HAAS

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Active substances for new drugs - purity determination with new DSC technology and separation process using liquid Flash chromatography

Objectives

Thermal analysis methods allow identification, determination of purity and compatibility of medicinal substance with the reference substance in the testing processes. Thanks to the diversity of these methods, it is possible to study the composition and physicochemical properties of new biologically active compounds, to study the thermostability of medicinal substances, predicting possible interactions between the drugs and the excipient, testing polymorphic forms and pre-formulation of new drugs. [1][2][3]

The main goal of the conducted measurements was to determine the purity of active substances used for drug manufacturing using differentia scanning calorimetry (DSC). This allowed testing a new type of DSC instrument for thermal analysis design made by Linseis that instead of a two-crucible setup uses a ceramic chip with a single crucible.

Materials and Methods

Measurements were conducted using differential scanning calorimeter Chip-DSC 10 (**Figure 1**) Linseis HAAS with a unique ceramic sensor, which already incorporates an in-build reference side (**Figure 4**). The experiment was done in crimped aluminum crucibles in the air. The heating rate was set to 20 K/min. Each measurement was performed three times using each time a sample of app. 4 - 7 mg mass.

Figure 1. Differential scanning calorimetry setup Chip-DSC 10 Linseis

Figure 2. Flash Chromatography setup SepaBean L Santai for purification and separation up to 1 l/min, up to 1 kg compound on 10 kg column

Results

Figure 3 shows measurements of 3 samples of selected active substances, which were run 3 times for each one. Figures 3A and 3B show the same substance without and with impurities, respectively. Figure 3C shows another active substance. The substance on graph 3A starts to melt at about 175,2°C and reaches its maximum rate at approx. 180°C. Melting enthalpy, so the information about the amount of energy needed to melt a unit mass of a given substance during melting, is about 125,2 mJ/mg. Measurements done for the same sample, but with impurities show two peaks. Melting of the substance of interest occurs at about 172,9°C and reaches its maximum at about 177,8°C. Enthalpy of the process was determined to be about 115 mJ/mg. The second, smaller peak resulting from the impurities, can be observed at a lower temperature value of about 155,9°C. The third sample with different substance starts melting at approx. 165,8 °C, with a maximum melting rate of about 173°C. The enthalpy of the melting process is about 104,1 mJ/mg. Three consecutively performed measurements show highly similar results, proofing measurement repeatability and efficiency. Detailed calculations are contained in the tables and charts.

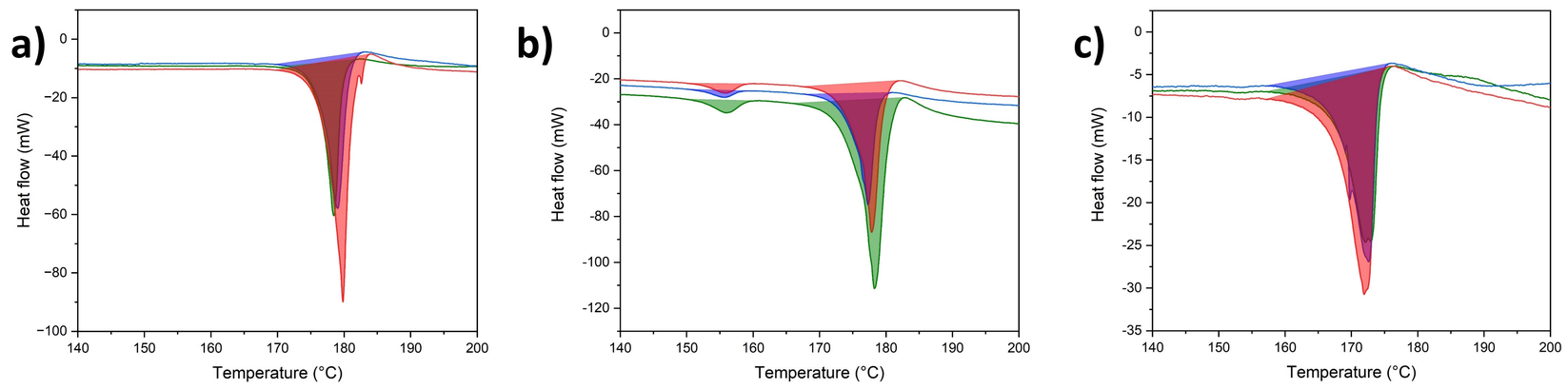
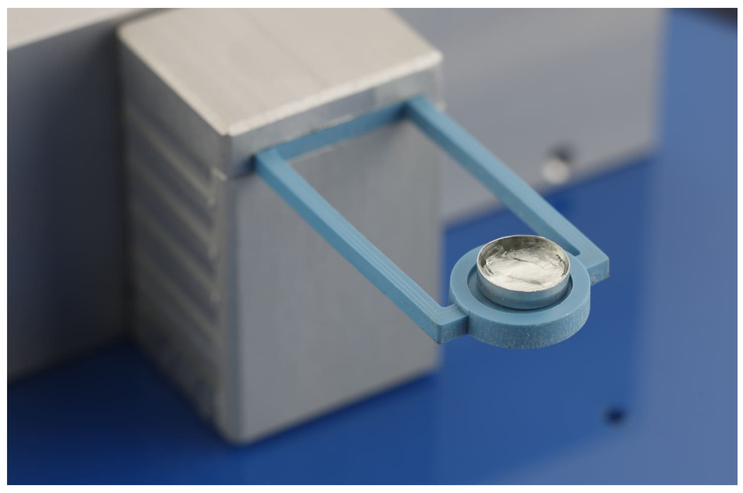


