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THERMAL CHARACTERISATION OF TORASEMIDE USING COUPLED TECHNIQUES

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Abstract

Thermal treatment of torasemide form A resulted in several effects which were divided into five steps. These were investigated and discussed applying TG-MS and TG-FTIR with additional information derived from SEM, hot-stage and FTIR microscopy. The investigated crystal form of torasemide represents a mixed solvate including ethanol and water. Its desolvation, the solid-solid transformation into the anhydrate mod. II and the melting of this anhydrate is elucidated using thermal analysis and microscopic observations (FTIR and hot-stage microscopy). The released and evaporated solvents were determined with coupled techniques. On further heating the structural identification of evolved gases allowed the analysis of the degradation pathway of torasemide up to 340°C.

Keywords: coupled techniques, desolvation, hot-stage microscopy, SEM, TG-FTIR, TG-MS, thermal decomposition, torasemide

Introduction

The determination of evolved gases using coupled TG-MS and TG-FTIR techniques is a well established and successfully applied method in the thermal analysis of organic or inorganic compounds, and therefore for the analysis of pharmaceuticals, too. The application of these simultaneous techniques allows the identification of the composition of gaseous products during degradation and the evaluation of the desolvation evaporates as a function of temperature [1–6]. Additionally, the potential of visualizing non destructive thermal events by hot-stage microscopy (HSM), which are often complex, superposed phenomena in DSC or DTA, has been described for decades as reflected in numerous publications [7–9].

The compound investigated in this study is the drug substance torasemide (Fig. 1), which is used as potential loop diuretic and antihypertensive agent. It is marketed as Demadex®, Toradiur®, Torem®, and Unat® in different European countries. In a former work [10] we extensively wrote about the different crystal forms of torasemide since this issue is of high interest with regard to the drug preformulation,

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which influences the drugs' security and efficiency as well as the application of patents for pharmaceutical industry. Two monotropically related modifications of the anhydrate were characterized (mod. I – *mp.* 158–161°C; mod. II – *mp*. 155–158°C). Additionally, a pseudopolymorphic crystal form (form A) was investigated which can be described as a channel inclusion compound containing fluctuating amounts (1.9–4.2%) of water and alcohol (methanol, ethanol, 1-propanol or 2-propanol).

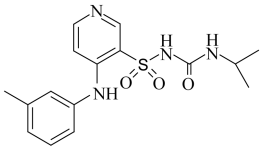

Fig. 1 Molecular structure of torasemide

The primary aim of the present study was to investigate the desolvation process of torasemide form A crystallized from water and ethanol, and to give a possible decomposition path for torasemide using coupled TG-MS and TG-FTIR methods. The results were supplemented by HSM and SEM observations.

Experimental

Materials and methods

Torasemide (mod. I, Batch No. EK 64/166) was provided by Roche Diagnostics GmbH, Mannheim, Germany. Torasemide form A, which was used as starting material for our studies, was prepared by rapid cooling of a hot saturated solution of torasemide in ethanol 96%/water (*v:v*=2:1) down to 7°C. After 24 h, crystals were filtered off, and stored at ambient conditions. All solvents and chemicals used for this study were of analytical grade.

Instruments

Hot stage microscopy (HSM) was performed using an Olympus BH-2 polarizing microscope (Olympus Optical Co., Ltd.) fitted with a Kofler hot-stage (Reichert, Vienna, Austria) and linked with a digital camera (Olympus BX50F, Olympus Optical Co., Ltd.) using the software Studio Lite and View Finder, Version 1.0. For visualizing the evaporation of gases the solid samples were immersed in silicon oil and covered with a cover slip.

The TG-MS coupled measurements have been carried out using TA Instruments (Newcastle, Delaware, USA) STD 2960 simultaneous TG-DTA unit with a heating rate of β=5 K min^{-1} and helium purging (10 L h^{-1}) and a Balzers Thermostar GSD 300T quadrupole mass spectrometer with a heated silica capillary inlet. This latter one was used in 'multiple ion detection' (MID) mode, when fragments with previously adjusted *m/e* values have been followed.

The TG-FTIR measurements have been carried out using TA Instruments (Newcastle, Delaware, USA) TG 2050 model with a heating rate of β=5 K min^{-1} and air (10 L h^{-1}) purging coupled to BioRad Excalibur FTS 3000 IR spectrometer with 4 cm^{-1} resolution and a heated stainless steel inlet.

The scanning electron microscopic observations have been performed on a Jeol JSM 5500LV apparatus after sputtering Au/Pd on the investigated samples.

