Institute for Pharmacy – Pharmaceutical Technology –, University of Leipzig, Germany

Quantification of omeprazole degradation by enteric coating polymers: an UV-VIS spectroscopy study

A. RIEDEL, C. S. LEOPOLD

Received April 19, 2004, accepted April 27, 2004

Prof. Dr. Claudia S. Leopold, Universität Leipzig, Institut für Pharmazie – Pharmazeutische Technologie – Schönauer Straße 160, D-04207 Leipzig, Germany
cleopold@rz.uni-leipzig.de

Pharmazie 60: 126–130 (2005)

The aim of this study was to investigate the degradation of the acid-labile proton-pump-inhibitor omeprazole in organic polymer solutions and aqueous dispersions of enteric coating polymers by UV spectroscopy. Furthermore, data were compared with those obtained in a previous HPLC study. For comparative purposes the cationic Eudragit® RS 100 and the monomeric acid acetic acid were included in this study. The discolorations of degraded omeprazole solutions were analysed by VIS spectroscopy. UV-VIS spectra were recorded after preparation of the solutions and after 180 min of storage. The change of absorption was calculated as the difference of the absorption values at 305 nm. Degradation of omeprazole depends on the amount of acidic groups in the polymer structure. This decomposition manifests itself in a shifting of the absorption maximum to lower wavelengths and a decrease of absorption intensity. UV-VIS spectroscopy was used to determine the extent of degradation induced by enteric polymers. A good correlation of these results with previous HPLC data was found when excluding UV absorbing polymers. Nevertheless, values obtained by UV-VIS spectroscopy were always lower than those obtained by HPLC. For evaluation of the discoloration of degraded omeprazole solutions, VIS spectroscopy is a simple and fast method.

1. Introduction

Omeprazole belongs to a class of antisecretory compounds, the substituted benzimidazoles, that suppress gastric acid secretion by specific inhibition of the H^+/K^+-ATPase enzyme system at the secretory surface of the gastric parietal cell (Clissold and Campoli-Richards 1986). Omeprazole degrades rapidly in aqueous solutions with low pH values (Pilbrant 1985; Mathew et al. 1995). Preformulation studies have shown that moisture, heat, solvents, and acidic compounds have deterious effects on the stability of omeprazole (Lövgren et al. 1987; Davidson and Mc Callum 1996). In other investigations, a degradation of omeprazole under exposure to UV-light, various salts (Ekpe and Jacobsen 1999) and some metal ions (Hamdan 2001) was found. The degradation of the proton pump inhibitor manifests itself in decreasing drug concentrations and increasing amounts of degradation products.

UV-VIS spectroscopy is often used for the assessment of identity and purity, for concentration measurements and structure information on pharmaceutical substances. It is also applied in dissolution studies, formulation and stability evaluations. Different omeprazole-γ-CD co-ground systems (Arias-Blanco et al. 1996), omeprazole-polymer complexes and an omeprazole containing enteric-coated granule formulation (Pilbrant 1985) were investigated regarding their dissolution profiles by UV-VIS spectroscopy. For stability studies of omeprazole derivative UV spectrophotometry was used (Castro et al. 1999; El-Kousy and Bebawy 1999; Wahbi et al. 2002). For quantification of omeprazole in pharmaceutical formulations sensitive VIS-spectrophotometric methods were developed based on its reaction with various reagents (Sastry et al. 1997; Salama et al. 2003). An *in vitro* study of the interactions between omeprazole and various metal ions was done by UV-VIS spectroscopy (Hamdan 2001). Omeprazole is officially listed in the United States Pharmacopoeia 27 (USP), and the European Pharmacopoeia 4.0 (Ph. Eur.). For identification of omeprazole, the European Pharmacopoeia recommends recording of an UV-VIS spectrum. The assessment of purity may also be done by measurement of the absorption of an omeprazole solution at 440 nm.

