

Formulation and stability evaluation of enteric-coated omeprazole formulations

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Omeprazole, a substituted benzimidazole, is a specific and non-competitive inhibitor of the enzyme H^+/K^+ -ATPase, known as the gastric proton pump. It is unstable in conditions of low pH and must be protected from the effects of gastric acid when given orally; thus, it is administered in the form of enteric-coated dosage forms. In this present study, various coating solutions were prepared in different concentrations and applied to previously subcoated omeprazole tablets to examine whether this coating prevented omeprazole from degrading in acidic media. Dissolution tests were conducted in acidic and basic media to determine the appropriate coating ratio. For stability evaluation, an accelerated stability test was performed on developed tablet formulations and commercially obtained capsules. Samples were examined with regard to visual appearance, omeprazole content and dissolution properties for a month. For formulation consideration, the most promising results were obtained from HPMCP₄ and CAP₄ (4% enteric coating with hydroxypropylmethyl cellulose phthalate solution and cellulose acetate phthalate solution, respectively) subcoated preparations. From the stability aspect only Losec capsules (Astro-Turkey, commercial product) seem to be dependable.

L'omeprazole, un benzimidazole substitué, est un inhibiteur spécifique/ H^+ , non compétitif, de la H^+/K^+ -ATPase, connue comme pompe des protons gastriques. Il est instable en milieux de faibles pH et doit être protégé des effets de l'acide gastrique lorsqu'il est administré par voie orale. Il est par conséquent administré sous forme entérique enrobée. Dans cette étude, différentes solutions d'enrobage ont été préparées à différentes concentrations et appliquées sur des comprimés d'omeprazole préalablement protégés par un sous-enrobage afin de déterminer si cet enrobage peut protéger l'omeprazole d'une dégradation en milieu acide. Des essais de dissolution ont été effectués en milieux acide et alcalin afin de déterminer les taux d'enrobage appropriés. Pour l'étude de stabilité, des essais de vieillissement accéléré ont été effectués sur les formules de comprimés étudiées et sur des capsules commerciales. Les échantillons ont été examinés en ce qui concerne l'aspect macroscopique, la teneur en omeprazole et les caractéristiques de dissolution sur un mois. Des résultats très encourageants ont été obtenus avec l'HPMCP₄ et le CAP₄ (4% d'enrobage entérique par une solution à base, respectivement, de phthalate d'hydroxypropylméthyl cellulose et d'acétate de cellulose) appliqué sur des comprimés comportant un sous-enrobage. Du point de vue de la stabilité, seules les capsules de Losec (produit commercial de Astra-Turquie) semblent donner de bons résultats.

Key words: Omeprazole — Tablets — Enteric coating — Stability.

Mots clés: Oméprazole — Comprimés — Enrobage entérique — Stabilité.

Enteric-coated dosage forms do not release the active ingredient until they have been transported down to the neutral reacting part of the small intestine, hence they offer the best possibilities for the protection of unstable drugs at low pH values [1]. The most important reasons for enteric coating can be summarized as follows:

- to protect acid-labile drugs from gastric fluid (e.g. enzymes and certain antibiotics),
- to prevent gastric distress or nausea due to irritation from a drug (e.g. sodium salicylate),
- to deliver drugs intended for local action in the intestines (e.g. intestinal antiseptics could be delivered to their site of action in a concentrated form and bypass systemic absorption in the stomach),
- to deliver drugs that are optimally absorbed in the small intestine to their primary absorption site in their most concentrated form,
- to provide a delayed-release component for repeat action tablets [2].

The choice of the polymer and the thickness of the coated layer

are critical to control the pH solubility profile of the enteric-coated dosage form.

