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Effect of pharmaceutical excipients on aqueous stability of rabeprazole sodium

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Abstract

The chemical stability of a proton-pump inhibitor, rabeprazole sodium, was evaluated in simulated intestinal fluid (pH 6.8) containing various 'Generally Recognized As Safe (GRAS)'-listed excipients, including Brij® 58, Poloxamer 188, Cremophor RH40, Gelucire 44/14 and PEG 6000. After incubation at 37 and 60 °C, the amounts of rabeprazole and its degradation product, thioether-rabeprazole, were quantitated by HPLC analysis. The main degradation product was separated and characterized by LC/MS. The degradation of rabeprazole followed first-order kinetics. In the absence of any excipients, the rate constants (k) obtained at 37 and 60 °C were 0.75 and 2.78 h^{-1}, respectively. In contrast, the addition of excipients improved its stability. Among several excipients tested in this study, Brij® 58 displayed the greatest stabilizing effect. For instance, at 37 and 60 °C, Brij® 58 reduced the k values to 0.22 and 0.53 h^{-1}, respectively. The stabilizing mechanisms of these hydrophilic polymeric excipients with optimal HLB values could be partially explained in terms of their solubilizing efficiency and micellar formation for thioether-rabeprazole. In conclusion, rabeprazole formulations that contain suitable excipients would improve its stability in the intestinal tract, thereby maximizing bioavailability.

Keywords: Aqueous stability; Pharmaceutical excipients; Rabeprazole; Thioether-rabeprazole; Stabilizing mechanism

1. Introduction

Stability is an important issue for the successful development of drug products (Kerns and Di, 2003). Unfortunately, almost all drugs in aqueous solutions are vulnerable to chemical degradation (Black et al., 1988; Badawy et al., 2001). If a drug is chemically degraded, its therapeutic efficacy begins to decline. Furthermore, drug degradation can accompany not only a loss in potency, but also formation of harmful and toxic byproducts (Loftsson and Brewster, 1996; Loukas et al., 1998). Therefore, maintaining drug stability is critical to successful product development. Drug stability in formulated solution has been investigated extensively (Yang and Macdonald, 2004). However, another important aspect of solution stability is in physiological fluids such as gastrointestinal fluids (Chong et al., 2003; Di et al., 2006). When taken orally, drugs are exposed to acidic and/or enzymatic conditions.

Rabeprazole sodium, 2-[[4-(3-methoxypropoxy)-3-methylpyridine-2-yl] methyl sulfinyl]-1*H*-benzimidazole (Fig. 1A), belongs to a class of proton-pump inhibitors (PPIs). It suppresses gastric acid secretion by specifically inhibiting the H^+/K^+-ATPase enzyme system at the secretory surface of the gastric parietal cell (Morii et al., 1990). Clinically, rabeprazole is used to heal, relieve symptoms and prevent a relapse of acid-peptic diseases, such as duodenal, gastric and oesophageal ulceration (Carswell and Goa, 2001). Of all PPIs tested, rabeprazole was the most potent acid inhibitor during the first day of dosing (Pantoflickova et al., 2003). Like other PPIs such as omeprazole and lansoprazole, when exposed to acidic or neutral environments, rabeprazole is converted to several degradation products. Compared to other PPIs, rabeprazole degrades at a faster rate (Richardson et al., 1998). Rabeprazole undergoes pre-systemic and mainly non-enzymatic metabolism that contribute to an absolute bioavailability of about 52% after oral administration of a 20 mg dose (Fuhr and Jetter, 2002). Therefore, a formulation that stabilizes rabeprazole needs to be developed.

The utilization of certain pharmaceutical excipients is known to improve the physical and chemical stability of many active components (Hancock et al., 1995; Costantino et al., 1998;

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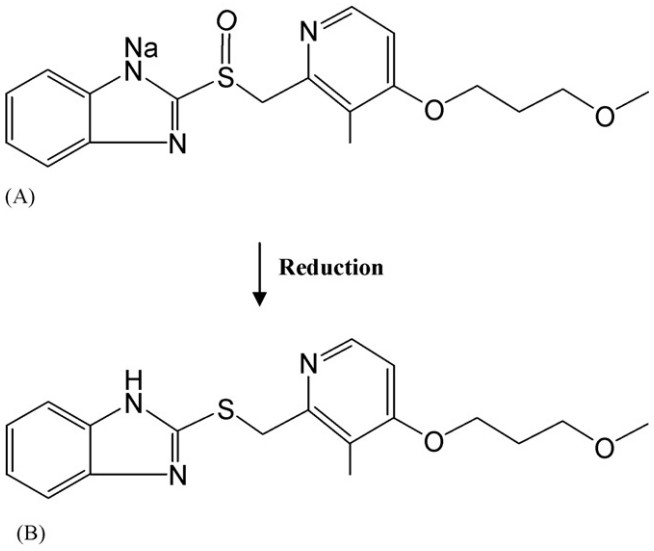


Fig. 1. Chemical structure of (A) rabeprazole sodium and (B) thioether-rabeprazole.

