DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY, 21(7), 781-792 (1995)

DEGRADATION RATES OF CAPTOPRIL IN AQUEOUS MEDIUM THROUGH BUFFER-CATALYSIS OXIDATION

David Chen[1], Huilan Chen, Hao Ku

Drug Delivery, Pharmaceutical R & D Laboratories
Development Center for Biotechnology
81 Chang Hsing Street, Taipei, Taiwan

ABSTRACT

Initial degradation rates of captopril (0.1 mg/mL) in acetate, citric, and phosphate buffer solutions with different buffer concentrations at 80 °C (μ=0.5) were studied at pH 6.0. All degradation reactions of captopril solutions fitted an apparent first-order plot. The degradation rates of captopril rose with increasing buffer concentrations. A mechanism involving the buffer-catalysis oxidation reaction of captopril was proposed in this study. The low apparent first-order degradation rates of captopril in citric buffer solutions might have been due to the chelating effect of the citric buffer, which reduced the metal-catalysis oxidation reaction of captopril. Therefore, using low concentrations of citric buffer to improve solution stability seems to be an appropriate approach in a liquid formulation development of captopril. To select citric buffer at a low concentration for the dissolution medium might be the right choice for a sustained-release formulation dissolution study of captopril.

[1] Author to whom correspondence should be addressed

INTRODUCTION

Because captopril USP is an angiotensin-converting enzyme inhibitor, it is often prescribed in tablet form to control hypertension. There is no commercial liquid product of captopril on the market in either oral or parenteral dosage form. Therefore, to study the stability of captopril in aqueous medium in order to develop a stable liquid product is an important topic in pharmaceutical industry. Also, today more and more drugs are being formulated in a long-acting solid dosage form for oral administration. For the development of an oral sustained-release dosage form of captopril, an appropriate dissolution medium in which captopril is stable during a longer-than-usual dissolution study must be selected. For this reason, to investigate the stability of captopril in different buffer solutions and then select the appropriate buffer system as the dissolution medium is an important subject for the formulator.

The oxidative rate of the degradation of captopril over the pH range 2.0-5.6 at 50 °C was first investigated by Timmius et al. [1] in 1982. They concluded that the oxidation reaction was the predominant route of degradation of captopril over this pH range and captopril disulfide was the major degradation product. In 1987, Lee and Notari [2] reported the stability study of captopril in aqueous solution in the pH range 6.6 to 8.0 and captopril disulfide was the sole degradation product through oxidation reaction in this pH range. In their study, they also observed that the reaction rate changed from the first-order reaction to the zero order reaction when the captopril concentration decreased below a minimum value. A mechanism involving cupric ion concentration, molecular oxygen-catalyzed oxidation and a rate-limiting step was proposed in their publication to explain their observation. Pramar et. al. [3] reported a stability study of several oral liquid formulations of captopril in 1992. They found that the decomposition of captopril in liquid formulation using water as the vehicle did not follow the first-order equation. The reason for not following the first-order equation was probably due to an uncontrolled factor, oxygen.

In the following study, acetate, citric and phosphate buffer solutions with different buffer concentrations were prepared. The pH values were adjusted close to the physiological pH of intestinal fluid, around pH 6.0. To avoid the degradation reaction order change from first order to zero order when the captopril concentration fell below a certain limit, only initial degradation rates of

captopril in each of these three buffer solutions were examined. Within the initial stage of the degradation reaction, only the first order degradation reaction of captopril was observed in all three buffer solutions that were studied. It is hoped that this solution stability study of captopril will serve two purposes. The first is to provide some stability information for the formulator to develop stable liquid formulation of captopril. The second is to generate some useful information for the pharmaceutical industry to select an appropriate dissolution medium for the development of oral sustained-release formulation of captopril.