In recent years, omeprazole has been widely used as a gastric acid secretion blocker and selectively inhibits the proton pump in the gastric mucosa [3-10]. Omeprazole degrades very rapidly in aqueous solutions at low pH values [1,3, 11, 12]. In aqueous solutions, the rate of degradation proceeds with a half-life of less than 10 min at pH values below 4, 18 h at pH 6.5 and about 300 days at pH 11 [1]. Omeprazole degradation is acid-catalysed; with an increase in the pH values, the rate of degradation decreases. In addition, the colour of the solution changes immediately to pale yellow upon the addition of the acid and on heating, the colour further changes to dark yellow, then becomes brownish [11]. Preformulation studies have shown that moisture, solvents and acidic substances have deleterious effects on the stability of omeprazole and should be avoided in pharmaceutical formulations. To overcome the stability problems of omeprazole, the best solution seems to be to prepare enteric-coated dosage forms. The preparation must be perfectly coated, since if any drug leaks out of the dosage

form in the stomach, it almost immediately degrades. Conversely, an acidic medium can diffuse into the dosage form through pinholes and/or other damage sustained during the enteric coating process [1].

Despite its importance as a therapeutic agent and its known instability, omeprazole and its formulations have been the subject of very few published stability investigations to date [3]. The aims of this study were:

- to examine whether the enteric coating prevents omeprazole from degrading in acidic media by applying various enteric coating solutions on previously subcoated omeprazole tablets,
- to determine the appropriate coating ratio in acidic and basic media by dissolution tests,
- to examine the stability of the tablet formulations developed and certain commercially available products by evaluating their visual appearance, content and dissolution properties.

I. MATERIALS AND METHODS

1. Materials

Omeprazole (Milen Merkez Pharmaceutical Company, Turkey), mannitol (Merck, Germany), microcrystalline cellulose (FMC Corp., United States), hydroxypropylmethyl cellulose (HPMC, Methocel K,M, Colorcon, United Kingdom), hydroxypropylmethyl cellulose phthalate (HPMCP-HP 55, Eastman Chemical Products Inc., Canada), Eudragit S-100 (Rohm Pharma, Germany), cellulose acetate phthalate (CAP, Eastman Chemical Products Inc., Canada), cetyl alcohol (Merck, Germany), ethanol 95% (Tekel, Turkey), phenacetin (Abbot, United States), acetonitrile (HPLC grade, Riedel, Germany), and methanol (HPLC grade, Merck, Germany). Other chemicals were of analytical reagent grade.

2. Methods

2.1. Formulation studies

2.1.1. Preparation of tablets

Omeprazole (20 mg), mannitol (83.5% w/w), lactose (anhydrous, 4% w/w) and sodium lauryl sulfate (0.25% w/w, as solubilizer) were mixed in a cylindric mixer for 10 min and granulated with hydroxypropylmethyl cellulose solution (1 % w/v in pH 11 phosphate buffer). After forcing the damp mass through a 1 mm screen by granulator (Erweka AR-400), the granules were tray-dried at 30°C until a constant weight was attained. Following sieving through an 0.75 mm screen, granules and 2.25% (w/w) microcrystalline cellulose (as antiadherent, disintegrant and lubricant agent) were blended in the cylindric mixer for 10 min, magnesium stearate (1 % w/w) was added and mixed thoroughly for an additional 5 min. The tablets were compressed on an eccentric tableting machine (Erweka AR-

400) equipped with 9 mm biconvex punches to obtain 200 mg tablets of hardness 7 kp.

2.1.2. Coating of tablets

2.1.2.1. Subcoating

The tablets were subcoated with hydroxypropylmethyl cellulose solution (due to the high viscosity of hydroxypropylmethyl cellulose solutions, 0.25% w/v in pH 7.4 phosphate buffer was selected as the result of preliminary formulation studies) based on the 1 % weight increase of the uncoated tablets by the use of a fluidized bed apparatus (Aymes, Turkey). The solution was atomized from the top of the apparatus at a rate of 1.5 ml/min. The inlet air temperature was set at 40°C. After 1 min of atomizing, the tablets were dried at 40°C for 2 min. The coating process continued for a total period of 20 min, including drying. The coated tablets were dried in the apparatus for 10 min after the completion of the coating, and further dried in a vacuum oven at 30°C until a constant weight was obtained.