Villalobos-Hernandez and Villafuerte-Robles, 2001). Pharmaceutical excipients interact with the active ingredients and/or serve as matrices that affect the critical quality attributes of drugs. This, in turn, enhances their chemical stability and/or bioavailability (Crowley, 1999). Pharmaceutical compositions that contain PPIs have been investigated, using various means to improve drug stability during storage (Ekpe and Jacobsen, 1999; Turkoglu et al., 2004). However, there are scanty reports addressing the issue of solution stability of PPIs. In particular, their stability in intestinal fluid should be thoroughly investigated, since all PPIs are sold as enterically coated dosage forms.

The purpose of this work was to study the effect of various pharmaceutical excipients on the aqueous stability of rabeprazole in simulated intestinal fluid (pH 6.8) at two different temperatures (37 or 60 °C). Five Generally Recognized As Safe (GRAS)-listed excipients were selected for the study: Brij® 58, Poloxamer 188, Cremophor RH40, Gelucire 44/14 and PEG 6000. Identification of main degradation product, thioether-rabeprazole by LC/MS and chromatograms as well as the stabilizing mechanism were also examined. In so doing, it was sought to develop formulation strategies to stabilize PPIs including rabeprazole. In addition, a simple and efficient stability-indicating methodology was developed.

2. Materials and methods

2.1. Materials

Rabeprazole sodium was purchased from Satya Sai Residency (Hyderabad, India). Brij® 58 (poloxyl 20 cetyl ether) and Poloxamer 188 (copolymer of ethylene oxide and propylene oxide) were purchased from Sigma (St. Louis, MO, USA). Cremophor® RH 40 (polyoxyl 40 castor oil) was obtained from BASF (Ludwigshafen, Germany). Polyethylene glycol 6000 (PEG 6000) and potassium dihydrogenphosphate were purchased from Showa (Tokyo, Japan). Gelucire® 44/14 (mixture of mono-, di- and tri-glycerides and mono- and di-fatty acid esters of polyethylene) was purchased from Gatteffosse (Saint Priest, France). Diethylamine was purchased from Junsei (Tokyo, Japan). HPLC-grade methanol and acetonitrile were obtained from Fisher (Seoul, Korea). All other chemicals were of reagent grade and used without further purification. The Puris-Esse® reverse osmosis system (Anyang, Korea) was operated to produce the water used in this study.

2.2. HPLC quantification of rabeprazole and its main degradation product

2.2.1. Chromatographic conditions

A reversed-phase HPLC system was used to quantify rabeprazole and its degradation product. The HPLC system (Waters, USA) consisted of a pump (Waters™ 600 Controller), a UV-VIS spectrophotometric detector (Waters™ 486 Tunable Absorbance Detector), an autosampler (Waters™ 717 plus Autosample), a degasser (Waters™ In-line Degasser), and an analytical column (Luna 5 μ C_{18} analytical column; 150 mm × 4.60 mm) protected by a guard column (Gemini C_{18}; 4 mm × 3.0 mm ID). The HPLC system was controlled by Borwin® 1.20 software. The optimized mobile phase in this study consisted of phosphate buffer (pH 7.2), methanol and acetonitrile (50:25:25, by v/v/v). The flow rate was fixed at 1.2 ml/min, and the column effluent was analyzed by an UV detector set at 284 nm. Aliquots (20 μl) were injected into the HPLC apparatus.

2.2.2. Validation of HPLC chromatographic method

The HPLC method was validated on the purpose of aqueous stability-indicating for rabeprazole. The validation parameters were addressed in terms of linearity, range, limit of detection, limit of quantitation, accuracy, precision, robustness and specificity.

2.2.2.1. Linearity and range. Standard calibration curves were prepared with six known concentrations of rabeprazole ranging from 0.1 to 20 μl/ml. The data of peak area versus drug concentration were treated by linear least square regression analysis.

2.2.2.2. Limit of detection and limit of quantitation. The limit of detection (LOD) and limit of quantitation (LOQ) were estimated following the same method as explained in Section 2.2.1. The signal-to-noise ratio for LOD and LOQ was considered 3:1 and 10:1, respectively.

2.2.2.3. Precision and accuracy. Intra-day precision and accuracy were determined by analysis of six different standard curves on the same day. Inter-day precision and accuracy were assessed by the triplicate analysis on 7 different days. A stock solution was prevented from light and stored at 4 °C. Working solutions for the standard curves were prepared freshly each day form the stock solution. Precision was determined by calculating the percent coefficient of variation (% CV) of peak areas. Accuracy was determined by comparing the measured concentration to its nominal value.

2.2.2.4. Robustness. The mobile phase composition consisting of phosphate buffer (pH 7.2), methanol and acetonitrile were varied in the range of ±5%, and the effects on the results were examined through their corresponding chromatograms. The robustness of the method was determined by calculating the percent coefficient of variation (% CV) of peak areas.

