DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY, 21(8), 965-971 (1995)

STABILITY OF OMEPRAZOLE SOLUTIONS AT VARIOUS PH VALUES AS DETERMINED BY HIGH-PERFORMANCE LIQUID CHROMATOGRAPHY

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ABSTRACT

A stability-indicating HPLC assay method for the quantitation of omeprazole has been developed. The developed method was used to study the effect of pH on the stability of omeprazole and to quantify the drug in capsules. The excipients present in the capsules did not interfere with the assay procedure. The pH-rate profile curve indicated that the maximum stability was at pH 11. Below pH 7.8, the decomposition was very fast. The decomposition constants have a direct relationship with the H^+ concentrations of the solutions.

INTRODUCTION

Omeprazole (Fig 1) is available as sustained release capsules. It is used against gastric ulcers. It is a new antisecretory compound that acts differently from the anticholinergics or H_2 histamine antagonistics. It is a gastric acid-pump inhibitor and acts by suppressing the gastric acid secretion by specific inhibition of the H^+/K^+ ATPase enzyme system at the secretory surface of the gastric parietal cell (1).

The purpose of these investigations was to i) develop a stability-indicating high performance liquid chromatography method for the quantitation of omeprazole, ii) quantify it in capsules, and iii) determine the effect of pH on its stability.

EXPERIMENTAL SECTION

Chemicals and Reagents: All the chemicals and reagents were either USP-NF or ACS grade and used without further purification. Omeprazole powder (Astra

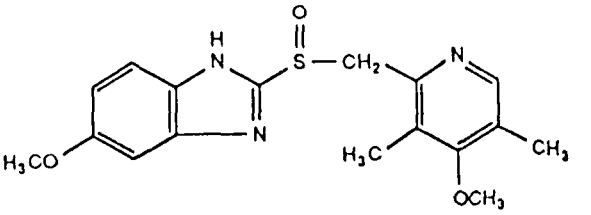

Figure 1: Structure Of Omeprazole

Hassle AB, Sweden) and methyl testosterone powder (Nutritional Biochemical Corporation) were used as received.

High-Performance Liquid Chromatography: A Waters ALC 202 HPLC system (Waters Associates, Milford, MA) equipped with a universal injector (Rheodyne Model 7125), a multiple wavelength detector (Schoeffel's SF 770, Applied Biosystems) and a recorder (Omniscribe 5213-12, Houston Instruments, TX) was used. A μBondapak C_{18} column (Waters, 30cm x 3.9mm i.d., 10μm) was the stationary phase. The mobile phase contained 40% (v/v) acetonitrile in 0.02M ammonium acetate in water (pH 7.1). The flow rate was 1.7 ml/min, and the sensitivity was 0.1 AUFS at 235 nm, the chart speed was 30.5 cm/h and the temperature ambient. The injection volume was 20 μl.

Preparation of Stock and Standard Solutions For the quantitation of capsules: The stock solution of omeprazole (1.0 mg/ml) was prepared in methanol. Before bringing to final volume, the pH was adjusted to ~ 10 with ~ 1N NaOH. The stock solution of the internal standard, methyltestosterone (1.0 mg/ml), was prepared in methanol using a simple solution method. These solutions were further diluted with water as needed. Before diluting to 25.0 ml, a 0.5ml quantity of ~ 1N NaOH was added to each solution to prevent the decomposition of omeprazole. The most commonly used standard solution contained 40 μg/ml of omeprazole and 80 μg/ml of methyltestosterone (internal standard).

Decomposition of Omeprazole: A 2.0 ml of the stock solution of omeprazole was mixed with 15 ml water and either ~1ml of ~1N H_2SO_4 or NaOH in a 150 ml beaker. The mixture was heated to boiling (~5 minutes), cooled and the pH adjusted to neutral using either ~1N NaOH or H_2SO_4. The solution was then brought to volume (50.0 ml) with water. The internal standard was not added in order to detect new peaks in the chromatograms.

Extraction from capsules: The contents of five delayed release capsules were ground to a fine powder and a quantity of the powder representing 25 mg of

omeprazole was accurately weighed. The powder was mixed with 20 ml of methanol, 0.2 ml of 2.5N NaOH, the mixture was stirred occasionally for 10 minutes, then brought to volume (25 ml) with methanol. The mixture was filtered (Fisher's 9-803-SE filter paper), the first 10 ml of the filtrate was rejected, and then collected for analysis. To 1.0 ml of the filtrate, 2.0 ml of the stock solution of internal standard and 0.5ml of ~1N NaOH were added and the volume brought to 25 ml with water.