MATERIALS AND METHODS

HPLC System

A high performance liquid chromatography (Spectra-Physics Pump p4000, Controller SN4000, Autosampler AS3000) equipped with a variable wavelength UV detector (Spectra-Physics UV1000) was used in conjunction with a Lichrospher 100RP-18 column (Merck 50995, 5 μm, 250 x 4mm). The areas under the chromatogram peaks were measured by an integrator (Spectra-Physic ISM100). A HPLC analytical method for captopril, published by Perlman and Kirschbaum [4], was modified slightly and used in this study. The mobile phase used was a 380:420:0.4 in volume mixture of methanol (BDH lot 1399968), water and orthophosphoric acid (85%, Merck 230K18268773). The mixed mobile phase was degassed under vacuum with a magnetic stirring plate (CORNING Stirrer/Hot plate). The variable wavelength detector was adjusted to 220 nm. The injection volume of the sample was 20 μL and the flow rate was 1.00 mL/min.

Determination of Metal Ions

The amount of copper and iron presented in potassium chloride (extra pure, Merck 739TA401735), potassium dihydrogen phosphate (Merck 212A646173), citric acid monohydrate (GR, Merck 238K18269444), and sodium acetate trihydrate (extra pure, food grade, Merck 204TA221465) were detected by an atomic absorption spectrophotometer (GBC 902 Double Beam). The total amount of iron and copper presented in each sample solution were calculated based on the amount of the solid chemical that had been used to prepare the solution and the atomic absorption assay results of these solid chemicals.

Sample Preparation

Three types of buffer solutions with different concentrations were prepared with sodium acetate trihydrate, citric acid monohydrate, and potassium dihydrogen phosphate. The pH was adjusted to 5.5, 6 and 6.5 with 1 N of sodium hydroxide or 6 N of hydrochloric acid by using a pH meter (Jenco model 6071). All of these buffer solutions were adjusted to 0.5 μ of ionic strength with potassium chloride. Sample solutions in screw-cap bottles were pre-heated to 80 °C before the captopril (EGIS/Hungary Lot# 601760292) was added into them. After the captopril was dissolved in each sample solution to give approximately 0.1 mg/mL by using a vortex apparatus (Genie 2 model G560), they were put into an 80 °C oven immediately. At each interval, sample solutions were withdrawn for HPLC assay and air was bubbled through the solution to ensure enough oxygen was in excess for an oxidation reaction.

RESULTS AND DISCUSSIONS

The catalytic effect of copper and iron on thiol oxidation, with copper being the most effective, was reported by Cullis et al. [5]. The concentration level of copper and iron in each sample of this study were determined and given in Table 1. Since the level of these two metals, particularly the copper level, were very low in the sample solution, no effort was made to reduce them for this study.

The first-order degradation plot of captopril in water with constant ionic strength (μ = 0.5) and pH adjusted to 6.0 at 80 °C was shown in Figure 1. The first-order degradation rate constant for captopril in 80 °C water at 0.1 mg/mL concentration was calculated to be 4.97×10^{-3} hr^{-1}. Captopril disulfide was identified to be the major degradation compound in the literature [1]. Because hydroxyl ions were present in the aqueous solution of this study, the following degradation mechanism for the oxidation of thiols described by Wallace and Schiesheim [6] could be used to explain the degradation pathway of captopril to captopril disulfide:

$$RSH + OH^- \Leftrightarrow RS^- + H_2O \quad (1)$$

$$RS^- + O_2 \rightarrow RS^{\bullet} + O_2^-$$

$$RS^- + O_2^- \rightarrow RS^{\bullet} + O_2^{2-}$$

$$2RS^{\bullet} \rightarrow RSSR$$

$$O_2^{2-} + H_2O \rightarrow 2OH^- + 1/2\ O_2$$

TABLE 1

The Content Level of Iron and Copper in Different Buffer Solutions were Determined. Each Sample was Adjusted to a Constant Ionic Strength (μ = 0.5) with Potassium Chloride.

