Institute of Pharmacy, Friedrich-Schiller-Universität, Jena, Germany

Investigations on the thermal behavior of omeprazole and other sulfoxides

K. M. ROSENBLATT, H. BUNJES, A. SEELING, H. OELSCHLÄGER

Received August 23, 2004, accepted August 30, 2004

Prof. Dr. Dres. h.c. H. Oelschläger, Institute of Pharmacy, Philosophenweg 14, D-07743 Jena, Germany

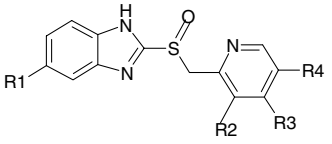
Pharmazie 60: 503–507 (2005)

Thermoanalytical and chromatographic investigations were performed to elucidate the reason for the uncommon thermal behavior of omeprazole prepared according to a newly developed route of synthesis. Differential scanning calorimetry revealed that the position of the melting endotherm of omeprazole strongly depended on the heating rate. High heating rates (20–30 °C/min) led to endothermic peaks at high temperatures (comparable to literature data), while lower rates induced a shift of the signal to lower temperatures. In thermogravimetric experiments weight loss was observed which started about 20 °C lower at the heating rate of 1 °C/min in comparison with the rate of 20 °C/min. Thermomicroscopic investigations indicated a decomposition prior to melting at low (1 °C/min) but not at high heating rates (20 °C/min). Investigation of the violet melt by HPLC and TLC showed that omeprazole was decomposed quantitatively. Decomposition started at 135 °C and depended on the rate of heating. The results indicate that eutectic behavior with decomposition products leads to a melting point depression of omeprazole upon slow heating. Similar behavior was observed for the related sulfoxides lansoprazole and pantoprazole which showed the same onset temperature for decomposition as omeprazole in chromatographic investigations. The heating rate dependent melting behavior was, however, much less pronounced for pantoprazole which has a melting range only slightly above the onset temperature for decomposition. In contrast, a constant value for the melting temperature could not be achieved for lansoprazole, the substance with the highest melting range under investigation, even at high heating rates up to 30 °C/min. In conclusion, a very dynamic method and exactly standardized measurement conditions, particularly with regards to heating rate, (e.g., in DSC) have to be employed to enable reliable determination of a melting point of these decomposable substances.

1. Introduction

The ultimate mediator of acid secretion is the H^+/K^+-ATPase (proton pump of the apical membrane of the parietal cell). This pump is unique to the parietal cells and a number of specific inhibitors of it have, therefore, been developed. The available compounds belong to the family of substituted benzimidazoles: omeprazole, lansoprazole, pantoprazole and rabeprazole. Esomeprazole is the more active S-enantiomer of omeprazole. These agents are especially useful in patients with hypergastrinemia and may be valuable in those patients whose peptic ulcer disease is not well controlled by H_2-antagonists. These benzimidazoles are prodrugs. They become protonated in the secretory canaliculi. The protonated compounds rearrange to form a sulfenic acid and a sulfenamide. The onset of action for rabeprazole is particularly rapid because it is transformed into the active form already at pH 4.9 in the parietal cells. The sulfenamide interacts covalently with sulfhydryl groups at critical sites in the luminal domain of the membrane-spanning H^+/K^+-ATPase with subsequent formation of a disulfide bridge. Full inhibition occurs with two molecules of inhibitor bound per molecule of enzyme.

