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Degradation of Omeprazole Induced by Enteric Polymer Solutions and Aqueous Dispersions: HPLC Investigations

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ABSTRACT Two reversed-phase high-performance liquid chromatography (RP-HPLC) methods were developed to investigate the degradation of the acid-labile proton-pump-inhibitor omeprazole in organic polymer solutions and aqueous dispersions of enteric coating polymers (Eudragit® L-100, S-100, CAP, HP-55, HPMCAS-HF, -LF, and shellac). The overall goal of the study was to determine the influence of the polymer structure on the degradation of omeprazole, i.e., whether the acid structure of the enteric coating polymers caused an instability of the proton pump inhibitor. Moreover, it was investigated whether a difference in omeprazole degradation could be detected between organic polymer solutions and aqueous dispersions. pKa values of the polymers and pH values of the aqueous dispersions were determined to see whether there was a correlation with the extent of degradation of omeprazole induced by enteric polymers. As the polymers containing phthalate moieties are very susceptible to hydrolysis, the influence of free phthalic acid on omeprazole stability was investigated. Finally, the degradation kinetics of omeprazole in organic polymer solutions were determined. Omeprazole degradation is more pronounced in aqueous polymer dispersions than in organic polymer solutions. The influence of organic polymer solutions on the stability of omeprazole depends on the amount of acidic groups in the polymeric structure, whereas the influence of aqueous polymer dispersions depends on the pH value of the dispersion. The amount of free acids present in some polymers as by-products also cause a degradation of the proton pump inhibitor. Among all investigated polymers, shellac showed the least influence on the stability of omeprazole. The decomposition of omeprazole in organic polymer solutions followed first-order kinetics. The decrease of omeprazole peak area in organic polymer solutions was in the order Eudragit® L-100> HPMCAS-HF>shellac.

KEYWORDS Omeprazole, Enteric coating polymers, HPLC, pK_a values, Kinetics

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INTRODUCTION

Omeprazole is a substituted benzimidazole that selectively inhibits the proton pump in the gastric mucosa (Clissold & Campoli-Richards, 1986). Omeprazole degrades rapidly in aqueous solutions at low pH values (Mathew et al., 1995; Pilbrant, 1985). Preformulation studies have shown that moisture, heat, solvents, and acidic substances have deleterious effects on the stability of omeprazole (Davidson & McCallum, 1996; Lövgren et al., 1987). Other investigators have observed a degradation of omeprazole under exposure to UV light, various salts (Ekpe & Jacobsen, 1999), and some metal ions (Hamdan, 2001). The degradation of the proton pump inhibitor manifests itself in a loss of drug content and increasing amounts of degradation products.

Many studies on the quantification of omeprazole and its degradation products or metabolites are based on high-performance liquid chromatography (HPLC) with ultraviolet (UV) detection. Omeprazole is officially listed in the United States Pharmacopoeia (USP) and the European Pharmacopoeia (Ph. Eur.). For the identification of omeprazole in the USP an HPLC chromatogram is required. The official HPLC assay described in the USP allows the separation of omeprazole from its degradation products as well as the quantification of the drug. As a purity test the Ph. Eur. also recommends an HPLC assay. Most of the employed HPLC methods use a reversed-phase column and a mobile phase that contains phosphate buffer with a pH of 7.4 or above. Ultraviolet detection is usually done at 235 nm (Mathew et al., 1995), 280 nm (Davidson & McCallum, 1996; Ekpe & Jacobsen, 1999; Storpirtis & Rodrigues, 1998), or above 300 nm (Lagerström & Persson, 1984; Persson et al., 1985; Quercia et al., 1997).

