

# Thermal Analysis in the Pharmaceutical Field



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THERMAL STABILITY

## Thermal Stability

### Stability – A Key Feature

Stability is of vital importance for the quality of drugs and drug products and plays a crucial role during the development, manufacturing and commercialization of pharmaceuticals. It has an impact on material attributes such as purity (see page 67 ff), safety, efficacy and product shelf-life (see page 169 ff).

Stability can be classified into the following categories:

- Chemical stability
- Physical stability
- Microbial stability

Microbial stability, however, cannot be covered by thermoanalytical methods.

Chemical stability is said to exist when a particular substance is not reactive during normal use. Or, conversely, chemical instability is said to be the case when a substance is able to undergo chemical reactions, such as oxidations (see pages 141 ff) or interactions between APIs and excipients (see page 237 ff). The reaction products formed may be toxic, reduce the potency of the drug or just make it aesthetically unacceptable. Sometimes, chemical stability is also equated to thermodynamic stability [45].

Physical stability can be related to such occurrences as transitions in the crystalline state (crystallization of an amorphous drug or the phenomenon of polymorphism – see page 199 ff), the loss of volatile matter or moisture adsorption. [1]

For finished drug products, the nature of preservatives used in the pharmaceutical preparation as well as the packaging can also be essential.

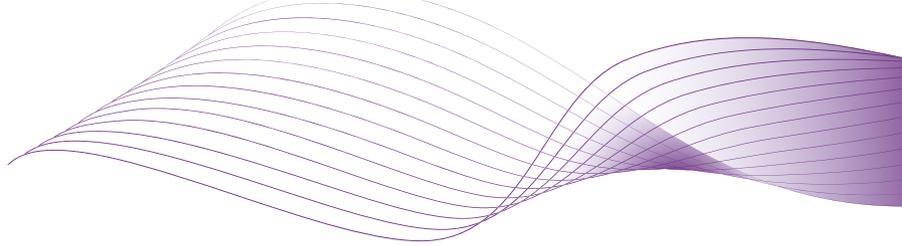
Both the ICH Guideline Q1A [2] and the WHO Technical Report No. 1010 [3] link the term 'stability' to environmental factors, such as temperature, humidity and light, which may influence the quality of a drug substance or drug product over time.

The term 'thermal stability' specifically refers to situations in which temperature is the influencing factor.

### Thermal Stability is the Ability of Compounds to Resist Heat Treatment

This means that a material is thermally stable as long as its structure and its properties are not affected when subjected to higher temperatures.

ASTM E2550 describes that "the assessment of material thermal stability" can be performed "through the determination of the temperature at which the material starts to decompose or react and the extent of the mass change using thermogravimetry" [4]. Thus, thermogravimetric analysis (usually under inert conditions, i.e., under the exclusion of air) is the method of choice for investigating thermal stability. Moreover, this makes it an important tool for estimating the maximum temperature of DSC tests as well as for DSC curve interpretation.



## Various Suitable Characteristic Temperatures

A degradation or decomposition effect can be characterized by various temperatures, as follows:

- By the onset temperature which is defined in ASTM E2550 as "the point on the TGA curve where a deflection is first observed from the established baseline prior to the thermal event".
- By the extrapolated onset temperature which is "the point of intersection of the starting-mass baseline and the tangent to the TGA curve at the point of maximum gradient" as mentioned in ISO 11358-1 [5] and DIN 51006 [6].
- By the DTG maximum (or minimum, depending on the direction of presentation). The DTG curve is the first derivative of the TGA curve versus time and the extremum represents the inflection point of the corresponding TGA curve.

All three temperatures are shown in figure 1. It illustrates the thermal behavior of pullulan in a nitrogen atmosphere. The different mass-loss steps are explained on page 116 ff using TGA-FT-IR. The effects between room temperature and 200°C are caused by the evaporation of water. Decomposition of the substance begins with the second mass-loss step; i.e., it occurs at 219°C (onset temperature as per ASTM E2550), 299°C (extrapolated onset temperature as per ISO 11358-1), and 315°C (minimum of the DTG curve).

Which temperature is the preferred one depends on the application as well as on the accuracy of determination. A peak temperature (DTG peak) is always mathematically well defined. The same is true of most of the extrapolated onset temperatures. The onset temperature, however, heavily depends on the magnification of the displayed curve and the data acquisition rate – yet it represents the true beginning of the mass-loss step under the selected measurement conditions.

