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Study of omeprazole stability in aqueous solution: influence of cyclodextrins

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Omeprazole (OME) is a proto type anti-secretary agent. This compound is very unstable, especially in acidic aqueous solutions. A stability indicating HPLC assay has been developed in order to investigate the effect of different factors on the stability of omeprazole. These factors included the pH with the tested values ranging from 6-10 and the temperature by monitoring the drug stability at 25, 37 and 40ºC. The study was then extended to investigate the effect of cyclodextrins, namely beta-cyclodextrin (β-CD), dimethyl-beta-cyclodextrin (DMβ-CD), hydroxypropyl-beta-cyclodextrin (HPβ-CD) and maltosyl-beta-cyclodextrin (Mβ-CD) on the stability of omeprazole. The results showed the dependence of drug stability on the pH and temperature with the degradation being significant below pH 7 and at higher temperature. The degradation kinetics follows the first-order kinetics. The addition of different cyclodextrins accelerates the degradation of drug, and this effect was in the following manner: β-CD> DMβ-CD> Mβ-CD> HPβ-CD. The effect of different concentrations of HPβ-CD on the degradation of drug was also studied. It was noted that the degradation of drug depends on the concentration of HPβ-CD up to 1.0 mM; above this concentration the degradation was constant.

Key words: Omeprazole – HPLC method – Cyclodextrin derivatives – Stability kinetics – Degradation – Complex formation.

Omeprazole (OME), an anti-secretary agent, is the prototype of proton pump inhibitors. It is widely used for the prophylaxis and treatment of peptic ulcers and symptomatic treatment of gastro-esophageal reflux [1]. It is a lipophilic drug with a major stability problem especially in an acidic solution with evidence of thermo-sensitivity being reported [2]. This compound is a heat-sensitive drug. Preformulation studies reflected the degradation effect of moisture, heat, solvents and acidic substances on the stability of omeprazole. Other investigators have observed a degradation of omeprazole under exposure to various salts and metal ions [3].

Cyclodextrins (CD) have been used to increase the aqueous solubility and stability of a wide variety of drugs [4-6]. CDs are cyclic oligosaccharides with a central cavity which can accommodate a wider variety of drugs, increasing their solubility and/or stability. On the other hand, in the case of ester hydrolysis, incomplete inclusion of the susceptible groups into the cavity may lead to acceleration of drug degradation. This acceleration can be attributed to the fact that partial inclusion of the target group will expose this group to stress conditions by sterically fixing the ester close to the proximity of the hydroxyl group of CDs [7]. It has also been shown that straight chain sugars that have an adjacent hydroxyl group such as dextrose can accelerate the degradation of drugs [8].

This study was designed to investigate the effects of temperature, pH of solution and different cyclodextrins on the stability of omeprazole in aqueous solution.

I. MATERIALS AND METHODS

1. Materials

Omeprazole (OME) was kindly donated by Tabuk Pharmaceutical Company (Tabuk, Kingdom of Saudi Arabia). Beta-cyclodextrin (β-CD) was purchased from the Sigma Chemical Company (St. Louis, MO, United States), dimethyl-beta-cyclodextrin (DMβ-CD) was purchased from Winlab, UK, hydroxypropyl-beta-cyclodxtrin (HPβ-CD) was supplied from Floka Japan (Tokyo, Japan) and maltosyl-beta-cyclodextrin (Mβ-CD) was obtained from Aldrich Chemica (Milan, Italy). HPLC solvent (acetonitrile) was purchased from BDH Laboratories Supplies (BDH Chemical Ltd., Poole, United Kingdom). All other chemicals and reagents were of analytical grades. HPLC water was used throughout this work.