To overcome the stability problems of the acid-labile substance omeprazole, the best approach appears to be the incorporation into enteric-coated dosage forms for protection from gastric acid. As enteric film-coating agents, the polymethacrylates Eudragit® L-100 and S-100 and the cellulose derivatives cellulose acetate phthalate (CAP), hypromellose phthalate (HPMCP, HP-50, HP-55), and hypromellose acetate succinate (HPMCAS-HF, -LF) are used. Lately, shellac has been rediscovered as a coating material. The chemical composition of shellac varies to some extent depending on the nature of the host trees, the species of the insect, and the environmental conditions. pH-sensitive enteric films consist of a long-chain polymer with ionizable carboxyl groups. Therefore, it has been assumed that the stability of omeprazole is affected by these polymers used to obtain gastric resistance (Gordon et al., 1995; Storpirtis & Rodrigues, 1998). To prevent potential omeprazole degradation, various patents suggest an inert subcoating layer, which separates the omeprazole core from the enteric coating (Erickson & Josefson, 1998; Lee et al., 2000; Lövgren et al., 1987). This subcoating, also called intermediate or separating layer, often consists of hypromellose (HPMC). Other patents describe chemically stable dosage forms without a separating layer, which contain basic excipients in the cores (Chen et al., 1997). One patent claims an intermediate layer, which is formed in situ as a result of the reaction of the alkaline core material and the acidic coating material. This in situ intermediate layer is supposed to be a water-soluble salt (Lundberg & Lövgren, 1996).

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 (Eudragit® L-100, S-100, CAP, HP-55, HPMCAS-HF, -LF, and shellac). A further goal was to clarify whether there is an influence of the polymer structure on the degradation of omeprazole, i.e., if the acid structure of the enteric coating polymers causes an instability of the proton pump inhibitor. Moreover, it was investigated whether a difference in omeprazole degradation can be detected between organic polymer solutions and aqueous dispersions. pK_a values of the polymers and pH values of the aqueous dispersions were determined to see whether there was a correlation with the degradation of omeprazole induced by enteric polymers. As the polymers containing phthalate moieties are very susceptible to hydrolysis, the influence of free phthalic acid on omeprazole stability was also investigated. Finally, the degradation kinetics of omeprazole in organic polymer solutions were determined.

EXPERIMENTAL

Materials

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-HPMCAS-LF HP-55 (Syntapharm, Germany/Shin-Etsu®, Japan), and CAP as in Aquateric® (Lehmann & Voss, Germany/FMC, Philadelphia, PA, USA). All polymers were donated from the manufacturers or distributors.

The solvents for the HPLC 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.

External standards were methyltestosterone and phenacetin (Fluka Chemie, Switzerland). Additional chemicals were phthalic acid, acetonitrile, monopotassium dihydrogenphosphate, and disodium hydrogenphosphate (all from Merck, Germany). All chemicals were of analytical grade.

A Bischoff HPLC equipped with a Bischoff UV detector Lambda 1000 and a Perkin Elmer UV-VIS spectrophotometer Lambda 12 used with 1 cm quartz cells were employed for drug quantification.

Methods

Preparation of the Organic Polymer Solutions and Aqueous Polymer Dispersions

Omeprazole was dissolved in methanol at a concentration of 2.0 mg/mL. Organic polymer solutions were prepared at a concentration of 6% (w/w) by adding the polymer to the respective solvents and stirring with a magnetic stirrer at least for 1 h. Aqueous polymer dispersions were prepared with distilled water at a concentration of 6% (w/w) and also stirred for at least 1 h.

Five mL of the methanolic omeprazole solution (2.0 mg/mL) were mixed with 20 mL of the polymer solutions. Five mL of this mixture were further diluted with the corresponding polymer solvent, resulting in an omeprazole concentration of 0.08 mg/mL.

Ten mL of the methanolic omeprazole solution were mixed with the aqueous polymer dispersions to 50 mL. Approximately 10 mL of this mixture were centrifuged for 15 min at 6000 rpm. Five mL of the clear supernatant were diluted with methanol, resulting in an omeprazole concentration of 0.04 mg/mL.

One g of the precipitate was dissolved in the corresponding polymer solvent. Five mL of this solution was further diluted to 25 mL with the same solvent.

Determination of Omeprazole Degradation by HPLC

A Bischoff HPLC pump equipped with a Bischoff Lambda 1000 spectrophotometer was used. The mobile phase was filtered and degassed. Twenty μL of the final solutions were injected into the HPLC using a Kromasil C18 column (250 × 4 mm, 5 μm) combined with a Kromasil 100 C18 precolumn. For investigation of omeprazole degradation in organic media, the following HPLC conditions were applied: mobile phase acetonitrile:buffer pH 7.4 (27:73 v/v); flow rate 1.3 mL/min; detection wavelength 305 nm; external standard phenacetin with a concentration of injection of 4 mg/mL. For investigation of omeprazole degradation in aqueous media, the following HPLC conditions were used: mobile phase acetonitrile:water (40:60 v/v); flow rate 1.7 mL/min; detection wavelength 235 nm; external standard methyltestosterone with a concentration of injection of 80 μg/mL. Injection concentrations of omeprazole were 80 μg/mL for the study in organic polymer solutions and 40 μg/mL for the investigations in aqueous polymer dispersions. The HPLC chromatograms were recorded immediately after preparation of the final solutions (1 min) and after 180 min of storage. The change of the peak area ratios of omeprazole and the external standard was calculated.

