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Chemical Stability and Mechanism of Degradation of Omeprazole in Solution

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ABSTRACT: The chemical stability and kinetics of omeprazole in buffer solutions at various pH values, 5.0, 7.0, 8.0, and 10.0, were studied at three different stress conditions, 25, 40, and 50 °C. It was found that the degradation reaction followed the pseudo first-order kinetics and was quite rapid at low pH values with a half-life of 43 min at pH 5.0 and 25 °C. In alkaline pH of 10.0 the drug was however remarkably stable with a half-life of 2.8 months at 25 °C. The energy of activation was pH-dependent and varied from 9.9 - 19.6 kcal/mol. The pH-log rate profiles in association with other thermodynamic activation parameters suggested that the main pathway of degradation reaction would be the hydrolysis with depending on hydronium ion concentration involving bimolecular reaction.

Key words: Omeprazole, stability, chemical kinetics, mechanism of degradation

INTRODUCTION

Omeprazole, a substituted benzimidazole, is the selective proton pump inhibitor in the gastric mucosa (1), which has become one of the best-selling pharmaceuticals worldwide. It was the first proton pump inhibitor to be marketed in Thailand and many other countries. The licensed indications and uses of omeprazole have increased significantly in various conditions requiring suppression of gastric acid secretion (2).

Omeprazole is very slightly soluble in water, but is highly soluble in alkaline solutions as the negatively charged ion. It is an ampholyte with $pK_a = 4$ (pyridinium ion) and 8.8 (benzimidazole). Since in solution omeprazole degrades rapidly at low pH values (3, 4), it is usually marketed as a gastro-resistant formulation in the form of enteric-coated beads containing the active ingredient. The beads are subsequently filled into capsules and packed in air-tight bottle with desiccant.

Despite its importance as a therapeutic agent and its known instability, very few stability investigations have been reported on omeprazole (3, 4). This study, therefore, was carried out to investigate the chemical kinetics as well as mechanism of degradation of this drug substance under various pH's and temperatures.

EXPERIMENTAL

Materials

Omeprazole used in this study was obtained from Astra Hassle, Sweden. Sodium tetraborate, potassium dihydrogen phosphate and potassium monohydrogen phosphate were from Merck and Riedel-De Haen Ag Seelze, Germany, respectively. Methanol was of HPLC grade and was obtained from J.T. Baker, U.S.A. Methylene chloride and ammonium hydroxide solution were of analytical grade and were obtained from Merck, Germany. All other chemicals were of analytical grade.

Chemical Stability and Kinetic Studies of Omeprazole in Solutions

The chemical stability and kinetics of omeprazole at pH 5.0, 7.0, 8.0, and 10.0 were studied at three different thermal stress conditions, 25, 40, and 50 °C. Aqueous solutions of omeprazole were prepared in phosphate buffers at pH 5.0, 7.0, and 8.0 with concentration of 100 mg/ml, and in borate buffer at pH 10.0 with concentration of 350 mg/ml. The concentration of all buffers used was 0.05 M. All of these solutions were filled and sealed in amber glass ampuls and stressed in water bath at constant temperature. Samples taken at

appropriate time intervals were assayed for omeprazole by using high-performance liquid chromatographic (HPLC) method.

Analysis of Omeprazole

The omeprazole concentration in the stressed samples was analyzed using a modification of the HPLC procedure described by Persson et al. (5). A 40-ml sample was injected into the HPLC system which consisted of a multiple solvent delivery system (Milton Roy CM 4000, U.S.A.), a sampling injector system (Milton Roy Auto Injector A 1000, U.S.A.), a programmable wavelength detector (Milton Roy LDC Analytical SM 4000, U.S.A.), and an integrator (Milton Roy CI-10B, U.S.A.). The pre-column (Silica, 5 mm, 30 mm length) and the column (Lichrosorb SI 60, 5 mm, 125 x 4 mm) were used. The compounds were eluted with a mobile phase of methylene chloride containing 2.5 % v/v of 5 % v/v concentrated ammonium hydroxide in methanol. The flow rate was 1.0 ml/min and the peak response was monitored with UV detection at 280 nm. The retention time of omeprazole was 10 min.

