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The Influence of Heating Rate on the Detection of Polymorphism, Butylated Hydroxyanisole

Sample: Butylated hydroxyanisole

Application: Inactive ingredient (antioxidant)

Conditions:
- Measuring cell: DSC820
- Pan: Aluminum 40 µl, hermetically sealed
- Sample preparation: As received, no preparation
- DSC measurement: Heating from 30 °C to 70 °C at 1, 2.5, 5, 10 und 20 K/min
- Atmosphere: Nitrogen, 50 cm³/min

Interpretation:
The DSC curves show the melting of butylated hydroxyanisole recorded at different heating rates. As expected the peak increases in size with increasing heating rates, which results in decreasing resolution. A second melting peak, which corresponds to the other modification of butylated hydroxyanisole, is observed only at lower heating rates. An additional factor of importance in the case of polymorphic transitions is the kinetics for transformation from one modification to the other. In the case described, the most favorable heating rate for the detection of the second transition is 2.5 K/min. The heat of fusion of the first crystal modification is best measured at 10 K/min. Further experiments are required to determine the heat of fusion of the second crystal modification.
### Evaluation

<table>
<thead>
<tr>
<th>Heating rate K/min</th>
<th>Onset 1 °C</th>
<th>ΔH J/g</th>
<th>Onset 2 °C</th>
<th>ΔH J/g</th>
<th>Weight mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>59.2</td>
<td>95.0</td>
<td>62.6</td>
<td>2.7</td>
<td>1.360</td>
</tr>
<tr>
<td>2.5</td>
<td>59.9</td>
<td>82.1</td>
<td>63.8</td>
<td>17.6</td>
<td>4.929</td>
</tr>
<tr>
<td>5</td>
<td>59.4</td>
<td>85.5</td>
<td>62.9</td>
<td>2.9</td>
<td>1.607</td>
</tr>
<tr>
<td>10</td>
<td>60.2</td>
<td>100.2</td>
<td>—</td>
<td>—</td>
<td>4.516</td>
</tr>
<tr>
<td>20</td>
<td>61.1</td>
<td>99.3</td>
<td>—</td>
<td>—</td>
<td>4.398</td>
</tr>
</tbody>
</table>

### Conclusion

With a suitable choice of the heating rates, it is possible to determine the melting point and the heat of fusion of the individual modifications of polymorphic substances, even when the melting points of the modifications lie close together.
16 Characterization of the Melting Behavior, Vanillin

Sample
Vanillin

Application
Flavoring agent

Conditions
Measuring cells: DSC or TGA
Pan: Aluminum 40 µl, with pierced lid or open
Sample preparation: As received, no preparation
DSC measurement: Heating from 30 °C to 250 °C at 10 K/min
TGA measurement: Heating from 30 °C to 250 °C at 10 K/min, blank curve corrected
Atmosphere: Nitrogen, DSC: 50 cm³/min, TGA: 20 cm³/min

Interpretation
The melting curve provides a survey of possible events that can occur during the measurement. This information can not be gained from simple melting point determinations with TOA. For instance the DSC curve shows a slight shift of the baseline after the melting process. The TGA curve shows no weight loss in this region, which indicates that the DSC baseline shift is caused by a change in the specific heat capacity \( c_p \). The SDTA signal of the TGA850 allows a qualitative evaluation of the melting behavior along with the TGA measurement.

An increasing weight loss occurs at temperatures above 150 °C because the vanillin evaporates and decomposes.

Evaluation
Onset temperature determination and integration of the melting peak of the DSC curve.

Melting point (onset) 81.8 °C
Heat of fusion \( \Delta H \) 133.5 J/g

Conclusion
The DSC is suitable for the rapid determination of melting points and heats of fusion. Additional information can be gained from a TGA measurement.
9 Sample Preparation, Butylated Hydroxyanisole

Sample | Butylated hydroxyanisole

Application | Inactive ingredient (antioxidant)

Conditions
- Measuring cell: DSC
- Pan: Aluminum 40 µl, hermetically sealed
- Sample preparation: As received (1) or crystals ground in a mortar (2)
- DSC measurement: Heating from 30 °C to 70 °C at 2.5 K/min
- Atmosphere: Nitrogen, 50 cm³/min

Interpretation
The two curves show the effects that sample preparation can have on the results. In both cases, two melting peaks can be observed that differ noticeably in temperature range and in the heats of fusion. The explanation lies in the polymorphic behavior of butylated hydroxyanisole. The two peaks correspond to the possible crystal modifications.

