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THE EFFECT OF 2-HYDROXYPROPYL-ß-CYCLODEXTRIN ON THE SOLUBILITY, STABILITY AND DISSOLUTION RATE OF FAMOTIDINE

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ABSTRACT

Famotidine was found to form an inclusion complex with 2-hydroxypropyl-ß-cyclodextrin (HPCD). Phase-solubility diagram was classified as type A_L with a stability constant for complex formation (K_{st}) of 100.50 M^{-1} at pH 7.4. Famotidine undergoes specific acid catalysis in strongly acidic solutions. Addition of HPCD to these solutions decreased the rate of drug degradation. The rate constant for degradation of complexed famotidine (k_c) and K_{st} were estimated from the relationship between the observed rate constant for overall drug degradation (K_{obs}) and HPCD concentration. An increase in ionization of famotidine resulted in a decrease in the magnitude of K_{st}. The dissolution rate of the prepared complex was significantly greater than that of the pure drug.

INTRODUCTION

Famotidine is a competitive inhibitor of histamine H_2-receptors and suppresses both the acid concentration and volume of gastric secretion [1,2]. Although

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famotidine reportedly undergoes minimal first-pass metabolism, its oral bioavailability is only 40-45%. Poor aqueous solubility and gastric degradation are believed to contribute to its low bioavailability [3,4].

Cyclodextrins are cyclic carbohydrates capable of forming inclusion complexes with several poorly water-soluble compounds, thereby enhancing their solubility and/or stability in an aqueous environment. ß-cyclodextrin has been shown to improve the solubility and dissolution rate of famotidine [5] .However, low aqueous solubility (about 1.8% w/v at 25°C), hemolytic activity, and potential for renal toxicity upon parenteral administration [6,7] has limited the widespread use of ß-cyclodextrin. 2-hydroxypropyl-ß-cyclodextrin (HPCD) is a highly water-soluble amorphous cyclodextrin which retains the ability to form inclusion complexes, but is devoid of any significant toxicity [7-9].

The purpose of this study was to improve the solubility and dissolution rate of famotidine through complexation with HPCD. Additionally, the effect of HPCD on the degradation of famotidine in an acidic environment was also investigated, since there has been, to date, no data reported on the aqueous stability of famotidine in the presence of a cyclodextrin.

MATERIALS

Famotidine and sulfamerazine were obtained from Sigma Chemical Co., St. Louis, MO. HPCD with a molecular weight of 1541 (corresponding to a degree of substitution of seven 2-hydroxypropyl residues per molecule) was kindly provided by American Maize-Products Co., Hammond, IN, and was used as received. Standardized hydrochloric acid (1N) was obtained from Fisher Scientific Co., Fair Lawn, NJ. Buffer substances and all other chemicals were of reagent grade. For the preparation of HPLC mobile phase, HPLC grade methanol and acetonitrile (Fisher Scientific Co.) were used. Distilled, deionized water was used for the preparation of buffer solutions as well as mobile phases.

METHODS

Apparatus

pH measurements were made at the temperature of study using a Chemcadet digital pH-meter equipped with a combination electrode (Cole-Parmer Instrument

Co., Chicago, IL). Dissolution studies were performed using a VanderKamp 600, six spindle dissolution tester (VanKel Industries Inc., Edison, NJ). For analysis of samples from dissolution study, a Response® UV-VIS spectrophotometer (Gilford Systems, Oberlin, OH) was used. HPLC set-up included a Varian 5000 pump, Valco injector, Varian UV-50 variable wavelength detector, Waters 740 data integrator and an Alltech Hypersil MOS, 5μ column (10 cm x 3.6 mm I.D.). The mobile phase was a mixture of 12% methanol, 2% acetonitrile and 0.25% glacial acetic acid in 0.1 M phosphate buffer (pH 4.6). 0.02 M triethylamine was added as an organic modifier. The flow rate was kept constant at 0.8 mL/min and the efluent was monitored at 267 nm. Retention times of the drug and sulfamerazine (internal standard) were 1.8 and 4.7 minutes, respectively.