RESULTS AND DISCUSSION

Rate of Degradation Reaction

It was found that omeprazole degraded quite rapidly in aqueous solutions especially at low pH values as shown in Figures 1 - 4, which are the typical pseudo first-order plots of omeprazole degradation at 25, 40, and 50 °C in buffer solutions of pH 5.0, 7.0, 8.0, and 10.0, respectively. Table 1 and 2 compile the pseudo first-order rate constants (k) and half-lives ($t_{1/2}$) of omeprazole degradation reaction in buffer solutions at specified pH's and temperatures, respectively. It is noted that the half-life of omeprazole in solution at pH 10.0 is appreciably long as about 3 months. Figure 5 shows the pH-log rate profiles of omeprazole at 3 different temperatures, revealing that the decomposition reaction was highly influenced by pH within the pH range studied. This indicates the acid-catalyzed hydrolysis. Since the pK_a of benzimidazole entity is 8.8, the possible degradation at pH below pK_a suggested hydrolysis with depending on hydronium ion concentration.

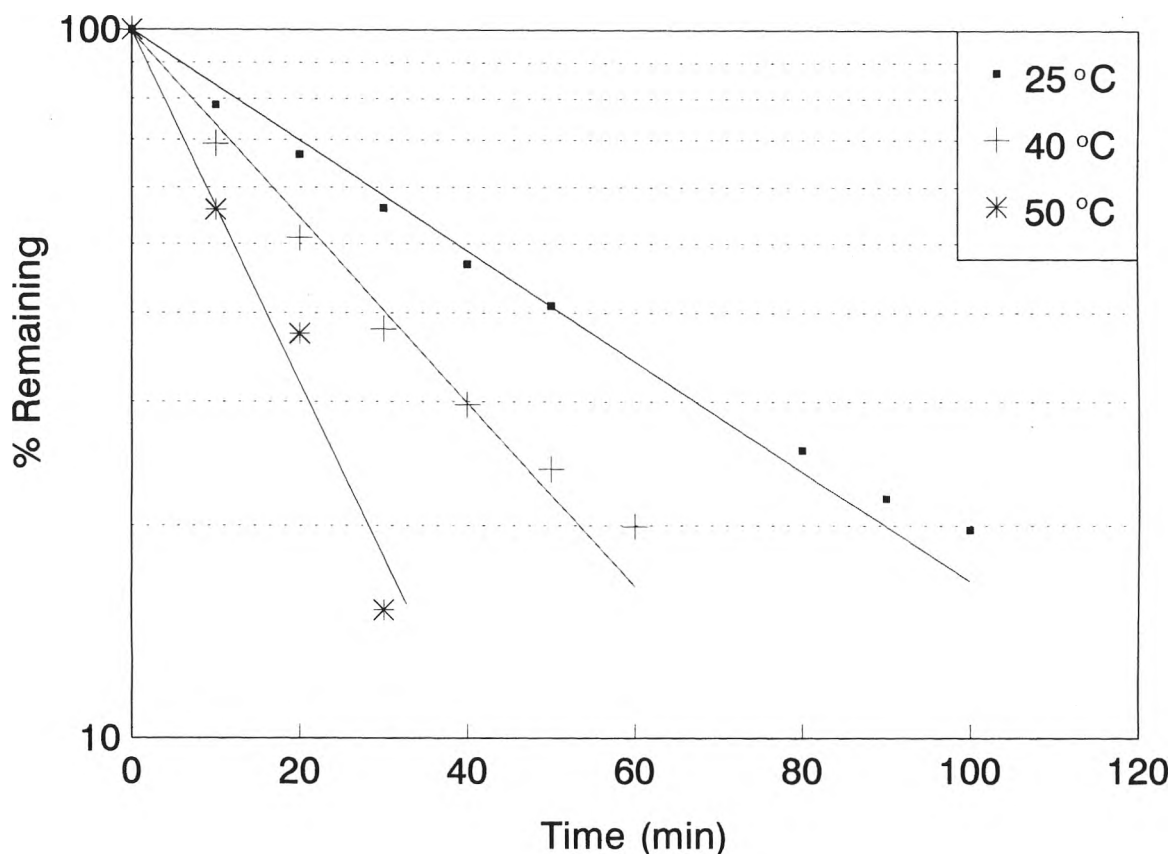


Figure 1 Typical pseudo first-order plots of omeprazole degradation at various temperatures in buffer solution with pH 5.0