2.1.2.2. Enteric coating

Subcoated tablets were coated with different enteric coating polymers (due to the high viscosity of the polymer solution, 3 and 5% concentrations were selected) (*table I*) based on the 1 % (HPMCP₁, ES₁, CAP₁), 2% (HPMCP₂, ES₂, CAP₂) and 4% (HPMCP₄, ES₄, CAP₄) weight increase of the subcoated tablets, by the use of a fluidized bed apparatus. Enteric coating solutions were atomized from the top of the apparatus at a flow rate of 1.5 ml/min. The inlet air temperature was set at 25°C. After 20 s of atomizing process, tablets were dried for 2 min. The coating process for hydroxypropylmethyl cellulose phthalate and cellulose acetate phthalate formulations containing 5% polymer were continued for a total period of 2.3, 4.5 and 7.1 min (including drying) for 1, 2 and 4% weight increase, respectively. In the case of formulation ES, which contained 3% polymer, this period was 2.4, 4.8 and 9.2 min (including drying) for 1, 2 and 4% weight increase, respectively. The remaining part of the process was as in subcoating.

2.1.3. In vitro release studies

Dissolution of the enteric coated tablets was determined using the USP XXII apparatus 2 at 37 ± 0.5°C with a paddle which rotated at 100 r/min. The dissolution medium was 0.1 N HCl solution and pH 7.4 phosphate buffer. A pH-changed dissolution procedure was used to simulate the pH change of the gastro-intestinal tract: 2 h of exposure to 0.1 N HCl (pH 1.2) solution, followed by adjustment with 0.2 M tribasic sodium phosphate solution to pH 7.4. At constant time intervals, 5 ml

Table I - Solutions used for enteric coating.

Formulation	Film former	Plasticizer	Solvent	Permeable barrier agent
HPMCP _{1,2,4} *	HPMCP (5%)	dibutyl phthalate** (10%)	acetone/isopropyl alcohol (1/1)	cetyl alcohol (0.5%)
ES _{1,2,4} *	Eudragit S-100 (3%)	dibutyl phthalate** (10%)	acetone/isopropyl alcohol (1/1)	
CAP _{1,2,4} *	CAP (5%)	diethyl phthalate** (10%)	acetone/isopropyl alcohol (1/1)	

*HPMCP_{1,2,4}, ES_{1,2,4}, CAP_{1,2,4}: enteric coating with formulations hydroxypropylmethyl cellulose phthalate, Eudragit S-100 and cellulose acetate phthalate, respectively, based on the 1/2/4% weight increase in subcoated tablets

**based on dry polymer weight

samples were removed from the release medium and assayed by means of UV spectrophotometry at 303 nm. The same procedure was used in the stability studies for the evaluation of dissolution properties.

2.2. Stability Studies

2.2.1. Samples

A total of four products were tested in the study. Two of them were obtained from the market (Losec Capsules, Astra-Turkey and Omeprazid capsules, Nobel-Turkey); the other two, formulated in the present study (coded HPMCP₄ and ES₄ tablets), were evaluated for their stability, since hydroxypropylmethyl cellulose phthalate and Eudragit S are more frequently used coating polymers than cellulose acetate phthalate. The tablets were stored in dark coloured glass bottles containing desiccant substances and closed tightly with an internal and external lid system.

2.2.2. Conditions for stability study

The samples were stored in two humidity cabinets (Niive, Turkey) at 40°C (± 1°C) and 75% relative humidity (± 3%). The cabinets were monitored by a thermometer calibrated to traceable standards and a hygrometer supplied with a certificate of compliance by the manufacturer.

2.2.3. Assay of omeprazole

The selective assay of omeprazole was carried out by HPLC according to the modified method of Kobayashi et al. [13]. The system consisted of a pump (Waters 510, Millipore), autosampler (Waters 717 Autosampler, Millipore), spectrophotometric detector (Waters 490-E, Millipore), column (Nucleosil C₁₈ 150 x 4.6 mm, Phenomenex) and an integrator (IBM PC/2,80,386, NEC). The chromatographic conditions for omeprazole assay were as shown in table II.

Table II - Chromatographic conditions for assay of omeprazole.

