Purity Determination and DSC Tzero™ Technology

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ABSTRACT

The determination of absolute purity by DSC has been an accepted technique since the mid 1960s. One source of error in the purity method, that has limited its applicability and accuracy, is uncorrected thermal lag. New DSC instrumentation incorporates these corrections directly into the heat flow signal. This superior approach leads to improved peak resolution and to more accurate purity analysis. It is likely that this advance will allow purity analysis to be performed at faster heating rates and the purity method will be extended to higher levels of purity.

INTRODUCTION

The melting of a pure material takes place over an infinitely narrow temperature range. The result is a sharp melting spike on a DSC trace at a temperature characteristic of that material. For a material that only has a small amount of impurity (that dissolves in the melt, but not in the solid) the melting point is depressed and the melting range is broadened. This is the basis of the calorimetric purity determination by observed melting point depression. The equations that predict the rate of heat flow versus temperature for melting a material (of given molecular weight, melting point, heat of fusion and purity) are derived from thermodynamic relationships, and predate the existence of commercial DSC's (*1*). A. P. Gray adapted these relationships to the non-ideal measuring systems of DSC's, in the 1960's (*2*). This purity method is thoroughly discussed and evaluated in ASTM Special Technical Publication (STP) Number 838 (*3*), and there is an ASTM standard method E 928 that details procedures and precautions with its use (*4*).

Although there are numerous theoretical and practical limitations of the method, it has proven a useful tool for quickly determining the absolute purity of purified organic materials, where the only impurities present are ones that are difficult to separate through ordinary separation techniques. The beauty of the method is that it determines from a single DSC run the extent of *impurity* to within 5 or 10 percent independently of which impurities are present. Figure 1 shows the melting endotherms of phenacetin (p-acetophenetidide) at three levels of impurity obtained from NIST for purposes of interlaboratory study (*5*). The purities are 99.97, 99.5 and 99.0 %.

It was clear from the earliest efforts to utilize the theoretical equations, that the thermal resistances and capacitances that are inherent to the DSC and sample encapsulation, affect the shape of a sharp melting peak. This is because the heat flow into the melting sample must flow across the thermal resistances of the DSC cell and across the small air gap that separates the DSC sensor-surface from the sample itself. This heat flow produces a temperature drop, known as *thermal lag*. Thus, the recorded temperature (of the sensor) is not the same as the actual sample temperature. Moreover, during melting of a pure material the actual sample temperature stops increasing during the melt and stays constant until the last bit of sample is melted. Meanwhile, the DSC set point temperature continues to increase linearly at the designated heating rate. The sample pan, which is in good contact with the sample, is thus being programmed at a *nonlinear* rate, producing a heat flow effect that distorts the peak shape.

One way to correct this thermal lag is to correct the purity calculation for the heat capacity of the sample pan and the thermal resistances in the system. To obtain these parameters with sufficient accuracy requires that the DSC user make additional DSC measurements of the contact resistance (R_0) and the heat capacity of the pan (Cp(pan)) at the temperature of the purity analysis. R_0 is obtained from the leading edge slope of the melting peak of a pure material melting in the same temperature range and using the same pan type. Cp(pan) can be obtained from the pan weight and the specific heat capacity of the pan material.

Another approach is to estimate these corrections and use conditions (small sample size, very slow heating rate) to minimize the effect. Besides taking more time, these conditions result in a much lower heat flow signal, resulting in noise and baseline curvature errors. These limitations have reduced the practicality of the technique and tempted users to take short cuts, resulting in compromised accuracy.