Recently, an alternative and efficient route for the synthesis of the first proton pump inhibitor omeprazole was described (Oelschläger et al. 1999). Even though the resulting product was clearly identified as omeprazole by HPLC and TLC and there were no indications for the presence of residual solvents, the capillary melting point of the newly synthesized substance was much lower (~145 °C) than the melting temperature reported in a common literature reference (156 °C) (O'Neill et al. 1996b). In the patent literature, different ranges of the melting temperature have been reported for omeprazole (140–147 °C, 147–150 °C, 152–157 °C) (Palomo 1992), whereas



	R1	R2	R3	R4
Omeprazole:	OMe	CH_3	OMe	CH_3
Lansoprazole:	H	CH_3	O–CF_3	H
Pantoprazole:	F, O, F	OMe	OMe	H

Ph. Eur. 4.00, USP 26 and JP 14 do not report a melting point. A preliminary investigation by differential scanning calorimetry of the newly synthesized sample in comparison to commercial omeprazole revealed about the same depression of the melting point for both substances. With IR spectroscopy and x-ray diffractometry no indications of polymorphism could be found which might have explained an uncommon behavior of the newly synthesized substance. To further elucidate the uncommon melting behavior of omeprazole, a systematic examination of the thermal behavior of omeprazole with several thermoanalytical and chromatographic methods was initiated, particularly under the aspect of a potential contribution of decomposition products. Two other sulfoxides, lansoprazole and pantoprazole were also included in the study due to their structural similarity and differing melting points. For lansoprazole a comparatively high melting temperature (m.p.: 178–182 °C) (O'Neill et al. 1996a) has been reported whereas that of pantoprazole (139–140 °C) (O'Neill et al. 1996c) is in a range lower than that of omeprazole.

For omeprazole in capsules and tablets it has been known that the substance shows a certain instability. As a result, the dosage forms become discolored and a reduction in drug content as well as the occurrence of decomposition products can be shown with liquid chromatography. The occurrence of these instabilities shows a certain relation to the manufacturer.

2. Investigations and results

The DSC curves of omeprazole display an endothermic peak followed by an exothermic event at most heating rates (Fig. 1). At the highest heating rates (20 and 30 °C/min), the onset of the endothermic peak is almost constant at about 157 °C. With decreasing heating rate, this peak shifts to lower temperatures. For example, the onset obtained with a heating rate of 2.5 °C/min is 10 K lower (at 147 °C) than that obtained at 20 or 30 °C/min. For lower heating rates, the exotherm following the endothermic peak becomes more pronounced until, at 1 °C/min, the endothermic peak completely disappears and only an exotherm (T_{onset}: 139 °C) remains.