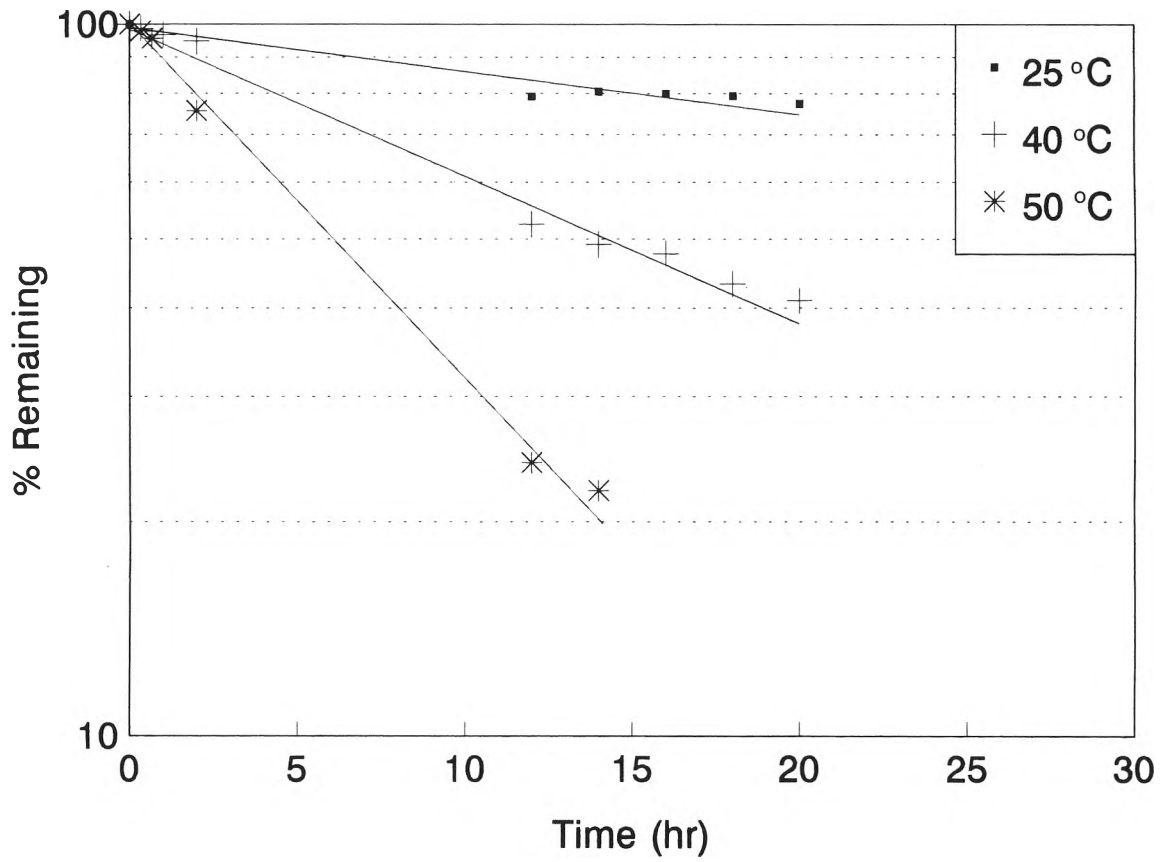


Figure 2 Typical pseudo first-order plots of omeprazole degradation at various temperatures in buffer solution with pH 7.0