Preparation of Solutions for pH Stability Studies: A stock solution containing 1.0 mg/ml of omeprazole in ethanol was prepared using a simple solution method. This stock solution was further diluted to a concentration of 0.1 mg/ml using different pH value buffers (Table 1). After the zero-day data (assays, physical appearances, and pH values), the solutions were stored in amber-colored glass bottles at room temperature. The data were recorded again at the appropriate intervals.

Preparation of Assay Solutions For Stability Studies: To a 2.0 ml quantity of the assay solution, 2.0 ml of the internal standard solution (0.2 mg/ml) in methanol, 0.1ml of ~1N NaOH and 0.9 ml of water were added. The diluted solution contained 40 µg/ml of omeprazole (based on the label claim). The concentration of the internal standard in each solution was 80 µg/ml.

Assay Procedure and Calculations: A 20 µl quantity of the assay solution was injected into the chromatograph using the conditions described. For comparison, an identical volume of the standard solution was injected. Since the ratio of peak heights were related to the concentrations of the drug (range tested 20-60 µg/ml), the results were calculated using a simple equation:

$$\frac{(Rph)_a}{(Rph)_s} \times 100 = \text{percent of the label claim found,}$$

where $(Rph)_a$ is the ratio of the peak heights of drug to internal standard of the assay solution and $(Rph)_s$, that of the standard solution.

RESULTS AND DISCUSSION

Assay Method: The developed HPLC assay method is accurate and precise with a relative percent standard deviation of 0.5% based on 5 readings. Linearity was obtained with a correlation coefficient of 0.999 for a concentration range of 20-60 µg/ml of omeprazole. The developed method appear to be stability-indicating since the peaks from the decomposition products separated from the drug peak (Figure 2C). The drug was highly sensitive to acid since the potency of drug remaining after hydrolysis with acid was zero (Figure 2C). On the other hand, the chromatogram obtained after hydrolysis with sodium hydroxide did not show any

TABLE 1

List Of Aqueous Solutions Of Omeprazole (0.1 mg/ml) Prepared For Stability Studies.

Solution No.	pH (±0.05)	Phosphate buffer conc (M)	Ionic Strength[a]
1	2.2	0.1	0.35
2	2.5	0.1	0.35
3	3.1	0.1	0.35
4	4.7	0.1	0.35
5	5.9	0.1	0.35
6	7.0	0.1	0.35
7	7.8	0.1	0.35
8	9.2	0.1	0.35
9	10.0	0.1	0.35
10	10.7	0.1	0.35
11	11.0	0.1	0.35

[a] Adjusted with KCl.

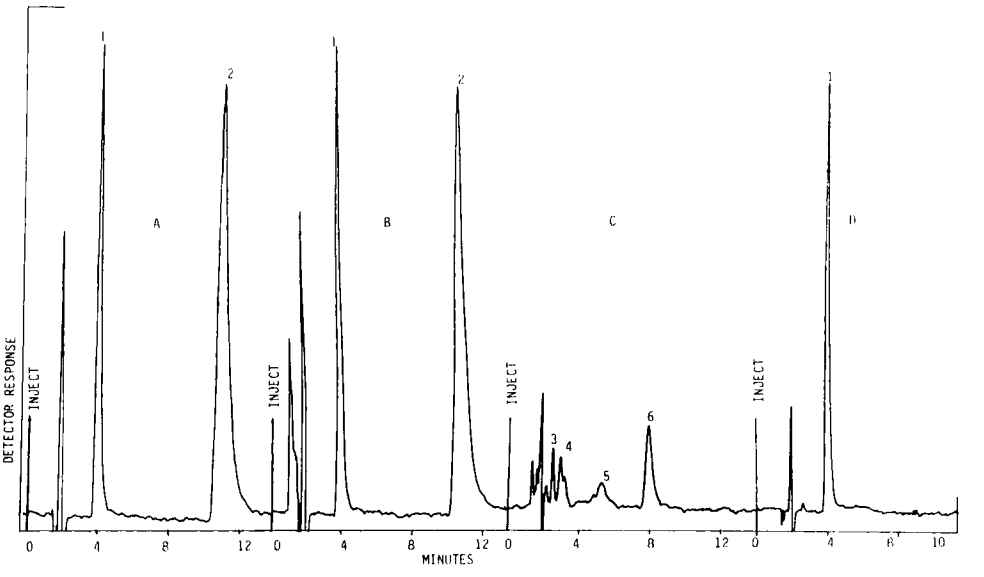

Figure 2: Sample chromatograms. Peak 1 is from omeprazole, Peak 2 from methyl testosterone (the internal standard), Peaks 3, 4, 5, and 6 from the degradation products of omeprazole. Chromatogram A is from a standard solution; B from a capsule; C from a solution decomposed using sulfuric acid; and D from a solution decomposed using sodium hydroxide. For chromatographic conditions, see text.