Based on this, the extrapolated onset temperature of the TGA curve along with the extremum of the DTG curve are generally used to describe mass-loss effects in the following examples. In addition, ASTM E2550 restricts application of the proposed method of thermal stability determination because "it is not suitable for materials that sublime or vaporize in the temperature of interest".

It is possible to differentiate between decomposition and sublimation or vaporization with evolved gas analysis, which consists of coupling a gas detector to the thermobalance that can identify the gaseous products released during measurement. More information about coupling is given on page 20 ff.

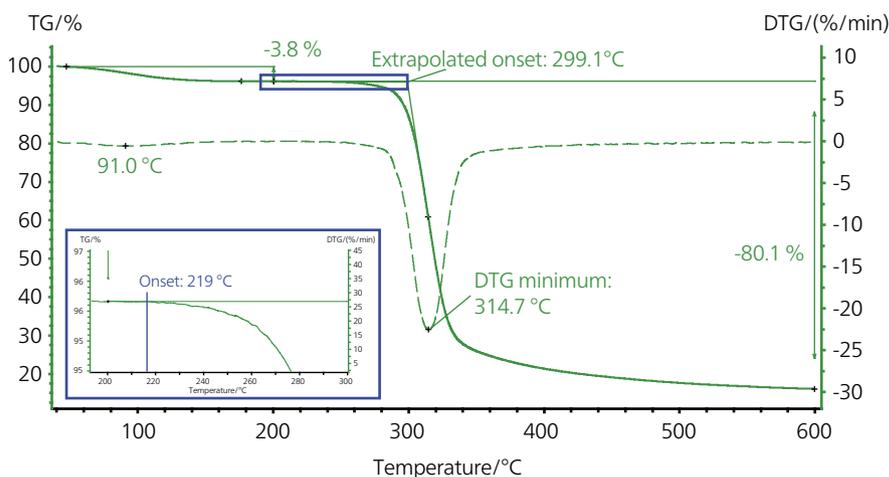


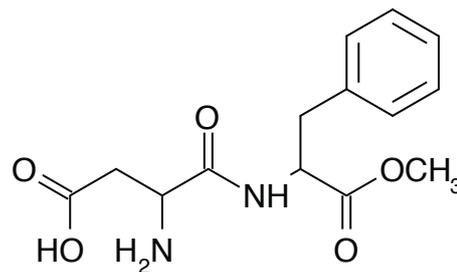
Figure 1. TGA measurement curve of pullulan. The first mass-loss step is due to the release of surface water (see TGA-FT-IR measurement on page 118). The second mass loss describes the thermal decomposition of the sample. The characteristic temperatures of the decomposition are 299°C (extrapolated onset temperature), 219°C (onset temperature according to ASTM E2550, see blue inset) and 315°C (maximum mass loss rate indicated by the DTG curve).

## Aspartame

### About Aspartame

Aspartame is a white powder discovered by accident in 1965 by James Schlatter. Because of its intense sweet taste, it is used as a sugar substitute in the food, beverage and pharmaceutical industry. The European food code for aspartame is E951. [7, 8, 9]

IUPAC name	Methyl L- $\alpha$ -aspartyl-L-phenylalaninate
CAS-No	22839-47-0
Molecular formula	$C_{14}H_{18}N_2O_5$
Molar mass	294.31 g/mol
Thermal properties	$T_m = 245 - 247^\circ\text{C}$ [9]
Drug class	Inactive ingredient



### Experimental

Method	TGA-FT-IR
Sample type/shape	White powder
Sample preparation	As received
Sample mass	7.46 mg
Crucible	Aluminum oxide, open
Temperature program	35°C ... 700°C, 10 K/min
Atmosphere	$N_2$ (40 ml/min)