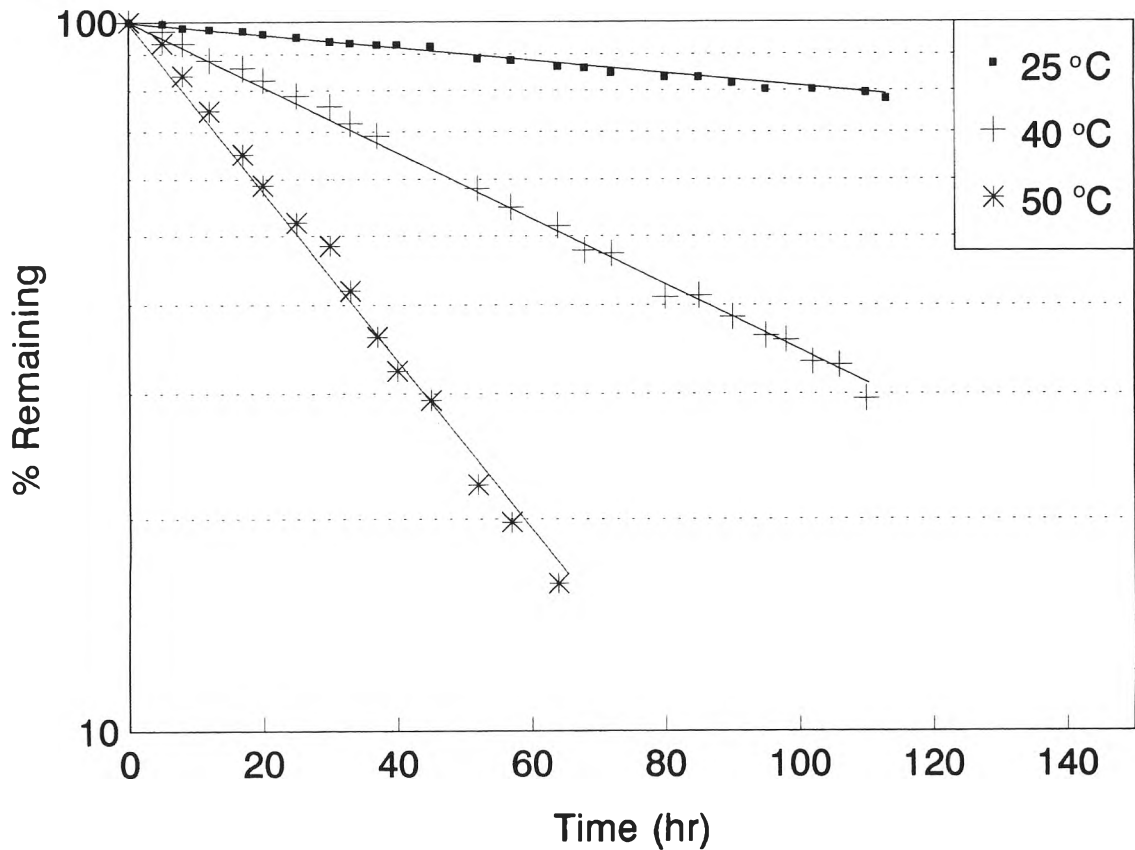


Figure 3 Typical pseudo first-order plots of omeprazole degradation at various temperatures in buffer solution with pH 8.0