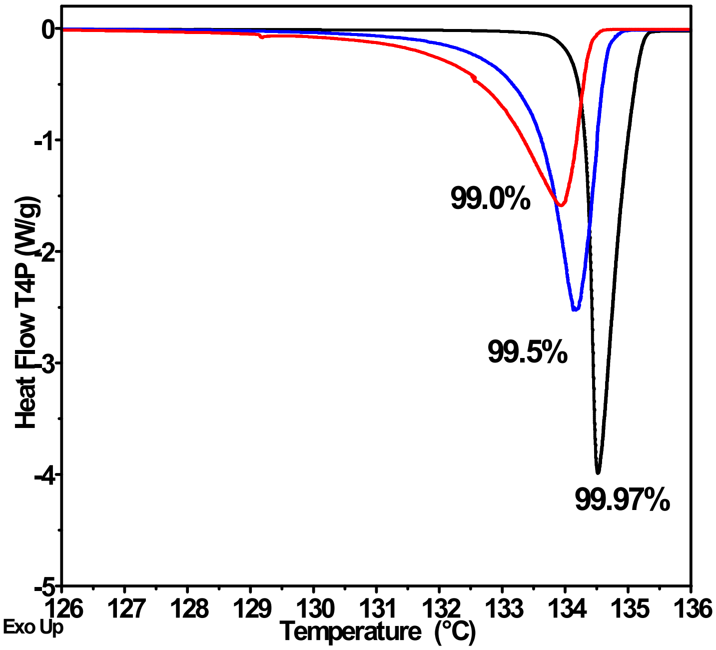

Figure 1 - DSC Melting Curves
of Phenacetin at Three Purity Levels

INSTRUMENTATION

Tzero™ Technology makes use of an alternative DSC cell design enabling the thermal resistances and capacitances to be accurately measured as part of a standard calibration process. This capability is accomplished by using a DSC sensor with an additional Tzero thermocouple positioned between the sample and reference sensor as the set point controller for the DSC, as shown in Figure 2. This physical arrangement, known as Tzero Technology, compensates for the thermal lags in the DSC. The heat flow is described by a four-term heat flow equation, rather than by the single-term equation conventionally assumed (*6*).

Advanced Tzero™ Technology employs a model of the entire DSC-Sample system and utilizes a more complete, four-term heat flow equation that effectively compensates for all thermal lag effects (*7*). As a result, all DSC melting peaks are automatically corrected for the thermal lag related errors. This is seen by comparing samples of high purity as shown in Figure 3. Comparing the onset and peak temperatures on these two plots (taken from the same DSC run, but using different sensor signals) shows how the peak shape, especially the leading edge, that should be vertical in this case, is more accurately represented using Advanced Tzero Technology. It is this leading edge of the purity peak that is analyzed in the purity software.

While the improvements in the DSC signals to remove peak distortion has the most dramatic improvement effect on the purity determination, there are some other aspects of Tzero Technology that warrant mention.

First, the use of the four-term heat flow equation also results in a flatter DSC baseline, since two of the four terms remove effects of asymmetry in the DSC. This asymmetry is the cause of baseline curvature, a dramatic limitation of some DSC instrumentation.

Second, improvements in the design of the furnace and cooling system of the Tzero DSC result in a much more reproducible baseline. This is because the cooling accessory is coupled to the furnace by nickel rods that offer a constant heat flow path despite the dimensional changes inherent in such extremes of temperature. The differential expansion is responsible in part for the shifting baselines of traditional DSC designs. Since baseline effects limit the *sensitivity* of a DSC, the result of this improvement in baseline reproducibly is improved sensitivity for measuring small samples.

Also, by reducing the negative aspects of extreme temperature gradients, the nickel rod coupling enables boosting the heating and cooling power, so that the system is capable of a greater range of heating and cooling rates, and of temperatures. By