Results and discussion

For the investigation of the desolvation process of torasemide form A, its physical purity was controlled by means of FTIR and XRPD and compared to previously published data [10]. Additionally, the crystals used as starting material were characterized by SEM (Fig. 2a and b) and microscopic observations with polarized light (Fig. 3a–f).

The prism-shaped crystals have sharp edges and faces. Crystals up to 1 mm in size were observed.

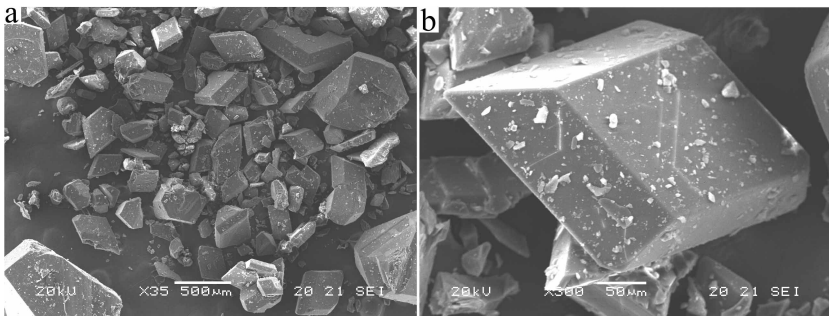

Fig. 2 SEM images of torasemide form A; a – *N*=35; b – *N*=300

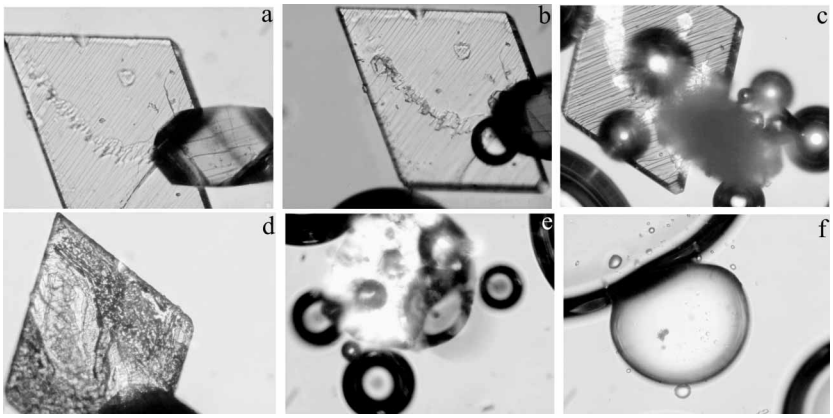

Fig. 3 Micrographs (*N*=200) of torasemide (starting material: form A) with polarized light recorded at different temperatures: a – 30°C; b – 90°C; c – 110°C; d – 130°C; e – 158°C; f – 165°C

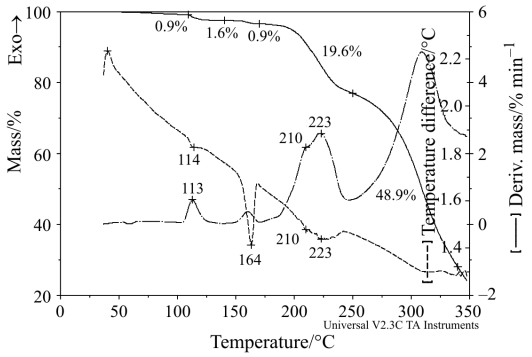

Fig. 4 Thermoanalytical curves of torasemide

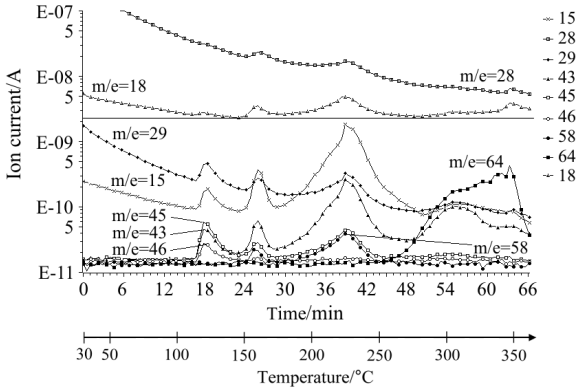

Fig. 5 MID profiles of torasemide

Based on the thermoanalytical curves (Fig. 4) and MID profiles (Fig. 5) the thermal behaviour of torasemide was divided into five steps, which are summarized in Table 1.