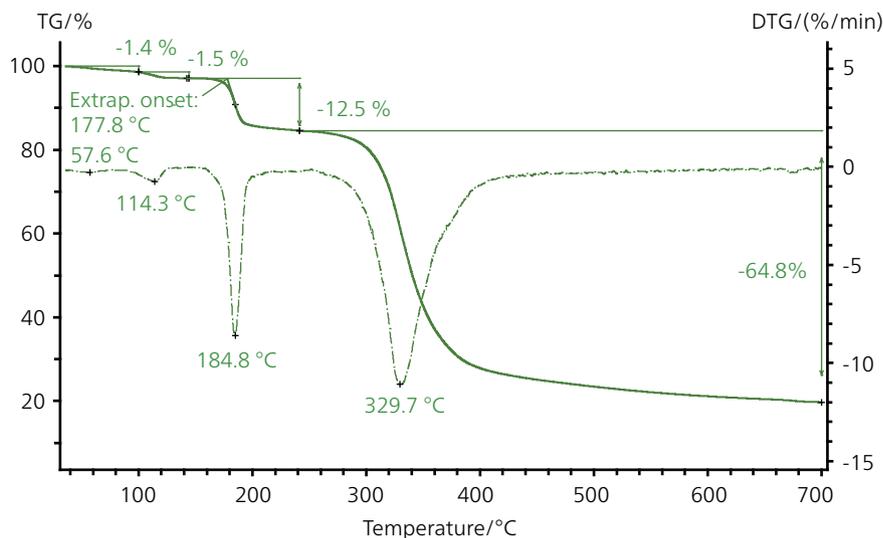
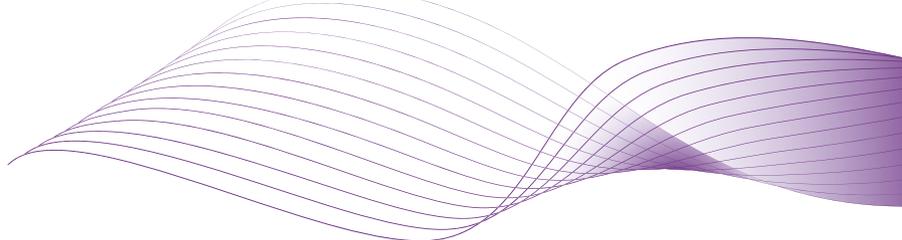


Figure 1. TGA curve of aspartame (solid line) and its first derivative (DTG, dash-dotted line)



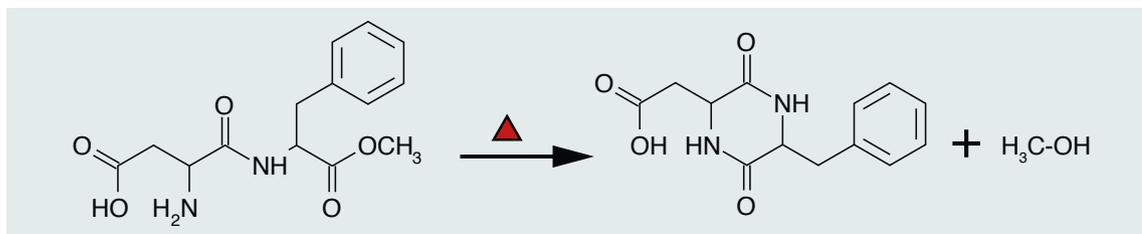
## Results:

### Initial mass losses due to water

Figure 1 depicts the TGA curve of aspartame during heating in nitrogen. Two mass-loss steps of 1.4% and 1.5% are detected at 58°C and 114°C (DTG peaks), respectively. They both result from the release of water. This can be deduced from the FT-IR spectra of the evolved gases at 60°C and 123°C (figure 3). The temperatures of these water releases indicate that it is surface water that is released during the first mass-loss step, while stronger bound water is released in the second step.

### Decomposition begins at 178°C

The first decomposition step at 178°C (extrapolated onset-temperature) leads to a mass loss of almost 13%. As explained on page 89, the substance loses thermal stability already at a lower temperature, i.e., at the temperature at which the TGA curve deviates from the baseline, thus at 158°C (see figure 2). The decomposition is associated with the release of methanol (figure 4) and the formation of a new substance, most probably 2,5-dioxopiperazine [7].



Release of methanol during heating of aspartame. It leads to a cyclization of the substance, forming 2,5-dioxopiperazine

The 2,5-dioxopiperazine formed melts at 247°C (peak temperature, see STA measurement on aspartame on page 47). The decomposition of this substance takes place at 330°C (DTG peak), inducing a mass loss of 65%. During decomposition, carbon dioxide and ammonia are released (see figure 5). The bands above 3000 cm<sup>-1</sup> are due to substances containing =C-H bonds. The effects in the wavenumber domain between 1600 and 1800 cm<sup>-1</sup> are typical for C=O bonds and/or aromatic rings. Figure 6 shows the FT-IR traces of methanol, carbon dioxide and ammonia along with the TGA curve of aspartame.