UV-VIS spectroscopy as the only method for drug concentration measurements has been shown to be insufficient in some cases. For example, a stability study by Tokumura et al. suggested increasing concentrations of amoxicillin using UV spectroscopy but a decreasing concentration of the drug determined by HPLC (Tokumura and Machida 2001). It is known that the spectra of omeprazole and its degradation products may show certain overlapping that interferes with direct quantification of omeprazole (Castro et al. 1999; El-Kousy and Bebawy 1999). Omeprazole shows an absorption maximum at 300 nm while its degradation products exhibit absorbance over the wavelength range of 200–400 nm (Castro et al. 1999). Therefore, many studies for quantification of omeprazole and its de-

gradation products (Mathew et al. 1995; Davidson and McCallum 1996; Storpirtis and Rodrigues 1998; Ekpe and Jacobsen 1999) or metabolites (Lagerström and Persson 1984; Amantea and Narang 1988; Kobayashi et al. 1992; Andersson et al. 1993) are based on HPLC with UV detection. For identification of omeprazole in the USP 27 an HPLC chromatogram is required. The official HPLC method allows the separation of omeprazole from its degradation products as well as the quantification of the drug. Most of the HPLC methods described for omeprazole degradation/metabolism use a mobile phase containing phosphate buffer with a pH of 7.4 or above. UV detection is done either at 235 (Mathew et al. 1995), at 280 nm (Arvidsson et al. 1991; Davidson and McCallum 1996; Storpirtis and Rodrigues 1998; Bozdag et al. 1999; Ekpe and Jacobsen 1999; Farinha et al. 2000) or above 300 nm (Lagerström and Persson 1984; Persson et al. 1985; Amantea and Narang 1988; Kobayashi et al. 1992; Andersson et al. 1993; Quercia et al. 1997).

Omeprazole is a white or off-white powder. It is very unstable under acidic conditions. Under the influence of acids omeprazole solutions turn to purple (Eger et al. 1999), yellow (Mathew et al. 1995; Eger et al. 1999), brown (Mathew et al. 1995) or dark red (Senn-Bilfinger et al. 1987). Pharmaceutical formulations containing proton pump inhibitors without stabilizing agents degrade under the influence of moisture and heat. These preparations turn to brown or dark brown (Lövgren et al. 1987; Tabata et al. 1994; Davidson and McCallum 1996).

In a previous study (Riedel and Leopold 2004) the influence of enteric coating polymers on the stability of omeprazole was investigated by HPLC. Because of published studies using UV-VIS spectroscopy for quantification of omeprazole (Pilbrant 1985; Arias-Blanco et al. 1996; Hamdan 2001), the aim of the present study was to compare these previous results with those obtained by UV spectroscopy and to clarify whether spectroscopy alone is a suitable method for the estimation of instability of the proton pump inhibitor. Instability of the proton pump inhibitor is accompanied by discolorations. They primarily indicate a decomposing process. Therefore, the discolorations of degraded omeprazole solutions are analysed by a simple and fast spectrophotometric method.

2. Investigations and results

2.1. Stability of omeprazole in different solvents

Omeprazole is stable in alkaline media. At pH 11 omeprazole has a half life of approximately 10 months (Pilbrant 1985). Therefore, no changes in the spectrum of an alkaline omeprazole solution can be observed within 180 min. As required by the Ph. Eur. 4.0, the spectrum of an alkaline omeprazole solution shows absorption maxima at 276 nm and 305 nm (Fig. 1). The ratio of the absorption values at these peaks has to be in the range of 1.6–1.8. The resulting ratio in this study is 1.744 ± 0.006 (Table 1), which is in accordance with the Ph. Eur. requirements. Omeprazole is poorly soluble in ethanol. In comparison to the spectrum of an alkaline aqueous solution, absorption values of an ethanolic omeprazole solution are lower at 276 nm and higher at 305 nm (Fig. 1). However, the spectrum still shows the typical curve shape after 180 min. Omeprazole is found to be stable in ethanol during the time period of investigation. The ratio of the absorption values at the two peaks is higher than 1.8 (Ta-