Buffer	pH	Conc. (M)	Content of Fe (ppm)	Content of Cu (ppm)
Water	6	-	0.429	0.030
Acetate	5.5	0.05	0.389	0.032
Acetate	5.5	0.2	0.271	0.037
Acetate	5.5	0.4	0.113	0.044
Acetate	6	0.05	0.389	0.032
Acetate	6	0.1	0.350	0.033
Acetate	6	0.2	0.271	0.037
Acetate	6	0.4	0.113	0.044
Phosphate	6	0.1	0.418	0.040
Phosphate	6	0.2	0.407	0.051
Phosphate	6	0.25	0.402	0.054
Phosphate	6.5	0.1	0.376	0.038
Phosphate	6.5	0.15	0.350	0.041
Phosphate	6.5	0.25	0.297	0.049
Citric	6	0.03	0.281	0.019
Citric	6	0.05	0.183	0.013
Citric	6	0.07	0.085	0.006
Citric	6	0.084	0.016	0.001

The degradation of captopril in acetate buffer and phosphate buffer solutions with different buffer concentrations at the initial stage of this stability study were shown in Figure 2, 3, 4 and 5. Initially, all degradation reactions of captopril at a 0.1 mg/mL concentration fitted an apparent first-order plot. Based on the observation from Table 2, the degradation rates of captopril in acetate and phosphate buffer solutions were faster than in water. Also, the increase of degradation rates of captopril were in direct proportion with the increase of buffer

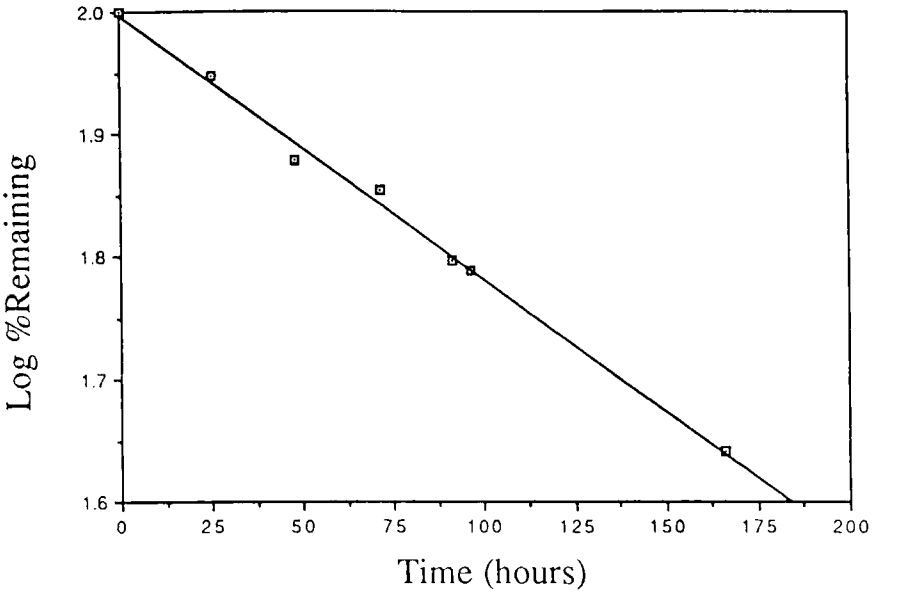

FIGURE 1 First Order Degradation Plot of 0.1 mg Captopril /mL in Water at 80 °C, μ=0.5 and pH was Adjusted to 6.0.