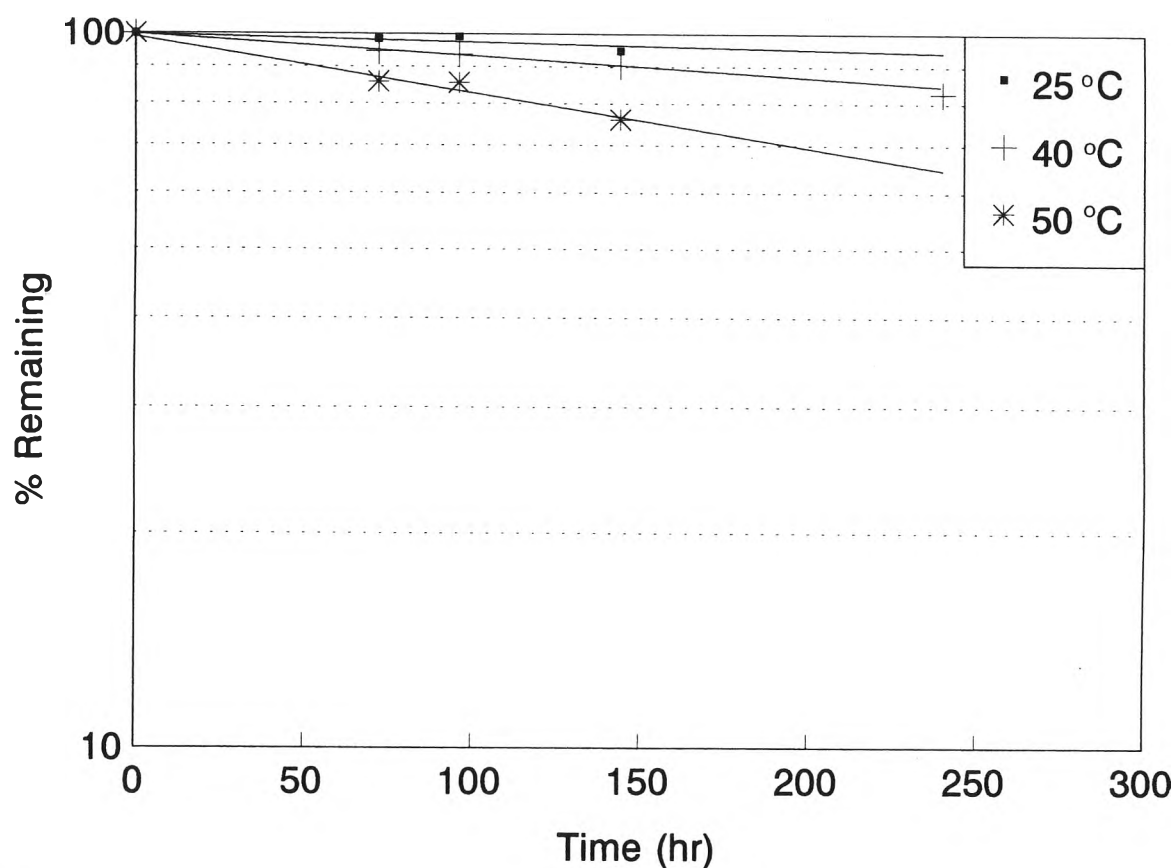


Figure 4 Typical pseudo first-order plots of omeprazole degradation at various temperatures in buffer solution with pH 10.0