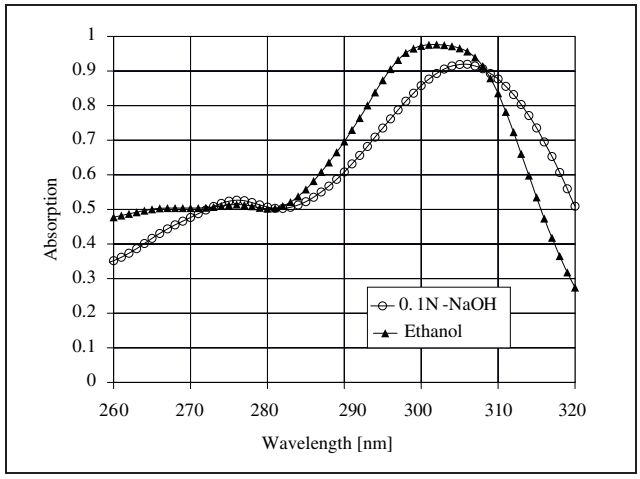

Fig. 1: UV spectra of omeprazole (0.02 mg/ml) in different solvents. As no changes occurred within 180 min, spectra drawn at 1 min are not shown

Table 1: Spectrophotometric data of omeprazole in different solvent systems at two different time points. Means ± SD, n = 6

	Absorption ratio ($A_{305\ nm}/A_{276\ nm}$) after 1 min	Absorption ratio ($A_{305\ nm}/A_{276\ nm}$) after 180 min
0.1N-NaOH	1.744 ± 0.006	1.742 ± 0.008
Ethanol	1.872 ± 0.007	1.878 ± 0.010
+ Eudragit® L 100 (6% w/w)	1.768 ± 0.019	1.125 ± 0.035
+ Eudragit® S 100 (6% w/w)	1.733 ± 0.019	1.128 ± 0.006
+ Eudragit® RS 100 (6% w/w)	1.853 ± 0.012	1.860 ± 0.018
+ Acetic acid (6% w/w)	1.718 ± 0.005	0.932 ± 0.003
Methylene chloride : isopropanol (1 : 1)	1.838 ± 0.001	2.068 ± 0.035
+ CAP (6% w/w)	n.d.	n.d.

n.d.: not determinable

Table 2: Correlation of the results obtained by UV spectroscopy and HPLC. Means ± SD, n = 6

	Change of UV absorption at 305 nm (%)	Change of HPLC peak area at 305 nm (%)	Correlation coefficient without CAP	Correlation cofficient with CAP
Methanol	0.37 ± 0.00	-1.83 ± 6.05	0.991	0.982
+ Eudragit® RS 100	0.84 ± 0.03	-0.10 ± 0.90		
+ Eudragit® L 100	18.64 ± 0.03	26.98 ± 5.10		
+ Eudragit® S 100	17.49 ± 0.03	18.24 ± 3.93		
+ Acetic acid	31.38 ± 0.01	45.70 ± 0.92		
Methylene chloride : methanol (4 : 1)	-0.45 ± 0.01	-2.69 ± 9.66		
+ CAP	11.72 ± 0.02	21.64 ± 6.32		

ble 1). This does not mean that the omeprazole identity test of the Ph. Eur. 4.0 is not fulfilled because this identity test is done with an aqueous alkaline omeprazole solution. Additional spectra of omeprazole in organic solvents are not mentioned in the Ph. Eur. and could not be found in the literature. For investigative purposes the change of absorption at 305 nm within 180 min is calculated (Table 2).

2.2. Stability of omeprazole in the presence of organic polymers

Eudragit® RS 100 is a cationic polymethacrylate without acidic carboxyl groups. As expected, the spectrum of omeprazole in the presence of Eudragit® RS 100 does not show any changes within 180 min (Fig. 2). It is similar to the spectrum obtained with an ethanolic omeprazole solution (Fig. 1). Omeprazole is found to be stable in an organic Eudragit® RS solution.

