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Practical Purity Determination by DSC

This application note details the practical aspects of purity determination by differential scanning calorimetry (DSC) and explains the way that the purity calculation works. This will give thermal analysts sufficient information to make successful purity determinations using their calorimeters and understand how to avoid some of the common errors that may be encountered.

Background

Historically, it has been observed that freezing points are depressed when impurities are present in a material, and later, pre-melting on re-heating an impure material was noted. With the introduction of the DSC1B, a method of quantifying the levels of impurity by differential scanning calorimetry was derived and demonstrated by Allan Gray[1,2], and modern calculations are an extension of Gray's method.

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Applicability

The purity calculation in differential scanning calorimetry (DSC) is applied to materials that are pure crystalline materials (i.e., discrete compounds) rather than polymeric materials or mixtures. Indeed, the purity of the material being analyzed should not be lower than 95 mole % (mol%). Below this level, the assumptions made in the calculation are not valid; preferably, the purity of the material under examination should be greater than 97 mol% so that errors are minimized.

The purity calculation works by analyzing the rate of melting of the sample, and from this, determining the depression of the melting point, which is caused by the presence of the impurity. This method, however, imposes conditions on the types of impurity, which are measurable. To summarize the scope of materials suitable to be analyzed by DSC for purity:

- The sample should be a pure crystalline material.

- The impurity should be soluble in the melted compound, but insoluble in the solid state, i.e. the impurity should not form solid solutions.

- The melting must be a first order transition.

- The compound being analyzed should be >95 mol% pure and preferably >97 mol% pure.

- Materials that decompose on melting may be analyzed with more advanced software (included with Pyris software); previously materials exhibiting this behavior were excluded.

- The material must all be in the same polymorphic form where polymorphs exist.

- The sample must be prevented from subliming where this occurs.

- The sample must not form conjugates with solvents (e.g., water).

- Liquid materials that form glasses on solidification cannot be analyzed in their amorphous state.

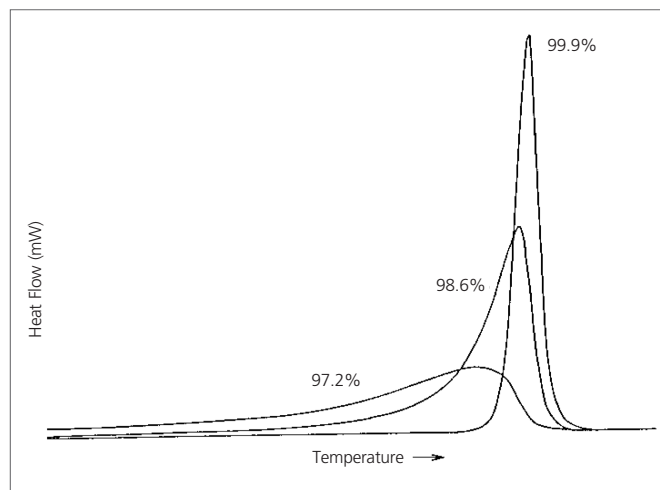- Composition of D-L isomers in materials is not measurable.

Figure 1. Effect of Purity on the Melting Peak of Benzoic Acid, more pure samples have broader melting peaks.

Provided the material under examination conforms to the requirements above, then the purity for that material can be determined by DSC.

Sample Preparation and Encapsulation

As with any thermal analysis measurement, correct sample presentation is of paramount importance, but in the case of purity determination, there is the need to ensure that conditions are optimum for the measurement.

The criteria to be met are:

- Use of a thin layer of sample to minimize temperature gradients within the sample.

- The sample should be evenly distributed over the base of the pan to insure good contact with the pan base.

- Sample pan bottom should be flat to ensure good heat transfer properties between the sample and the sample-holder sensor.

- Sample should be contacted by the sample pan lid to promote fast heat flow through the pan and good thermal contact within the sample.