Mobile phase	acetonitrile-pH 8 phosphate buffer 25/75 (v/v)
Flow rate	1 ml/min
Injection volume	20 µl
Internal standard	phenacetin
UV wavelength	280 nm
Operating temp.	ambient

The sample solution (200 µg/ml) was prepared by ultrasonic extraction of quantity of mixed beads from six capsules or of powder from six ground tablets equivalent to 20 mg of omeprazole, in 60 ml of phosphate buffer (pH 11) for 10 min. After the addition of 20 ml of 95% ethanol, ultrasonication continued for additional 5 min and the extract was diluted in the same buffer to 100 ml, finally filtered through Whatman No. 1 paper. Eventually, the filtrate (0.5 ml) was combined with phenacetin solution (0.5 ml, 200 µg/ml) to form the internal standard and diluted with water to 100 ml.

The standard omeprazole solution was prepared by dissolving about 20 mg of omeprazole and 20 mg of phenacetin in 20 ml of 95% ethanol, then diluting to 100 ml in a volumetric flask with pH 11 phosphate buffer. A set amount (0.1 ml) of this

solution was diluted with water to 50 ml in a volumetric flask. The chromatogram of the standard omeprazole solution presented in figure 1. The retention times for omeprazole and the internal standard (phenacetin) were 10.24 and 7.50 min, respectively.

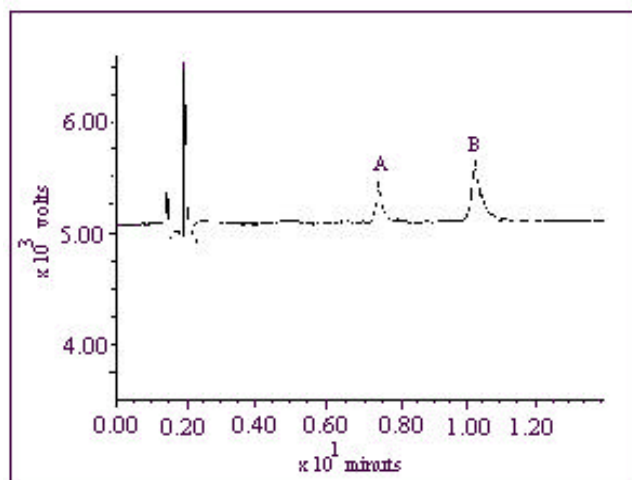


Figure 1 - Chromatogram of the standard solution of omeprazole. A: phenacetin, B: omeprazole, 400 ng/ml. For the chromatographic conditions, see table II.

The sample and the standard solutions (20 µl) injected separately and the quantity of omeprazole was calculated from the ratio of the peak area of drug to internal standard.

After the injection of sample solution, no interferences observed related to the excipients such as cellulose, disodium hydrogen phosphate, hydroxypropyl cellulose, hydroxypropylmethyl cellulose, lactose, mannitol and sodium lauryl sulfate present in the delayed release capsules and in our preparations.

The decomposed omeprazole solution was prepared by dissolving about 20 mg omeprazole in 20 ml of 95% ethanol and diluting to 100 ml in a volumetric flask with USP XXII pH 3 buffer. Then, to determine the probable interference between the standard omeprazole peak and the degradation products of omeprazole formed, the sample was injected into an HPLC column immediately after its preparation: 30 min and 3 h (at room temperature). Following these injections, a decrease was observed due to degradation in the area of the standard omeprazole peak as a function of time and could not be detected after 3 h. Under these HPLC conditions, no interaction was detected between the degradation products and omeprazole (figure 2).

2.2.4. Stability testing protocol

Prior to the stability study, all samples were evaluated with respect to visual appearance, omeprazole content and dissolution characteristics. Samples were stored at 40 ± 1°C and 75% relative humidity (± 3%) for a total period of four weeks for stability evaluation; each week, samples were analysed to check their stability. Dissolution results were given as mean ± SEM and compared by means of Student's t-test. A p value below 0.1 was considered significant.