Eudragit® L 100 and Eudragit® S 100 are acidic polymethacrylates. The influence of Eudragit® L 100 on the stability of omeprazole is shown in Fig. 3. The absorption maximum at 305 nm is shifted to lower wavelengths (hypsochromia). Moreover, a reduction of the absorption intensity within 180 min can be observed (hypochromia). The absorption at 305 nm decreases by $18.6 \pm 0.0\%$ within 180 min (Table 2). In the presence of Eudragit® S 100 a similar shift of the absorption peaks and a reduction of the absorption intensity could be observed. As expected, both effects are less pronounced with Eudragit® S 100 than with Eudragit® L 100 (Table 2). As no spectrum changes are observed in the presence of Eudragit® RS 100, acidic groups in the polymer structure are responsible for omeprazole degradation and the polymethacrylate backbone does not affect the stability of omeprazole. The polymethacrylate Eudragit® S 100 only contains 30% of acidic groups compared to 50% of acidic groups in Eudragit® L 100 and has therefore a less pronounced effect on the stability of omeprazole.

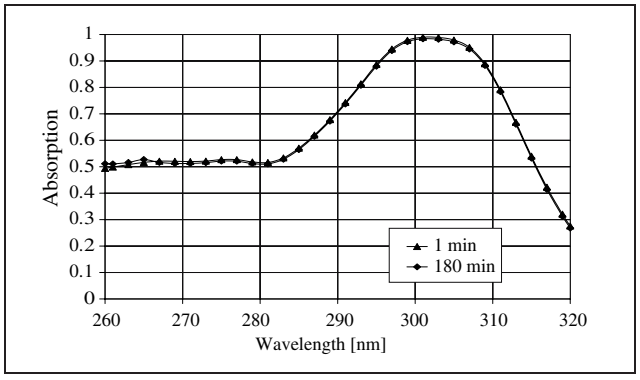

Fig. 2: UV spectra of omeprazole (0.02 mg/ml) in ethanolic Eudragit® RS 100 solution (6% w/w) at two different time points

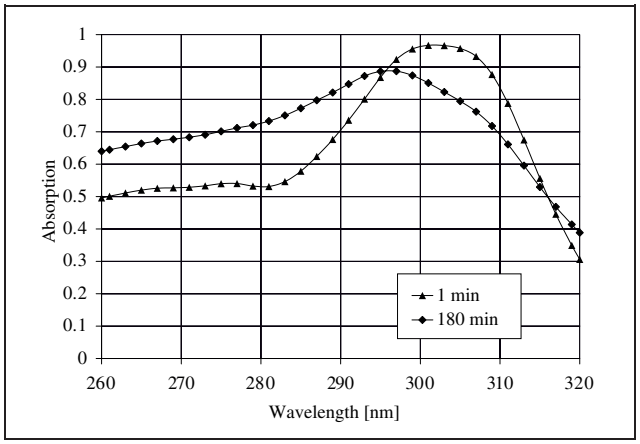

Fig. 3: UV spectra of omeprazole (0.02 mg/ml) in ethanolic Eudragit® L 100 solution (6% w/w) at different time points

The acidic cellulose ester CAP is also investigated in the study. As it could be shown that the solvent mixture does not influence omeprazole stability, a spectrum of omeprazole in an organic CAP solution is recorded after 1 min and after 180 min. Because of the phthalate moieties in CAP, the polymer shows a high UV absorption at wavelengths < 300 nm. The omeprazole spectrum is superimposed by the CAP spectrum. The absorption value at 305 nm changes to $11.7 \pm 0.0\%$ within 180 min (Table 2). This observation neither correlates with the amount of acidic groups in the polymer structure nor with the results of previous HPLC investigations (Riedel and Leopold 2004).

