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Monitoring the Polymorphism of Paracetamol by Means of DSC

Paracetamol (acetaminophen) is the most commonly used medication for pain and fever in both the United States and Europe. However, it is not worth getting a headache when you think about its physicochemical properties. Thermal analysis, and especially differential scanning calorimetry (DSC), is of great help.

July 16, 2020 by Gabriele Kaiser

Paracetamol (acetaminophen) is the most commonly used medication for pain and fever in both the United States and Europe [1]. However, it is not worth getting a headache when you think about its physicochemical properties. Thermal analysis, and especially differential scanning calorimetry (DSC), is of great help.

Paracetamol is known to have three polymorphs [2]:

- Stable form I (monoclinic)
- Metastable form II (orthorhombic) and
- Unstable form III

Form I has a lower heat capacity than form II. Below -120°C, the form II modification becomes more stable than form I [3]. In addition, form II contains well-defined slip planes in its crystal structure which may facilitate direct compression for tablet production [4].

Thermal Behavior of Paracetamol

In the following example, 2.09 mg of paracetamol was heated twice from room temperature to 200°C in aluminum crucibles and a nitrogen atmosphere. The cooling step in between was also performed at 10 K/min.

In the 1st heating step, an endothermal effect is visible with an extrapolated onset temperature of 169°C. This correlates well to the melting point of form I (6). During the subsequent controlled cooling step (not shown here), no crystallization takes place. This means that the paracetamol is still amorphous at the beginning of the 2nd heating step.

In the 2nd heating, an exothermal effect (with a peak temperature of 82°C) appears first which is related to a cold or post crystallization process. But with increasing heating, it turns out that there is not the same modification present as before because the corresponding melting effect is shifted to lower values. The extrapolated onset temperature of 157°C is characteristic for form II [5]. Thus, the metastable form II was formed during post crystallization.

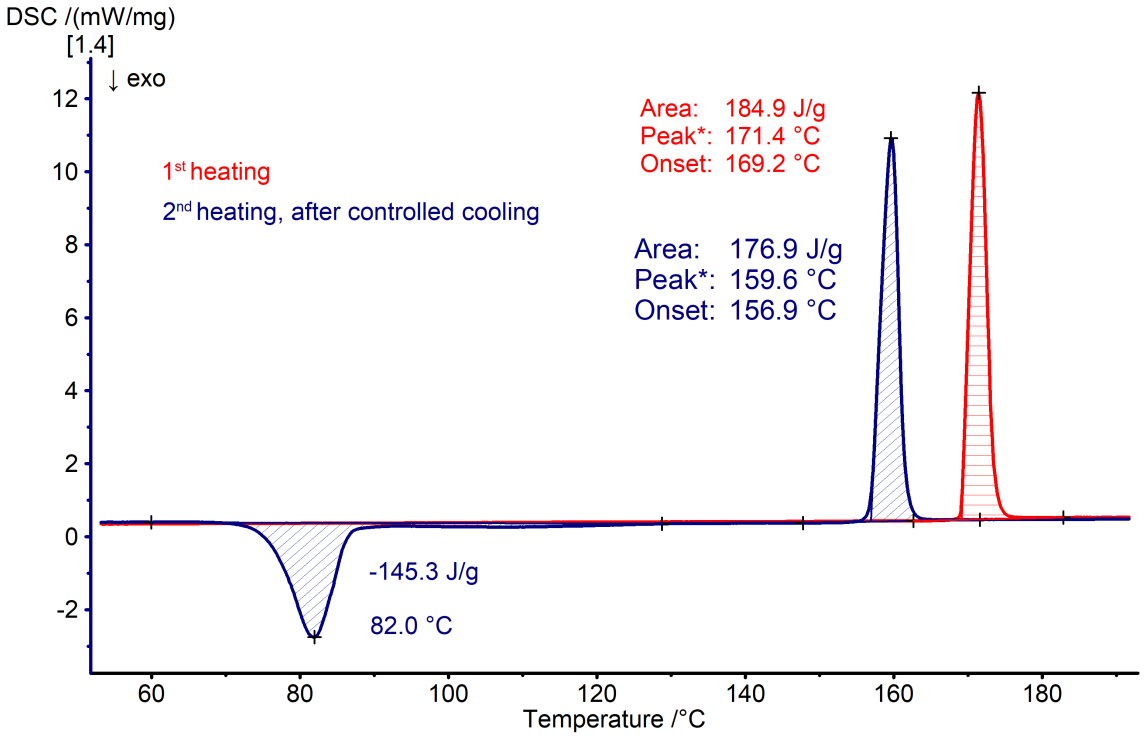

Fig. 2: DSC measurement on paracetamol, depicted are the DSC curves of the 1st (red) and the 2nd heating (dark blue); the y-axis scaling is valid for both curves; measurement conditions see text

More information about application possibilities of thermal analysis in the pharmaceutical field can be found here.

Literature:

[1] https://en.wikipedia.org/wiki/Paracetamol

[2] Bashpa, K. Bijudas, Anjali M Tom, P.K. Archana, K.P. Murshida, K. Noufala Banu, K.R. Amritha, K. Vimisha, Polymorphism of paracetamol: A comparative study on commercial paracetamol samples, International Journal of Chemical Studies, Vol. 1, Issue 6 (2014),

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[3] Sacchetti, Thermodynamic Analysis of DSC Data for Acetaminophen Polymorphs, J. Therm. Anal. and Cal., 63; p 345 – 350
[4] Kachrimanis, D. Braun, U. Griesser, Quantitative analysis of paracetamol polymorphs in powder mixtures by FT-Raman spectroscopy and PLS Regression, J Pharm Biomed Anal. 2007; 43; p 407 –412
[5] Polymorphism in the Pharmaceutical Industry, edited by R. Hilfiker and M. van Raumer, pp 435/436, Wiley-VCH, 2019

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