The resolution R between two chromatographic peaks was calculated according to Eq. 1

$$R = 2(t_2 - t_1)/(W_1 + W_2) \qquad (1)$$

where t_1 and t_2 are the retention times and W_1 and W_2 the respective peak widths.

Determination of the Amount of Free Phthalic Acid in Aquateric® and HP-55

According to the product specifications of Aquateric, between 0.500 g and 1.000 g of the polymer powder was weighed into a tared 250 mL narrow-mouth, stoppered glass flask and diluted with deionized water to 200 g. The flask was stoppered, shaken on a laboratory shaker for 30 min, and then placed on a magnetic stirrer. While stirring, 25-mL

samples were withdrawn and transferred to a tared 50 mL volumetric flask. Five mL of 1 N HCl were added, diluted with water to 50 mL, and thoroughly mixed. A portion of the mixture was centrifuged for 15 min at 5000 rpm. The absorbance of the supernatants was measured in a 1-cm quartz cell at 275 nm with 0.1 N HCl as reference using a Perkin Elmer UV-VIS spectrophotometer Lambda 12. The phthalic acid content of Aquateric® and HP-55 was calculated according to Eq. 2.

$$\textit{phthalic acid content}\ [\%] = \frac{A \cdot 100}{B \cdot C} \qquad (2)$$

where A=phthalic acid concentration (mg/mL) determined from a phthalic acid calibration curve, B=weight of the 25-mL sample (g) and C=polymer weight (g).

Determination of the Omeprazole Degradation Rate

The degradation rate was determined by investigation of the organic omehrazole solution in presence of 6% (w/w) Eudragit® L-100, HPMCAS-HF, and shellac, respectively, over 24 h. The HPLC chromatograms were recorded at various time points.

Determination of the pH Values

The pH values of the plain solvents, the omeprazole-free organic polymer solutions, and the omeprazole-free aqueous polymer dispersions were determined at ambient temperature with a Mettler DL70 ES titration apparatus, which was equipped with a DG113-SC glass electrode for titrations under waterless conditions and a DG111-SC glass electrode for aqueous systems (Mettler Toledo, Germany).

Determination of the pKa Values by Acid-Base Back Titration

According to Schmidt-Mende (2001), an amount of polymer corresponding to $2 \cdot 10^{-4}$ mol carboxyl groups was dissolved in an excess of 0.1 N NaOH, diluted with distilled water to 20 mL, and stirred 5–10 min until complete dissolution. Immediately thereafter, 0.1 N HCl was added by the titration apparatus Mettler DL70 ES with a titration speed of 0.33 mL/min. The pH values during the titration were measured potentiometrically with the DG111-SC glass electrode.

RESULTS AND DISCUSSION

pH-sensitive enteric films consist of a linear polymer chain with ionizable carboxyl groups. The methacrylic acid content in Eudragit® L-100 is between 46% and 50% (Table 1) and the polymer dissolves at a pH above 6. The methacrylic acid content in Eudragit® S-100 is only between 28% and 31% and it therefore dissolves at a pH above a 7. Among the investigated cellulose derivatives, CAP has the highest amount of acidic groups, particularly covalently bound phthalic acid. The acid content of HP-55 is between 21% and 27%. The HPMCAS-HF shows the lowest acid content and therefore dissolves at the highest pH. With regard to shellac, no general information on the amount of acid groups can be found because of its natural origin.

Stability of Omeprazole in Organic Polymer Solutions

As with the USP HPLC method, the HPLC method used in this study does not allow the identification of the decomposition products of omeprazole. However, it is a suitable technique for separation of omeprazole from its decomposition products and for quantification of omeprazole in the presence of enteric polymers in organic media. Interference with neither degradation products of omeprazole nor with the by-products and excipients in the polymers was observed. The mobile phase used provided a good resolution between the omeprazole peak and the external standard peak (R=*4.82*). Linearity of the calibration curve was obtained with a correlation coefficient of 0.999 for a concentration range of 16–160 µg/mL of omeprazole.

