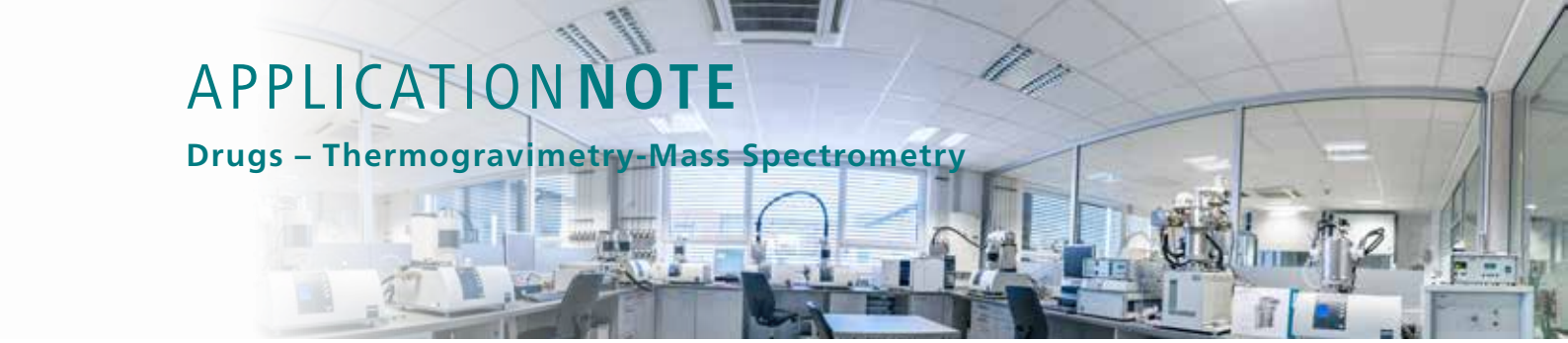

Mass Spectrometry Coupled to Thermogravimetry for the Study of Residual Solvents in Drugs

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Introduction

The solvent content of drugs is strictly controlled, as residual solvents may affect the efficacy of the treatment and even let the drug produce a certain degree of toxicity. The manufacturing process of active pharmaceutical ingredients (APIs) will inevitably use water or organic solvents, such as ethyl acetate, acetone and others. Many of these organic solvents are toxic. Therefore, the measurement of residual solvents (qualitative and quantitative) has become an important issue.

The pharmaceutical industry commonly uses gas chromatography (GC) methods to measure residual solvents. However, the GC method has its drawbacks: The measurement temperature needs to not be too high when a conventional headspace injection is used, and the sample must be stabilized within the temperature range of the test. The sample needs to be dissolved prior to testing, which does not allow for complete "in-situ testing" – and predictably, the state of sample dissolution, solvent selection, etc., are all important factors in measuring residual solvents. It can be expected that sample preparation and solvent selection have a certain impact on the test.

Experimental

At this point, an STA *Jupiter*® system was coupled to an *Aëolos*® quadrupole mass spectrometer to obtain meaningful results on the residual solvent content and identity. The sample was heated to observe the mass-loss process and simultaneously the gases released were transferred into the mass spectrometer (MS) to analyze the species of the evolved gas.

In this case, the mass spectrometer recorded mass numbers m/z 17, m/z 18, m/z 28 (CO, N_2), m/z 40 (Ar), m/z 43, m/z 44 (CO_2), m/z 45, m/z 61, m/z 70, and m/z 88, which detected permanent gases and the release of typical solvents like water (m/z 17, 18), acetone (m/z 43) and ethyl acetate (m/z 43, 45, 61, 70, 88).

Measurement Parameter

Measurement mode:	TGA-QMS
Heating rate:	10 K/min
Sample mass:	9.67 mg
Temperature range:	35°C to 220°C/250°C
Gas atmosphere:	Argon