2.2.2.5. Specificity. The specificity of the method was ascertained by analyzing the drug-free solutions containing each excipient at a concentration of 5%. Aliquots of these drug-free samples were centrifuged and directly injected into HPLC to determine whether there was any interfering peak at the retention time of rabeprazole or its main degradation product.

2.3. Identification of rabeprazole and its main degradation product by LC/MS

Liquid chromatography–mass spectrometry (LC/MS) was used to identify rabeprazole and its main degradation product. Mass spectra were acquired using a Finnigan TSQ Quantum Ultra AM triple stage quadrupole mass spectrometer (San Jose, CA, USA) equipped with an electrospray ionization (ESI) interface. The vaporizer temperature was set at 100 °C and nitrogen was applied as the sheath gas. The heated capillary was maintained at 350 °C. Mass analysis was performed in the positive ion mode with the source current set at 5 mA; the potential of the tube lens was set at 82 V. The *m/z* scanning ranged from 100 to 500. The type of column and the mobile phase composition were consistent with the conditions described above.

2.4. Aqueous stability in the presence of pharmaceutical excipients

The stability of rabeprazole was tested in the absence and presence of the following pharmaceutical excipients: Brij® 58, Poloxamer 188, Cremophor RH 40, Gelucire 44/14 and PEG 6000. In a typical experiment, each excipient was dissolved in simulated intestinal fluid (0.05 M phosphate buffer at pH 6.8) to a concentration of 5% (w/v). The final concentration of rabeprazole was maintained at 0.2% (w/v) during the stability test. Samples were incubated in a shaking reaction incubator (BS-06, Lab. Companion, USA) at either 37 or 60 °C. At specified time intervals, the reaction was terminated with a strong alkaline liquid, 0.1% methanolic diethylamine (As mentioned earlier, rabeprazole was particularly prone to degradation at acidic/neutral pHs. To retard rabeprazole instabilization, the reaction medium pH was made to be alkaline by the use of a 0.1% methanolic diethylamine). The mixture was then centrifuged to remove insoluble materials, and the supernatant was injected into the HPLC.

2.5. Stabilizing mechanism of pharmaceutical excipients

Rabeprazole was dissolved in simulated intestinal fluid to obtain a final drug concentration of 0.2% (w/v) in the absence of excipient. Samples were incubated in a shaking reaction incubator at 37 °C for 6 h to maximize the formation of thioether-rabeprazole. Subsequently, the excipients (5%, w/v) were then dissolved in the above reaction mixtures and further incubated for 2 h. The resulting mixtures were then centrifuged to remove insoluble materials, and the concentration of thioether-rabeprazole was determined before and after the addition of each pharmaceutical excipient by HPLC without addition of 0.1% methanolic diethylamine. During stability tests, the pH of aqueous rabeprazole solutions was also monitored. The decomposition rates and shelf lives of rabeprazole were then evaluated on the assumption that it followed a first-order reaction.

2.6. Data processing

The best-fit straight line was determined by the least squares method. Data obtained from the experiments were subjected to ANOVA tests for statistical analyses. *P*-values of ≤ 0.05 were regarded as statistically significant.

3. Results and discussion

3.1. HPLC quantification of rabeprazole and its main degradation product

3.1.1. Validation of HPLC method

Chromatographic determinations of rabeprazole and its metabolites have been reported elsewhere (Nakai et al., 1994; Miura et al., 2005). However, no study has reported a simple *in vitro* method enabling dual determination of rabeprazole and its main degradation product. The following are the results of the validation of our HPLC analytical methodology. Table 1 summarizes chromatographic validation parameters.

3.1.1.1. Linearity and range. The calibration graph over the concentration range of 0.1–20 μg/ml was found to be linear. Linearity was evaluated by determining six standard working solutions containing 0.1, 0.5, 1, 5, 10 and 20 μg/ml of rabeprazole sodium in six replicates. Peak area and concentration was subjected to least square linear regression analysis to calculate the correlation coefficient, slop and intercept. A good linear relationship was validated by the high value of correlation coefficient ($r^2 = 0.99999$). The slop obtained was 3.8×10^{-5} and the intercept was 1.3×10^{-2}. The data were validated by means of variance analysis (ANOVA), which showed no significant difference in the linearity deviation ($P < 0.05$).