TABLE 2

Assay Results Of Omeprazole Solutions At Different pH values At 25°C

pH	% drug remaining at time (days)									
	0	1	5	8	14	21	28	46	67	93
2.2	ppt									
2.5	ppt									
3.1	ppt									
4.7	ppt									
5.9	74.21									
7.1	93.60	70.85								
7.8	100.00	93.11	55.99	41.42	25.97					
9.2	100.00	99.95	90.03	84.65	76.39	61.31				
10.0	100.00	100.48	99.02	97.89	95.31	90.92	88.85			
10.7	100.00	100.37	99.54	100.75	-	99.91	97.98	93.76	92.71	88.26
11.0	100.00	99.07	98.80	100.43	-	99.45	96.78	96.41	97.25	94.01

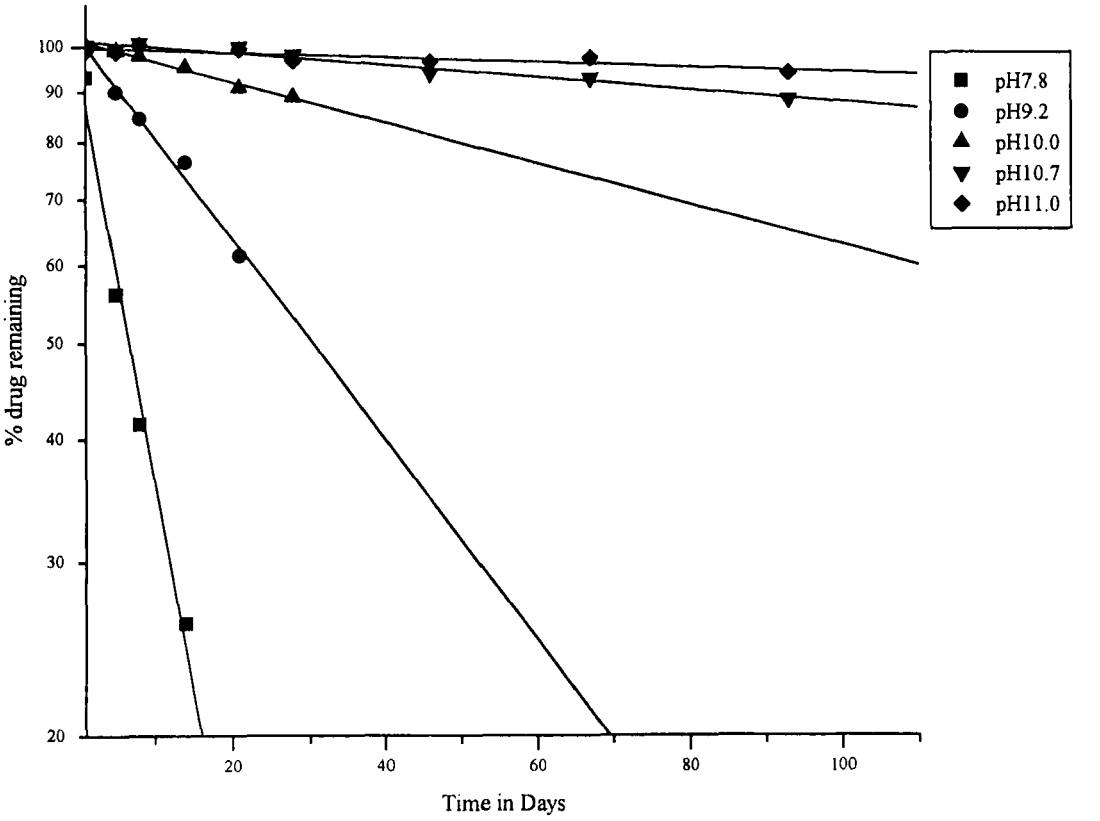

Figure 3: First-Order Plots Of Omeprazole Degradation At Different pH Values.