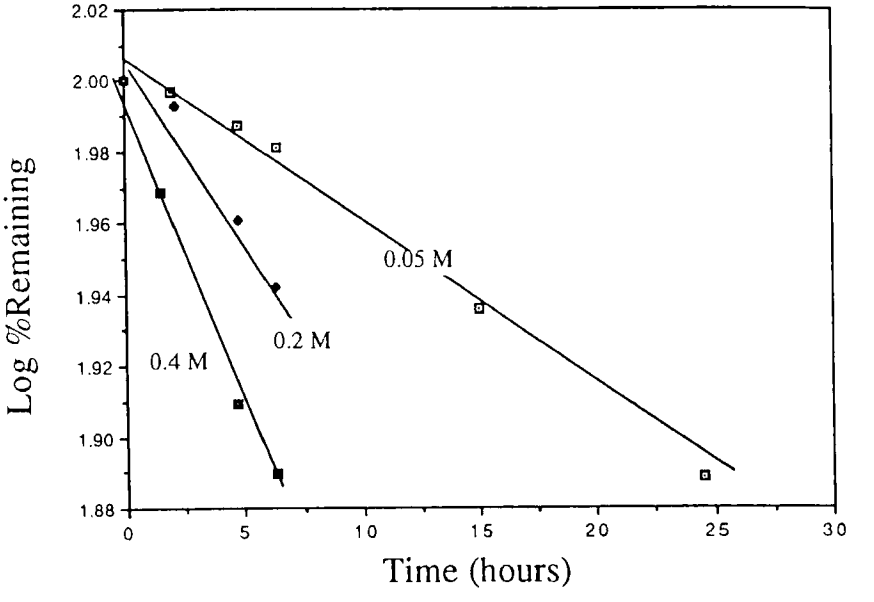

FIGURE 2 Apparent First-Order Degradation Plots of 0.1 mg Captopril/mL in pH 5.5 Acetate Buffer Solution at 80 °C. Acetate Buffer Concentrations were 0.05 M, 0.2 M, and 0.4 M. μ=0.5.

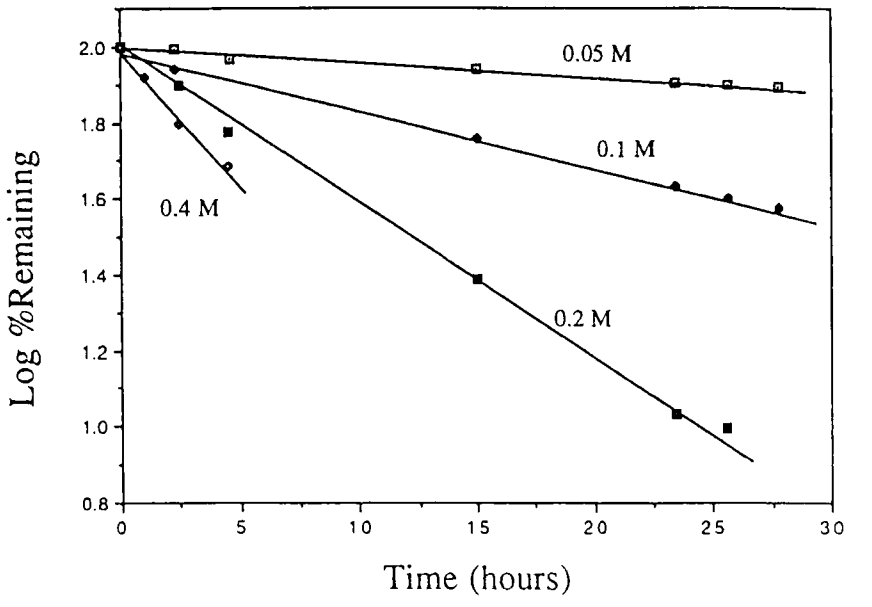

FIGURE 3 Apparent First-Order Degradation Plots of 0.1 mg Captopril/mL in pH 6.0 Acetate Buffer Solution at 80 °C. Acetate Buffer Concentrations were 0.05 M, 0.1 M, and 0.2 M and 0.4 M. μ=0.5