To meet the above criteria, PerkinElmer recommends that the sample size be kept small, typically between 1 mg and 3 mg, and that sample pans are selected as follows:

a). Universal Crimper Aluminum Pans (Robotic Crimper)
Use two pans of the same size nested together. Typically the 50 µl pans (part number B014-3017 or B014-3021) are preferred due to the depth of the side wall. If heating the sample above 120 °C, consider piercing the top pan in the center to allow air inside the pan to expand. Alternatively, consider using the 50 µl pans with holes (B014-3019) as the top pan. Note that having the top pan with holes will allow any material ejected from within the pan to be collected in the well at the top of the pan, removing the need to clean out the sample furnace after such a spillage. This spillage can also indicate an interpretation of any anomalies seen on the DSC curve.

b). Volatile Aluminum Pans - Part Number 0219-0062
Use two sample pan bases nested inside each other, sealed to prevent material from escaping. Again, if heating above 120 °C, consider piercing the top pan before it is sealed to allow for expansion of the gases within the pan. These pans were used for this data.
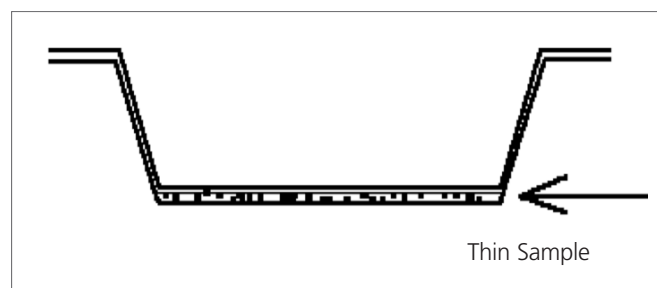

Thin Sample

Figure 2. Preferred purity encapsulation using two stacked and sealed hermetic pans.

c). Other Pan Types

Other pans should be selected where circumstances require their use, but allowance should be made for the differing thermal resistances. Pans of materials other than aluminum of the types given above are acceptable, but it should be noted that aluminum has a relatively higher thermal conductivity compared with other materials and this will affect the R_o values obtained. The prime reason for considering using pans of different design is to prevent volatilization (sublimation) from occurring. In this case it may be necessary to use a large volume, stainless steel pan in order to contain the sample in the temperature range required. It will be necessary to determine R_o for this type of pan.

Determination of Thermal Resistance Constant, R_o

The thermal resistance constant, R_o, is a measure of the rate of heat transfer between the sample holder of the DSC and the sample itself. The rate of heat transfer is affected, among other things, by the flatness of the base of the sample pan; the thermal conductivity of the sample pan material; sample size; sample pan type; and by the heating rate. Once determined, R_o is used in the purity calculation to correct the calculated sample melting point for 100% pure material. If not measured correctly, it will lead to inaccurate purity measurements and other anomalies, so it is important that R_o be measured accurately under the conditions that the sample is to be analyzed.

To measure the thermal resistance constant, prepare a 3 mg piece of indium metal and flatten it on a sheet of glass before encapsulating it in a suitable DSC pan. The indium sample should then be analyzed at the same heating rate as the pure sample to be tested (see Figure 3 for typical result). Perform the Slope calculation in the Pyris software. The value of R_o is taken as the value for the Inverse slope in the units of °C/W.

Typical values are between 20 °C/W and 80 °C/W, but these values are for guidance and are very sample pan-type dependent.

Selection of Heating Rate

The scanning rate selected will, to some extent, depend on the purity of the sample being analyzed. In general, the higher the expected purity, the slower the scanning rate selected. Normally, the lowest and highest heating rates used are 0.2 °C/min for purities approaching 100 mol%, and 5 °C/min for the least pure materials i.e., between 95 mol% and 97 mol% pure. The reason for selecting differing heating rates is because the melting peak signal is reduced significantly as purity decreases. To minimize this, scanning faster gives a better signal to noise ratio.