Figure 3. Three consecutive measurements of the selected samples: a) SM_I_1, b) SM_I_2, c) SM_I_3



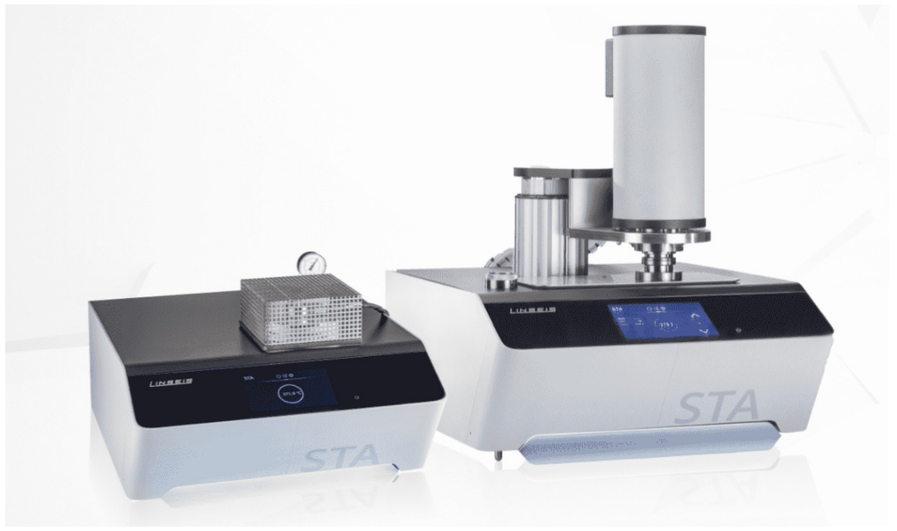


Figure 4. Selected sample of compound in aluminium sample pan on differential calorimeter Chip-DSC Linseis ceramic sensor, simultaneous thermal analysis STA for mass changes and decomposition research

Conclusions

The DSC method can be used for the qualitative analysis of products and indicates the level of their purity. The examined Chip design allows high heating and cooling rates without any external chiller. It significantly increases efficiency of the research time, enabling screening of larger number of samples and in case of damage or contamination, it can be easily replaced by user.

The measurements show that the novel design of the Chip-DSC with a ceramic chip can work as well as the other DSC setup. Even small amounts of impurities can be detected within minutes. Fast measurements, low cost, and small size of the device make it available also for small laboratories that need to quickly examine the purity of the received materials or synthesized substances. To learn more about the samples, further analysis is planned using additional techniques, thermogravimetry (TGA and STA), or evolved gas coupled techniques, TGA+FTIR or TGA+MS. Further purification of impurities will be performed with liquid Flash Chromatography, on selected Flash columns – 12 g in research scale, 5-10 kg Santai Flash chromatography columns for scale up and production scale (**Figure 2)**.

References:
[1] A. Stebnicka, I. Mucha, Zastosowanie analizy termicznej w farmacji,, Farmacja Polska, Tom 70 · nr 8 · 2014 str. 460-465
[2] M. Nowak, B. Cichy, Szerokie spektrum możliwości analizy termicznej w badaniach i przemyśle CHEMIK 2014, 68, 3, 216-223
[3] K. Łapiński, R. Tomikowska, Analiza termiczna – badania z zastosowaniem różnicowej kalorymetrii skaningowej i termograwimetrii z technikami łączonymi, ISBN 978-83-947942-0-0, 05.2017