2.3. Comparison of the UV data with previous HPLC investigations

In a previous study it could be shown that the influence of enteric coating polymers in organic solutions on the stability of omeprazole depends on the amount of acidic groups in the polymer structure (Riedel and Leopold 2004). According to that HPLC study, the influence of the cellulose ester CAP on the stability of omeprazole is between that of Eudragit® L and S (Table 2). As expected, the non-acidic polymer Eudragit® RS 100 does not cause any change of the omeprazole peak (Table 2). The area of the omeprazole peak changes in the presence of the acidic polymethacrylates Eudragit® L 100 and Eudragit® S 100 to $27.0\% \pm 5.1$ and $18.2\% \pm 4.0$, respectively. It is noticeable that the calculated changes in UV absorption are lower than the changes in the peak areas obtained by HPLC (Table 2). This can be explained by the above mentioned phenomenon of spectrum overlapping by degradation products of omeprazole. Therefore, UV absorption values apparently include the contribution of absorption by degradation products. These degradation products are separated with HPLC. The quantitative results obtained by HPLC are therefore more reliable. Nevertheless, a correlation coefficient of the obtained UV and HPLC data is found to be 0.991 excluding CAP and only 0.982 including CAP (Table 2). This lower value may be explained by the phthalate moieties in the CAP backbone. The structures show a high UV absorption at wavelengths < 300 nm. Although for final calculations only absorption values at 305 nm are used, a contribution of the phthalate structures to the overall UV absorption cannot be ruled out completely.

2.4. Stability of omeprazole in the presence of ethanolic acetic acid

Acetic acid is a monomeric organic acid with a pK_a of 4.71. It is included in this study to compare the influence of polymeric acids with that of monomeric acids. Omeprazole degrades rapidly in the presence of acetic acid as can be seen from the values in Table 1. The initial ratio of the absorption values at the two peak maxima (1.718 ± 0.001) is reduced already after 1 min in comparison to the solvent ethanol. Within 180 min absorption at 305 nm decreases by $31.4 \pm 0.0\%$. Again, results obtained by HPLC show a more pronounced influence of acetic acid on the omeprazole peak area change than UV data (Table 2). The

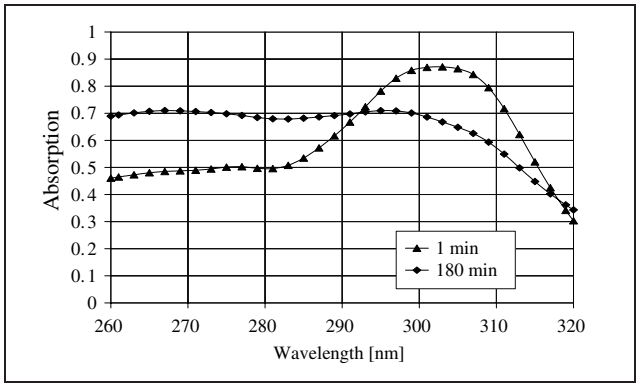

Fig. 4: UV spectra of omeprazole (0.02 mg/ml) in ethanolic acetic acid (6% w/w) at two different time points

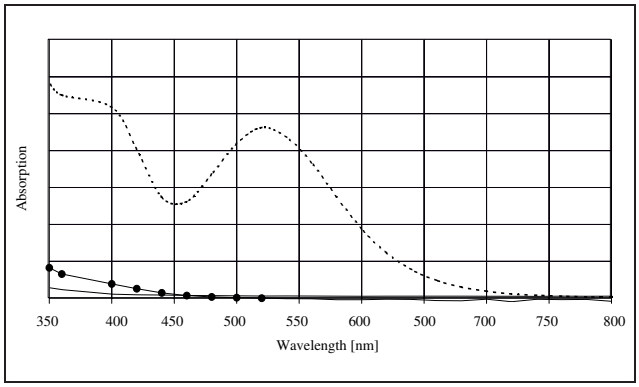

Fig. 5: VIS spectra of omeprazole (0.02 mg/ml) in organic CAP solution (6% w/w) at two different time points and plain CAP solution as reference — plain CAP (Aquateric®) –●– 1 min ---- 180 min

omeprazole spectra recorded in the presence of this monomeric acid show a similar change within 180 min as spectra recorded in presence of the polymeric acids (Fig. 4). The absorption maximum at 305 nm is shifted to lower wavelengths. Moreover, a reduction of the absorption intensity within 180 min can be observed. Both effects are more pronounced in the presence of acetic acid than with polymeric acids. The characteristic two peak maxima of omeprazole can hardly be detected. Both methods, UV spectroscopy as well as HPLC, show that the monomeric acid acetic acid causes the fastest and most pronounced decomposition of omeprazole compared to polymeric acids. This can be explained by the better accessibility of the carboxyl group in a monomeric structure. Long polymer chains may shield these acidic groups and the polymer appears to be less acidic.