A further reason for increasing the heating rate as the purity is reduced is to keep the analysis times acceptable. As purity decreases, the melting can become broadened by many degrees, so choosing a faster scanning rate can help to keep the analysis times practical.
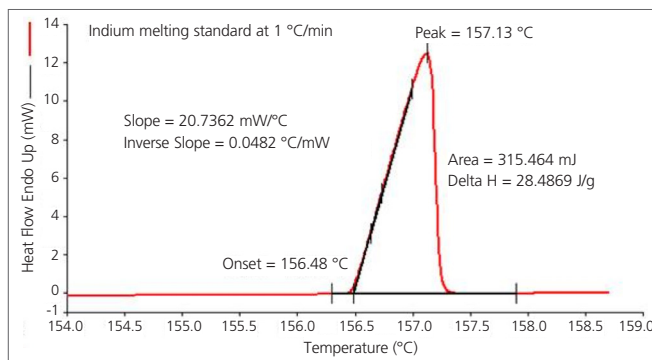

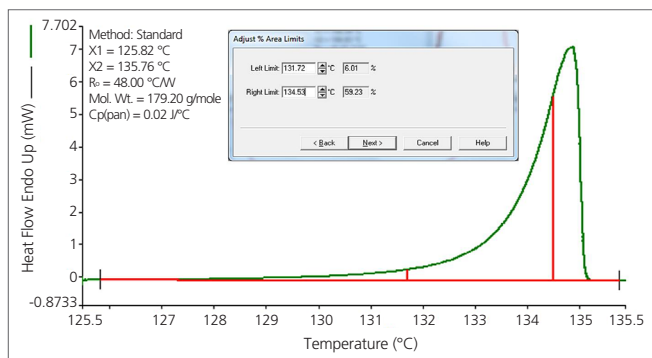*Figure 3.* Calculation of R_o from the data of Indium run at 1 °C/min in a double hermetic pan.

Figure 4. Peak calculation and partial areas selection for purity determination of Phenacetin scanned at 1 °C/min.

It should be noted that with more modern equipment, the need to change the scanning rate to adjust the sensitivity is reduced since sensitivities are significantly better than when the purity theory was first proposed and developed. Slower scan rates allow more area (enthalpy) for each partial area used for calculation, hence, a better opportunity for better accuracy.

Selection of Temperature Range for the Analysis

The temperature range over which samples are analyzed should also be given some consideration. With very pure materials, such as the indium calibration reference material, the amount of pre-melting is minimal and DSC runs can be started within a few degrees of the expected onset of melting, and continue for several degrees after the peak has ended and returned to the baseline.

For impure materials, great care must be taken to start the heating well before the apparent start of melting, since the presence of the impurity can depress the melting point by many degrees. Often, this is not apparent because the amount of material melting, is very small, but does, however, play a significant part in the determination. For very impure materials, be prepared to start the run up to 20 °C or even 30 °C before the expected melting, but to keep the analysis times acceptable, choose a faster scanning of up to 5 °C/min for this example. Another consideration is that the underlying baseline in an absence of the sample should be essentially straight. Faster heating rates provide more signal from the sample and less error contribution from noise or curvature in the instrument baseline.

Always continue the run for a few degrees past the end of the melting peak - this allows the baseline to be properly determined. It is preferable not to heat too far beyond the end of the peak since the materials often examined for purity tend to be thermally unstable and overheating will cause them to decompose. In the case of unknown samples, it can be desirable to check the thermal stability using Thermogravimetric analysis (TGA) to insure that the sample is stable in the temperature range for the purity analysis.

Peak Area Calculation

As with the temperature range to perform the analysis over, correct selection of the temperature limits will play a vital part in obtaining accurate purity data. Selecting a suitable left-hand limit will play a more significant role than the right-hand limit and, in general, will move the left limit to lower temperatures as the sample purity decreases. In some cases, the left-hand temperature of the calculation may be set to 10 °C - 20 °C before the apparent onset of melting with no ill effects.

Partial Area Calculation

First selecting, the left and right limits for the peak area calculation, selection of the partial area over which the data for the Van'T Hoff plot will then be selected. In this instance, the default left and right limits represent 6% and 59% of the peak area, respectively. The lower limit default is chosen to be above the pre-melting, which will be present, and the upper limit is chosen to be before the peak maximum. You should also select the upper limit before the inflection point on the leading edge. For very pure samples, the portion of the curve to analyze is the curved section leading up to the linear section.