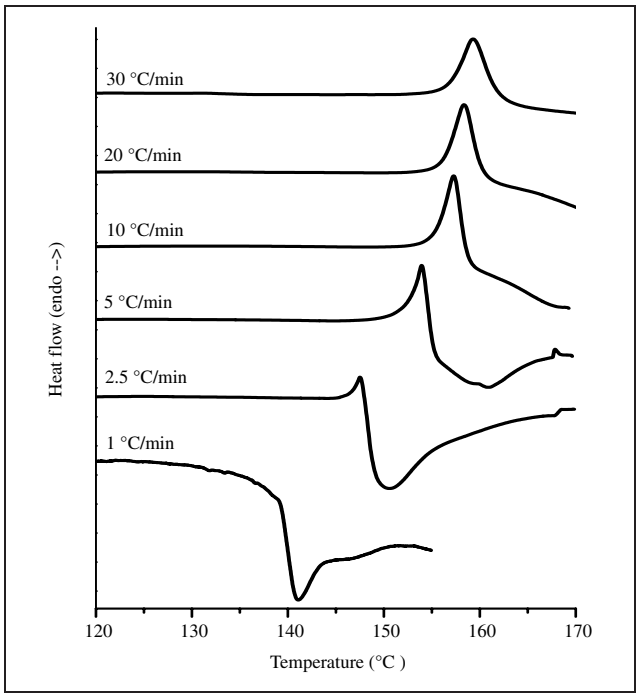


Fig. 1: DSC curves of omeprazole obtained with different heating rates

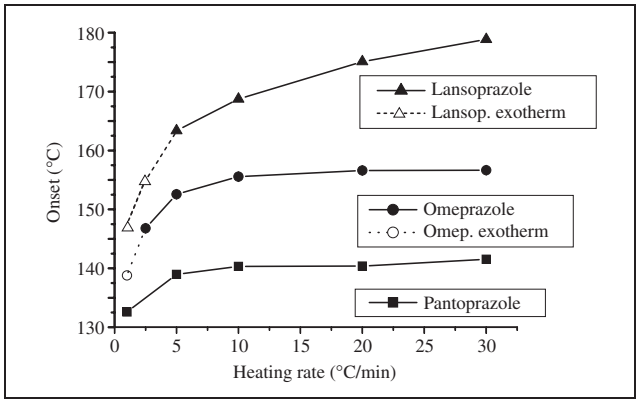


Fig. 2: Onset values of the thermal transitions of the three prazoles as observed by DSC (endothermic transitions: full symbols, exothermic transitions: open symbols; omeprazole n = 3–4; pantoprazole and lansoprazole n = 1)

Lansoprazole and pantoprazole have a DSC melting behavior qualitatively similar to omeprazole (endotherm followed by exotherm). For pantoprazole, the heating rate dependent shift of the endothermic event is less pronounced than for omeprazole (Fig. 2). The onset values already reach constant values at a heating rate of 10 °C/min (141 °C). At the lowest heating rate of 1 °C/min there is still an endothermic peak (T_{onset}: 133 °C). The exothermic peak is less pronounced than for omeprazole. For lansoprazole the heating rate shows the largest effect on the thermal behavior out of the three prazoles under investigation. Even with the highest heating rates (20 and 30 °C/min), no constant onset values for the endotherm are reached. The onset temperatures at these heating rates still differ by 4 K (175 resp. 179 °C). At a heating rate of 2.5 °C/min and lower the endothermic event disappears. In contrast, the exotherm is already clearly visible at a heating rate of 30 °C/min.

For omeprazole, thermomicroscopic investigations were performed at heating rates of 1 and 20 °C/min. With the high heating rate, the colorless crystals melted at about 158 °C and started to become dark during the melting process (Fig. 3). In contrast, the crystals already began to darken around 140 °C using the low heating rate. They were almost black when they melted at about 148 °C.

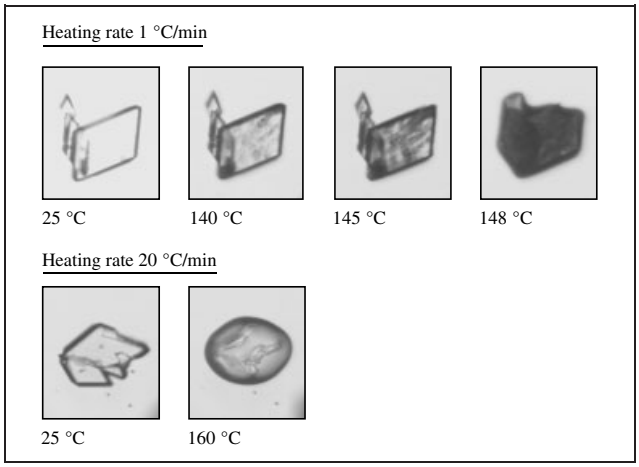


Fig. 3: Thermomicrographs of omeprazole crystals heated at different rates

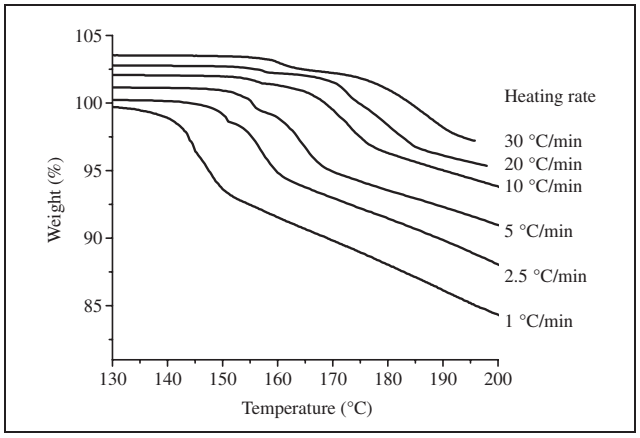


Fig. 4: Thermogravimetric curves of omeprazole obtained at different heating rates. The curves are displaced along the ordinate for better visualization