2.5. Examination of the discolorations of omeprazole in the presence of organic polymer solutions

As omeprazole shows discolorations during storage (Lövgren et al. 1987; Davidson and McCallum 1996), the examination of the color of omeprazole containing formulations appears to be a useful tool to quantify the extent of degradation caused by acidic agents. For the examination of purity of omeprazole solutions the Ph. Eur. 4.0 recommends the measurement of absorption at 440 nm. Absorption must not be higher than 0.10. This limit is in accordance with the content of impurities F or G as mentioned in the Ph. Eur. 4.0. In Table 3 the wavelengths of the absorption maxima of the omeprazole solutions and the corresponding colors are listed. Immediately after preparation of the omeprazole-containing polymer solutions (1 min) almost all solutions are colorless and clear. The methanolic shellac solution is yellow but clear. Within 180 min of storage various discolorations can be observed. Eudragit® L 100 and S 100 cause a dark purple discoloration in methanolic solution. CAP causes a more intense purple color. The solutions which contain the HPMCAS polymers are red or purple. HP-55 causes a yellow-green discoloration within 180 min. The yellow shellac solution becomes light orange. No changes of the color are observed under the influence of the non-acidic polymethacrylate Eudragit® RS 100. The analysis of the discolorations by VIS spectroscopy over time shows different absorption maxima or slight absorption shifting to higher wavelengths. In Fig. 5 the spectrum of an omeprazole containing CAP solution at different time points is shown in comparison to a plain CAP solution. Decomposition of omeprazole occurs immediately after mixing the drug with the organic CAP solution. After 1 min a slight increase in VIS absorption can be seen and the initially colorless solution becomes yellowish. Within 180 min a sharp absorption peak can be detected at 525 nm. Therefore the color of the mixture is purple after storage. The plain solvents are colorless and do not show any spectrum change within 180 min. According to the literature (Senn-Bilfinger et al. 1987; Brändström et al. 1989), an isomeric thion is likely to be the major decomposition product, as the color of most of the investigated omeprazole solutions are purple. Other discolorations such as the yellow-green color observed with HP-55 may be caused by the same decomposition product, only dissolved in a different solvent. The isomeric thion is known to turn its color from purple into yellow (Senn-Bilfinger et al. 1987; Brändström et al. 1989). Solvents may affect this color change.

Table 3: VIS spectroscopic evaluation of discolorations of omeprazole-containing organic polymer solutions at two different time points. Means ± SD, n = 3

Omeprazole-containing polymer solution	Start of detectable absorption after 1 min at wavelength (nm)	Color of solution	Start of detectable absorption after 180 min at wavelength (nm)	Color of solution
Eudragit® L 100	< 400	Colorless	529 ± 0	Purple
Eudragit® S 100	< 400	Colorless	527 ± 1	Purple
Eudragit® RS 100	< 400	Colorless	< 400	Colorless
HPMCAS-HF	< 400	Colorless-opaque	526 ± 2	Purple
HPMCAS-LF	< 400	Colorless-opaque	522 ± 1	Purple
CAP (Aquateric®)	< 422	Colorless-yellowish	525 ± 1	Purple
HP-55	< 400	Colorless-opaque	< 451	Yellow, Yellow-green
Shellac	< 470	Yellow	< 500	Red, orange

3. Discussion

UV-VIS spectroscopy is often regarded as an insufficient method for quantification of drug concentration. In this study, values obtained by UV-VIS spectroscopy have been shown to be lower than those obtained by HPLC. This observation may be explained by overlapping UV spectra of the degradation products of omeprazole which can only be separated by HPLC. Nonetheless, a good correlation ($R = 0.991$) is found when excluding UV absorbing polymers. Apparently, overlapping of the omeprazole spectrum by its decomposition products does not affect the data as much as assumed. The degradation of omeprazole in organic polymer solutions depends on the amount of acidic groups in the polymer structure. Monomeric acids cause a similar change of UV-VIS spectra of omeprazole as polymeric acids. However, this change is much less pronounced with polymeric acids because of sterical interactions. For a quantification of omeprazole decomposition HPLC is recommended. For evaluation of the discoloration of degraded omeprazole, VIS spectroscopy is a simple and fast method to estimate omeprazole stability.