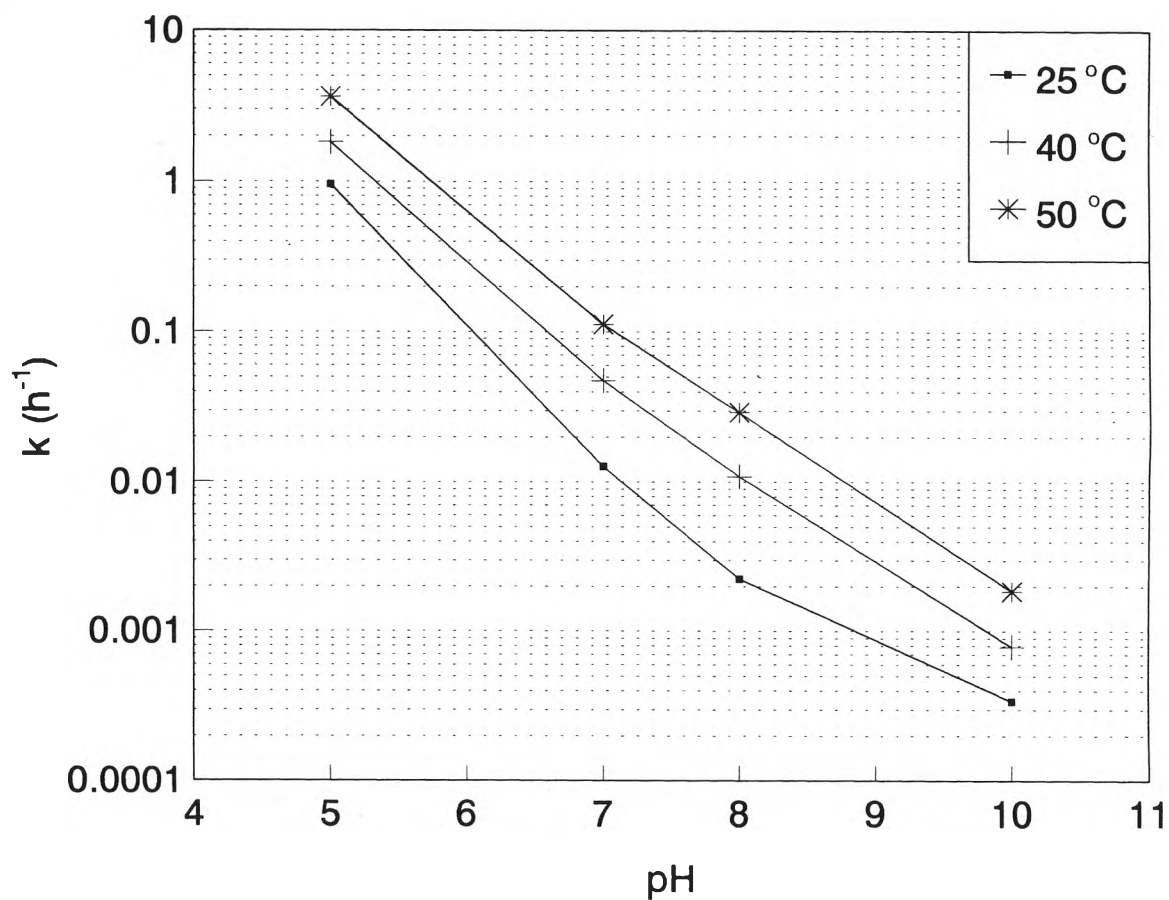


Figure 5 pH-log rate profiles of omeprazole at various temperatures

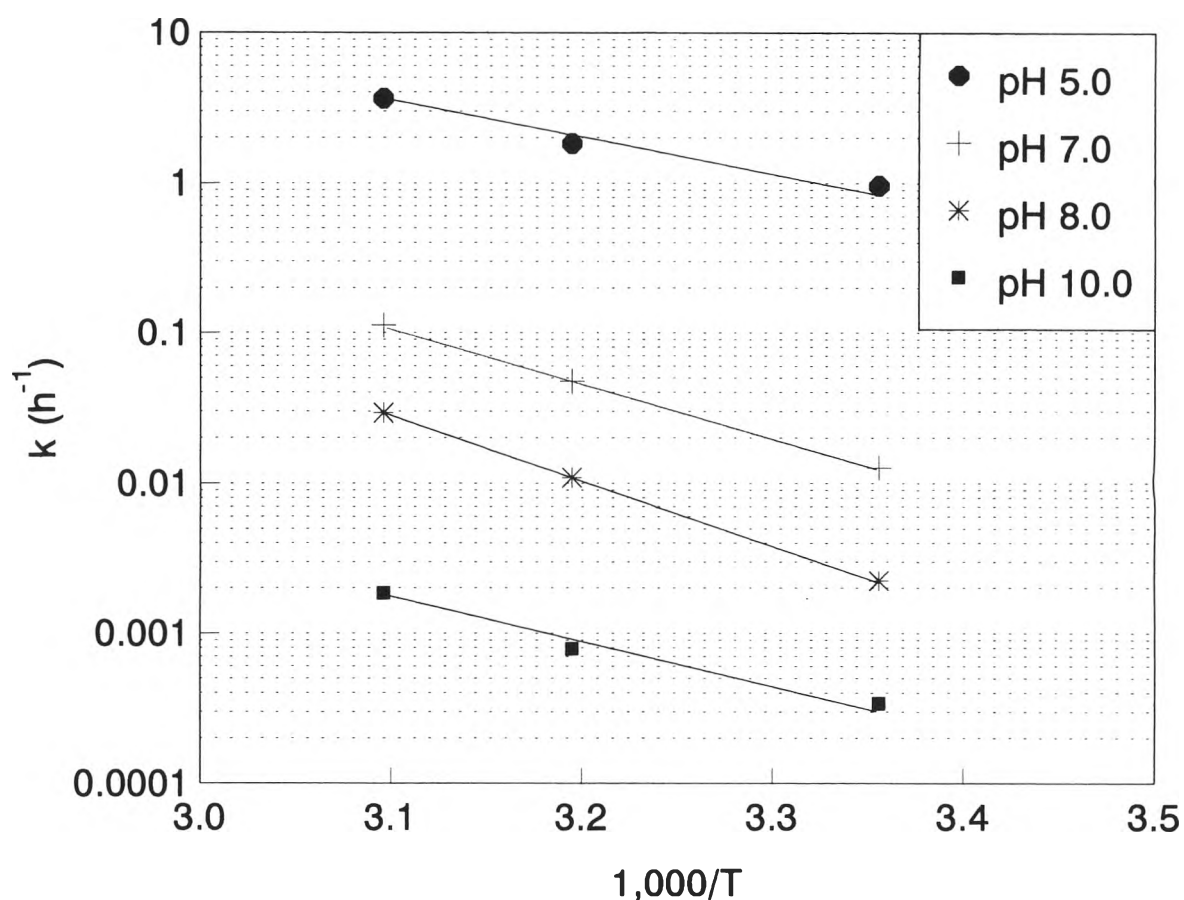


Figure 6 Arrhenius plots of omeprazole degradation at various pH's

Table 1. Pseudo First-Order Rate Constants (k) of Omeprazole Degradation Reaction in Buffer Solutions at Various pH's and Temperature

pH	k (h ⁻¹) at Various Temperatures (r ²)		
	25 °C	40 °C	50 °C
5.0	9.60 x 10 ⁻¹ (0.9180)	1.82 (0.9004)	3.63 (0.9577)
7.0	1.27 x 10 ⁻² (0.8888)	4.74 x 10 ⁻² (0.9764)	1.12 x 10 ⁻¹ (0.9756)
8.0	2.24 x 10 ⁻³ (0.9920)	1.09 x 10 ⁻² (0.9826)	2.92 x 10 ⁻² (0.9539)
10.0	3.40 x 10 ⁻⁴ (0.7215)	7.85 x 10 ⁻⁴ (0.9955)	1.85 x 10 ⁻³ (0.9762)

Table 2. Half-Lives (t_{1/2}) of Omeprazole in Buffer Solutions at Various pH's and Temperature

pH	t _{1/2} at Different Temperatures		
	25 °C	40 °C	50 °C
5.0	43 min	23 min	11 min
7.0	55 h	15 h	6 h
8.0	13 days	64 h	24 h
10.0	2.8 months	37 days	16 days

Temperature Dependence and Mechanistic Interpretation of Degradation Reaction

In order to investigate the effect of temperature on degradation of omeprazole, the treated kinetic data at all temperatures studied were employed in Arrhenius plots as shown in Figure 6. The energy of activation (E_a) values were obtained from the slopes of these plots. All other thermodynamic activation parameters, *i.e.