Table 1
Summary of chromatographic validation parameters

Parameter	Data
Linearity range (μg/ml)	0.1–20
Correlation coefficient	0.99999 ± 0.00001
Slop	$3.8 \times 10^{-5} \pm 1.1 \times 10^{-7}$
Intercept	$1.3 \times 10^{-2} \pm 1.6 \times 10^{-2}$
Limit of detection (ng/ml)	10
Limit of quantitation (ng/ml)	20
Robustness (% CV)	1.7
Specificity	Specific

Table 2
Precision and accuracy of intra-day and inter-day for chromatographic validation

Concentration (μg/ml)	Intra-day ($n=6$)		Inter-day ($n=3$)	
	Precision (%)	Accuracy (%)	Precision (%)	Accuracy (%)
0.1	0.7	101.1 ± 0.6	1.3	100.6 ± 0.9
0.5	0.8	99.0 ± 0.8	1.5	100.3 ± 1.5
1	0.5	101.4 ± 0.5	1.4	100.5 ± 1.1
5	0.3	100.7 ± 0.3	1	100.0 ± 0.8
10	0.5	100.9 ± 0.5	0.7	100.3 ± 0.6
20	0.4	99.8 ± 0.4	0.4	99.7 ± 0.2

3.1.1.2. Limit of detection and limit of quantitation. The LOD and LOQ were validated to be 10 and 20 ng/ml.

3.1.1.3. Robustness. The percentage CV of peak areas calculated for variation in the mobile phase composition (±5%) was found to be less than 2%. The low values of % CV as shown in Table 1 supported the robustness of this analytical method.

3.1.1.4. Specificity. No significant interfering peaks were observed at the retention times of either rabeprazole or its main degradation product in drug-free solutions containing each excipient (5%).

3.1.1.5. Precision and accuracy. The precision and accuracy was determined at six different concentration levels and expressed in terms of % CV of rabeprazole peak area (Table 2). The % CV values for both intra-day ($n=6$) and inter-day ($n=3$) on seven different days were all found to be less than 2%. Also, this proposed method was found to afford the accuracy of 99–102%.

3.1.2. Application of the HPLC method to quantification of rabeprazole and its main degradation product

Fig. 2 shows typical chromatograms of aqueous rabeprazole solutions incubated at 37 °C for up to 60 min in the absence of any stabilizing excipients. The amount of rabeprazole (retention time = 5.4 min) decreased rapidly, whereas the content of a main degradation product (retention time = 14.2 min) increased. Interestingly, our HPLC analysis provided that the addition of Brij® 58 into the aqueous rabeprazole solution reduced the amount of the main degradation product. Also, Brij® 58 did not accompany any peak interfering rabeprazole and its main degradation product.

3.2. Identification of rabeprazole and its main degradation product by LC/MS

Unlike other PPIs, rabeprazole is reduced to thioether-rabeprazole via a non-enzymatic pathway. Thioether-rabeprazole is a potent inhibitor of H. pyroli growth (Fujioka et al., 1993). To characterize the main degradation peak observed in Fig. 2, LC/MS was employed in this study. The signal intensity of rabeprazole in the positive mode was reported to be much higher than that in the negative mode, due to the

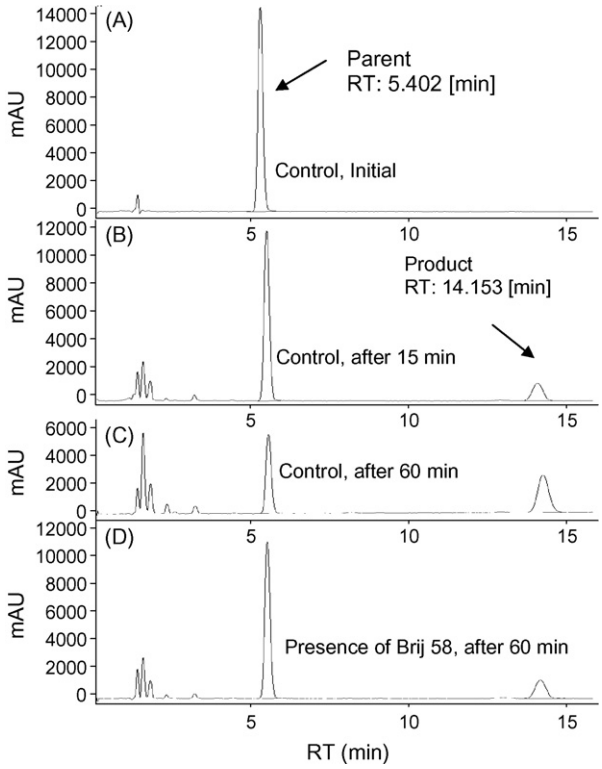


Fig. 2. HPLC chromatograms of rabeprazole solutions incubated for (A) 0, (B) 15 and (C) 60 min in the absence of excipient and (D) 60 min in the presence of Brij® 58.

three nitrogens in its structure (Zhang et al., 2004). As seen in Fig. 3, an intense peak appeared in the positive ion mode. The ion spectrum of rabeprazole had a protonated molecular ion $[M+H]^+$ that was identified at *m/z* 360. Also, the ion spectra of $[M+Na]^+$ and $[M+K]^+$ were observed at *m/z* 382 and 398, respectively (Fig. 3A). In comparison, the ion spectrum of the degradation product had a protonated molecular ion $[M^+ + H]^+$ at *m/z* 344. Its corresponding $[M+Na]^+$ and $[M+K]^+$ spectra were at *m/z* 366 and 382 (Fig. 3B). These data prove that the major degradation product observed in Fig. 2 is thioether-rabeprazole with the molecular formula of 2-[[4-(3-methoxypropoxy)-3-methylpyridine-2-yl]methylthio]-1*H*-benzimidazole. Therefore, the chromatographic method developed in this study was used to simultaneously measure the amounts of rabeprazole and thioether-rabeprazole.