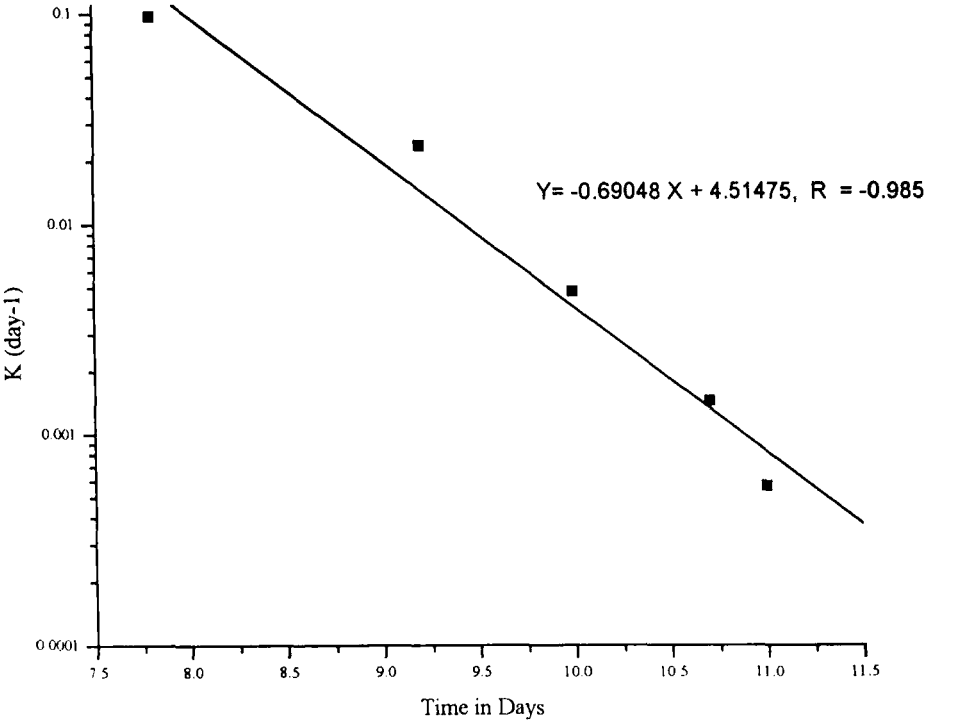

Figure 4: pH-rate Profile Curve of Omeprazole In 0.1M Phosphate Buffer.

peaks from the decomposition products (Figure 2D). Omeprazole appears to be very stable under basic conditions.

The results indicate that the developed method can be used to quantify omeprazole in capsules. The percent of omeprazole in the capsules were found to be 100.6% of the label claim. The procedure for the extraction of the drug from the capsules is very simple. There were no interferences from the excipients such as cellulose, disodium hydrogen phosphate, hydroxypropyl cellulose, hydroxypropyl methylcellulose, lactose, mannitol and sodium lauryl sulfate present in the delayed release capsules (Figure 2B).

When studying decomposition, it was observed that the color of the solution changed immediately to pale yellow on addition of the acid. On heating, the color further changed to a dark yellow and then to a brown precipitate.

The pH of the mobile phase was 7.1 because the drug was very unstable at lower pH values even for a short period of time. The internal standard did not interfere with any of the degradation products (Figure 2). The pH of the standard and the assay solutions were adjusted to about 10 with sodium hydroxide in order to minimize degradation of omeprazole.

Effect of pH on the stability of omeprazole: Solutions between pH 2.2 and 4.7 (Solutions 1-4, Table 1) degraded within few hours and the solutions showed precipitation and complete degradation of omeprazole in less than 4 hours. As the pH was increased from pH 5.9 to 7.0, the solutions were unstable even for a day (Table 2). Precipitation occurred after one day in the pH 5.9 solution. In all the solutions, precipitation was found after the drug had decomposed by ~25%. In solutions of pH values 7.8 to 11.0, the omeprazole followed first-order law (Figure 3). It was determined that the stability improved with increase in pH (Table 2). The maximum stability was observed at pH 11, the highest value studied.

The pH-rate profile curve of omeprazole (Figure 4) shows that degradation is acid catalyzed. As the pH value increased, the rate of degradation decreased. The H^+ values had a direct relationship with K_{obs} values (Figure 4). The maximum pH values studied in these investigations was 11 since the pH values above 11 are not practical physiologically.

REFERENCE

1. Anon. Product insert # 7748206, Merck & Co., Inc., West Point, PA 19486, USA.