2. HPLC analysis method

Omeprazole samples were analyzed using a modified reversed-phase high performance liquid chromatography (HPLC) method [9] employing a water instrument with a Shimadzu UV detector set at 302 nm and a water US-60 injector. The samples were eluted at a flow rate of 1.0 mL/min at room temperature, under isocratic conditions. Separation was achieved using octadecylsilane column μ-Bondapak C18 column (Waters Assoc.; 10 μm, 150 mm × 3.9 mm id). The mobile phase consisted of acetonitrile: phosphate buffer pH 7.5 (25:75% v/v). Standard calibration curves, based on the average of the peak height of different concentrations using a known amount of drug in the concentration range of 0.5-5.0 μg/mL, were used to determine the intra- and inter-day precision of the method. Standard solutions were prepared daily by dissolving the appropriate amount of drug in ethanol to yield the final solution (10 μg/mL), and the calibration curves were constructed before each sample set was analyzed to ensure reproducibility of the analysis.

3. Kinetic study

3.1. Degradation of omeprazole in aqueous solutions (effect of pH)

The effect of pH (6.0, 7.5, 9 and 10) of the medium on the stability of omeprazole was carried out at constant temperature of 25ºC. Solutions of omeprazole were prepared in the selected buffer at different pH values. The solutions were placed in brown glass vials covered with Teflon lined screw caps and stored at 25ºC in a thermostatically controlled oven (Heraeus thermostatic oven, Karl Kolb Scientific technical supplies, Buchschlag-Frankfurt, Germany). At different time intervals, 0, 24, 48, 72, 96, 120, 168 h, samples were taken out of the oven, frozen immediately and kept in a freezer (- 20ºC) until they were analyzed.

3.2. Effect of temperature

Solutions of omeprazole (1.0 mL, 50 μg/mL) were added to pre-

pare 10 mL of the phosphate buffer solution (pH 7.5) (0.02 M, ionic strength = 0.08) and were placed in the brown glass vials covered with Teflon lined screw caps and stored at 4°C (in a refrigerator) and 25, 37 and 40°C in a thermostatically controlled oven (Heraeus thermostatic oven, Karl Kolb Scientific technical supplies, Buchschlag-Frankfurt, Germany). Samples were collected at different time intervals (0, 24, 48, 72, 96, 120, 168 h). Similar procedures were used as before.

3.3. Effect of cyclodextrin structure

Solutions of omeprazole (1.0 mL, 50 μg/mL) were diluted to 100 mL using a phosphate buffer solution with a pH of 7.5 (0.02 M, ionic strength = 0.08) containing 10 mM of either β-CD, DMβ-CD, HPβ-CD or Mβ-CD (10 mL). The solutions were placed in the brown glass vials covered with Teflon lined screw caps and stored at 37°C in a thermostatically controlled oven. At different time intervals 0, 24, 48, 72, 96, 120, 168 h, samples were taken and then analyzed.

3.4. Effect of HP-BCD concentration

The effect of HPβ-CD concentration on the degradation rate of OME was carried out at 37°C. Drug samples (10 mL) were prepared as before but the vehicle was phosphate buffer solution with a pH of 7.5 containing different concentrations of HPβ-CD (0.1, 1.0, 10 mM), which were then placed in the brown glass vials covered with Teflon lined screw caps and stored at 37°C in a thermostatically controlled oven. The samples were treated as described before and analyzed by the HPLC.

4. Determination of the stability constant (K_c) of the complexes

4.1. Partition coefficient method

The stability constants (K_c) of the complexes between omeprazole and each CD were determined using the partition coefficient method [10]. The partition coefficient of omeprazole between n-octanol and aqueous buffer solution pH 7.5 was determined in the absence and presence of CDs at 25°C. Aqueous buffer solutions containing known amounts of OME with or without CD were added separately to equal volumes of n-octanol in screw-capped tubes. The mixtures were shaken for 1 h in a thermostated water bath at 25ºC. The aqueous phase was separated using a separating funnel, then the concentration of omeprazole was determined by the HPLC method. The partition coefficient of the OME was calculated in the absence (PC) and presence of CDs $(PC)_{CD}$. This calculation involved dividing the concentration of drug in the oil phase by that in the aqueous phase. The stability constants (Kc) of complexes between drug and each CD were calculated according to the following equation:

$$(PC)_{CD}/(PC) = 1 + K_C[CD]_{ini} \qquad \textbf{Eq. 1}$$

where $[CD]_{ini}$ is the initial concentration of CD.