*, enthalpy of activation (ΔH^\ddagger), Gibbs free energy of activation (ΔG^\ddagger), and entropy of activation (ΔS^\ddagger), were calculated according to the following Equations 1 - 3,

$$\Delta H^\ddagger = E_a - RT \quad (\text{Eq. 1})$$

$$\Delta G^\ddagger = -RT \ln (kh/ k_b T) \quad (\text{Eq. 2})$$

$$\Delta S^\ddagger = (\Delta H^\ddagger - \Delta G^\ddagger)/ T \quad (\text{Eq. 3})$$

Table 3. Thermodynamic Activation Parameters of Omeprazole Degradation

pH	E_a (kcal/mol)	ΔH^\ddagger (kcal/mol)	ΔG^\ddagger (kcal/mol)	ΔS^\ddagger (cal/mol/k)
5.0	9.94	9.35	22.33	- 43.51
7.0	16.62	16.03	24.89	- 29.70
8.0	19.63	19.04	25.92	- 23.08
10.0	12.74	12.15	27.03	- 49.94

The large positive values of Gibbs free energy of activation (ΔG^\ddagger) in Table 3 reflect the non-spontaneous nature of such degradation reaction and certain amount of energy must be required before it is capable of undergoing reaction. The values of enthalpy of activation (ΔH^\ddagger) shown in Table 3, which according to the Transition State Theory represent the net result of energy release or uptake during simultaneous bond forming and breaking when the activated complex is formed. This is consistent with the extent of the bimolecular reaction taking place during the transition state.