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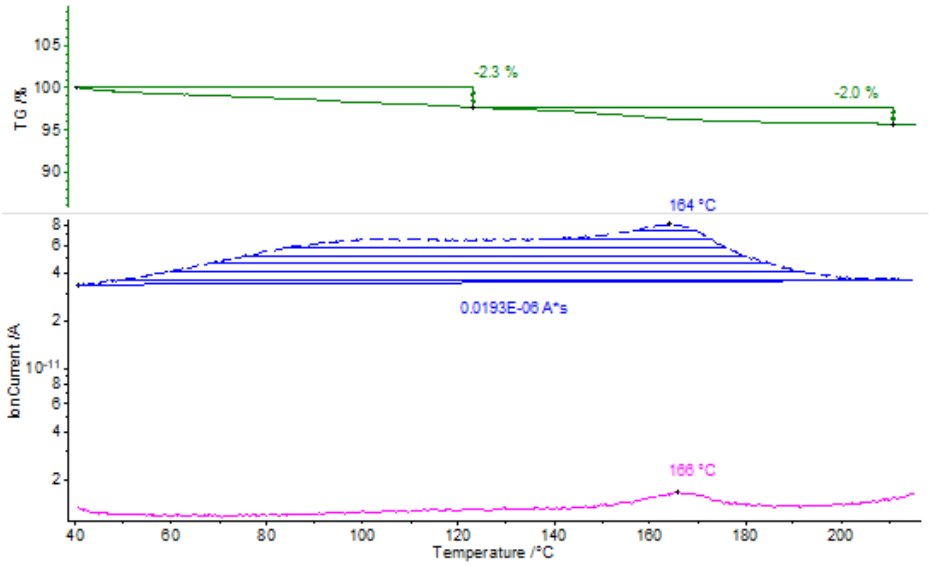
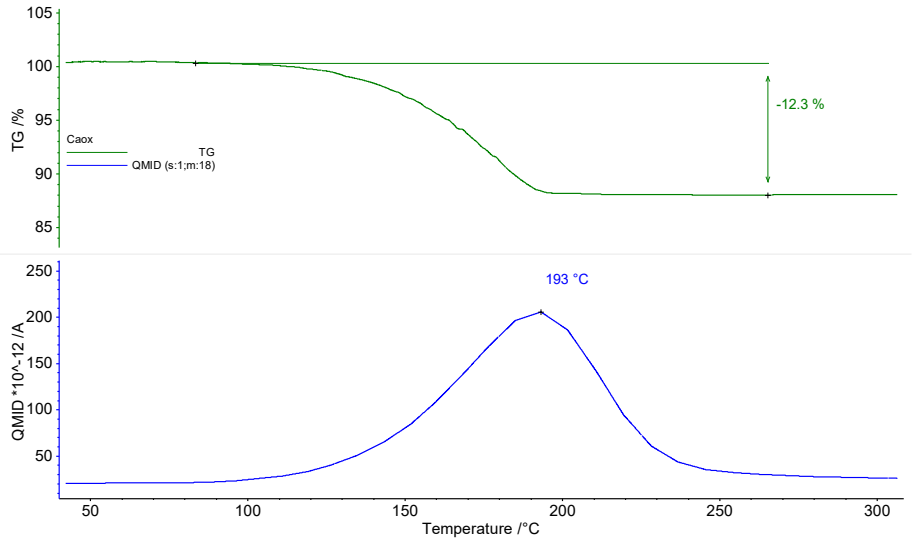
Results and Discussion

The results are shown below; the thermogravimetric plot (green curve) illustrates that the sample loses mass in two steps of 2.3% and 1.98% in the range of RT-200°C, and the total weight loss amounts to 4.28%*9.67 mg=0.4138 mg. Analysis of the obtained MS data revealed an increase of m/z 18, which correlates well with the mass-loss steps. This mass number proves the release of water; see blue curve. In addition, a very small peak was found at m/z 43, indicating that small amounts of other solvents were present.

The amount of water released could be quantified with the help of the known standard material, calcium oxalate monohydrate, releasing 12.3% of water in the range between room temperature and 250°C; see figure 2.



1 Temperature-dependent mass change (TGA, green) and ion currents of m/z 18 (water, blue) and m/z 43 (acetone, ethyl acetate, pink)