4.2. Phase solubility method

Phase solubility studies were carried out at room temperature (25ºC) according to the Higuchi and Connors method [11]. Excess amounts of OME were added to brown glass bottles containing phosphate buffer 0.02 M (pH 9.5) in the presence of different concentrations of CDs (0, 1, 2, 3, 4, 8, 10 mM). The bottles were shaken in a thermostatically water bath shaker for 72 h at 37ºC. The samples were taken, filtered through a 0.45 μm and assayed. The stability constants (K_s) were calculated according to the following equation:

$$K_s = \text{slope}/[S_0\ (1 - \text{slope})] \qquad \textbf{Eq. 2}$$

where S_0 is OME solubility in water and calculated from intercept.

II. RESULTS AND DISCUSSION

The reversed phase HPLC method adopted in this article enabled satisfactory quantitative analysis of omeprazole to be achieved within the selected concentration range. *Figure 1* shows a typical chromatogram for the intact drug dissolved in phosphate buffer pH 7.5 (retention time = 6.4 min ± 0.1, n= 6). Standard curves were linear with correlation coefficient of 0.9980 ± 0.0015. The intraday and interday precision and accuracy of the method are shown in *Table I*. The method was found to be precise as the intraday relative standard deviation percent (RSD %) of six replicate determinations for one day at the concentration was in the range of 5.5-8.1%, while the interday precision ranged from 5.7-8.2%. The accuracy was calculated as the percent of drug recovered after analysis. The intraday accuracy was in the range of 99.8-101.1%, with interday being in the range of 99.8-100.4%. Moreover, this method was suitable for quantitating the amount remaining of the drug subjected to different storage conditions without interference of the decomposition products (*Figure 1*).

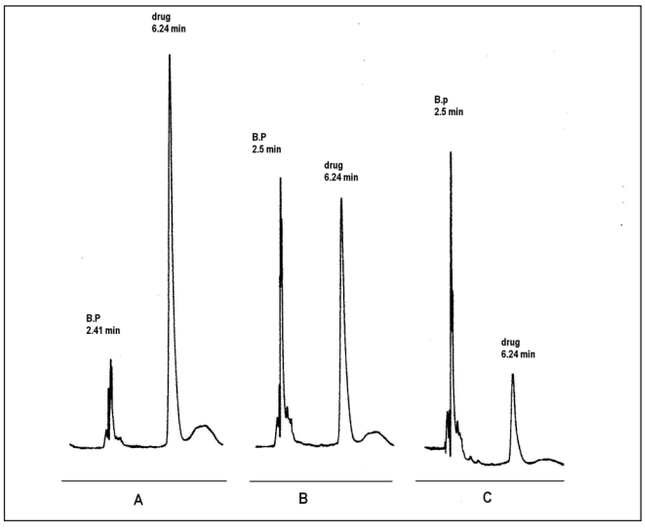

Figure 1 - Typical high-performance liquid chromatography of omeprazole in phosphate buffer solution at pH 7.5 at 37ºC stored for (A) one day (B) 3 days (C) 7 days.

Table I - The intra- and inter-day variations and accuracy of omeprazole (n = 6).

Conc. (µg/mL)	Intra-day		Inter-day	
	Precision (RSD, %)	Accuracy (%)	Precision (RSD, %)	Accuracy (%)
0.5	7.5	101.1	8.2	100.4
1.0	8.1	99.8	7.8	100.1
2.0	6.5	99.9	6.8	99.8
3.0	6.8	100.1	6.7	99.9
4.0	7.1	100.1	7.1	99.8
5.0	5.5	99.9	5.8	99.8

The stability study was carried out at different pH values, namely 6, 7.5, 9, and 10, which covered the neutral and alkaline medium. OME is known to be very unstable in acidic medium [2]. It was found that the degradation of OME at these different pH values followed first-order kinetics (correlation coefficient (r) between 0.992-0.996). The first-order kinetic parameters are listed in *Table II*. The data revealed an improvement in OME stability when the medium pH was increased (*Table II*). The small values of reaction rate constant of degradation of OME indicate longer half-life and shelf life. These findings are in agreement with Mathew *et al*. [12] who reported that the degradation of omeprazole is acid catalyzed and is very stable at high pH.