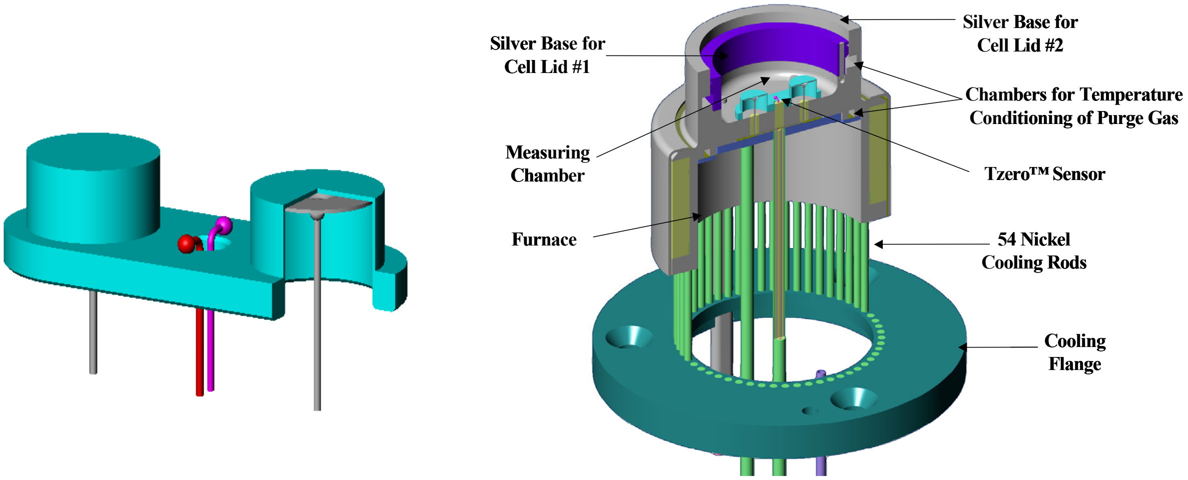

Figure 2 - Tzero™ Sensor (Left) Q Series™ DSC Cell (Right)

improving the furnace control feedback loop, using the Tzero sensor and heater (PID) control, the equilibration time has also been dramatically improved.

PURITY DETERMINATION

A traditional DSC curve and purity calculation are seen in Figure 4. The sample is a 1 mg sample of over-the-counter ibuprofen pain medication. The sample weight has been adjusted to take into account the inert ingredients in the formulation. These ingredients are sufficiently dissimilar to the active ingredient that there is no mutual dissolution either in the solid or liquid phase. Hence, the weight fraction of the excipient does not affect the purity analysis. This lack of melting depression by the inert ingredients is normally the case for drug formulations, since without mutual dissolution chemical interaction is unlikely. Were it otherwise, drug-excipient interaction would reduce product shelf life.

The heating rate used in Figure 4 is the common 1 °C/min (*3*). The sample was hermetically sealed to ensure there is no loss of volatiles, the heat of which might effect the purity determination. Unfortunately, as with most hermetic pans, the mass of the pan is greater than that of a standard pan, and the coupling to the DSC is poorer. Both of these would ordinarily be negatives for a purity analysis, since the thermal lag corrections are proportional to these factors. However, because of Advanced Tzero™ Technology both of these effects are addressed in the DSC signals.

The purity calculation data in Figure 4 is the van‘t Hoff plot, the fitting of the partial area data versus the temperature corresponding to those partial areas. That is, each of the data points reflects a determination of the fraction of the total area, the fraction of the material that has melted up to that temperature. For high purity samples the partial area measurements are very small. (The corresponding points on the DSC curve are closely spaced in the region of the pre-melting tail.) Any errors in the DSC signal may cause scatter or bias in the partial area data. Hence, to obtain reliable purity determination data requires much of a DSC.