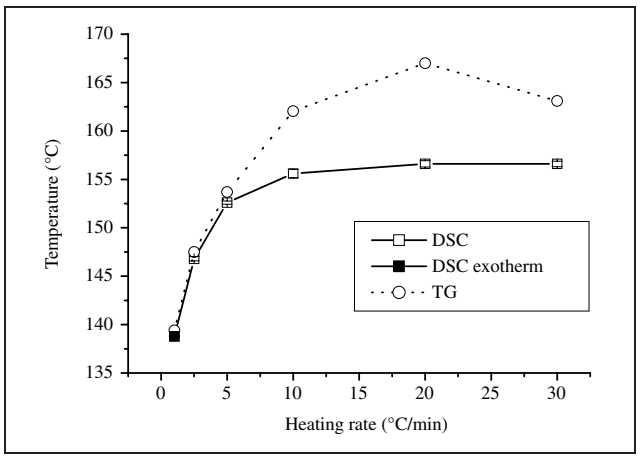


Fig. 5: Comparison of the DSC onset temperatures (onsets of the endothermic peaks except for full symbol: exothermic onset) with the values of 1% weight loss measured with TG

Omeprazole was also investigated by thermogravimetry combined with DTA. The DTA signals show qualitatively and quantitatively almost the same effects as the DSC results with respect to the transition temperatures. The thermogravimetric curves reveal a weight loss upon heating. The temperature at which the weight loss begins depends on the heating rate (Fig. 4). For lower heating rates, the loss of weight starts at lower temperatures and reaches higher values in comparison with the weight loss observed at higher heating rates. To compare the thermogravimetric results with the DSC onset values, the temperatures of 1% weight loss were determined. For the lowest heating rate (1 °C/min), the point of 1% weight loss is almost identical (139 °C) with the onset of the exotherm in the DSC (Fig. 5). For the heating rates 2.5 and 5 °C/min the thermogravimetric values are very similar to the onset of the DSC endotherms. In contrast, the temperatures of 1% weight loss are substantially higher than the DSC onset temperatures at higher heating rates (10 °C/min and above).

The thermogravimetric curves show several steps during heating. There are two steps of different sizes for all heating rates except 1 °C/min which leads to only one large step. The size of these steps seems to depend on the heating rate. The large (second) step appears at lower temperatures for lower heating rates and increases in size. A different shape of the steps is probably the reason for the low 1%-weight loss temperature observed at a heating rate of 30 °C/min. The cause of these steps is currently unknown and was not investigated in detail.

When heating the white crystals of any of the prazoles, their color turns over violet to black and a characteristic, mercaptane-like smell develops. The melting temperatures obtained with the Kofler bench were 156 °C ± 0.8 °C for omeprazole (n = 20), 180 °C ± 1.0 °C for lansoprazole (n = 20) and 143 °C ± 0.6 °C (n = 3) for pantoprazole.

In order to get information on the dependence of the melting point values on differences in the individual handling of the method and the device, the melting temperatures of omeprazole and lansoprazole were measured by 10 persons (untrained on the device) 5 times each. In this investigation, the median value for omeprazole is 159 °C ± 1.6 °C (n = 50; range: 156–162 °C), lansoprazole has a melting point of 181 °C ± 1.2 °C (n = 50; range: 178–184 °C).

For the interpretation of the melting point depression of the three sulfoxides, samples were kept for 10 min at different temperatures and analyzed by HPLC. As expected, the AUC values of the decomposition products, which started to appear at 135 °C, increased with temperature, until, e.g., for omeprazole no more sulfoxide was detectable at 155 °C. The other two sulfoxides were also completely decomposed within 10 min at this temperature. As an example for complete decomposition a chromatogram of omeprazole melt 10 min at 155 °C is shown in Fig. 6.