Evaluation
<table>
<thead>
<tr>
<th>Sample preparation</th>
<th>Onset 1, °C</th>
<th>ΔH, J/g</th>
<th>Onset 2, °C</th>
<th>ΔH, J/g</th>
</tr>
</thead>
<tbody>
<tr>
<td>as received</td>
<td>59.3</td>
<td>78.2</td>
<td>63.3</td>
<td>27.6</td>
</tr>
<tr>
<td>ground in a mortar</td>
<td>55.1</td>
<td>96.8</td>
<td>61.7</td>
<td>1.7</td>
</tr>
</tbody>
</table>

Conclusion
A difference in sample preparation (especially mechanical treatment) can lead to different results. This is particularly the case with substances that exhibit polymorphism.
10 Influence of the Sample Weight, Butylated Hydroxytoluene

Sample: Butylated hydroxytoluene

Application: Inactive ingredient (antioxidant)

Conditions:
- Measuring cell: DSC with IntraCooler
- Pan: Aluminum 40 µl, hermetically sealed
- Sample preparation: As received, no preparation
- DSC measurement: Heating from 50 °C to 80 °C at 2.5 K/min
- Atmosphere: Air, stationary environment, no flow

Interpretation:
The curves show the melting peaks as a function of sample weight. As expected, the peaks in the original presentation (ordinate in mW) increase in height but also in width with increasing weight. Because of this the resolution decreases. In contrast, the normalized presentation shows that the lowest sample weight gives the highest peaks.

Evaluation:
The onset temperature and heat of fusion of the peaks are determined. The mean values of a number of measurements are presented in the table.

<table>
<thead>
<tr>
<th>Sample weight (mg)</th>
<th>Onset, °C</th>
<th>Heat of fusion, ΔH, J/g</th>
</tr>
</thead>
<tbody>
<tr>
<td>18 ± 0.3</td>
<td>69.4 ± 0.1</td>
<td>85.6, 84.7, 85.6</td>
</tr>
<tr>
<td>8.5 ± 0.3</td>
<td>69.6 ± 0.1</td>
<td>83.9, 84.5</td>
</tr>
<tr>
<td>4.0 ± 0.4</td>
<td>69.5 ± 0.1</td>
<td>82.6, 84.1, 83.6</td>
</tr>
</tbody>
</table>

Conclusion:
The sample weight influences the shape of the melting peak. The time required for melting is longer for larger samples because a greater amount of heat has to be transferred. As a result of this, the peaks are shifted to higher temperature. For comparison purposes, the measurement of samples of similar weight is recommended. Samples that are too large are disadvantageous: the peaks become broad (lower resolution) and non-uniform melting leads to irregularly shaped peaks.
11 Influence of the Pan on the Determination of Moisture Content, Cellulose

Sample  Microcrystalline Cellulose (Avicel)

Application  Inactive ingredient (gel binder, adsorption agent, flow improver)

Conditions  Measuring cell: TGA with sample robot
              Pan: Aluminum 100 µl, without a lid or with a pierced lid. The lid was pierced automatically immediately before the measurement (needle diameter 1 mm).
              Sample preparation: As received, no preparation
              TGA measurement: Heating from 30 °C to 300 °C at 20 K/min, all measurements are blank curve corrected.
              Atmosphere: Nitrogen, 80 cm³/min

Interpretation  Cellulose and its derivatives easily take up water from the surroundings or release water depending on the humidity in the laboratory.
28 Kinetic Analysis of Decomposition, Acetylsalicylic Acid