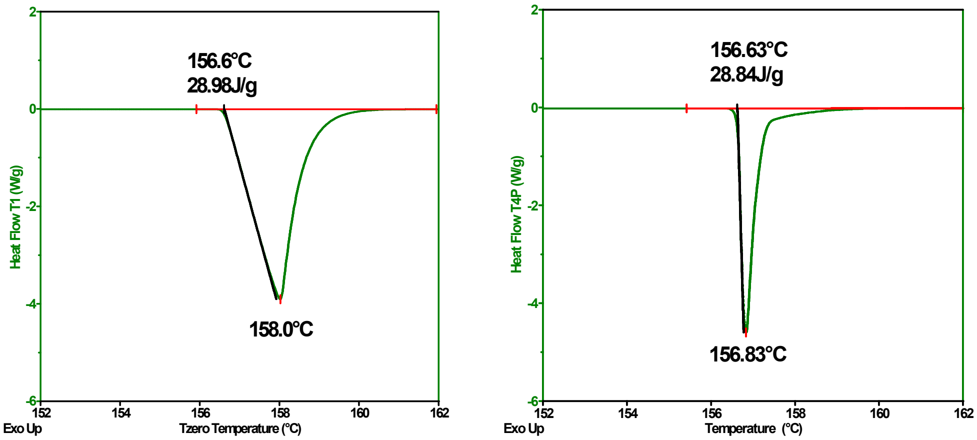

Figure 3 - 3.5 mg Indium by Traditional DSC (left) and Using Advanced Tzero™

High resolution. The area of each incremental partial area "slice" of the peak should represent only the data in that narrow temperature range. If a DSC lacks resolution it means that each data point has been smeared (averaged) to some extent with its neighbors. The Q1000 DSC with Advanced Tzero Technology is shown to give the highest resolution of any DSC when compared using the TAWN resolution index (*6*). This is a critical need for purity analysis.

- **Low Noise.** Noise in the DSC signal will cause scatter in the partial area data and reduce the accuracy of the determination. Noise will also prevent the analysis of small samples, that are preferred for this analysis, and often a small sample is all that is available. (If the DSC data is smoothed, it will change the results of the purity calculation.)
- **Straight Baselines.** As can be seen in Figure 4, the melting starts very gradually. From theoretical considerations, a 99 % pure material is 20 % melted by 3 ºC below the melting point (*7*). So in fact, every DSC melting peak with an impurity has a long, gradual, low-temperature "tail" that is part of the overall melting. It is important to start the peak baseline well below the extrapolated onset to the peak. Baseline curvature or drift will not only adversely affect the total area of the peak, but more importantly, it will bias the partial area data, that when fitted to the van't Hoff equation will cause error in the determination of purity.

One of the biggest limitations to accurate purity analysis is the distortion of melting peak shape by the temperature gradient between sample and sensor. Even correcting this in the purity software doesn't completely correct for this problem because of uncertainties in leading edge slope values used. Advanced Tzero automatically addresses these effects by using the full four-term heat flow equation, evaluated through calibration. Moreover, removing the distortion provides additional benefits for purity determination especially for high purity materials. That is, for these analyses the information of the impurity is mostly held in the small portion of the leading edge of the melting peak. So, to obtain the best analysis, the user selects limits for the partial area calculation that cover this portion of the melting peak (see Figure 5, right hand side). From the Advanced Tzero data from a Q1000, this can be seen as the data up to the

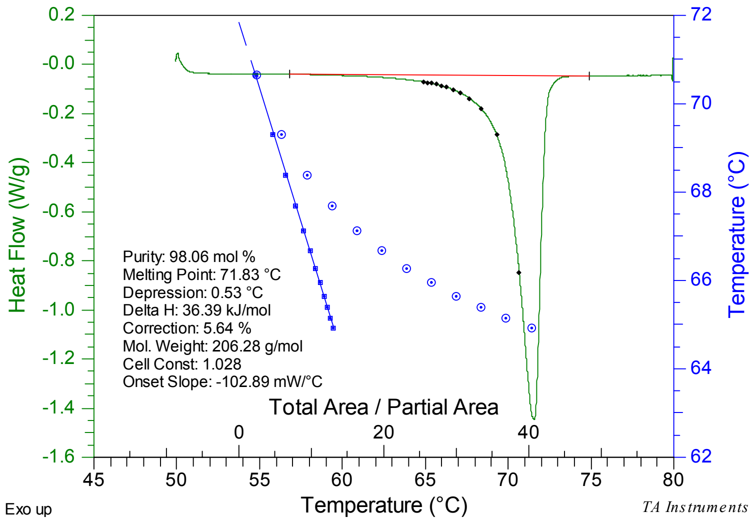

Figure 4 - Purity Analysis of Ibuprofen

inflection point of the leading edge. But for a conventional DSC it is difficult to assess this point because of the heat flow distortion. The left side of Figure 6 shows the leading edge of the melting peak for the same DSC run but analyzing the traditional one term heat flow relationship. This is the signal analyzed by all conventional DSC's including power compensation and heat flux designs.