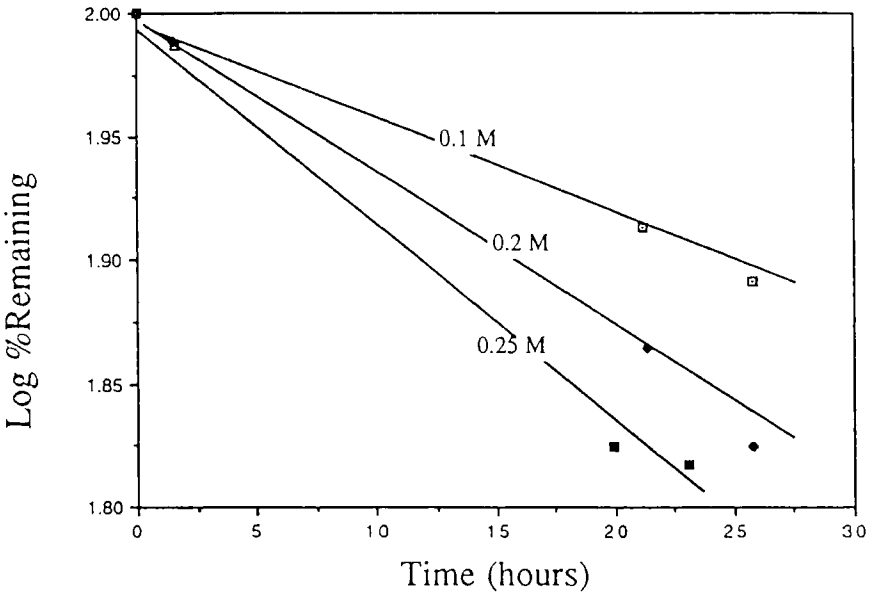

FIGURE 4 Apparent First-Order Degradation Plots of 0.1 mg Captopril/mL in pH 6.0 Phosphate Buffer Solution at 80 °C. Phosphate Buffer Concentrations were 0.1 M, 0.2 M, and 0.25 M. μ=0.5.

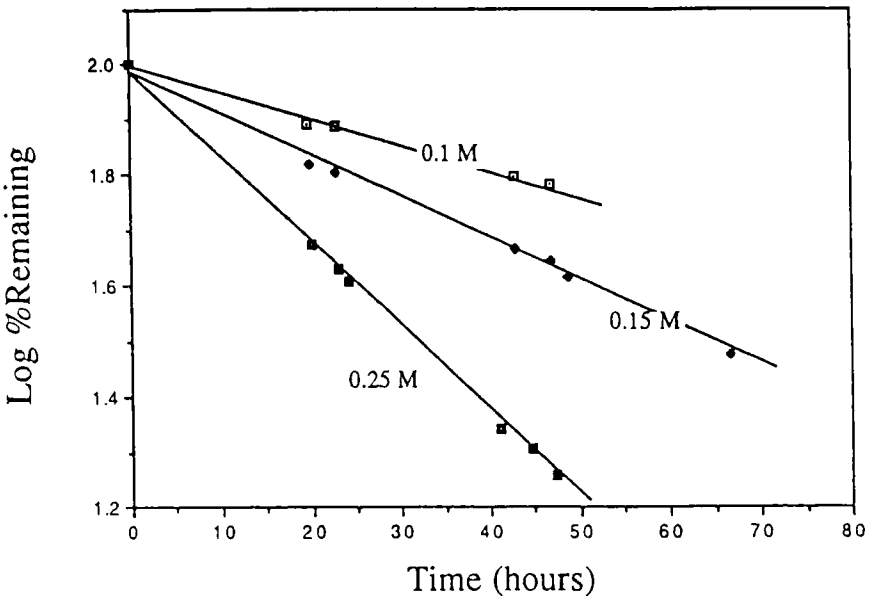

FIGURE 5 Apparent First-Order Degradation Plots of 0.1 mg Captopril/mL in pH 6.5 Phosphate Buffer Solution at 80 °C. Phosphate Buffer Concentrations were 0.1 M, 0.15 M, and 0.25 M. μ=0.5

concentration at any given pH. To rationalize this degradation behavior, the following degradation mechanism was proposed. The degradation pathway of captopril to captopril disulfide in these buffer solutions was not only the one described in Eq. (1). Another buffer-catalysis oxidation mechanism might have been undergoing simultaneously to facilitate the degradation of captopril in buffer solution, as described in the following equations:

$$RSH + A^- \Leftrightarrow RS^- + HA \quad (2)$$

$$RS^- + O_2 \rightarrow RS^{\bullet} + O_2^-$$

$$RS^- + O_2^- \rightarrow RS^{\bullet} + O_2^{2-}$$

$$2RS^{\bullet} \rightarrow RSSR$$

$$O_2^{2-} + H_2O \rightarrow 2OH^- + 1/2\ O_2$$

$$HA + OH^- \Leftrightarrow A^- + H_2O$$

HA: CH_3COOH, H_3PO_4 or $H_2PO_4^-$ A^-: CH_3COO^-, $H_2PO_4^-$ or HPO_4^{2-}

TABLE 2

Initial Degradation Rates (K_{obs}) of 0.1 mg Captopril/mL at 80 °C in various Buffer Solutions. μ=0.5. K_{obs} were Obtained from the Slopes of the First-Order Degradation Plots Through a Linear Regression Analysis.

Buffer	pH	Conc. (M)	K_{obs} (1/hr) x 10^3	Correlation Coefficient
Water	6	-	4.97	0.996
Acetate	5.5	0.05	10.87	0.990
Acetate	5.5	0.2	21.66	0.955
Acetate	5.5	0.4	40.59	0.994
Acetate	6	0.05	8.67	0.982
Acetate	6	0.1	34.62	0.998
Acetate	6	0.2	91.34	0.997
Acetate	6	0.4	161.22	0.988
Phosphate	6	0.1	9.31	0.997
Phosphate	6	0.2	15.26	0.997
Phosphate	6	0.25	18.98	0.992
Phosphate	6.5	0.1	10.55	0.995
Phosphate	6.5	0.15	17.52	0.995
Phosphate	6.5	0.25	35.88	0.999
Citric	6	0.03	1.11	0.991
Citric	6	0.05	1.85	1.000
Citric	6	0.07	4.29	0.993
Citric	6	0.084	4.98	0.997

This type of buffer-catalyzed initiation of the reaction sequence to captopril oxidation of which is proposed in this study, is consistent with the observation that degradation rates increased when the buffer concentration increased.

The apparent first-order degradation plots of 0.1 mg captopril/mL at pH 6.0 citric buffer with different citric buffer concentrations were shown in Figure 6. The initial degradation rates (Kobs) of captopril in citric buffer increased from 1.11 x 10^{-3} hr^{-1} to 4.98 x10^{-3} hr^{-1} (Table 2). This observation could be explained