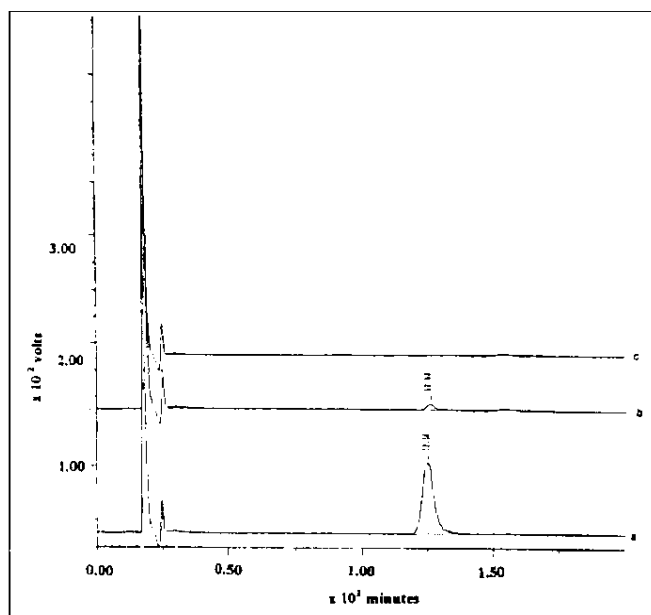


Figure 2-Chromatogram of the decomposed omeprazole solution, a: initial omeprazole solution (400 ng/ml), b: after 30 min, c: after 3 h.

II. RESULTS AND DISCUSSION

1. Formulation studies

An enteric-coated dosage form should not allow significant release of drug in the stomach yet provide rapid dissolution of the polymer layer while releasing the drug at adesired site in the intestine. Hydroxypropylmethyl cellulose phthalate, polyvinyl acetate phtalate and methacrylic acid/methyl methacrylate copolymers are frequently used for enteric coating. These polymers are weak acids, containing carboxyl groups in a substantial proportion of their monomeric units. Rapid dissolution of these polymers requires pH values that are much higher than those normally present in the stomach.

The design of an enteric coated dosage form with optimal properties in terms of low drug release during gastric residence combined with rapid disintegration at intestinal pH, requires consideration of the pH, generated at the core surface, polymer pKa, solubility and thickness of the coating layer [14].

In our study, omeprazole tablets were subcoated with hydroxypropylmethyl cellulose solution (0.25 % w/v in pH 7.4 phosphate buffer) based on the 1 % weight increase. Preliminary studies indicated this was sufficient to protect the active ingredient from the weak acidic characteristics of the enteric coating material. Subsequently, the enteric coating process was carried out on subcoated omeprazole tablets. pH-changed dissolution tests were performed to determine appropriate polymer and coating ratios which are among the most important factors for an enteric-coated dosage form to have optimal properties.

The omeprazole tablet designed should obey the « delayed release (enteric-coated) articles-general drug release standard » in the USP XXII; no individual value should exceed 10 % when dissolved in the acidic phase after 2 h of operation and no less than 75% should be released in buffer solution after continuous operation on the apparatus for 45 min. The dissolution profiles

and evaluation of data on the enteric-coated omeprazole tablets at pH 1.2 and 7.4 are summarized in *figure 3* and *table III*. As the drug was not stable in the acidic dissolution medium (pH 1.2), quantitative determination was undertaken immediately after the samples were removed. From these data it was concluded that the hydroxypropylmethyl cellulose phthalate coded formulations, HPMCP₁, and HPMCP₂, did not meet the requirements of the USP XXII, since the dissolved level was less than 75% in 45 min and the released amount was more than 10% in the acidic phase after 2 h. Meanwhile, HPMCP₄ met the USP XXII criteria in the acidic and the basic phase. For the ES-coded formulations (ES₁, ES₂, ES₄), the released amount did not meet the requirements of the USP XXII, since the dissolved level was less than 75% for basic media. ES₁ and ES₂, tablets did not meet the requirements of the USP XXII, since the dissolved level was more than 10% in the acidic phase, but the released amount was less than 10% in the acidic phase