Sample: Acetylsalicylic acid

Application: Analgesic

Measurement:
- Measuring cell: TGA850
- Pan: Aluminum 100 µl, with pierced lid
- Sample preparation: As received, no preparation
- TGA measurement: Heating from 25 °C to 300 °C at 1, 2.5, and 10 K/min, all measurements are blank curve corrected
- Atmosphere: Air, 50 cm³/min

Interpretation:
The first diagram (28a) shows the effect of the heating rate on the decomposition of acetylsalicylic acid. The decomposition, that is the resulting weight loss, is shifted to higher temperature with increasing heating rates. The DTG curves, i.e. the first derivative of the TGA curves, are formed in order to calculate the percentage conversion curves that are used for further kinetic analysis. The DTG curves together with the choice of a suitable baseline allow the separation of the first decomposition step from further overlapping decomposition reactions (the TGA curves do not terminate horizontally).

Interpretation:
The second diagram (28b) shows the complete evaluation using the model-free kinetics method. The conversion curves are calculated from the DTG curves using the baseline type ‘integral horizontal’. These conversion curves are, in turn, the basis for the model-free kinetics for the calculation of the activation energy. This lies in the range 100 – 140 kJ/mol and is a function of conversion, indicating a complex reaction. The activation energy allows a simulation of the decomposition reaction for other conditions (temperature and time). This is shown graphically and in tabular form in so-called iso-conversion plot and tables. In this presentation, the time required for the substance to reach a given percentage conversion (or in other words degree of decomposition) at a given temperature is evident.
**Evaluation**

The activation energy is determined as a function of the percentage conversion. The details are given in the diagrams.

Prediction of the storage time/storage temperature for a conversion of 1, 2, 3 or 4% (applied kinetics). It is evident from the table, that a conversion of 1% is reached when the substance is stored at 15.2 °C for 10 000 hours; 1 year has 8760 hours.

<table>
<thead>
<tr>
<th>Time</th>
<th>Conversion</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1%</td>
</tr>
<tr>
<td>10 000 h</td>
<td>15.3 °C</td>
</tr>
<tr>
<td>20 000 h</td>
<td>10.6 °C</td>
</tr>
<tr>
<td>30 000 h</td>
<td>8.0 °C</td>
</tr>
</tbody>
</table>

Please note: Extrapolation of results from reactions performed in the liquid state to the solid state have a high degree of uncertainty.

**Conclusion**

The example shows that thermal analysis and the application of model-free kinetics is an efficient means of estimating the potential storage lifetime of pharmaceutical preparations at a minimum expense. The TGA can of course only be used when the decomposition is coincidental with a significant weight loss.

It must be emphasized that this procedure can never replace a proper long-term test. The method is more useful for the preliminary selection of formulations. The formulations that exhibit good properties can then be subjected to the time-consuming and expensive final tests.
35 Polymorphism, L-Polylactide

Sample: L-Polylactide

Application: Inactive ingredient

Conditions:
- Measuring cell: DSC
- Pan: Aluminum 40 µl, hermetically sealed
- Sample preparation: As received
- DSC measurement: Heating from 30 °C to 300 °C at 10 K/min
- Atmosphere: Nitrogen, 50 cm³/min

Interpretation:
The form of the DSC curve is typical for substances that undergo transformations in the melt. A separation of the two peaks depends on the crystallization rates of the modifications. In spite of the good peak separation, the measured heat of fusion of the first modification is too low: firstly, because an unknown quantity of the high-melting modification is already present, secondly, because the exothermic crystallization of the high-melting form takes place at the same time as the melting of the first form, and thirdly, because a solid-solid transition can occur. The second peak is usually too small, because the transformation or crystallization is incomplete when heating dynamically. For this reason both heats of fusion are displayed in brackets.

In order to produce the high temperature form, the sample could be annealed at 160 °C in a similar way to that described in application example 33.
**Evaluation**  Several different baseline options have to be applied in order to evaluate the melting peak correctly. For the first peak the type ‘horizontal left’ is used and for the second peak the type ‘horizontal right’.