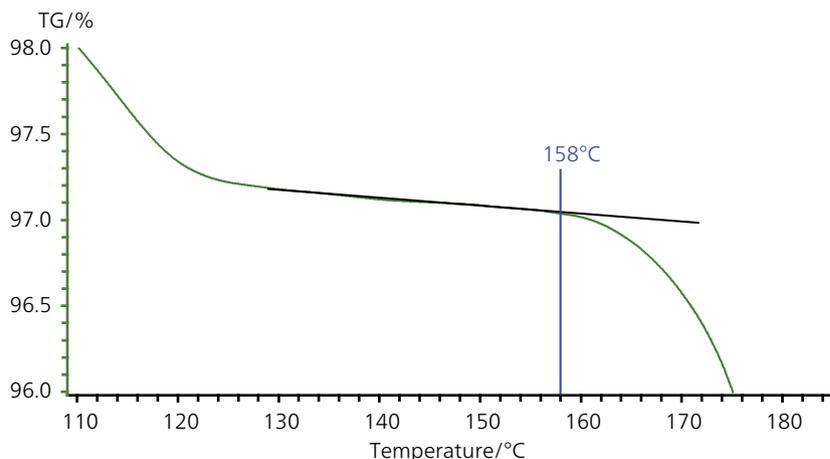


Figure 2. Zoom excerpt from figure 1 for determination of the thermal stability

## Aspartame

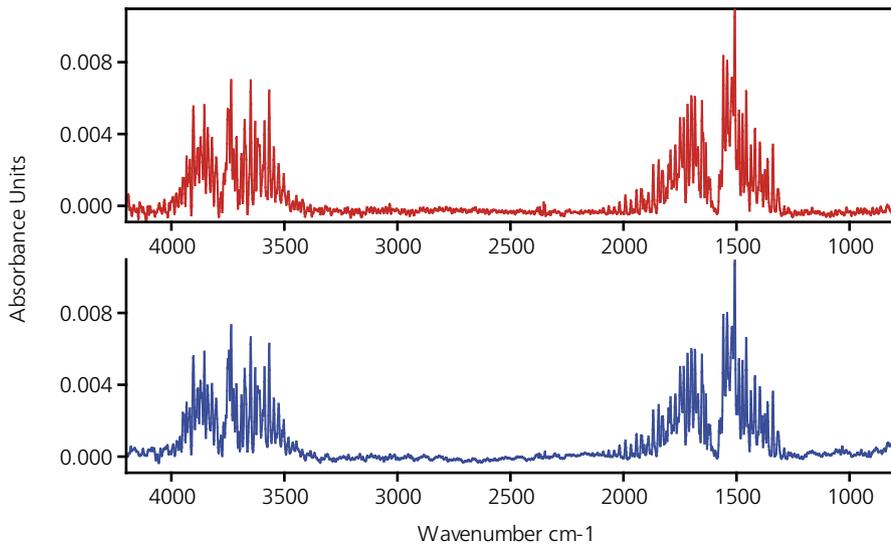


Figure 3. FT-IR spectrum of the products released at 60°C (red curve, top) and 123°C (blue curve, bottom). The absorption bands detected at both temperatures are typical for water. The comparison spectrum of water is depicted on page 108.

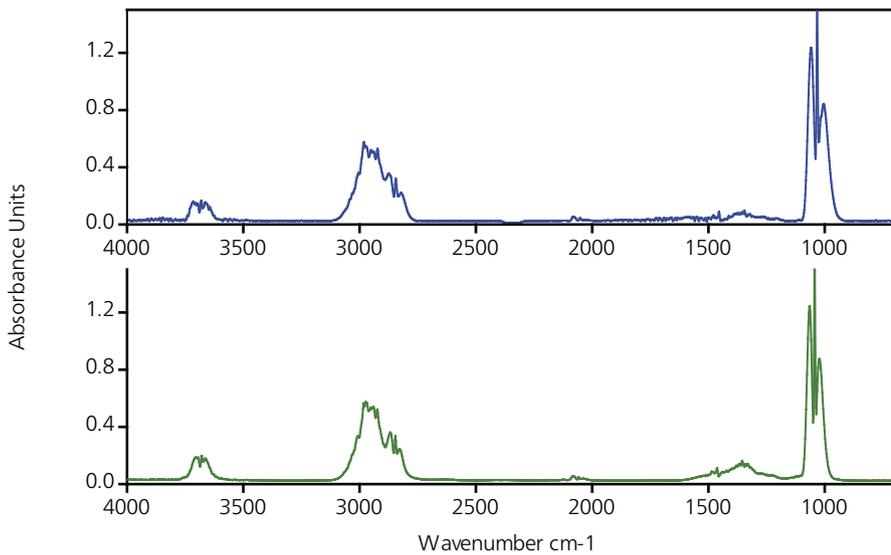


Figure 4. FT-IR spectrum of the products released at 184°C (blue curve, top) compared to the library spectrum of methanol (green curve, bottom)

