

Q&A with Ardena Experts

Insights into Thermogravimetric and Evolved Gas Analysis

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What role does thermal analysis play in solid-state research?

Thermal analysis plays a crucial role in solid-state research. It helps determine how an API behaves when exposed to temperature changes. This includes analyzing mass loss during heating, identifying the melting point, potential phase transitions, and degradation temperature. Common thermal analysis techniques include thermogravimetric analysis (TGA), differential scanning calorimetry (DSC), and hot-stage microscopy (HSM).

Can you explain what TGA is and how it works?

TGA is short for thermogravimetric analysis. During a TGA measurement, the sample is placed on a microbalance in a temperature-controlled chamber. The sample is heated up to a certain temperature while the mass is continuously monitored by the balance. The results are presented as a curve that plots the sample's mass against temperature, showing both absolute and normalized weight.

How are released volatiles analyzed during thermal analysis?

To determine the nature of the volatiles that are released during heating, the evolved gases can be analyzed. The TGA could be coupled to an Infra-Red Spectrometer (IR) or Mass Spectrometer (MS). At Ardena, we use a MS as it is very sensitive towards the detection of solvent molecules. The MS is coupled to the exit of the heating chamber through a capillary which is held at elevated temperatures to prevent condensation of the solvent gases during the transfer of the TGA to the MS detector.

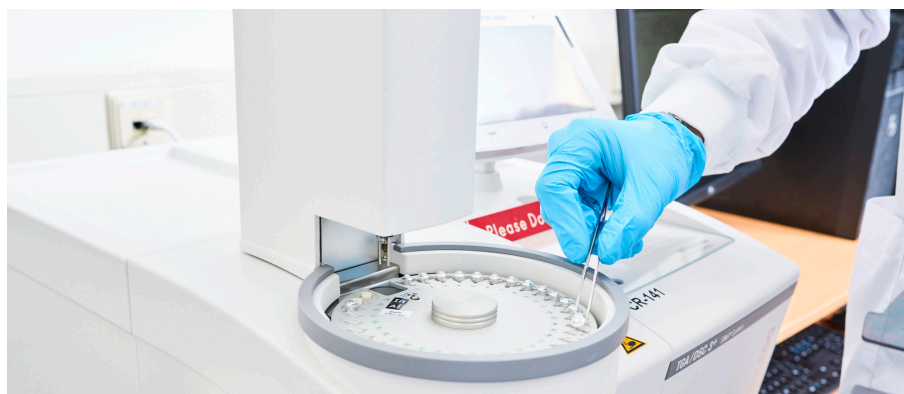
Why might TGA-MS be necessary for analyzing solid forms?

TGA-MS provides valuable insights into mass loss during heating. For instance, if no mass loss is detected until degradation, it indicates the solid form is likely an anhydrous, non-solvated form. Conversely, if a mass loss is observed by TGA before complete degradation, the MS signals can help identify whether the volatiles are due to water or a solvent, and which solvent. This is useful to determine if a solid form is a (stoichiometric) hydrate or solvate.

Moreover, often based on the mass loss behavior we can tell whether the water or solvent molecules are part of the crystal structure or only present at the surface of the API solids (residual), indicating whether the solid has been dried properly.

What equipment do you use for TGA-MS, and what are the typical settings?

At Ardena we use a TGA/DSC 3+ STARe system (Mettler-Toledo GmbH, Switzerland) with small furnace. The TGA curve presents the weight vs temperature (absolute weight and normalized). Typically, the sample weight is between 1 – 2 mg and 100 μ L aluminum crucibles are used. The seals are pin holed by the sample robot just before insertion into the sample chamber. Samples are heated from 25 to 300°C at a heating rate of 10°C/min. Simultaneously to the TGA curve, a DSC curve is recorded.



The gases evolved from the TGA samples are analyzed by an Omnistar GSD 350 mass spectrometer (Pfeiffer Vacuum GmbH, Germany). This MS is a quadrupole mass spectrometer, which analyzes masses in the range of m/z 0-200.

What are the capabilities of Ardena's TGA-MS system?

We can monitor the weight loss of any solid sample between 25 – 1000°C, either during a dynamic heating range or at an isothermal temperature. We can confirm the type of volatiles that are being released during mass loss.

Are there any limitations to the TGA-MS technique?

We typically scan for mass fragments of volatiles/solvents that we expect based on the components used during experimentation. If the volatiles are unknown, it is more challenging to determine the nature of the volatiles.