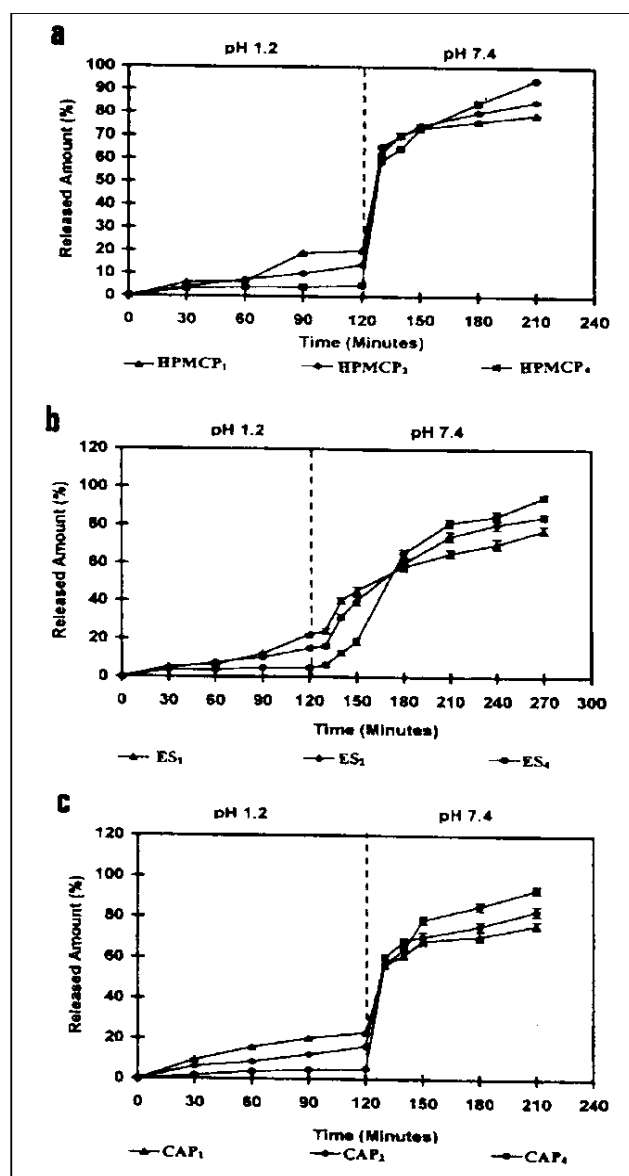


Figure 3 - Dissolution profiles of omeprazole tablets coated with (a) formulation HPMCP_{1,2,4}, (b) formulation ES_{1,2,4}, and (c) formulation CAP_{1,2,4} (see *table I*). Bars indicated SEM; n = 6.

Table III - Evaluation of the release data of formulations.

Formulation	% Released		Meeting USP XXII standards	
	Acidic phase	Basic phase	Acidic phase	Basic phase
HPMCP ₁	20	73	-	-
HPMCP ₂	14	74	-	-
HPMCP ₄	<10	>75	+	+
ES ₁	22	55	-	-
ES ₂	15	58	-	-
ES ₄	<10	>75	+	-
CAP ₁	23	70	-	-
CAP ₂	16	73	-	-
CAP ₄	<10	>75	+	+

*HPMCP_{1,2,4}, ES_{1,2,4}, CAP_{1,2,4}: enteric coating with formulations hydroxypropylmethyl cellulose phthalate, Eudragit S-100 and cellulose acetate phthalate, respectively, based on the 1/2/4% weight increase in subcoated tablets

(+) meeting, (-) not meeting USP XXII standards, respectively

for the ES₄ formulation. For cellulose acetate phthalate coded preparations, similar to hydroxypropylmethyl cellulose phthalate, CAP₁ and CAP₂ subcoded formulations did not meet the requirements, while CAP₄ was in agreement with the requirements.