3.3. Effect of pharmaceutical excipients on the aqueous stability of rabeprazole

Rabeprazole stability results were attained by incubating aqueous solutions at 37 and 60 °C for 60 min (Fig. 4). When the test medium did not contain any pharmaceutical excipients, the concentration decreased to 45.38 ± 4.75%. At the same time, a considerable amount (16.68 ± 3.62%) of thioether-rabeprazole was detected. Also, the aqueous stability of rabeprazole was affected by temperature and at 60 °C, the drug degraded

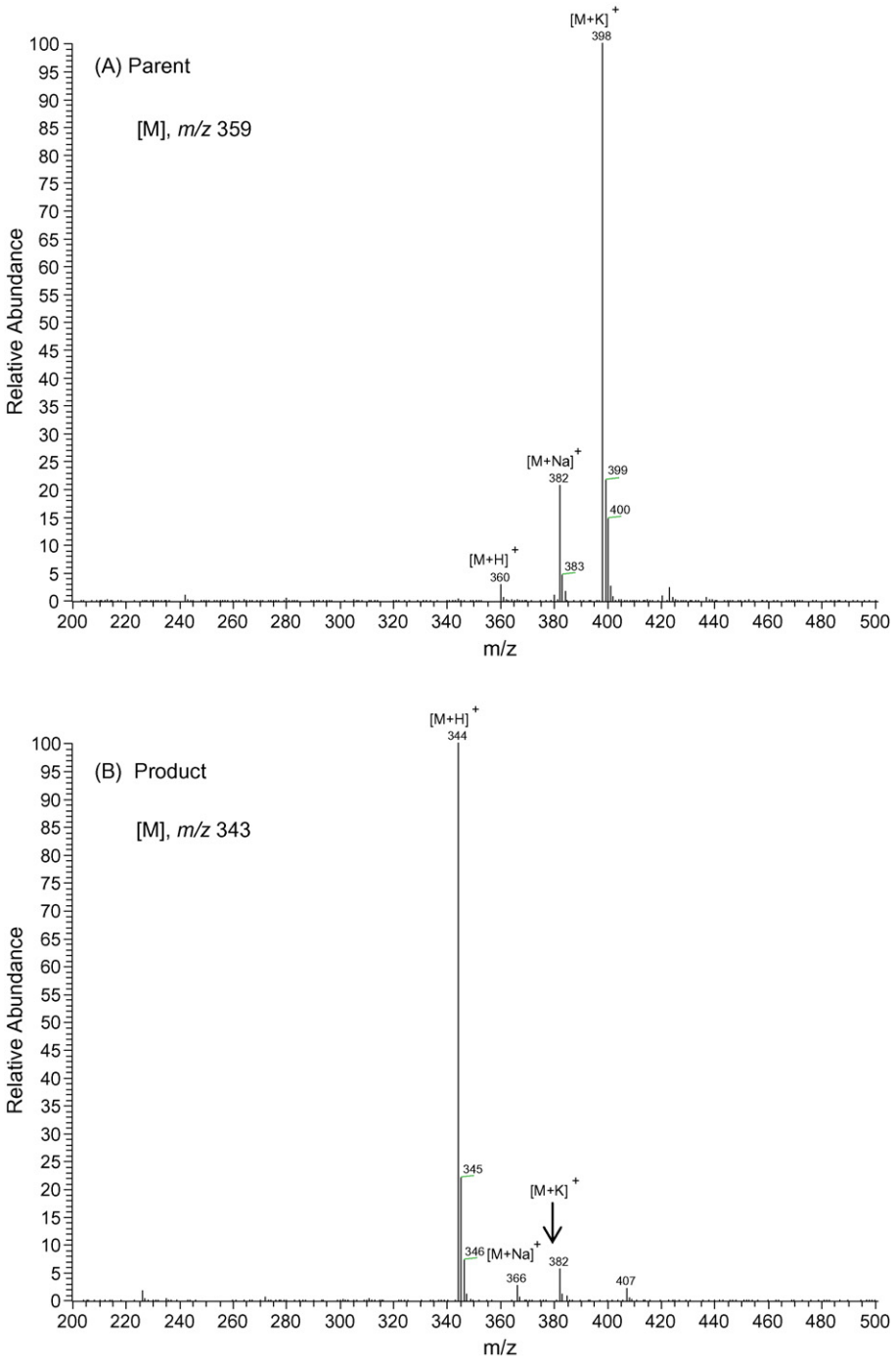
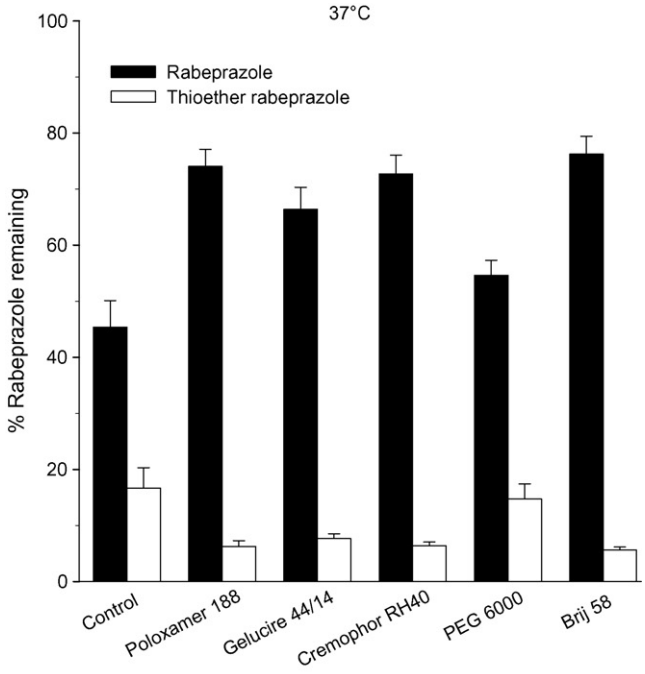