TABLE 1 Characteristics of Enteric Coating Polymers According to Product Specifications

	Amount of free carboxyl groups [%]	Dissolution pH
Eudragit® L-100	46–50	6.0
Eudragit® S-100	27–30	7.0
CAP (Aquateric®)	30–40	6.0
HP-55	21–27	5.5
HPMCAS-HF	4–8	7.0
HPMCAS-LF	14–18	5.0
Shellac	[a]	[a]

[a]No specification.

Methanol is one of the recommended solvents for omeprazole, the polymethacrylates, HPMCAS, and shellac. The external standard phenacetin was eluated before omeprazole at a retention time of about 10 min. The retention time of omeprazole was about 15 min. Neither changes of the retention time nor of the peak areas could be observed during the time course of the experiments. Therefore, omeprazole was stable in methanolic solution for at least 180 min. The same results were obtained with the solvent mixtures methylene chloride:methanol (4:1 v/v) and acetone-methanol (1:1 v/v), where the former mixture was used as solvent for CAP and the latter for HP-55.

The acidic polymethacrylates Eudragit® L-100 and Eudragit® S-100 showed a pronounced influence on the decomposition of omeprazole (Fig. 1). In contrast, the cationic nonacidic polymethacrylate Eudragit® RS-100 did not cause degradation of omeprazole (Fig. 1). As expected, the influence of the acidic polymethacrylates manifested itself in decreasing peak areas during the time course of the experiments. After 180 min the omeprazole peak area was reduced while the phenacetin peak area remained constant. The peak area decrease induced by Eudragit® L-100 was more pronounced than with Eudragit® S-100 (27.0%±5.1 and 18.2%±3.9, respectively). Because of the absence

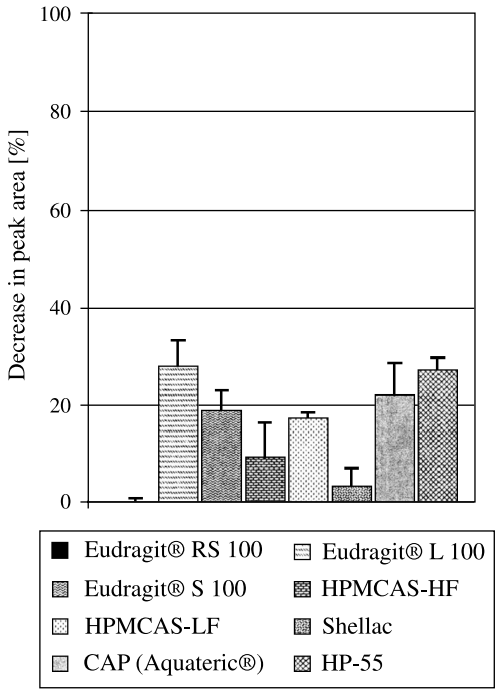

FIGURE 1 **Decrease in Peak Area [%] of Omeprazole in Various Organic Polymer Solutions (6%, w/w) within 180 min. Means±SD, n=3–8.**

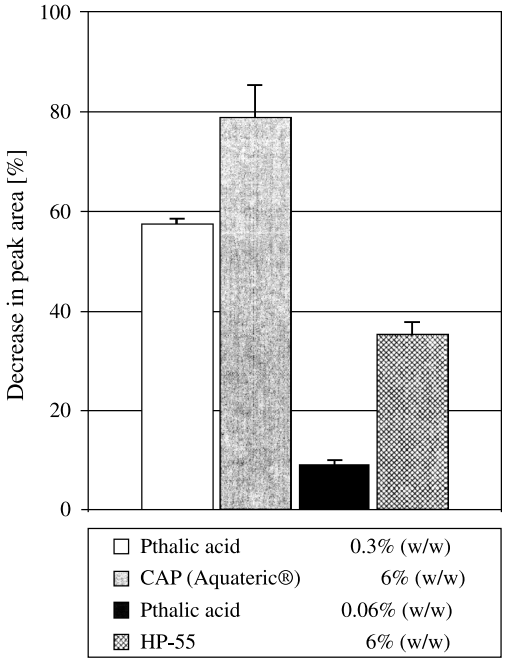

FIGURE 2 **Decrease in Peak Area [%] of Omeprazole in Various Phthalic Acid Solutions and Organic Polymer Solutions (6%, w/w) within 180 min. Means±SD, n=3–8.**

of acidic groups in the polymer structure, Eudragit® RS-100 did not show any influence on the peak area of omeprazole.