In summary, in the formulations tested, hydroxypropylmethyl cellulose phthalate, cellulose acetate phthalate and Eudragit S in 4% (HPMCP₄, ES₄, CAP₄) enteric coating percentages met the requirements of the USP XXII in the acidic phase. For basic phase, hydroxypropylmethyl cellulose phthalate and cellulose acetate phthalate met the requirements of the USP XXII, but Eudragit S did not. A similar situation was discussed in a study by Kane *et al.* [15]; this might be due to the lower solubility of hydroxypropylmethyl cellulose phthalate and cellulose acetate phthalate at lower pH values when compared to Eudragit S (hydroxypropylmethyl cellulose phthalate is soluble at pH 5.4, Eudragit S is soluble at pH 7.0, and cellulose acetate phthalate is soluble at pH 5.5).

Finally, it can be stated that hydroxypropylmethyl cellulose phthalate and cellulose acetate phthalate appeared to be proper excipients for the enteric coating of omeprazole. Although, among the tested formulations, 1 and 2% of enteric coating was not adequate for subcoated tablets, better results were obtained by 4% enteric coating. Öztürk *et al.* [14] evaluated the release kinetics of weak acidic substances from enteric-coated dosage forms and reported that the thickness of the enteric coating is one of the most important parameters affecting the release of the active material. Similar to our study, Bums *et al.* [16] reported that the optimum conditions were provided by increasing the coating ratio from 3 mg/cm² to 8 mg/cm², as more than 10% of the release of the drug was realized in the acidic phase of dissolution in the case of 3 mg/cm² coating. Studies are present in the literature concerning drugs similar to omeprazole, which are unstable in the acidic pH of the stomach and whose stability is improved by enteric coating [17-22].

2. Stability studies

2.1. Assay method

The assay of omeprazole by HPLC was sufficiently accurate

and precise (a relative percent standard deviation of 0.5%) based on six readings. Linearity was obtained with a correlation coefficient of 0.999 for a concentration range of 100 to 1000 ng/ml of omeprazole.

2.2. Appearance

In Losec capsules, there was no significant colour change as a sign of instability in the capsule content after a month;

however, a pale yellow color was observed in the Omeprazid capsules at the end of third week. In the ES-coded formulation, the colour showed a variation to a pale yellow at the second week and to yellow at the fourth week. In the HPMCP₄-coded formulation, a change in colour, slightly yellowish, was observed at the end of the first week, whereas a variation completed in the third week was detected in a shorter period when compared to ES₄. With respect to colour change, Losec capsules seem to be the most stable among the tested samples. In a similar study by Davidson and McCallum [3], the authors stated that the visual examination data for omeprazole preparations supported the assay and dissolution results.

2.3. Assay of omeprazole content

The assay results of each sample at each time point, expressed as a percentage of the label claim and of the initial value, are listed in *table IV*. In both formulations, the degradation was more than 10% (for formulations HPMCP₄ and ES₄, 16.85 and 10.50%, respectively), whereas in the commercial products it was lower. However, the measured degradation amount for Losec capsules was lower than that of Omeprazid capsules (0.18 and 6.70%, respectively). When HPMCP₄ and ES₄-coded preparations were compared with commercial products, the loss of omeprazole was highest in the HPMCP₄ formulation and the lowest in Losec capsules. Davidson and McCallum [3] reported similar data previously.

Table IV - Assay results of omeprazole preparations, presented as percent of label claim (%LC) and initial value (%T₀).

Codes	Time (week)				
	Initial time (%LC)	% LC (%T ₀)			
		1	2	3	4
HPMCP ₄	100.18	95.45	91.40	85.50	83.15
ES ₄	100.04	96.15	93.30	91.40	89.5
Losec caps.	100.00	99.90	99.85	99.85	99.82
Omeprazid capsules	100.00	99.60	98.45	95.25	93.30

2.4. Release of omeprazole

A summary of the percentage of the label claim of omeprazole released from the dosage forms in pH 7.4 phosphate buffer after a 2 h pre-exposure to simulated gastric fluid (also called the acid resistance test) is shown in *figure 4*. The results are given for the mean and range of the six individual capsules or tablets. Evaluation of the release results is shown in *table V*. As the data were evaluated with regard to acid resistance (the amount which dissolves in the acidic phase), a statistical difference was found between the initial, second and fourth weeks in all the

preparations. In HPMCP₄ and ES₄-coded preparations, concerning acid resistance, USP limits were not exceeded in the initial and second weeks, but these limits were exceeded in the fourth week. In Losec and Omeprazid capsules, the USP limits were obeyed for the specified time. When the data were evaluated in the basic phase, no change was observed for Losec and Omeprazid capsules in the above-stated periods, but in HPMCP₄ and ES₄-coded preparations, there was a change which could be characterized by the elongation of the release rate in the fourth week (figure 4, a and b). In the literature [23, 24], in an accelerated stability study realized with enteric coated aspirin tablets, alterations in the dissolution rates of the tablets as a function of time were reported.