2 Temperature-dependent mass change (TGA, green) and ion current of m/z 18 (water, blue) of calcium oxalate monohydrate.

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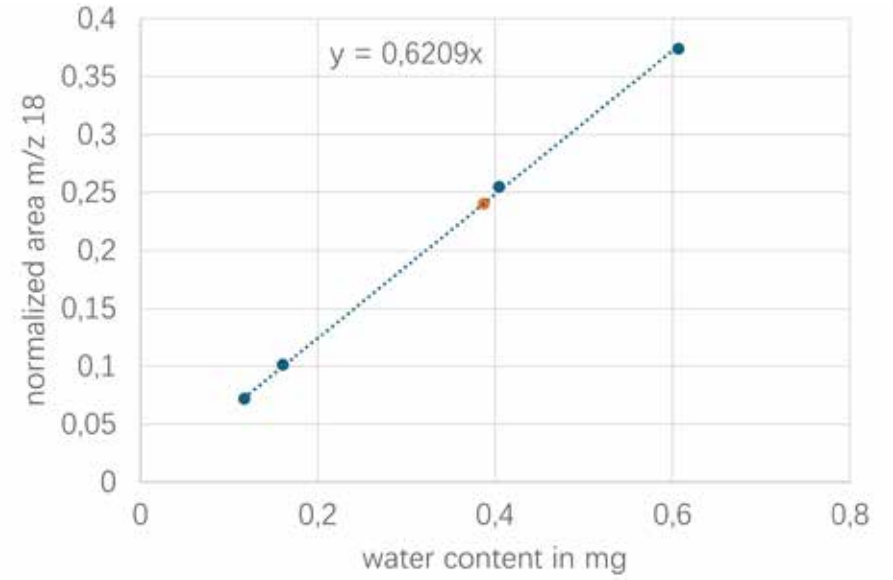
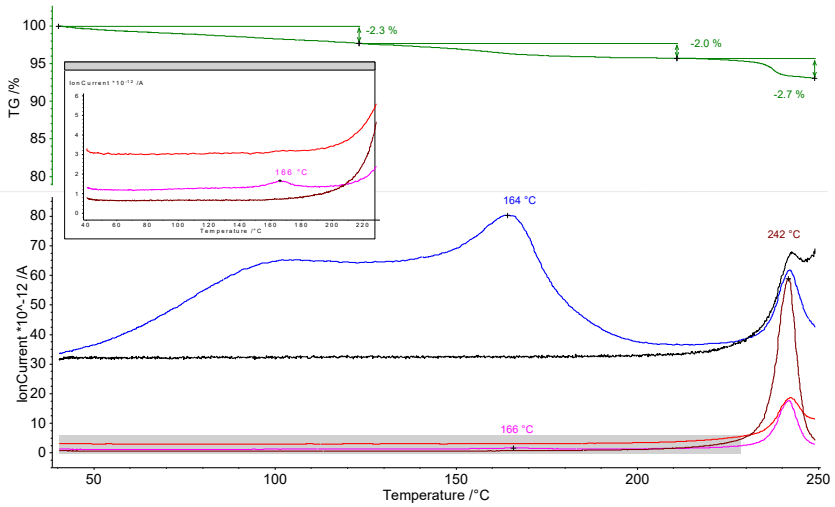
A calibration curve was generated using several different sample masses of calcium oxalate monohydrate, relating the amount of water released to the areas under the curve of m/z 18; see figure 3. Using this correlation, the amount of water released from the pharmaceutical sample was quantified to 0.387 mg (orange data point). Thus, it can be interferred that the amount of additional solvent, e.g., acetone or ethyl acetate, was about 0.027 mg.

A second sample of the same material was heated to 250°C. Another mass-loss step appeared in the thermogravimetric curve with a mass loss of 2.7% above 220°C. Here, the ion current signal shows the simultaneous increase of several mass numbers such as m/z 18, m/z 28, m/z 43, m/z 44 and m/z 45 that cannot be related to a single solvent; see figure 4. This indicates that the third weight-loss step is not simply volatilization of solvent, but decomposition of the sample.



3 Correlation of the water content to the peak area of the ion current m/z 18.



4 Temperature-dependent mass change (TGA, green) and ion currents of m/z 18 (water, blue), m/z 28 (black), m/z 43 (pink), m/z 44 (red) and m/z 46 (brown).

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Conclusion

These measurements demonstrate the ability of TGA-MS coupling to detect and analyze trace amounts of evolved gases. In particular, the detection sensitivity of toxic solvents in pharmaceuticals is reliably high enough to partially replace the quite complex GC-MS headspace method which is typically used in the pharmaceutical fields. A calibration curve can be used to determine the amount of a particular molecule, such as water. The advantage of this coupling technique is that traces of these critical gases can be detected and quantified without any pretreatment of the pharmaceutical sample. In addition, the evaporation of residual solvents can be clearly separated from the onset of the sample decomposition.

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