The acidic cellulose esters investigated in this study also influenced stability of omeprazole (Fig. 1). In the presence of the succinate esters HPMCAS-HF and -LF, the retention times of the external standard and omeprazole again remained constant. However, the solvent mixtures used for CAP and HP-55 caused a shift of the omeprazole peak to a lower retention time (about 10 min) without affecting drug stability. The HPMCAS-HF and -LF, which caused a peak area decrease of 8.9%±7.0 and 16.7%±1.0, respectively, had a less pronounced effect on the decomposition of omeprazole than the acidic polymethacrylates (Fig. 1). This decrease in peak area corresponds to the amount of acidic groups in the polymer structure (Table 1). Surprisingly, the cellulose esters CAP and HP-55 appear to have the greatest influence of the peak area of omeprazole (decrease in peak area 78.9%±6.3 and 35.3%±2.5, respectively) (Fig. 2). This observation cannot be explained by the amount of acidic groups in the polymer structure. Although CAP has more acidic groups than HP-55, the highest amount of carboxyl groups is contained in Eudragit® L-100 (Table 1). The cellulose esters CAP and HP-55 are known to be susceptible to hydrolysis (Bodmeier & Chen, 1991;

Davis, 1986). During storage, free phthalic acid is formed, which could explain the high degradation rate of omeprazole caused by these two polymers.

Under the influence of a methanolic shellac solution, only a negligible change of the omeprazole peak area (3.3%±3.5) could be observed after 180 min (Fig. 1). Hence, it showed the lowest influence on omeprazole decomposition compared to the other acidic polymers.

Determination of the Influence of Acidic Impurities Contained in the Polymers

Product specifications of CAP (Aquateric®) allow a maximum content of free phthalic acid of 4%. In the present study, a content of free phthalic acid of 3.25% was found. To investigate the effect of phthalic acid on omeprazole stability, omeprazole was mixed with a phthalic acid solution of 0.3%, which corresponds to the free phthalic acid concentration in a 6% (w/w) Aquateric® solution. Interestingly, a decrease of omeprazole peak area of nearly 60% caused by free phthalic acid was observed (Fig. 2). HP-55 contains about 1% of free phthalic acid (Goskonda & Lee, 2000). This value can be confirmed in the present study. As described for Aquateric®, omeprazole was mixed with a phthalic acid solution of 0.06% to quantify the effect of the acid on omeprazole degradation. Here, the peak area of omeprazole was reduced by nearly 10% (Fig. 2). Therefore, the amount of free phthalic acid in these polymers contributed to, the overall degradation of omeprazole observed with CAP (Aquateric®) and HP-55. After mathematical elimination of the phthalic acid degradation effect, the influence of CAP and HP-55 on omeprazole stability was between that of Eudragit® S-100 and L-100 (Fig. 1). Thus, the decomposition of omeprazole in the presence of organic polymer solutions correlates with the amount of acidic groups in the respective polymer structure.

Stability of Omeprazole in Aqueous Polymer Dispersions

Enteric coating polymers are acidic polymers containing free carboxyl groups. These film-forming polymers are undissolved even at a pH between 6 and 7 for the most part, and therefore are poorly water soluble. However, they can be dispersed in water. In contrast to commercially available aqueous dispersions of film-forming polymers, the investigated aqueous polymer dispersions are not manufactured by emulsification of the polymers. Aqueous dispersions are suspensions and therefore an investigation of both the aqueous supernatants and the precipitates is necessary. Only CAP is used as the commercial product Aquateric® powder, which already contains all required excipients for preparation of an aqueous dispersion.

Investigation of the Supernatants

The resolution of the omeprazole peak and the peak of the external standard methyltestosterone ($R=6.60$) confirms the suitability of the applied HPLC conditions used in this study. Interference with neither degradation products of omeprazole nor with the by-products and excipients in the polymers was observed. Linearity of the calibration curve was obtained with a correlation coefficient of 0.999 in a concentration range of 16–160 µg/mL of omeprazole.