Molecular Weight Entry

The purity calculation determines the mol% purity based on the primary material present, and to produce a value, it requires a value for the molecular weight of the sample. Since the material is a discrete organic compound, it is likely that the molecular weight is known or can be determined.

The Van'T Hoff Plot

The Van'T Hoff plot is a graphical display of the data from the purity determination and allows the operator to assess the validity of the data produced. It compares the actual measured data for the reciprocal of the fraction of the sample peak melted ($1/_F$) with the temperature at which that amount of melting is observed. This data is usually non-linear, becoming increasingly non-linear as the sample purity reduces. In Figure 5, it can be seen that there are two sets of plotted data indicated by a blue square sign (observed data) and a red square sign (corrected/linearized data). When the adjusted data conform to a straight line it is a confirmation that the experimental conditions and the purity determination are proper.

The curvature observed in the uncorrected data in the Van'T Hoff plot is a consequence of the pre-melting, which is undetectable by the DSC. It can be made worse by starting the DSC run too
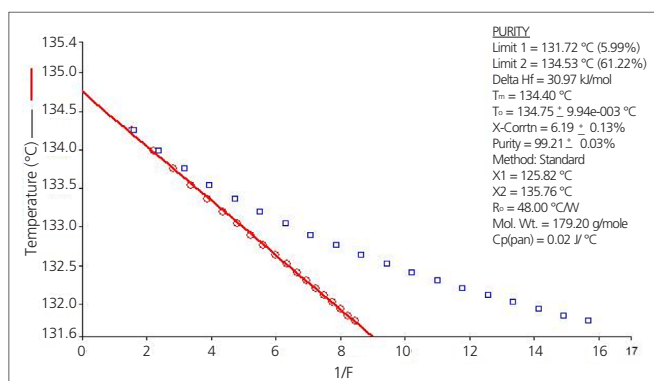

Figure 5. Van'T Hoff plot for purity determination of Phenacetin.

Table 1. Acceptable values for calculated x-correction.

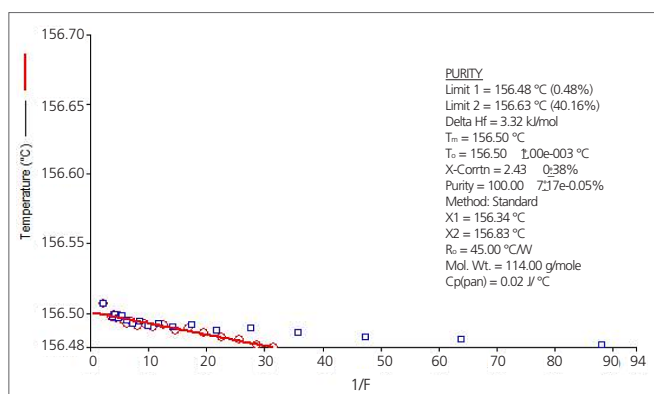| X-Correction range	Validity of Data
0% - 5%	Purity values are likely to be accurate
5% - 10%	Purity values may be of acceptable accuracy
10% - 15%	Purity values will not be accurate
>15%	Purity values will be unacceptable

Figure 6. Purity of 99.9999% pure Indium run at 0.4 °C/min with correctly selected R_o.

close to the main peak, or by selecting the left limit for calculating the peak area too near the main melting peak. Both will result in an abnormally large x-correction being calculated.

Based on the curved data in the Van'T Hoff plot, the DSC Purity software attempts to linearize the data by estimating the amount of melting that has gone undetected by the DSC (because it is distributed over a wide temperature range) and, in doing so, produces a straight line fit. The amount of "missing area" due to this pre-melting, added as part of the estimation process, is given as the "x-correction". It follows, therefore, that very large x-corrections are undesirable and may indicate problems in either the experimental procedure, the peak calculation, or indicate that the sample is too impure to be determined by DSC.