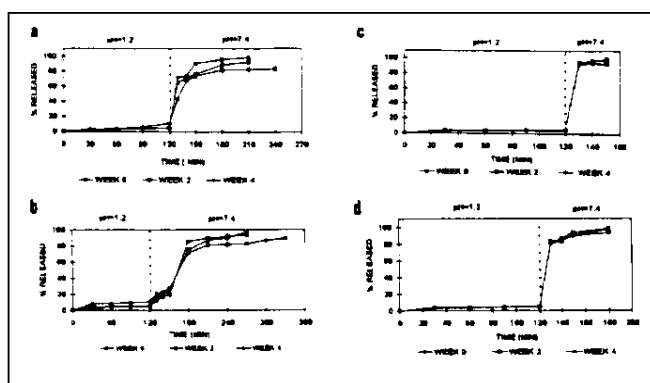


Figure 4 - The variation observed by time in dissolution profile of (a) HPMCP₄ coded preparation, (b) ES₄ coded preparation, (c) Losec capsules and (d) Omeprazid capsules (at 40°C and 75% relative humidity). Bars indicate SEM; n = 6.

When appearance, assay and dissolution characteristics were evaluated together, the results supported each other. At 40°C and 75% relative humidity, degradation was highest for the HPMCP₄ preparation, whereas the change of colour and with respect to acid resistance, the deviation from the USP XXII limits was the highest. With respect to these criteria, ES₄, Losec Omeprazid capsules followed the HPMCP₄ coded formulation.

In our study, better results were obtained with the commercial products which contain enteric-coated pellets, rather than the enteric-coated tablet formulations. Enteric coating of a particular

system seems to be more advantageous from a technological point of view (in the commercial product, pellets in the capsule) than the enteric coating of a single unit (tablets), as a small error in the enteric coating process of a single unit will affect the result on a large scale; studies in the literature support this view [25,26]. On the other hand, differences between the stability of commercial products with similar formulations may also arise from the technology used in production. As a result, the enteric-coated pellets in a capsule might be suggested as a (multiparticulate systems) better alternative than tablets from the formulation and stability aspect.

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Table V - Evaluation of the release data obtained from stability studies.

Form.	% Released								Meeting USP XXII requirements					
	Time (week)								Time (week)					
	Acidic phase				Basic phase				Acidic phase			Basic phase		
	Initial time	2	4	variation (p<0.1)	Initial time	2	4	variation (p<0.1)	initial time	2	4	initial time	2	4
HPMCP ₄	4.89	4.97	11.12	yes	92.51	81.57	77.64	yes	+	+	-	+	+	+
ES ₄	4.93	4.98	10.57	yes	81.03	87.96	76.87	yes	+	+	-	+	+	+
Losec	4.58	4.89	4.97	yes	98.96	97.20	94.02	no	+	+	+	+	+	+
Omeprazid	4.49	4.51	4.98	yes	98.39	97.29	93.12	no	+	+	+	+	+	+

Form.: formulation

HPMCP₄ and ES₄: Our preparations, coated with HPMCP and Eudragit S-100, respectively, based on the 4% weight increase in subcoated tablets

Losec and Omeprazid: commercial capsule products

(+) meeting, (-) not meeting USP XXII standards, respectively

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ACKNOWLEDGMENTS

This work was supported by a grant from Tubitak, the Scientific and Technical Research Council of Turkey (Project No. SBAG-AYD-38). The authors would like to thank Eczacıbaşı Pharmaceutical Company and İlsan İltas Pharmaceutical Company for providing omeprazole.