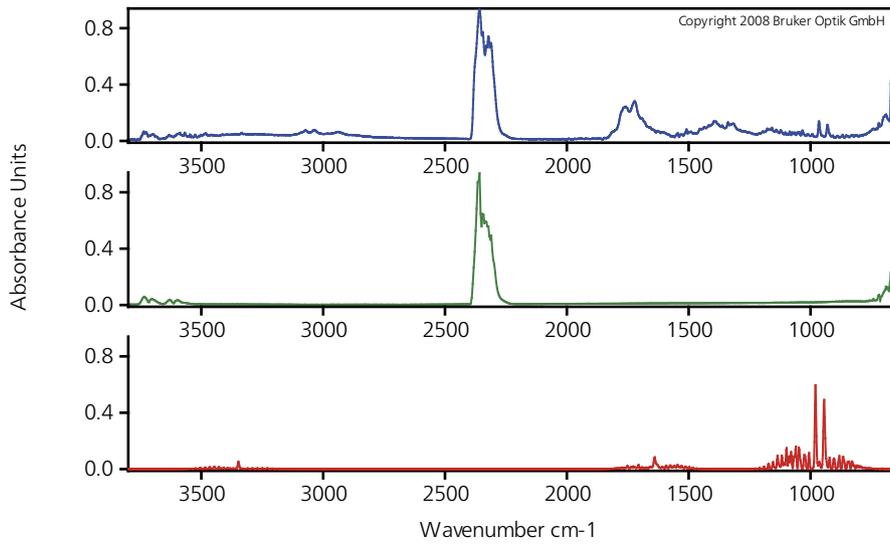
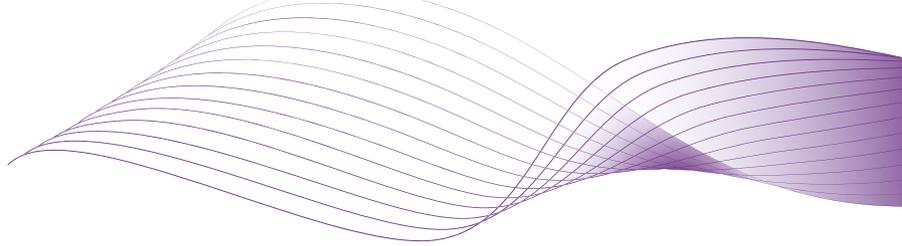


Figure 5. FT-IR spectrum of the products released at 329°C (blue curve, top) compared to the library spectra of CO<sub>2</sub> (green curve, middle) and NH<sub>3</sub> (red curve, bottom)

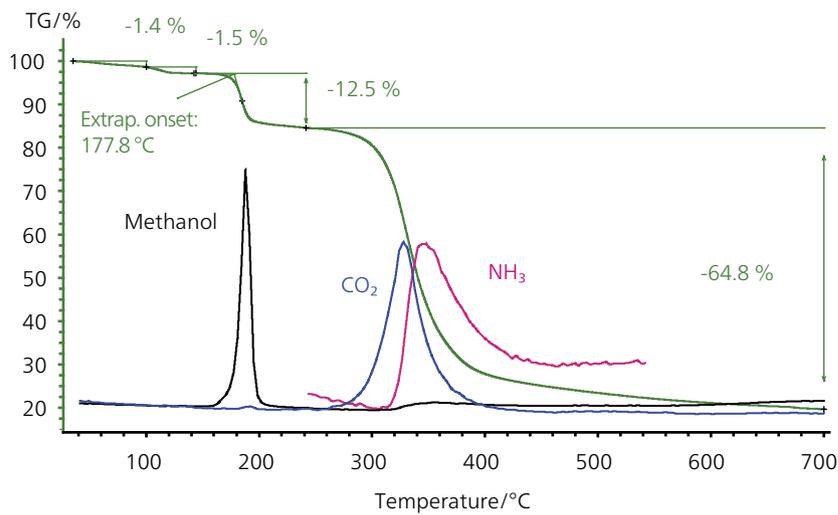


Figure 6. TGA curve of aspartame displayed with FT-IR traces of methanol, CO<sub>2</sub> and NH<sub>3</sub>