Detecting reaction products caused by interactions between the active drug and another potential formulation component is one of the uses of the DSC purity determination (*8*). The procedure for this calls for determining the purity of the active component, then grinding it with all the components, aging the mixture at an elevated temperature, and then rerunning the mix to assess additional impurities. If there is no loss of purity it is an indication that the components in the formulation are stable and will resist shelf-life degradation of the active component. Figure 6 shows two samples of an over-the-counter ibuprofen formulation, one from a container well past the expiration date. The lower temperature curve is from the aged sample and indicates a change in its purity. (*This figure is meant to demonstrate the technique, and not meant to infer that the lower purity product is in any way hazardous or less effective.)*

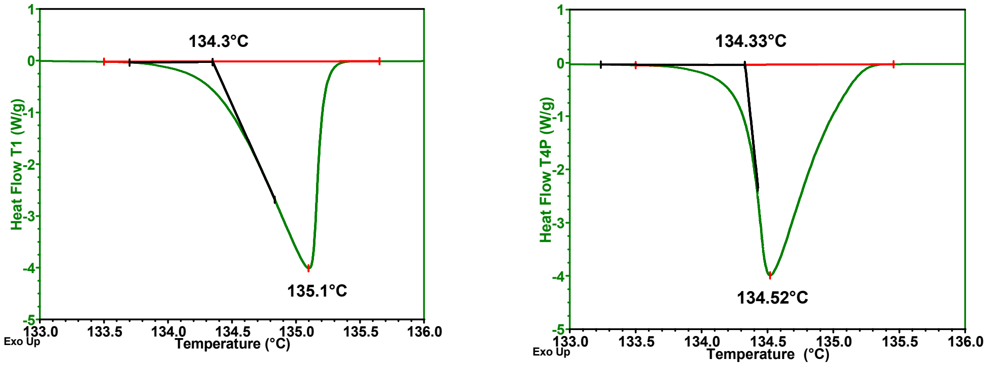

Figure 5 - Melting of 99.97% Phenacetin Using Traditional DSC (Left)
And Using Advanced Tzero™ DSC (Right)

CONCLUSIONS

DSC has long been used to determine purity in pharmaceutical components and formulations. To obtain accurate data requires careful technique. Q Series DSCs, known as Advanced Tzero Technology, make the gathering of accurate purity data easier. By compensating for thermal lag errors, the Q1000 DSC, with Advanced Tzero™ Technology reduces many of the prior limitations of the purity technique.

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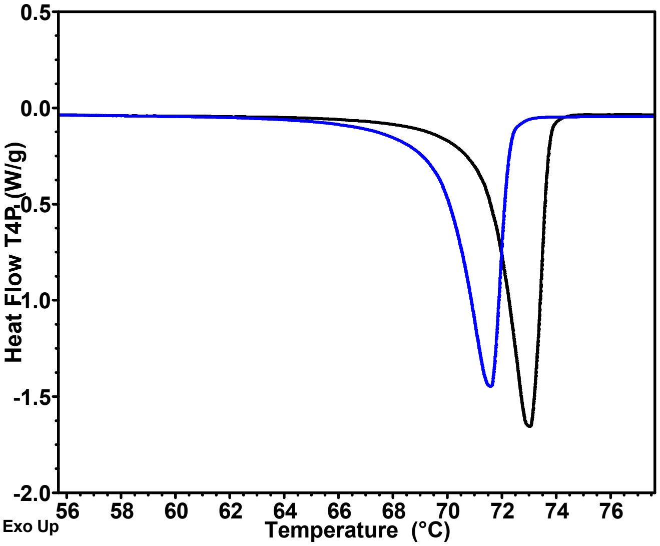

Figure 6 -Ibuprofen Formulation. Two samples: One Past the Manufacturer's Expiration Date

KEYWORDS

differential scanning calorimetry, melting, purity, pharmaceuticals