Step 1

Between 30 and 110°C (t=0–16 min, Fig. 4) 0.9% of mass loss was recorded. By means of the Gram-Schmidt curve [11] a continuous water evolution could be detected in the range of 30 to 110°C assigned to adsorbed water on torasemide crystal form A (Fig. 6). Moreover a continuous water evolution along the whole temperature interval (30–340°C, 0–62 min, Figs 4 and 6a) was observed, as it has been indicated also by the MID line at *m/e*=18 in Fig. 5. (The thin dotted line just below the water line is a guide for eye. Furthermore, the authors wish to focus one's attention that for the evolution of water and the total evolved gases the Gram–Smith curves are described in two different sensitivities, so their direct comparison may lead to false conclusions. Here just their tendencies are important.) By polarized HSM the transparent crystals of form A could be observed in the whole range of step 1 without changing their crystal form (Fig. 3a, b). A slight loss of evaporated gases is visible as small bubbles while heating up (Fig. 3b), which is in agreement with the TG-curve (Fig. 4).

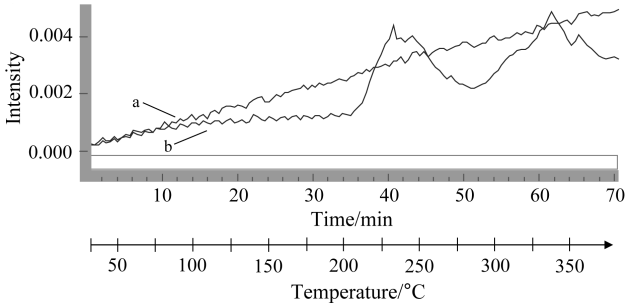

Fig. 6 Gram–Schmidt curve of a – water and b – total vapour evolution from torasemide

Step 2

Increasing the temperature up to 140°C 1.6% further mass loss was observed (Fig. 4, Table 1). By the evaluation of the MID curves (Fig. 5) the simultaneous evaporation of water (*m/e*=18) and ethanol (*m/e*=46, 45, 43, 29, 28 and 15) was detected (Table 2, Fig. 5).

The release of ethanol and water was additionally proven by TG-FTIR coupled technique, as can be seen in the FTIR curve of the evolved gases recorded at 130°C (20 min, Fig. 7). The absorption band at 1060 cm^{-1} is belonging to the C–O–H deformation vibration, while the other band at 2980 cm^{-1} is belonging to the CH_3–CH_2– stretching vibration of ethanol. Further, the release of the solvents included in the crystal lattice of torasemide form A could easily be observed by HSM (Fig. 3c). By embedding a few crystals in silicon oil the release of the evaporate is clearly visible by the formation of numerous bubbles. Simultaneously with the desolvation of crystal form A a solid-solid transformation into the anhydrate mod. II takes place. This

Table 1 Classification of steps taken from Figs 4 and 5 of torasemide (the last line corresponds to observations obtained from HSM)

	Step 1	Step 2	Step 3	Step 4	Step 5
Time/min	0–16	16–22	22–28	28–44	44–62
Temperature/°C	30–110	110–140	140–170	170–250	250–340
Mass loss/%	0.9	1.6	0.9	19.8	48.9
Evolved fragments, with representative *m/e* units	H_2O, *m/e*=18	H_2O, *m/e*=18	H_2O, *m/e*=18	H_2O, *m/e*=18	H_2O, *m/e*=18
		EtOH, *m/e*=46	EtOH, *m/e*=46		
		45, 43, 29, 28, 15	45, 43, 29, 28, 15		
			TOR, *m/e*=58	TOR, *m/e*=58	TOR, *m/e*=64
			43, 28, 15	43, 28, 15	58, 43, 28, 15
Crystal form	form A		mod. II	amorphous→decomposing→gaseous	

Table 2 Assignment of leaving fragments

Water	Ethanol		Torasemide	
m/e=18 H_2O	*m/e*=15	$-CH_3$	*m/e*=15	$-CH_3$, –NH
	m/e=28	$-C_2H_4$	*m/e*=28	–C=O
	m/e=29	$-C_2H_5$	*m/e*=43	$-C_3H_7$, $-NH-C_2H_4$
	m/e=43	$-C_2H_2-OH$	*m/e*=45	$-NH_2-C_2H_5$
	m/e=45	$-C_2H_4-OH$	*m/e*=58	$-NH-CH-(CH_3)_2$
	m/e=46	$-C_2H_5-OH$	*m/e*=64	SO_2