As distilled water often shows weak acidic properties (Münzel et al., 1959), a degradation of omeprazole can even occur in the dispersion medium water.

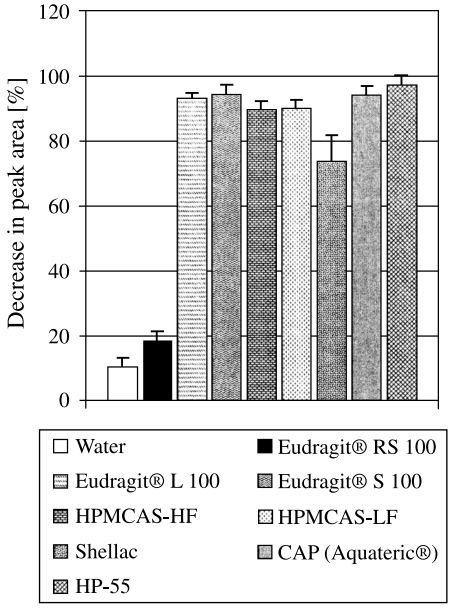

FIGURE 3 **Decrease in Peak Area [%] of Omeprazole in Various Aqueous Dispersions (6%, w/w) within 180 min According to the HPLC Method for Aqueous Systems. Investigation of the Supernatants. Means±SD, n=3–8.**

Omeprazole was eluated before the external standard at a retention time of about 3 min. The external standard methyltestosterone has a retention time of about 13 min. Only marginal changes of the omeprazole peak area were observed in the presence of water (Fig. 3). Hence, omeprazole was only slightly unstable in water within the time course of the experiment. A more pronounced effect on the peak area of omeprazole was found in an aqueous Eudragit® RS-100 dispersion (Fig. 3), which is in contrast to the experiments in organic solutions. An almost complete disappearance of the omeprazole peak was observed in aqueous dispersions of the acidic polymers (Fig. 3). There was no difference between the influence of the acidic polymethacrylates and the acidic cellulose esters on omeprazole degradation. Eudragit® L-100 and CAP caused a decrease of the omeprazole peak area of about 93% and 94%, respectively. The natural polymer shellac decreased the peak area of omeprazole to a lower extent (only 74.0%±7.7). In aqueous solutions the omeprazole degradation rate was characterized by a half-life of less than 10 min at pH values lower than 4 (Pilbrant, 1985). As all acidic polymers in aqueous dispersions used in this study caused very low pH values of about 3 (Table 2), a nearly complete degradation of omeprazole within 180 min was expected. Distilled water, the aqueous Eudragit® RS-100 dispersion, and the aqueous shellac dispersion showed higher pH values than the other polymer dispersions (Table 2). Here, the loss of omeprazole was less pronounced (Fig. 3). In addition, adsorption of omeprazole to latex particles had to be taken into consideration. Ruiz et al. (2000) found that adsorption of omeprazole to Aquateric® was greatest (90%) at a pH of 4–5. It has been suggested

TABLE 2 pK_a **Values and pH Values of the Investigated Polymers (Means±SD, n=3)**

	pK_a (H_2O)	pH[a]
Water	–	5.71±0.04
Eudragit® RS-100	–	5.86±0.02
Eudragit® L-100	6.45±0.03	3.05±0.00
Eudragit® S-100	6.66±0.05	2.99±0.00
CAP (Aquateric®)	4.71±0.04	2.82±0.02
HP-55	4.83±0.04	3.35±0.00
HPMCAS-HF	5.15±0.05	3.85±0.00
HPMCAS-LF	5.09±0.05	3.53±0.00
Shellac	6.72±0.02	5.11±0.00

[a]Aqueous polymer dispersion 6% (w/w).