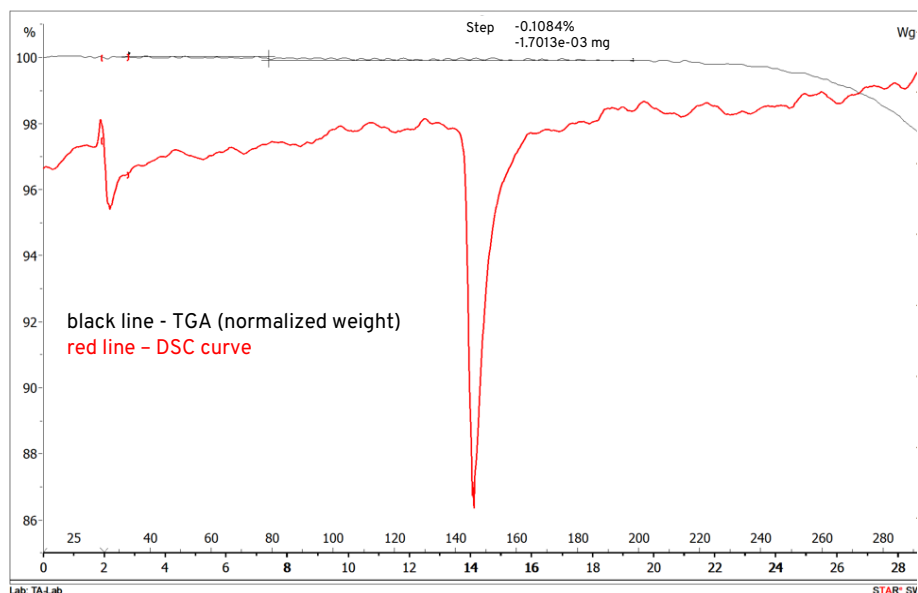
The MS works very well for detection of volatile solvents, it does not give information on the degradation fragments of the compound itself during the degradation process.

The sample chamber is purged with nitrogen to prevent any reactions with oxygen/air during the measurement. The corresponding mass fragments of 14 and 28 can obscure mass fragments of certain solvent molecules that have these fragments in their MS spectrum.

Can you provide examples of TGA-MS analysis?

The TGA example below shows the thermal behavior of an anhydrous non-solvated solid form. The percentage weight loss (left y-axis) and the heat flow (right y-axis) is expressed as a function of time and temperature (x-axis).

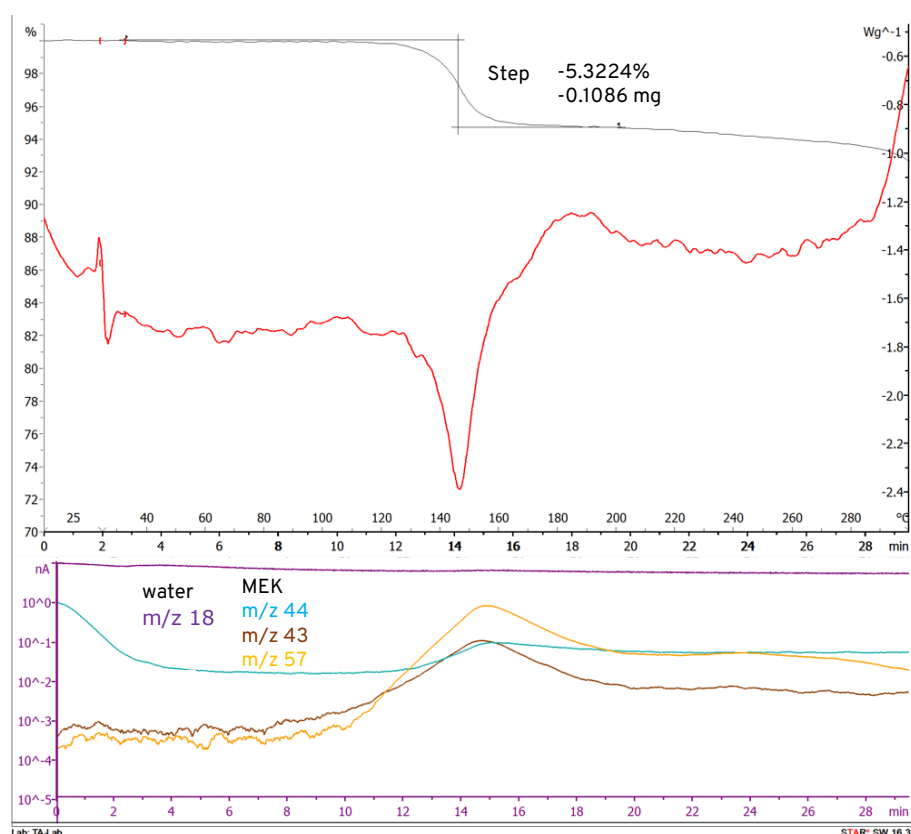
There is negligible mass loss observed between 25 and 200°C, after which the solid starts to degrade (black line). The simultaneously measured DSC trace (red line) shows an endothermic melting event with a peak temperature at ~142°C.



In the following example, a sudden mass loss of 5.3% is observed between 100 and 170°C. According to the mass fragments observed in the MS spectrum, these masses belong to methyl ethyl ketone (MEK). Considering the MW of the API is ~600 g/mol, the mass loss equals 0.5

molecule of MEK per molecule of API. Based on the sudden mass loss, accompanied by a broad endothermic event in the DSC curve, this solid is likely a hemi-MEK solvate. Since there are no other thermal events (e.g.: melting) recorded until 290°C, the solid loses its crystal structure when the solvent molecules are released and starts to degrade around 290°C.

The initial drop in m/z 44 observed in the MS spectrum between 0 to 2 min, is due to the removal of air (CO₂) from the sample chamber, due to purging with N₂.



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