Parallel TLC-investigations revealed the existence of more than 30 decomposition products, some of which showed intensive fluorescence in long-wave UV-light. The differences in the literature melting points, depending on the method, seem thus to result from eutectic behavior of the sulfoxides with decomposition products.

3. Discussion

The thermoanalytical behavior of all three substances under investigation highly depends on the heating rate. Considering the results for omeprazole obtained by the differ-

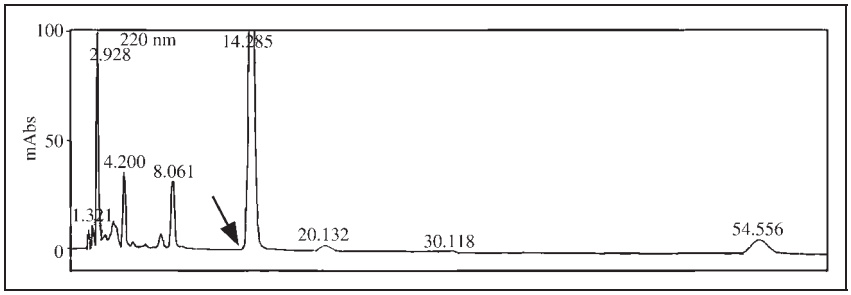


Fig. 6:
HPL-chromatogram of an omeprazole melt (10 min at 155 °C); the arrow marks the position of the peak of omeprazole (t_R = 13,9 min)

ent methods, the complex thermal behavior observed upon heating in the DSC can be interpreted as follows: The endothermic event which corresponds to the literature melting point (Budavari 1991b) when recorded at high heating rates is confirmed to be related to the melting of the substance by the results from thermomicroscopy. The exotherm can be assigned to a decomposition process that is clearly observable in thermomicroscopy (darkening of the crystals or melt, respectively) as well as on the Kofler bench. The thermomicroscopic investigations revealed that the darkening of omeprazole crystals depended on the heating rate. Upon heating with 1 °C/min, a melting process of the crystals could still be observed in the microscope although there was no endothermic DSC signal. It can be assumed that the DSC exotherm overlaps with the endotherm resulting from melting of the substance. The decrease in size of the endothermic DSC peak for the heating rate of 2.5 °C/min in comparison with higher heating rates may also result from an overlap of the endothermic and exothermic signal.

The microscopic results show that the melting point is shifted to a lower temperature when decomposition of the substance starts before melting (at 1 °C/min) indicating that the melting point depression may be due to eutectic behavior of the drug substance with its decomposition products. This assumption is supported by thermogravimetric data, which reveal a weight loss as part of the decomposition process. When the weight loss starts around the DSC onset temperatures of the endothermic event (heating rates 1–5 °C/min), the melting temperature is depressed, while it reaches constant values for higher heating rates, when the weight loss starts above the onset temperatures of the melting endotherm (Fig. 4). It can thus be assumed that the melting point obtained with the high heating rates is the "true" melting point because, in these cases, there are no decomposition products present which could have an eutectic influence on the melting temperature.

HPLC and TLC data reveal that the temperature of beginning decomposition is almost the same for all three sulfoxides. They also indicate that the amount of decomposition products depends on how long and at which temperature the substance remains above the decomposition temperature. Obviously, the time span for which the sample remains above this temperature is much longer for lower heating rates in thermoanalytical investigations. Larger amounts of decomposition products lead to a greater eutectic effect, which results in an increased lowering of the melting point.

Due to the larger difference between decomposition temperature and melting point, the effect is more pronounced for the sulfoxides with higher melting points. The low melting substance pantoprazole (m.p. 139–140 °C) is not subjected to temperatures above the decomposition temperature for a long time before melting even at rather low heating rates. Therefore, the melting point deviations between different heating rates are quite small for this drug. For the highest melting substance, lansoprazole, however, a plateau for the melting temperature is not even reached with the highest heating rates. A heating rate as high as 30 °C/min obviously still leaves too much time for decomposition of this substance.