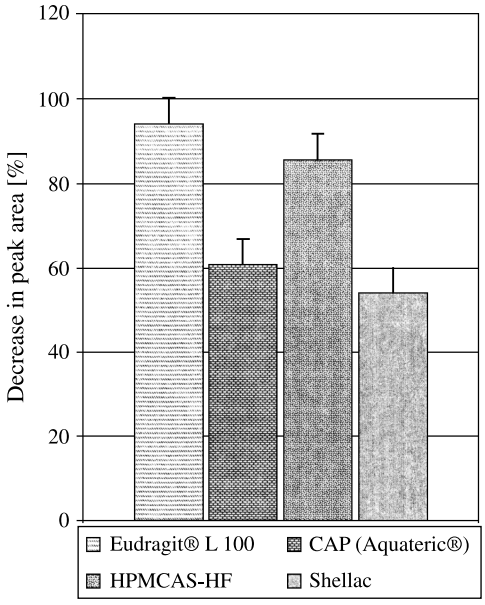

FIGURE 4 **Decrease in Peak Area [%] of Omeprazole in Various Aqueous Dispersion Systems (6% w/w) within 180 min According to the HPLC Method for Organic Systems. Investigation of the Precipitates. Means±SD, n=4.**

that this high adsorption value may be due to electrostatical interactions, as omeprazole and Aquateric® have opposing charges at a pH of 4.5 (Ruiz et al., 2000).

Investigation of the Precipitates

Omeprazole is poorly soluble in water. Therefore, a decrease of the omeprazole peak area can be caused by precipitation of the drug as well as by adsorption to the water-insoluble polymer particles. Indeed, omeprazole was detected in the precipitates. Surprisingly, undissolved omeprazole also underwent a degradation of at least 50% in the presence of acidic polymers (Fig. 4). This again may be due to the very low pH values. Unfortunately, the investigations of the precipitates only allow estimations of omeprazole degradation, because of water residues in the precipitate samples that could not easily be removed without affecting omeprazole stability.

Determination of the Degradation Kinetics of Omeprazole in Organic Polymer Solution

It is well known that the degradation of omeprazole is acid catalysed (Mathew et al., 1995; Pilbrant, 1985). In aqueous solution, the decomposition of omeprazole

follows first-order kinetics or pseudo first-order kinetics (Mathew et al., 1995; Pilbrant, 1985). Moreover, in two studies (Mathew et al., 1995; Pilbrant, 1985), a relationship between the logarithm of the observed rate constant for degradation and the pH was found. With increasing pH values, the degradation rate decreases.

To investigate the degradation of omeprazole in organic polymer solutions, the degradation of omeprazole in solutions of Eudragit® L-100, HPMCAS-HF, and shellac was investigated over 24 h. For comparative purposes, the degradation of omeprazole in plain methanol was also measured. The decomposition of omeprazole in organic polymer solutions also followed first-order kinetics. This is in accordance with results published by Bränström et al. (1989) who investigated the decomposition of omeprazole and analogues under acidic conditions. According to this study, the degradation rate was proportional to the concentration of omeprazole. Semilogarithmic plots of drug concentration vs. time for the degradation of omeprazole in different organic systems are shown in Fig. 5. As mentioned above, omeprazole degrades within a few hours in organic polymer solutions. The results described earlier are confirmed by this study: Again, an organic Eudragit® L-100 solution caused the most pronounced omeprazole degradation and shellac the least pronounced. The solvent methanol had only a negligible influence on the stability of omeprazole within 24 h. Omeprazole degradation rates increased in the following order: methanol< shellac solution<HPMCAS-HF solution<Eudragit® L-100 solution (Fig. 5). The originally colorless solutions become yellowish (methanol), brown (shellac), and dark purple (HPMCAS-HF and Eudragit® L-100). The observed first-order degradation rate constants (k_{deg}) were obtained from the above-mentioned semilogarithmic plots by determination of the slope of the regression line and used to calculate the degradation half lives (Table 3). Omeprazole degraded at a half-life of 8 days in methanol. In methanolic shellac solution, omeprazole had a degradation half-life of almost 31 h. In methanolic HPMCAS-HF solution, the degradation half-life of omeprazole was about 21 h, and in methanolic Eudragit® L-100 solution, approximately 8 h. As the applied HPLC method did not allow a separation of the degradation products, the structure of the degradation products was not determined. However, an isomeric thion is likely to be the major decomposition product, as the color of the omeprazole solutions turned from purple to yellow over time. This observation is in accordance with the literature (Brändström et al., 1989; Senn-Bilfinger et al., 1987).