The purity can then be determined from the slope of the corrected linear data on the Van'T Hoff plot. The theoretical melting point of 100% pure material is also obtained from the plot as the point where the fraction melted ($1/_F$) is zero. This value is given as part of the purity calculation printout and is shown as T_o. The observed melting point of the sample (from the extrapolated onset of the leading edge of the DSC peak) is given as T_m on the purity calculation output.

Assessing the Validity of Purity Data

Having produced a purity analysis, it is important to review the data produced and assess its validity. There are several features on the Van'T Hoff plot that should be examined before accepting the data and these are outlined below:

- Is the T_o higher than the T_m? This indicates that the R_o used in the calculation is likely to be valid although not an absolute guarantee. The effect of R_o is more pronounced where the purity is nearer 100 mol%.

- Is the x-correction small? See Table 1.

- Are there any anomalies on the DSC curve that could affect the results?

If all of the above factors are correct, then the accuracy assessment must be that the data is likely valid. The sample should previously have been assessed for suitability of analysis by DSC for purity, and preferably some samples "doped" with a suitable impurity to check whether the calculation performs as expected.

Identifying Common Problems in Purity Determination

Reference to Figure 6 and Figure 7 demonstrates the effect of changing the value of R_o. On the same indium data analyzed using different R_o settings, all other values remain identical between the two plots. It will be obvious that the indium, at 99.9999% pure, should give a purity of a similar value when analyzed by the purity software. For very pure materials the R_o should correspond to a slope slightly greater than the greatest slope in the leading edge of the melting curve.

Examination of the data presented in Figure 6 and Figure 7 will reveal that in Figure 6, where the value of R_o is apparently close, the x-correction is low and the calculated theoretical melting of indium T_o and the observed melting T_m are identical. In Figure 7, the calculated theoretical melting of 100% pure indium is lower than the observed "impure" melting - this, is impossible, since melting point actually increases with increased purity and the $\frac{1}{F}$ behavior shown in Figure 7 indicates that R_o was incorrectly set!

Note that PYRIS for Windows does not display the Van'T Hoff plot if the slope is negative and an error message is displayed instead.
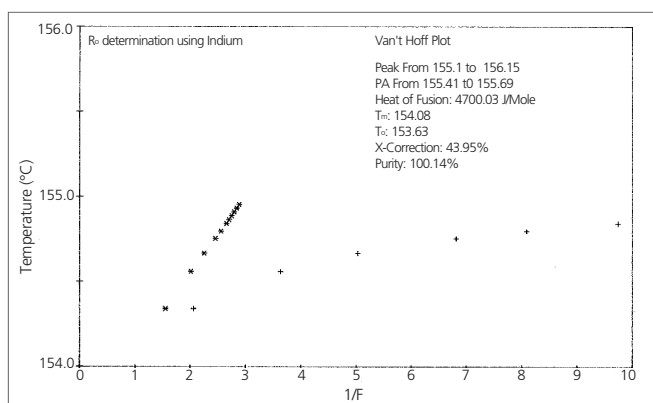

Figure 7. Purity of 99.9999% pure Indium with wrongly selected Ro – $\frac{1}{F}$ Slope is negative. (In Pyris software an error message is displayed instead of the above result.)

Another clue to the problem noted in Figure 7 is that the x-correction is very large, again indicative of an incorrect value for R_o, although this can also indicate a sample of very low purity.

Conclusion

The purity calculation can offer a rapid and convenient way of determining the purity of a material without the need to develop a High-Performance Liquid Chromatography (HPLC) method for each individual component possible and without the need to identify each component in an HPLC chromatogram. The calculation can cope with a range of different purity levels and sample preparation and handling is minimized.

References

1. Purity Determinations by Thermal Methods, ASTM STP838, ASTM International, West Conshohocken, PA,19428.

2. P. Gabbott, Editor, Principles and Applications of Thermal Analysis, Wiley-Blackwell:Oxford, 2007.

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