4. Experimental

Omeprazole used in this study was purchased from Midas, Germany/Uquifa, Spain. The film-forming polymers were Eudragit® L 100, Eudragit® S 100, Eudragit® RS 100 (Röhm, Germany), Shellac 101 EP (Syntapharm, Germany), HPMCAS-HF, HPMCAS-LF, HP-55 (Syntapharm, Germany/ShinEtsu, Japan), and CAP as in Aquateric® (Lehmann & Voss, Germany/FMC, USA). All polymers were donated by the manufacturers or distributors. Glacial acetic acid was purchased from Merck, Germany.

Solvents for UV spectroscopy are ethanol for the polymethacrylates and methylene chloride: isopropanol (1 : 1) for cellulose acetate phthalate (CAP). Solvents for the HPLC studies were methanol (analytical grade) for the polymethacrylates and methylene chloride : methanol (4 : 1) for CAP (Riedel A and Leopold CS 2004). The solvents for the discoloration study were methanol (analytical grade) for the polymethacrylates, HPMCAS and shellac, methylene chloride : methanol (4 : 1) for CAP, and acetone : methanol (1 : 1) for HP-55.

4.1. Preparation of omeprazole polymer solutions

Omeprazole is dissolved in ethanol at a concentration of 0.2 mg/ml. Organic polymer solutions at a concentration of 6% (w/w) are prepared by adding the polymers to the respective solvents and stirring with a magnetic stirrer for at least 1 h. 5 ml of the omeprazole solution are mixed with either 45 ml of the organic polymer solution, with 45 ml of the plain solvents or for comparative purposes with 0.1 N NaOH and ethanolic acetic acid (6% w/w), respectively. For the duration of the study all solutions are stored at ambient temperatures and prevented from light.

4.2. Determination of omeprazole degradation

A spectrum is recorded at wavelengths between of 260 nm and 320 nm immediately after preparation of the test solutions (1 min) and after 180 min of storage. The change of absorption is calculated as the difference of the absorption values at 305 nm. UV absorption is measured with a Perkin Elmer Lambda 12 spectrophotometer at a scan speed of 60 nm/min with 1 cm quartz cells. For details on the HPLC investigations see Riedel and Leopold (2004). Briefly, a reversed phase HPLC method with UV detection is employed and chromatograms are recorded at a wavelength of 305 nm.

References

Amantea MA, Narang PK (1988) Improved procedure for quantitation of omeprazole and its metabolites using reversed-phase high-performance liquid chromatography. J Chromatogr Biomed Appl 426: 216–222.

Andersson T et al. (1993) High-Performance Liquid-Chromatographic assay for human liver microsomal omeprazole metabolism. J Chromatogr Biomed Appl 619: 291–297.

Arias-Blanco MJ et al. (1996) Preliminary study of different omeprazole/gamma-CD co-ground systems. Int J Pharm 143: 113–118.

Arvidsson T et al. (1991) Peak distortion in the column liquid-chromatographic determination of omeprazole dissolved in borax buffer. J Chromatogr 586: 271–276.

Bozdag S et al. (1999) Formulation and stability evaluation of enteric-coated omeprazole formulations. STP Pharma Sci 9: 321–327.

Brändström A et al. (1989) Chemical reactions of omeprazole and omeprazole analogues. I. A survey of the chemical transformation of omeprazole and its analogues. Acta Chem Scand 43: 536–548.

Castro D et al. (1999) Comparison of derivative spectrophotometric and liquid chromatograpic methods for the determination of omeprazole in aqueous solutions during stability studies. J Pharm Biomed Anal 21: 291–298.