Fig. 3. Identification of rabeprazole and its main degradation product by LC/MS.

more dramatically. However, the addition of pharmaceutical excipients to the aqueous rabeprazole solution improved its stability. Among various excipients, the greatest stabilizing effect was attained with Brij® 58. Fig. 5 shows the amount of rabeprazole remaining and thioether formed as a function of time. At the absence of any pharmaceutical excipients, the decreased amount of rabeprazole (6.5 ± 2.2) was accompanied by the increased amount of thioether-rabeprazole (23.3 ± 4.0), however, the enhanced amount of rabeprazole (61.1 ± 3.2) accompanied by the inhibited amount of thioether-rabeprazole (8.5 ± 2.1) was found at the presence of Brij® 58 in the test medium after incubation at 60 °C for 60 min. Therefore, the stabilizing effect of Brij® 58 was proved by evaluating both the mass of drug remaining and the main degradation product forming. However, it should be mentioned that combined value (69.6%) of the 60 min data does not account for 100% mass balance. This means that the thioether form of rabeprazole is one of several degradation products. The identification of other degradation products deserves further investigation.



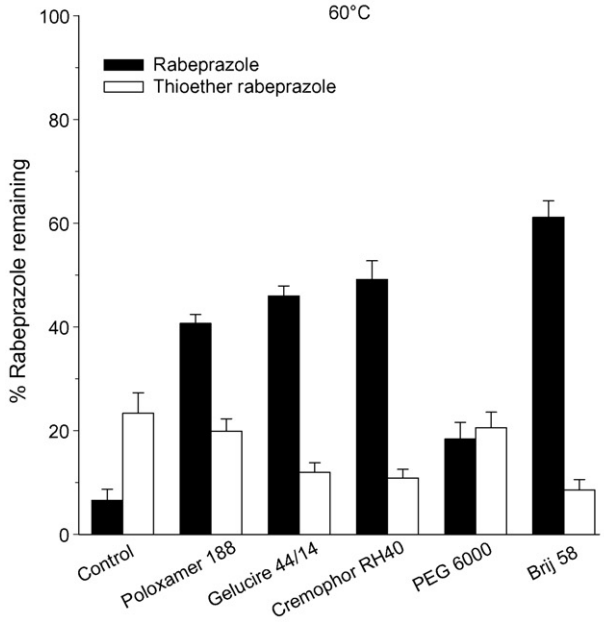


Fig. 4. Effects of excipients on the amounts of rabeprazole and thioether-rabeprazole after 60 min incubation at 37 and 60 °C, respectively. Closed bar indicates the percentage of rabeprazole remaining, while the open bar shows the formation of thioether-rabeprazole, as determined by HPLC analysis. The data obtained in the absence of excipient were expressed as control.

3.4. Effect of pharmaceutical excipients on degradation kinetics of rabeprazole

The accelerated testing method for pharmaceutical products that is based on principles of chemical kinetics was used to measure the stability of the drug under said conditions (Santoro et al., 1992; Sabry et al., 2003). To estimate the kinetic parameters of rabeprazole in the absence or presence of excipients, the logarithm of % residual rabeprazole was plotted versus time. The