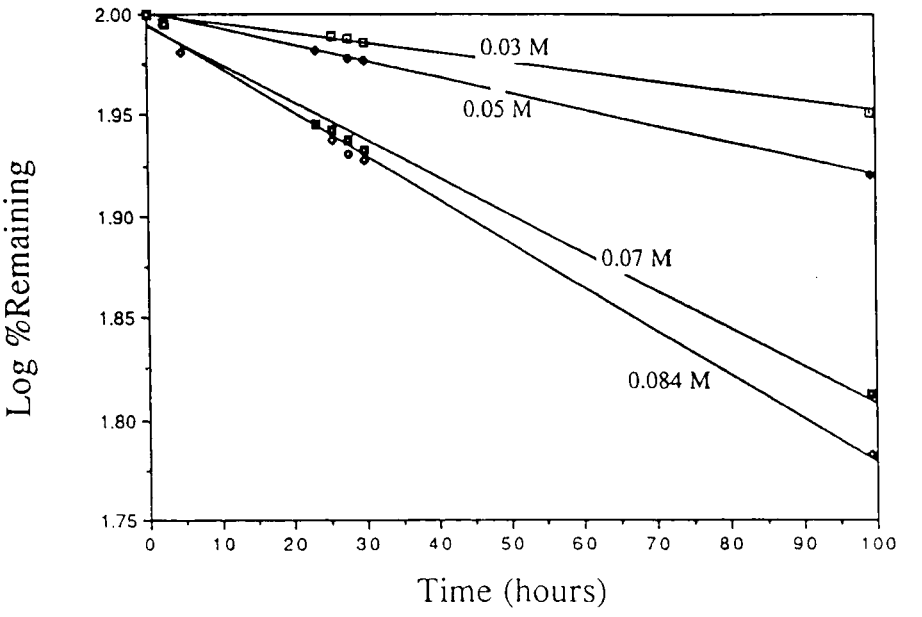

FIGURE 6 Apparent First-Order Degradation Plots of 0.1 mg Captopril/mL in pH 6.0 Citric Buffer Solution at 80 °C. Citric Buffer Concentrations were 0.03 M, 0.05 M, 0.07 M and 0.084 M. μ=0.5.

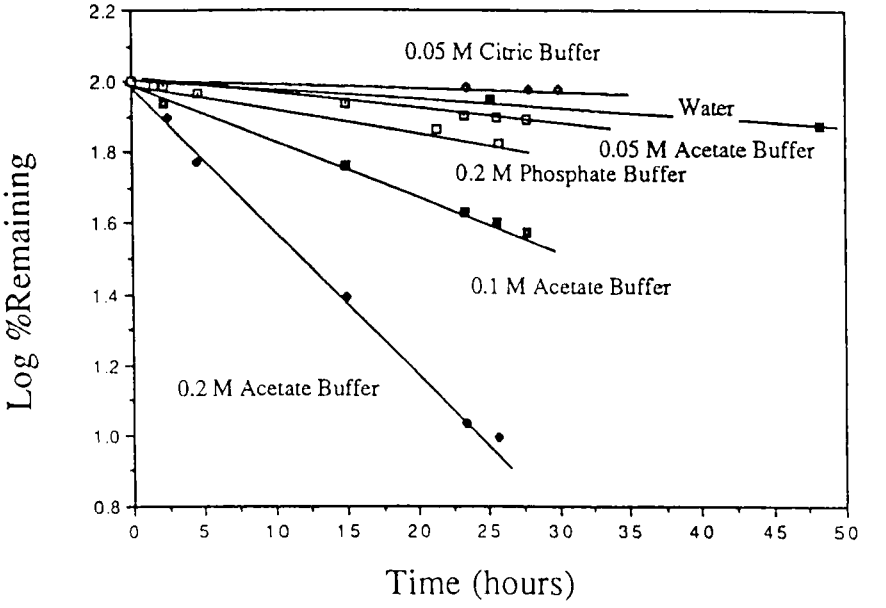

FIGURE 7 Apparent First-Order Degradation Plots of 0.1 mg Captopril/mL in pH 6.0 Buffer Solutions at 80 °C. μ=0.5.