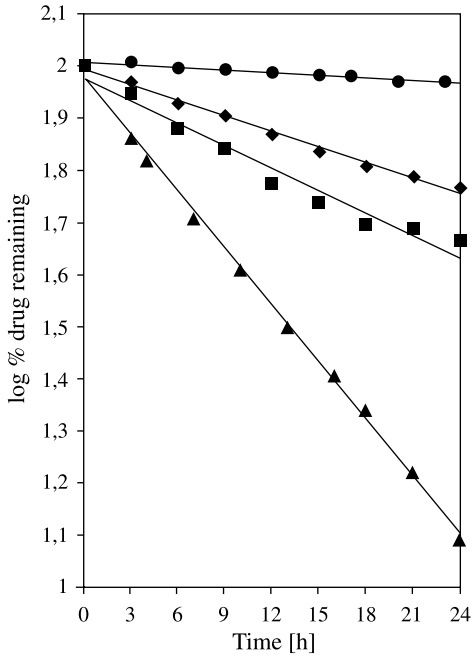

FIGURE 5 Degradation of Omeprazole in Different Organic Solutions. (●) Methanol, (◆) Methanolic Shellac Solution (6% w/w), (■) Methanolic HPMCAS-HF Solution (6% w/w), (▲) Methanolic Eudragit® L-100 Solution (6% w/w) within 24 h. Means ± SD, n = 3.

TABLE 3 First-Order Degradation Rate Constants (k_{deg}) and Degradation Half-Lives ($t_{1/2}$) of Omeprazole in Organic Polymer Solutions (6% w/w)

	k_{deg}	$t_{1/2}$
Methanol	0.004 h^{-1}	8.29 d
Eudragit® L-100	0.083 h^{-1}	8.31 h
HPMCAS-HF	0.033 h^{-1}	21.24 h
Shellac	0.023 h^{-1}	30.80 h

Determination of the pK_a Values of Enteric Coating Polymers

In order to obtain gastric resistance, enteric polymers should have a pK_a between 4 and 6 Chambliss (1987). A modified acid-base titration according to Parke and Davis (1954) was used to determine the pK_a values of Eudragit® L-100, S-100, HPMCAS-HF, LF, CAP, HP-55, and shellac. The pK_a value was determined from the linearized titration

curve of log (1 − t)/t vs. pH as the point of intersection with the abscissa (Schmidt-Mende, 2001), where t is the degree of titration.

The polymethacrylates Eudragit® L-100 and S-100 show pK_a values above 6.4, where Eudragit® L-100 has a lower pK_a value than Eudragit® S-100 (Table 2). These results are in accordance with those by Schmidt-Mende (2001). With pK_a values above 5, the succinate esters HPMCAS-HF and -LF are less acidic than the phthalate esters CAP (pK_a=4.71) and HP-55 (pK_a=4.83). The pK_a values of the succinate esters decrease with an increasing amount of free acid groups (Table 1). Therefore, HPMCAS-HF (pK_a=5.15) is less acidic than HPMCAS-LF (pK_a=5.09). As a film-forming polymer in Aquateric®, CAP shows the lowest pK_a value (pK_a=4.71), which is comparable to that of acetic acid. All investigated cellulose esters are more acidic than the polymethacrylates. This was also found by Schmidt-Mende (2001). For shellac, a pK_a range between 6.9 and 7.5 can be found in the literature without mentioning the applied method (Chambliss, 1987). With the acid-base back titration used in this study, a pK_a of 6.72 was determined for shellac. Consequently, shellac showed the highest pK_a value compared to the other investigated polymers.

CONCLUSION

Two HPLC methods to determine the degradation of omeprazole in organic polymer solutions and aqueous polymer dispersions were developed. These HPLC methods allowed the separation of omeprazole from its decomposition products and the quantification of omeprazole in the presence of enteric polymers in organic solvents. Interference with neither the degradation products of omeprazole nor with the by-products and excipients in the polymers was observed. Omeprazole was stable in the investigated organic solvents for at least 180 min. Omeprazole degradation was more pronounced in aqueous polymer dispersions than in organic polymer solutions. The influence of organic polymer solutions on the stability of omeprazole depended on the amount of acidic groups in the polymeric structure, whereas the influence of aqueous polymer dispersions depended on the pH value of the dispersion. The amount of free acids that were present in some polymers as by-products had to be taken into consideration. These acids also caused a degradation of omeprazole. Among all investigated enteric polymers, shellac showed the lowest influence on omeprazole degradation. The decomposition of omeprazole in organic polymer solutions followed first-order kinetics.

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