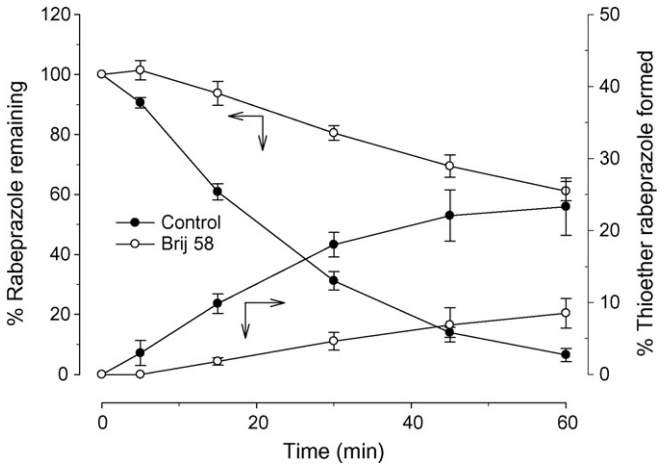


Fig. 5. Changes in the amounts of rabeprazole and thioether-rabeprazole at 60 °C as a function of incubation time. Ascending curves demonstrate the degradation patterns of rabeprazole, while descending curves indicate the formation patterns of thioether-rabeprazole. The stability studies of rabeprazole were carried out in the absence (●) and presence (◯) of Brij® 58. Inhibition by Brij® 58 were expressed as not only the degradation of rabeprazole but also the formation of thioether-rabeprazole.

data were then curve-fitted by linear regression analysis. Fig. 6 shows typical degradation profiles of rabeprazole in the presence of pharmaceutical excipients at both 37 and 60 °C. All plots were linear at both temperatures, indicating that the degradation of rabeprazole followed first-order kinetics. From the slopes of the straight lines, rate constants (k) and half-lives ($t_{1/2}$) were calculated. Calculation of Ea is also possible at 37 and 60 °C according to the Arrhenius equation. The kinetic parameters obtained are given in Table 3. ANOVA analysis substantiated that the solution stability of rabeprazole was statistically improved by addition of pharmaceutical excipients.

3.5. Stabilizing mechanism of pharmaceutical excipients

Comparison of the retention times of rabeprazole and its thioether form suggests that the latter is more hydrophobic than the former (see Fig. 2). In fact, thioether-rabeprazole gradually saturated and then precipitated out of the stability test medium as incubation progressed. The continuous phase separation of thioether-rabeprazole from the aqueous phase due to its poor aqueous solubility was considered as one factor to facilitate the reaction. Therefore, it was anticipated that preventing the phase

Table 3
Degradation rate constant (k), half life ($t_{1/2}$) and activation energy (E_a) obtained from solution kinetics of rabeprazole with or without pharmaceutical excipients

Excipient	37 °C		60 °C		E_a (kJ mol^{-1})
	k (h^{-1})	$t_{1/2}$ (h)	k (h^{-1})	$t_{1/2}$ (h)	
Control	0.75	0.93	2.78	0.25	49.05
Poloxamer 188	0.37	1.86	0.91	0.76	33.36
Gelucire 44/14	0.29	2.39	0.77	0.90	36.61
Cremophor RH40	0.26	2.64	0.72	0.96	37.58
PEG 6000	0.50	1.39	1.75	0.39	47.05
Brij® 58	0.22	3.13	0.53	1.32	32.28

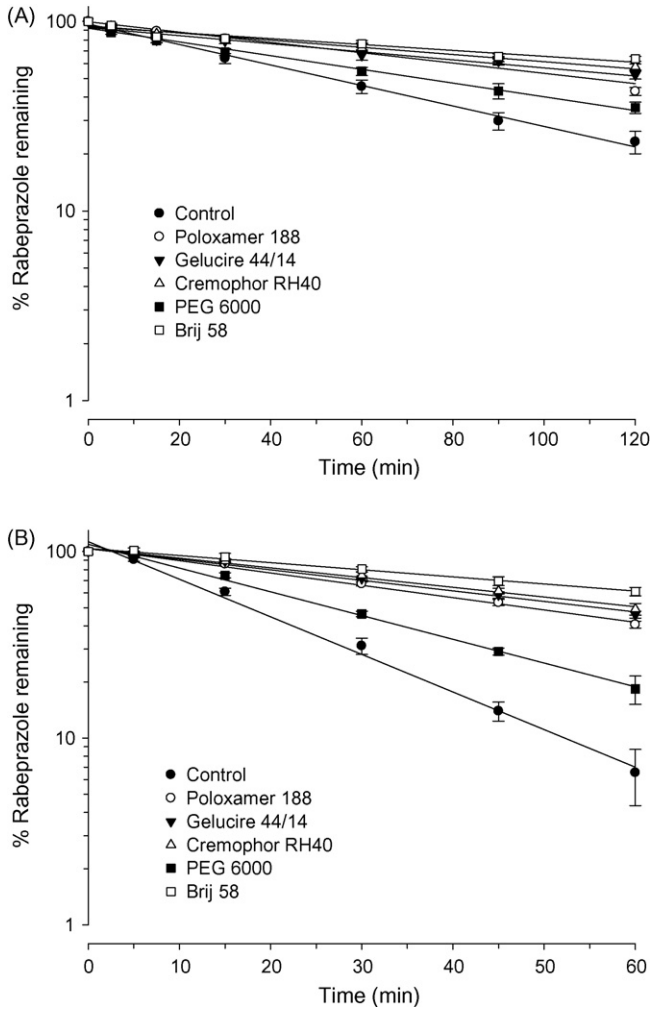


Fig. 6. Logarithm of percentage of rabeprazole remaining against incubation time, assuming first-order degradation plots at (A) 37 and (B) 60 °C, respectively.