Phase-solubility study

This study was performed according to the method reported by Higuchi and Connors [10]. Famotidine in an amount that exceeded its solubility (100 mg) was accurately weighed into each teflon-lined screw-capped scintillation vial, to which was added 5 mL of pH 7.4 phosphate buffer containing various concentrations of HPCD (0 - 0.143 M). The vials were agitated at 37 ± 0.5°C for 72 hours to ensure equilibrium. Following equilibration, contents of the vials were filtered through 0.45 μ membrane filter. Aliquots of the filtered solutions were diluted (when necessary) with mobile phase, mixed with internal standard and injected onto the HPLC. Calibration curve obeyed Beer's law for the entire range of famotidine concentration encountered in the study. Two determinations were made at each HPCD concentration, and the mean famotidine concentration plotted against the corresponding HPCD concentration to generate the phase-solubility diagram.

Kinetic Studies

Three HCl solutions, 0.01, 0.05 and 0.1 N, were prepared from standardized 1 N HCl through appropriate dilutions. A constant ionic strength of 0.3 was maintained in these solutions by adding appropriate amounts of KCl. pH of these solutions was measured before and after the kinetic study and was found to be 2.02, 1.41 and 1.14, respectively.

Studies were initiated by adding 0.1 mL of a 0.01 M stock solution of famotidine in N,N-dimethylformamide to 9.9 mL of preequilibrated acid solutions in screw-capped scintillation vials. The vials were kept in a thermostated water-bath

at 37 ± 0.5°C. Thirty μL samples were withdrawn at appropriate intervals and analyzed for undecomposed famotidine by HPLC.

Effect of HPCD on the Specific Acid Catalysis of Famotidine

Accurately weighed amounts of HPCD (0 - 2.1 g) were added to 10 mL volumetric flasks along with 0.1 mL of a 0.01 M famotidine stock solution. The final volume of the flasks was adjusted with 0.01 N HCl, and the contents transferred to screw-capped scintillation vials placed in a thermostated water-bath at 37 ± 0.5°C. At various intervals, thirty μL aliquots were withdrawn and immediately frozen to stop further reaction. Thawed samples were mixed with internal standard and analyzed for undegraded famotidine by HPLC.

Dissolution Rate Studies

These studies were performed using a USP type II dissolution apparatus according to the method outlined for famotidine in USP XXII. Nine hundred milliliters of phosphate buffer (pH 4.5) served as the dissolution medium. The stirring speed was 50 rpm and the temperature was kept constant at 37 ± 0.5°C. Samples tested include pure famotidine, famotidine-HPCD inclusion complex and a 1:1 physical mixture of famotidine and HPCD. The inclusion complex was prepared by a published method[5]. All samples (passed through 40 and retained on 80 mesh USP Standard) contained an equivalent of 12.5 mg of famotidine. At appropriate time intervals, aliquots were withdrawn using a glass wool-plugged pasteur pipette and analyzed spectrophotometrically at 267 nm.

RESULTS AND DISCUSSION

Figure 1 shows the phase-solubility diagram of famotidine in phosphate buffered (pH 7.4) HPCD solutions (0 - 0.143 M) at 37 ± 0.5°C. It indicates the formation of a soluble complex having a first-order dependence on HPCD concentration and classifies the diagram as type A_L[10]. At 0.143 M HPCD, the solubility enhancement for famotidine was approximately ten fold.The apparent stability constant for complex formation (K_{st}) was calculated from figure 1 based on the equation:

$$K_{st} = \frac{\text{Slope}}{\text{Intercept } (1 - \text{Slope})}$$

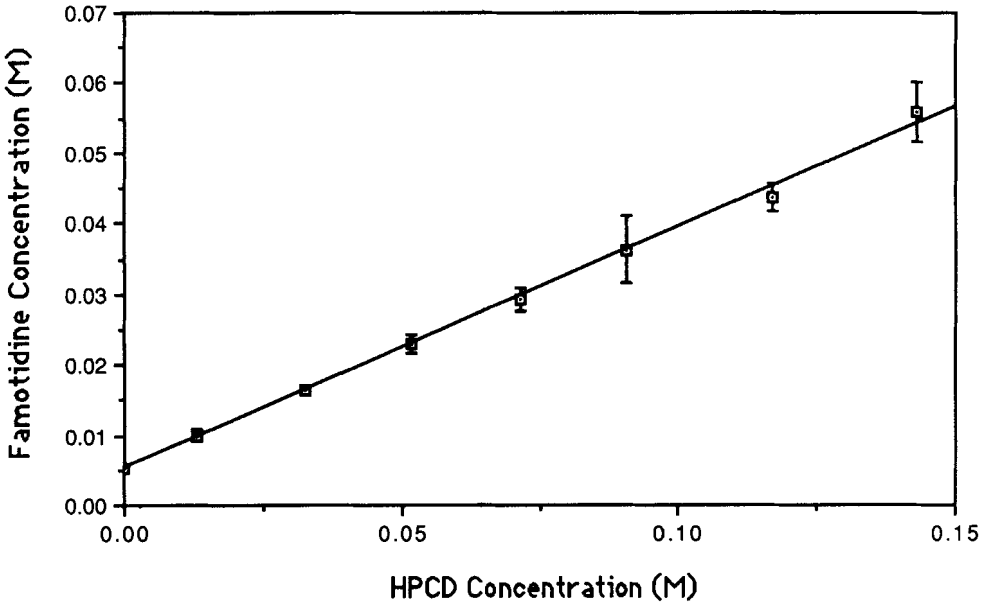


FIGURE 1

Phase-solubility diagram for famotidine-HPCD system in pH 7.4 phosphate buffer at 37° ± 0.5°C. Each data point is the mean of two determinations. The error bars denote S.D.

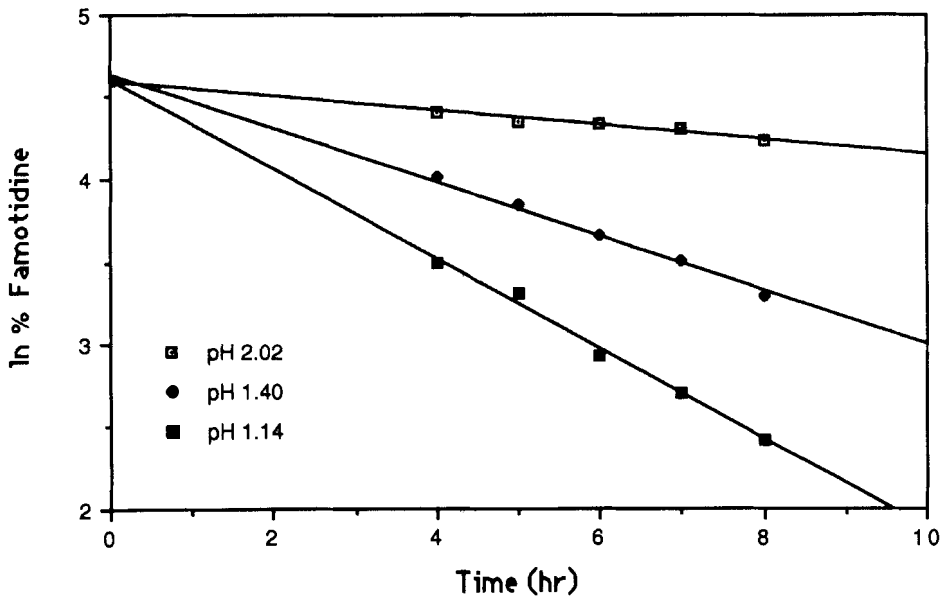


FIGURE 2

Plot showing the pseudo-first order degradation of famotidine at 37 ± 0.5°C and three different pHs (μ = 0.3).

TABLE 1

Effect of pH on the observed pseudo-first order rate constant (K_{obs}) for famotidine degradation at 37 ± 0.5°C (μ = 0.3).

HCl (N)	pH	K_{obs} (hr^{-1})
0.01	2.02	0.044
0.05	1.40	0.162
0.10	1.14	0.272

and was found to be 100.50 M^{-1}. The stoichiometry of the inclusion complex was assumed to be 1:1 based on Figure 1.

The degradation of famotidine in hydrochloric acid solutions followed pseudo-first order kinetics as evident from the linear plot in Figure 2. Table 1 shows the observed pseudo-first order rate constants (K_{obs}) for drug degradation at the three pHs studied.

A plot of log K_{obs} versus pH (Figure 3) is linear with a slope of 0.9 indicating specific acid catalysis of famotidine. The rate constant for specific acid catalysis (K_H+) is calculated to be 2.93 M^{-1} hr^{-1} based on the equation:

$$\log K_{obs} = \log K_H^+ - pH$$

Introduction of up to 0.136 M of HPCD to the reaction medium did not affect the order of the reaction as linear relationships were obtained in all cases between logarithm of percent drug remaining versus time. Increasing the HPCD concentration decreased the rate of degradation of famotidine at pH 2.02 and 37 ± 0.5°C. A non-linear relationship between K_{obs} and HPCD concentration was obtained as depicted in Figure 4. This result is consistent with the reaction kinetics postulated in Scheme I, where k_o is the observed rate constant for degradation of free drug, k_c is the rate constant for degradation of the complexed drug, and K_{st} is the apparent stability constant for complex formation, assuming 1:1 complexation [11].

