to assess the purity of organic substances including pharmaceuticals. The PerkinElmer Pyris software features purity determinations directly in the DSC software, which greatly facilitates ease-of-use. In addition to the standard van't Hoff approach, the PerkinElmer software also features multiple linear regression analysis for the determination of purities for materials, which undergo simultaneous melting and decomposition. The PerkinElmer power compensated DSC provides the highest possible resolution (e.g., greatest peak intensities and narrowest peak half-widths) for the best possible accuracy and precision. The power compensated DSC approach yields well-defined partial heat of melting intervals, critical for the proper determinations of purity, without the 'smearing' that can occur with heat flux DSC devices. In addition, the PerkinElmer power compensated DSC features the high performance platinum resistance thermometer (PRT) temperature sensors, which provide greater sample temperature accuracy and reproducibility as compared to the lesser performing thermocouple systems.

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