Clissold SP, Campoli-Richards DM (1986) Omeprazole – A preliminary review of its pharmacodynamic and pharmacokinetic properties, and therapeutic potential in peptic ulcer disease and Zollinger-Ellison syndrome. Drugs 32: 15–47.

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

Eger K et al. (1999) Benzimidazol-Derivate. In: (ed.) Arzneistoffanalyse, 4. Auflage, Stuttgart, p. 537–541.

Ekpe A, Jacobsen T (1999) Effect of various salts on the stability of lansoprazole, omeprazole, and pantoprazole as determined by high-performance liquid chromatography. Drug Dev Ind Pharm 25: 1057–1065.

El-Kousy NM, Bebawy LI (1999) Stability-indicating methods for determining omeprazole and octylonium bromide in the presence of their degradation products. J AOAC Int 82: 599–606.

Farinha A et al. (2000) Dissolution of omeprazole from delayed-release solid oral dosage forms. Drug Dev Ind Pharm 26: 785–790.

Hamdan II (2001) *In vitro* study of the interaction between omeprazole and the metal ions Zn(II), Cu(II), and Co(II). Pharmazie 56: 877–881.

Kobayashi K et al. (1992) Simultaneous determination of omeprazole and its metabolites in plasma and urine by reversed phase high performance liquid chromatography with an alkaline-resistant polymer coated C18 column. J Chromatogr Biomed Appl 117: 299–305.

Lagerström P-O, Persson B-A (1984) Determination of omeprazole and metabolites in plasma and urine by liquid chromatography. J Chromatogr Biomed Appl 309: 347–356.

Lövgren KI et al. (1987) EP 0 2479 83 B1

Mathew M et al. (1995) Stability of omeprazole solutions at various pH values as determined by High-Performance Liquid Chromatography. Drug Dev Ind Pharm 21: 965–971.

Persson B-A et al. (1985) Determination of omeprazole and metabolites in plasma and urine. Scand J Gastroenterol 20: 71–77.

Ph. Eur. (2002) edition 4.0.

Pilbrant A (1985) Development of an oral formulation of omeprazole. Scand J Gastroenterol 20: 113–119.

Quercia RA et al. (1997) Stability of omeprazole in an extemporaneously prepared oral liquid. Am J Health Syst Pharm 54: 1833–1836.

Riedel A, Leopold CS (2004) Degradation of omeprazole induced by enteric polymer solutions and aqueous dispersions: HPLC investigations. Drug Dev Ind Pharm, submitted.

Salama F et al. (2003) Validation of the spectrophotometric determination of omeprazole and pantoprazole sodium via their metal chelates. J Pharm Biomed Anal 33: 411–421.

Sastry CSP et al. (1997) Spectrophotometric methods for the determination of omeprazole in bulk form and pharmaceutical formulations. Talanta 44: 1211–1217.

Senn-Bilfinger J et al. (1987) (H^+-K^+)-ATPase inhibiting 2-[(2-pyridylmethyl)sulfinyl]benzimidazoles. 2. The reaction cascade induced by treatment with acids. Formation of 5H-pyrido[′,2′:4,5][1,2,4]thiadiazono-[2,3-a]benzimidazol-13-ium salts and their reaction with thiols. J Org Chem 52: 4582–4592.

Storpirtis S, Rodrigues D (1998) In vitro evaluation of dissolution properties and degradation products of omeprazole in enteric-coated pellets. Drug Dev Ind Pharm 24: 1101–1107.

Tabata T et al. (1994) Manufacturing method of stable enteric granules of a new antiulcer drug (lansoprazole). Drug Dev Ind Pharm 20: 1661–1672.

Tokumura T, Machida Y (2001) UV absorption should not be applied for determining amoxycillin in acidic dissolution test medium. Int J Pharm 228: 1–4.

USP (2004) edition 27.

Wahbi A-AM et al. (2002) Spectrophotometric determination of omeprazole, lansoprazole and pantoprazole in pharmaceutical formulations. J Pharm Biomed Anal 30: 1133–1142.