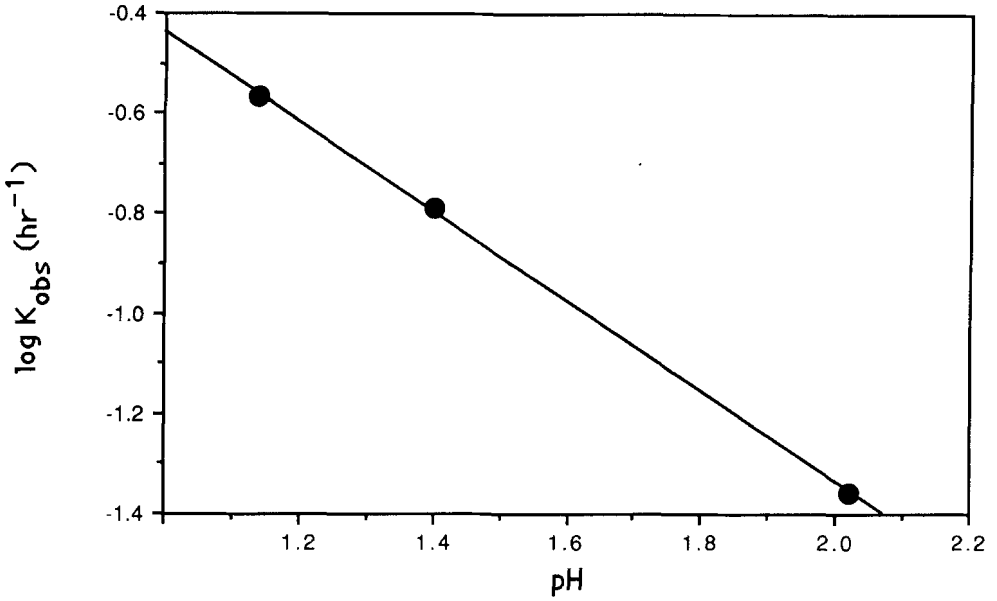


FIGURE 3

Plot showing the specific acid catalysis of famotidine at 37 ± 0.5°C (μ = 0.3).

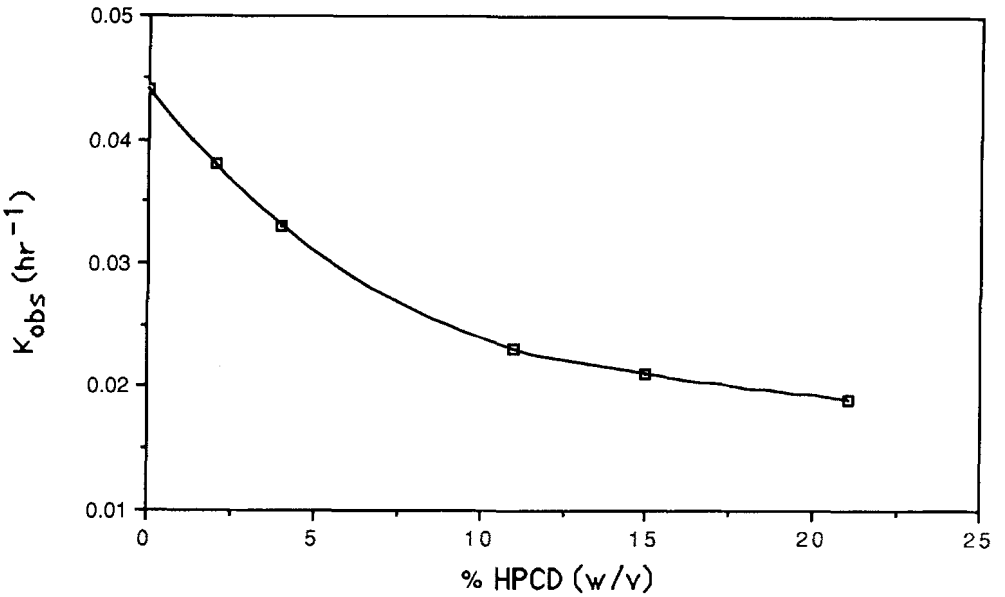
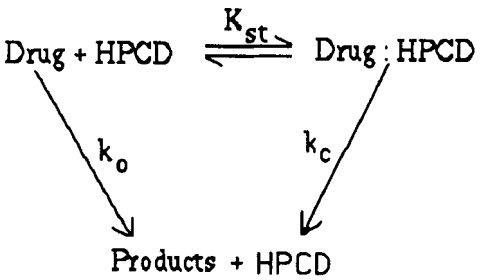


FIGURE 4

Plot showing non-linear dependency of K_{obs} for famotidine degradation at pH 2.02 and 37 ± 0.5°C on HPCD concentration.