<table>
<thead>
<tr>
<th></th>
<th>Onset, °C</th>
<th>ΔH, J/g</th>
</tr>
</thead>
<tbody>
<tr>
<td>First peak</td>
<td>151.0</td>
<td>(24.4)</td>
</tr>
<tr>
<td>Second peak</td>
<td>168.4</td>
<td>(58.9)</td>
</tr>
</tbody>
</table>

**Conclusion**  The example demonstrates that polymers can also exhibit polymorphism.
22 Glass Transition and Moisture Content, Hydroxypropoxymethylcellulose Phthlate (HPMC-PH)

Sample
Hydroxypropoxymethylcellulose phthalate (HPMCPH HP 55)

Application
Inactive ingredient (tablet coating substance)

Conditions
- Measuring cells: DSC or TGA
- Pans: Aluminum 40 µl or 100 µl, both with pierced lids
- Sample preparation: The samples were stored under different relative humidity conditions in exsiccators
- DSC measurement: Heating from 30 °C to 150 °C, cooling to 30 °C, 5 minutes isothermally at 30 °C, then heating to 300 °C at 20 K/min
- TGA measurement: Heating from 30 °C to 300 °C at 20 K/min
- Atmosphere: Nitrogen, DSC: 50 cm³/min, TGA: 80 cm³/min

Interpretation
TGA (diagram 22a)
The diagram shows the TGA curves of samples that were stored under different relative humidity conditions. The moisture content of a sample can be determined from the first step of the corresponding TGA curve. The values obtained correlate with the storage conditions.
Interpretation

DSC (diagram 22b)

The diagram shows the first and second heating curves of two different samples. Since the measurements were done in a pans with pierced lids, the moisture was able to evaporate in the first heating run. This process can be observed as a large endothermic peak. This correlates with the amount of water released. Apart from this, the peak partially overlaps the glass transition of the ‘wet sample’. The glass transition (Tg) is therefore determined using the second heating run, in which the moisture has already escaped.

Evaluation

<table>
<thead>
<tr>
<th>Storage</th>
<th>TGA</th>
<th>DSC</th>
</tr>
</thead>
<tbody>
<tr>
<td>7 days over P₂O₅</td>
<td>1.18</td>
<td>129.6</td>
</tr>
<tr>
<td>1 day over P₂O₅</td>
<td>1.39</td>
<td>—</td>
</tr>
<tr>
<td>Untreated</td>
<td>2.50</td>
<td>—</td>
</tr>
<tr>
<td>1 day at 95% r. h.</td>
<td>8.28</td>
<td>—</td>
</tr>
<tr>
<td>7 days at 95% r. h.</td>
<td>9.50</td>
<td>130.7</td>
</tr>
</tbody>
</table>

Conclusion

Cellulose-based polymers take up moisture easily. The uptake is dependant on the storage conditions. The moisture-free sample is normally used for determining the glass transition temperature (Tg). This is done by evaluating the second heating run. If the glass transition temperature has to be determined with different moisture contents, then sealed pans have to be used.
23 Quality Control, PE Films

Samples PE-LLD, PE-LD, PE-HD

Application Packaging material

Conditions Measuring cell: DSC
Pan: Aluminum 40 µl, hermetically sealed
Sample preparation: Samples cut out of the films
DSC measurement: Heating from 30 °C to 160 °C, cooling to 30 °C, then heating to 160 °C, all steps with heating or cooling rates of 10 K/min
Atmosphere: Nitrogen, 50 cm³/min

Interpretation DSC is specified in the USP for the physical testing of polyethylene containers: the quality of packaging material is of decisive importance for the protection of raw materials and end products. In particular, primary packaging material i.e. packaging material that comes into direct contact with the product must be perfect as far as quality is concerned, must satisfy the specified requirements and must not react with the material that it is designed to protect. The first heating run serves to eliminate any (unknown) thermal history so that samples of different quality can be properly compared with each other in the second heating run. The melting peak maximum and the crystallinity (calculated from the heat of fusion), are used as quality criteria.

Evaluation The crystallinity of a sample is determined by comparing its measured heat of fusion with that of 100% crystalline PE which is assumed to have a heat of fusion of 290 J/g. This is demonstrated as example with one of the curves.