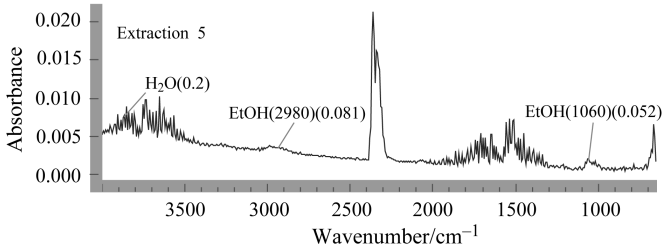

Fig. 7 FTIR spectrum of evolved vapours at 130°C (20 min)

transformation is indicated by a continuous loss of the crystals' transparency, which starts at 110°C (Fig. 3c) and is finished simultaneously with the end of the desolvation at about 130°C (Fig. 3d). The identification of currently existing anhydrate mod. II was given by FTIR-microscopy [10].

Step 3

The same solvents (ethanol and water) were detected in step three (between 140 and 170°C, 22–28 min) causing 0.9% further mass loss in the TG curve. From the comparison of the MID peak areas belonging to *m/e*= 45 and 46 it can be stated that the amount of evolving ethanol in step 2 is approximately 5–10 times greater than in step 3. As to the water (*m/e*=18) content a reverse phenomenon was recorded (Fig. 5). In this temperature interval it can be concluded from the TG and MID curves at *m/e*=18 and *m/e*=45 and 46 that the estimated amount of ethanol is at least five times less than that of the evaporated water (Figs 4 and 5). According to the observations with HSM the melting process of torasemide mod. II takes place within this step (155 to 160°C, Fig. 3e, f). The process of melting is indicated by the presence of the endothermic peak on the DTA curve at 164°C. In contrast to the starting material form A, the currently present anhydrate (mod. II) does not contain solvent molecules in its crystal lattice [12]. Therefore, the evolved substances correspond to the remaining solvent molecules released from the anhydrate particles during their melting. Looking at the MID curves at *m/e*=46, 45, 43 and 15 in steps 2 and 3 an anomaly was recognized in the areas of the corresponding peak areas. Whereas the *m/e*=45 and 46 profiles, which are representative of the leaving ethanol are running paral-

lel and exhibit a decreasing tendency, the lines at *m/e*=43 and 15 are obviously increasing (Fig. 5, step 3). Although these curves belong to the same specific mass units, they definitely have to originate from other sources than that of the ethanol, e.g. from a partial sublimation of torasemide during its melting.

Step 4

The first stage of decomposition takes place between 170–250°C (28–44 min). The corresponding mass loss is about 20%. At least two consecutive endothermic processes (peaks at 210°C and 223°C, Fig. 4) are observed in the DTA curve. On MID curves the representative fragments at *m/e*=58, 45, 43, 29, 28 and 15 are detectable corresponding to the leaving of the aminopropyl group (–NH–C_3H_7) and its fragments (e.g. –NH_2-C_2H_5, –NH-C_2H_4, –C_3H_7, –C_2H_5, –C_2H_4, –CH_3, –NH, respectively; Fig. 8). The leaving of this group theoretically results in 16.6% of mass loss. So far it can be stated that the measured but somewhat higher mass loss (20%) is caused by the overlapping of the first and second stage (steps 4 and 5) of decomposition (Fig. 4).

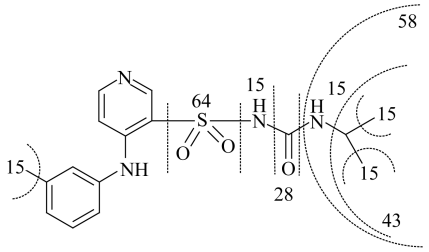

Fig. 8 Structure with degradation mechanism

Step 5

In the final step between 250 to 340°C almost 50% of mass loss was recorded. This can be attributed to the overall decomposition of torasemide. According to the MID curves fragments of –C=O, –NH–, and SO_2 (*m/e*=28, 15 and 64, respectively) were identified, as it has been indicated in Fig. 8.

Conclusions

The high potential advantage of the combination of conventional thermoanalytical techniques (DTA, TG/DTG, HSM) with mass spectrometry and FTIR could be demonstrated in the case of the drug substance torasemide. It aided the interpretation of the course of the investigated thermal reactions. Whereas HSM was an essential analytical tool to unravel the first thermal steps (steps 1–3), i.e. desolvation, transformation, and melting process, by visualizing them, the TG/MS and TG/FTIR couplings provided structural identification of compounds evolving during desolvation, melting and especially during thermal decomposition (steps 4 and 5), which enabled the analysis of the degradation mechanism of torasemide (Fig. 8).

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