Scheme I

Based on Scheme I, the rate expression for the change of total drug concentration, $[Drug]_T$ is:

$$\frac{-d\,[Drug]_T}{dt} = k_o[Drug] + k_c[Drug:HPCD] \qquad (1)$$

Rearrangement and manipulation of equation 1 with the equation for K_{st} based on Scheme I yields [12]:

$$\frac{k_o}{k_o - K_{obs}} = \frac{k_o}{K_{st}(k_o - k_c)[HPCD]} + \frac{k_o}{(k_o - k_c)} \qquad (2)$$

Figure 5 is a Lineweaver-Burk plot of the rate data according to equation 2. The value of k_o was observed to be 4.4×10^{-2} hr^{-1}. The value of k_c was calculated to be 1.97×10^{-3} hr^{-1}, and that of K_{st}, calculated by dividing the ordinate intercept by the slope, was found to be 12.98 M^{-1}. This indicates that free famotidine degrades faster than complexed famotidine and that complex formation increases famotidine stability by 22 fold at pH 2.02 and 37 ±0.5°C. K_{st} is significantly larger at pH 7.4 (phase-solubility data) than at pH 2.02 indicating that the ionized form of famotidine does not form a stable inclusion complex with HPCD.

Figure 6 shows the dissolution profiles of drug, physical mixture, and the prepared complex at pH 4.5 and 37 ± 0.5°C. It is evident that both the complex and physical mixture demonstrate a significant enhancement in the dissolution rate compared to the free drug. The enhanced dissolution rate of the complex can be attributed to an increase in solubility and a decrease in crystallinity. An

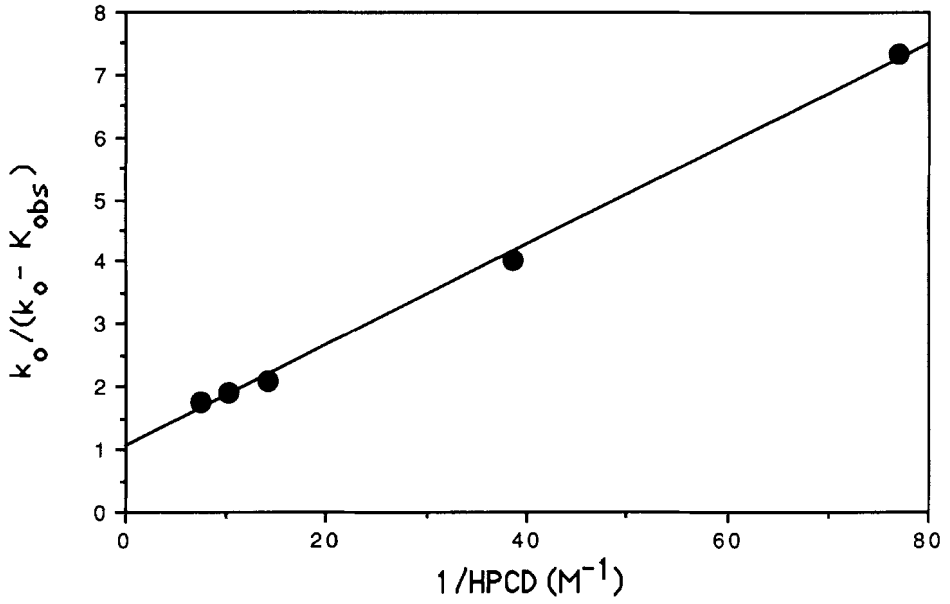


FIGURE 5

Lineweaver-Burk plot of the rate data in figure 4 according to equation (2).