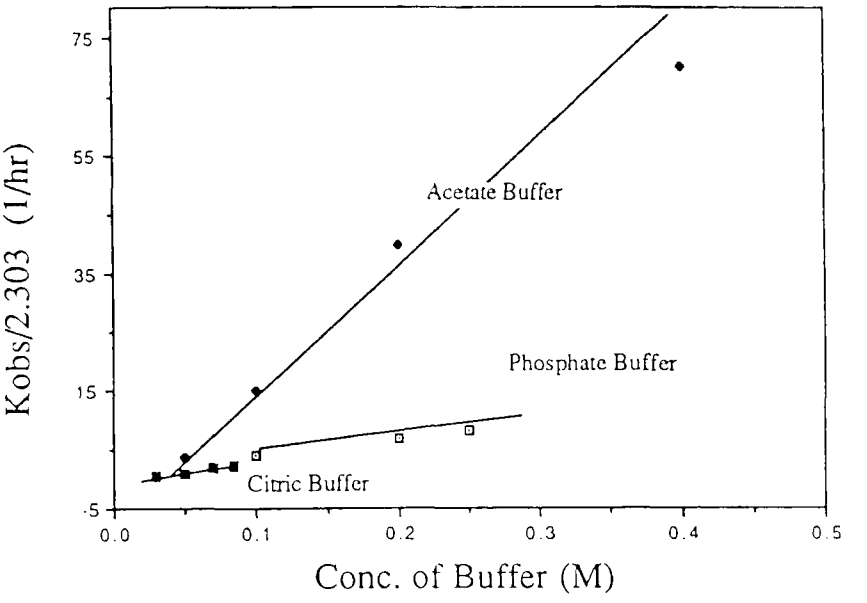

FIGURE 8 Apparent First-Order Degradation Rate Constants (K_{obs}) of 0.1 mg Captopril/mL vs. Buffer Concentrations Plots. pH=6.0, Temp.= 80°C, μ=0.5.

through Eq. (2). However, the low degradation rates of captopril in citric buffer could not be explained through Eq. (1), since Kobs for captopril in water at pH 6.0 was 4.97×10^{-3} hr^{-1} as shown in Table 2. In order to explain the low degradation rates of captopril in citric buffer solutions, the following mechanism was proposed. The citric buffer might act as a chelating agent which reduced the catalytic effect of metal ions during the captopril oxidation. This metal-catalyzed reaction on thiol oxidation has been studied by Cullis et. all. (5) and was described through the following equations:

$$RS^- + M^{(n+1)+} \rightarrow RS^{\bullet} + M^{n+} \quad (3)$$

$$2RS^{\bullet} \rightarrow RSSR$$

$$M^{n+} + 1/2\ O_2 \rightarrow M^{(n+1)+} + 1/2\ O_2^{2-}$$

Eq. (3) could be used to explain the reason why degradation rates of captopril in citric buffer solutions were slower than in water alone.

In conclusion, it is best to select citric as the buffer to improve the stability of captopril in liquid formulation development, as shown in Figure 7 and 8. It is because citric buffer can reduce the metal-catalytic effect on captopril oxidation. However, the formulator should keep in mind that citric buffer also has a buffer-catalytic effect on captopril oxidation as described on Eq (2). An excess of much citric buffer might also reduce the stability of captopril in an aqueous medium. Therefore, to formulate with a citric buffer at a low concentration seems to be the appropriate approach for the liquid formulation development of captopril.

In terms of selecting the dissolution medium, the time required for 2% of captopril degraded at 80 °C were calculated based on the K_{obs} for 0.2 M acetate buffer, 0.2 M phosphate buffer and 0.05 M citric buffer at pH 6.0, as shown in Table 2. Using the first-order equation, the theoretical time required for 2% of captopril degraded at 80°C will be 0.22 hrs., 1.32 hrs., and 10.92 hr. for 0.2 M acetate buffer, 0.2 M phosphate buffer and 0.05 M citric buffer at pH 6.0 respectively. At 37°C the degradation rate of captopril in aqueous medium will be much slower than at 80°C. Using a citric buffer at a low concentration as the dissolution medium (37 °C) would be a good choice for a sustained-release formulation dissolution study of captopril.

REFERENCES

[1] P. Timmins, I. M. Jackson, and Y. J. Wang, *Int. J. Pharm.*, **11**, 329 (1982)

[2] T. Lee and R. E. Notari, *Pharm. Res.*, **4**, 98 (1987)

[3] Y. Pramar, V. D. Gupta, and C. Bethea, *J. Clin. Pharm. Ther.*, **17**, 185 (1992)

[4] S. Perlman and J. Kirschbaum, *J. Chromatogr.*, **206**, 311 (1981)

[5] C. F. Cullis, J. D. Hopton, C. J. Swan, and D. L. Trimm, *J. Appl. Chem.*, **18**, 335 (1968)

[6] T. J. Wallace and A. Schriesheim, *J. Org. Chem.*, **27**, 1514 (1962)