separation of thioether-rabeprazole would inhibit the destabilization of rabeprazole. To test this concept, the concentrations of solubilized thioether-rabeprazole in the reaction mixtures were measured before and after addition of an excipient to the medium. Table 4 indicates that the concentration of solubilized thioether-rabeprazole might affect the aqueous stability of rabeprazole. The ratio of the concentration of solubilized thioether-rabeprazole in the presence of an excipient to that in its absence was termed the solubilization ratio. Interestingly, PEG 6000 displaying the poorest stabilizing effect provided the smallest solubilization ratio (1.87 ± 0.02). This could be contributed to its hydrophilic characteristics in comparison with the other excipients which are all nonionic surfactants possessing amphipathic characteristics. Therefore, PEG 6000 lacks the surface active property to solubilize thioether-rabeprazole in an aqueous medium. In addition, PEG 6000 was widely reported to enhance drug dissolution as a hydrophilic carrier by making solid dispersions (Cirri et al., 2007). Accordingly, the slightly increased solubility of thioether-rabeprazole after incorporation of PEG 6000 may be due to its macromolecular structure that serves as a carrier.

Hydrophile-lipophile balance (HLB) value can be used as an empirical index to select various surfactants (Lin, 1996; Dinarvand et al., 2005; Okubo et al., 2006). According to the classical HLB scale, surfactants with HLB values higher than 9 are hydrophilic and act as O/W emulsifiers and solubilizing agents. Because all the surfactants selected in the present study have relatively high HLB values, it was expected that they would provide considerable solubilizing effects on thioether-rabeprazole in the testing media. Interestingly, Poloxamer 188 with the highest HLB value did not serve as a best solubilizer for thioether-rabeprazole. It is likely that one of the stabilizing mechanisms of these hydrophilic polymeric surfactants could be explained in terms of their solubilizing efficiency on thioether-rabeprazole accompanied by optimal HLB values.

On the other hand, critical micelle concentration (CMC) is another frequently used surfactant property. Above this concentration, polymers present in their surfactants form micelles (Zhong et al., 1992; Heerklotz and Seelig, 2000). In the present study, all the surfactants had lower cmc values than their operating concentrations (5%, w/v) as shown in Table 4. As a result, all the surfactants formed micelles in the aqueous solutions. Furthermore, Poloxamer 188 having a highest HLB value failed to provide the best solubilizing effect might be contributed to its relatively high CMC value. Furthermore, Brij® 58 has the lowest CMC value (0.0004%, m/v) so that it would give better possibility for forming micelles to solubilize more thioether-rabeprazole than the others. This event seems to contribute to stabilizing rabeprazole against chemical degradation in the aqueous solution.

The monitoring of the stability test medium pH under various conditions proved that its pH was not affected after addition of the excipients (Table 4). It was thus concluded that the stabilizing effect of these pharmaceutical excipients on the degradation of rabeprazole in aqueous solution is attributed to the combination of their physicochemical properties in terms of amphipathic property, HLB and CMC value.

Table 4
Physicochemical properties of pharmaceutical excipients and their solubilizing effect on thioether-rabeprazole

Excipient	MW	HLB	CMC (%, w/v)	Apparent pH	Solubilization ratio[a]
Poloxamer 188	7680–9510	29	0.096–0.118	6.994 ± 0.004	5.19 ± 0.16
Gelucire 44/14	–	14	0.03	6.948 ± 0.002	5.20 ± 0.07
Cremophor RH40	7000–9000	14–16	0.039	6.968 ± 0.001	4.78 ± 0.09
PEG 6000	7300–9300	–	–	7.011 ± 0.001	1.87 ± 0.02
Brij® 58	1122	15.7	0.00044	6.970 ± 0.001	5.62 ± 0.36

[a] Solubilization ratio indicates the ratio of solubilized thioether-rabeprazole concentration in the presence of pharmaceutical excipients to that in the absence of pharmaceutical excipient.

4. Conclusions

The present study demonstrates the stabilizing effect of several pharmaceutical excipients on rabeprazole stability in simulated intestinal fluid. Among various excipients, Brij® 58 exhibited the most powerful stabilizing effect on rabeprazole. Such formulations could stabilize rabeprazole in the intestinal tract, thereby improving its bioavailability. Also, the simple and efficient HPLC methodology developed in this study made it possible to measure rabeprazole and its main degradation product, thioether-rabeprazole. This would permit easy comparisons of the stabilizing effects of a variety of excipients on the aqueous rabeprazole stability.

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