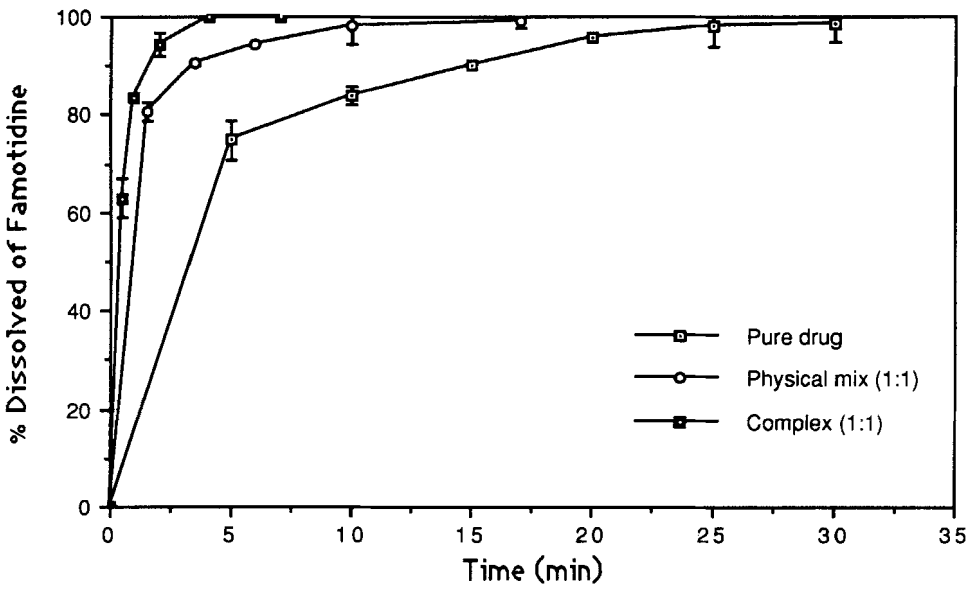


FIGURE 6

Dissolution profiles of pure famotidine, physical mixture and inclusion complex in pH 4.5 phosphate buffer at 37 ± 0.5°C. Each data point is the mean of two determinations. The error bars indicate S.D.

improvement in the wettability of famotidine particles due to quick dissolution of HPCD in the microenvironment is believed to account for the increased dissolution rate of the physical mixture [13].

CONCLUSIONS

Famotidine was found to form an inclusion complex with HPCD, with the generation of an A_L type phase-solubility diagram. At 0.143 M HPCD, the solubility enhancement for famotidine was approximately ten fold. Complexed famotidine degraded at a slower rate than uncomplexed famotidine at pH 2.02 and 37 ± 0.5°C. The complex is markedly more soluble than the pure drug resulting in an increase in its dissolution rate. It appears that increase in ionization of famotidine results in a significant decrease in its stability constant for complex formation with HPCD. Studies are currently underway to characterize the complex formation of famotidine with other amorphous cyclodextrin derivatives with a goal of enhancing its oral bioavailability.

ACKNOWLEDGMENTS

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REFERENCES

1. Physicians' Desk Reference, 44th edition, Medical Economics Company Inc., NJ (1990) pg. 1428.
2. K. Heinrich, Pharm. Int., 7, 213 (1986).
3. H. Kromer and U. Klotz, Int. J. Clin. Pharmacol. Ther. Toxicol., 25, 453 (1987).
4. M. Suleiman, N. Najib, M. Hassan and M. Hamid, Int. J. Pharm., 54, 65 (1989).
5. M. Hassan, M. Suleiman and N. Najib, Int. J. Pharm., 58, 19 (1990).
6. A. Yoshida, H. Arima, K.Uekama and J. Pitha, Int. J. Pharm., 46, 217 (1988).

7. Encapsin® HPB, Promotional Literature from Janssen Biotech N. V. Drug Delivery Systems, Belgium, June 1990.
8. J. Pitha, T. Irie, P. Sklar and J. Nye, Life Sci., 43, 493 (1988).
9. M. Brewster, K. Estes and N. Bodor, Int. J. Pharm., 59, 231 (1990).
10. T. Higuchi and K. Connors, in "Advances in Analytical Chemistry and Instrumentation", C. N. Reilley (ed.), Interscience, New York 1965, pg. 132.
11. A. Green and J. Guillory, J. Pharm. Sci., 78, 427 (1989).
12. T. Loftsson, S. Bjornsdottir, G. Palsdottir and N. Bodor, Int. J. Pharm., 57, 63 (1989).
13. A. H. Goldberg, M. Gibaldi, J. L. Kanig and M. Mayersohn, J. Pharm. Sci., 55, 581 (1966).