A heating rate dependent melting temperature has also been observed with other decomposable substances. E.g., the melting behavior of diclofenac sodium (with more complex peaks than those of the prazoles depending on the atmosphere used for the experiments) depends on the heating rate (Tudja et al. 2001). In own investigations on ascorbic acid and acetylsalicylic acid a heating rate dependent position of the melting transition (but no exothermic events) was found in DSC (data not shown) which was, however, reproducible when constant measurement conditions were used.

Due to the eutectic induced melting point depression, the melting point of decomposing substances should be determined with a highly dynamic method, which reduces or eliminates the formation of decomposition products before melting. As a simple method, the determination of the instantaneous melting point with the aid of a Kofler bench was considered for the three prazoles under investigation. But literature already points out that the melting temperature of decomposable substances lowers with increasing time on the bench and therefore recommends to read the melting point 10 seconds after positioning the sample on the bench (Schenk 1991). As expected, the melting temperatures for all sulfoxides obtained with this method are comparatively high. The results were, however, spread over a rather wide temperature range, suggesting problems inherent to the method. It was, e.g., observed that the melting point highly depends on the amount of substance used (the more substance used, the higher the melting point). The skillfulness in handling the powder and the flow properties of the powdered substance have a great influence on the amount of substance on the bench and thus on the melting point. Moreover, positioning of the powder on the bench takes some time so that the powder is subjected to elevated temperatures for different periods of time in different areas of the bench. In addition, the color change of the crystals makes the differentiation between darkening and melting difficult. Therefore, even though the Kofler bench method reduces thermal stress during the determination of the melting point it does not give highly reproducible and thus reliable results. This is at least partly due to difficulties in achieving reproducible experimental conditions.

When the melting point of decomposable substances has to be determined, DSC measurements employing a high heating rate and constant measurement parameters seem to be a better alternative provided that the heating rate is optimized in test experiments. In some cases, when no constant values for the melting temperature can be obtained even with high heating rates in DSC (as was observed with lansoprazole), the determination of a reliable melting point becomes very difficult. At least the measurement conditions have to be given in such cases along with the thermoanalytical results to make the comparison of data from different sources possible.

In conclusion, DSC at high heating rates may be a useful method to determine melting points of decomposable substances provided that the measurement conditions are optimized and standardized, e.g., in the pharmacopoeia. On the other hand, methods employing slow heating rates (e.g., the capillary method of the Pharmacopoeia Europea) are not useful for this purpose since the eutectic behavior with decomposition products will lead to erratic results.

4. Experimental

4.1. Materials

Omeprazole was synthesized according to the procedure described by Oelschläger et al. (1999). Lansoprazole was provided by Takeda Chemical Industries, Osaka, I and pantoprazole acid was prepared from pantoprazole-sodium-sesquihydrate Altana Pharma Deutschland, Konstanz by addition of 0.1 M HCl to the aqueous solution and extraction with dichloromethane (dried with Na_2SO_4).

4.2. Methods

4.2.1. DSC

The samples (0.2–0.8 mg) were placed in aluminium crucibles, sealed and scanned from 20 °C up to about 20 °C above the determined signal with different heating rates in a Perkin Elmer Pyris 1 DSC.

4.2.2. Thermomicroscopy

A Leica DMRXP microscope with a Lincam THMS 600 programmable hot stage was used. Heating at 20 °C/min started at 25 °C and was continued up to a few degrees above the melting point. Heating at 1 °C/min started at 100 °C, from 25–100 °C the sample was heated with 20 °C/min. DSC measurements confirmed that the thermal behavior of omeprazole subjected to this modified heating protocol did not differ from that of a sample investigated starting at 20 °C with 1 °C/min.

4.2.3. Thermogravimetry/Differential Thermal Analysis

Thermogravimetric measurements were performed under an atmosphere of air with a TGA/DTA 320 with diskstation 5200 H (Seiko, Tokio, Japan). The samples weighed about 3 mg and were placed in an open aluminium pan. Samples were measured from 40 °C to around 200 °C using the same heating rates as in DSC. DTA signals of indium were used for temperature calibration.