Moreover, the entropy of activation (ΔS^\ddagger), which takes into account the steric factor and the proper orientation of reactant molecules with adequate energy in order for the reaction to occur, in this case exhibits large negative values especially at low pH. This is to be expected for a reaction involving large and somewhat complex molecules like omeprazole since more molecular orientation prior to reaction is likely to be required. The values of ΔS^\ddagger are larger at high concentration of hydronium ions than at low concentration. This may be attributed to the tremendous reduction in disorder of the

system when bringing 2 species together to form the activated complex.

where R is the gas constant (1.987 cal/mol/K), T is temperature in degree Kelvin (K), k is the pseudo first-order rate constant of degradation reaction, h is the Planck constant (6.626×10^{-34} Js), and k_b is the Boltzmann constant (1.381×10^{-23} J/K).

The values of these thermodynamic activation parameters are given in Table 3. It can be seen that the energy of activations (E_a) of omeprazole decomposition at various pH's have the magnitude within the range of 9.9 - 19.6 kcal/mol, indicating the solvolytic type of reaction (6). The values of E_a are also shown to gradually increase with increasing pH up to the pK_a of benzimidazole moiety (8.8) of omeprazole. These results suggest that the reaction is likely to be catalyzed by acid pH.

system when bringing 2 species together to form the activated complex.

CONCLUSION

The degradation reaction of omeprazole in solution was experimentally found to follow the pseudo first-order kinetics and seemed to be acid-catalyzed reaction. The order of magnitude of the activation energy and thermodynamic activation parameters indicate bimolecular solvolytic type of reaction.

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ความคงตัวของคีมีและกลไกการเสื่อมสลายของโอมิพราโซลในสารละลาย

650/97 น โอมิพราโซล

ณรงค์ สาริสุต ทัดทรง ท้วทพิย และ ศิริพจน์ เชื้อเจริญ

ภาควิชาเภสัชอุตสาหกรรม คณะเภสัชศาสตร์ มหาวิทยาลัยมหิดล กรุงเทพฯ 10400

บทคัดย่อ: จากการศึกษาความคงตัวและจลนศาสตร์ทางเคมี ของยาโอมิพราโซล ในสารละลายบัฟเฟอร์ค่า pH ต่างๆ คือ 5.0, 7.0, 8.0, และ 10.0 ที่อุณหภูมิ 25 °, 40 °, และ 50 ° ซ. พบว่าปฏิกิริยาการเสื่อมสลายเป็นไปตาม จลนศาสตร์อันดับหนึ่งปรากฏ และมีอัตราเร็วสูงที่ค่า pH ต่ำ โดยมีค่าครึ่งชีวิตเท่ากับ 43 นาที ที่ pH 5.0 และอุณหภูมิ 25 ° ซ. ส่วนใน pH เป็นดั่งที่ 10.0 ยากลับมีความคงตัวสูง โดยมีค่าครึ่งชีวิตเท่ากับ 2.8 เดือน ที่ 25 °ซ. นอกจากนี้ยังพบว่าค่าพลังงานก่อกัมมันต์เปลี่ยนแปลงไปตาม pH และมีค่าอยู่ในช่วง 9.9 - 19.6 กิโลแคลลอรี่/โมล จากการพิจารณาโปรไฟล์ของ pH กับอัตราเร็ว ร่วมกับ ค่าปัจจัยทางเทอร์โมไดนามิกส์ ของการเกิดปฏิกิริยา บ่งชี้ว่า วิธีทางที่สำคัญของปฏิกิริยาการเสื่อมสลายควรจะเป็น ไฮโดรไลซิส ที่ขึ้นกับความเข้มข้นของอนุมูลกรด และเกิดจากโมเลกุล 2 ชนิด เข้าทำปฏิกิริยากัน

กัญแจคำ: โอมิพราโซล ความคงตัว จลนศาสตร์ทางเคมี กลไกการเสื่อมสลาย