4.2.4. Kofler bench

The instantaneous melting point was determined with a Kofler bench (Wagner & Munz, Munich, Germany). The Kofler bench is a metallic bench with a temperature gradient from 50–250 °C and a gradation of 2 °C. To determine the melting point, the substance is spread on the bench in a thin line of around 2 cm (10–20 °C) length in the area of the expected melting point. According to the instruction of the manufacturer for the investigation of decomposing materials, a delay time of ten seconds was used after positioning of the sample on the bench before reading the melting temperature.

4.2.5. HPLC

Analyses of the samples were performed on a Shimadzu LC-10AS-Chromatograph with UV-Detector SPD-M10A (DAD) (Shimadzu Europe/Duisburg); Column: LiChrospher® RP-8, 125 × 4, 5 µm (Merck/Darmstadt); Eluent: CH_3CN/phosphate buffer pH 7,6 (27 : 73); flow rate 1 ml/min; vol. of injection: 20 µl. For stability testing samples were stored for 10 min at different temperatures beginning from 135 °C up to 157 °C (steps: 5 °C) and were then dissolved in acetonitrile/water 1 : 1 and diluted with eluent to a concentration of about 100 µg/ml. In comparison with the obtained degradation products the melting points of the sulphoxides were determined by the capillary method (Ph. Eur. 4.00; 2.2.14 [Method I]) and the resulting oils were diluted in the eluent and analyzed as above.

4.2.6. TLC

The same samples as for HPLC were examined by TLC, using a TLC silicagel F_{254} plate. The test solutions were prepared by dissolving about 10 mg of the heated substances as well as the residue of the melting point determinations (capillary method) in 1.0 ml of MeOH. 10 µl of each solution were applied to the plate and the chromatogram was developed over a path of 10 cm using ethylacetate as eluent. The plate was allowed to dry in air and examined in daylight and ultraviolet light at 254 nm and 366 nm.

Acknowledgements: We thank Prof. C. Müller-Goymann, Institute of Pharmaceutical Technology, University of Braunschweig, for the possibility to perform TGA/DTA measurements and J. Schildt for technical assistance.

References

Davidson AG, McCallum A (1996) A survey of the stability of omeprazol products from 13 countries. Drug Dev Ind Pharm 22: 1173–1185.

O'Neill M, Smith A, Heckelman PE (Eds.), (2001a) Lansoprazole. The Merck Index, 13th Ed., p. 961, Merck Research Laboratories, Whitehouse Station, NJ.

O'Neill M, Smith A, Heckelman PE (Eds.), (2001b) Omeprazole. The Merck Index, 13th Ed., p. 1224–1225, Merck Research Laboratories, Whitehouse Station, NJ.

O'Neill M, Smith A, Heckelman PE (Eds.), (2001c) Pantoprazole. The Merck Index, 13th Ed., p. 1256, Merck Research Laboratories, Whitehouse Station, NJ.

Oelschläger H, Seeling A, Seeling B, Westesen K, Bunjes H (1999) Selektive Oxidation von 5-Methoxy-2-[(3,5-dimethyl-4-methoxy-2-pyridyl)methylthio]-1-H-benzimidazol zu RS-5-Methoxy-2-[[(3,5-dimethyl-4-methoxy-2-pyridyl)methyl]sulfinyl]-1-H-benzimidazol (Omeprazol). Pharmazie, 54: 734–737.

Palomo Call A (1992) EP 484265 Al 920506; C.A. 117, 111603.

Schenk D (1991) Thermische Verfahren; In: Nürnberg E, Surmann P (eds.) Hagers Handbuch der pharmazeutischen Praxis, Vol. 2: Methoden, 5th Ed., p. 65, Springer-Verlag Berlin Heidelberg.

Tudja P, Khan M, Mestrovic E, Horvat M, Golja P (2001) Thermal behaviour of diclofenac sodium: decomposition and melting characteristics. Chem Pharm Bull 49: 1245–1255.