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DRIED MOLASSES AS A DIRECT COMPRESSION MATRIX FOR ORAL CONTROLLED RELEASE DRUG DELIVERY II: RELEASE MECHANISM AND CHARACTERISTICS OF THEOPHYLLINE FROM A MOLASSES-HPMC MATRIX

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ABSTRACT

Controlled release tablets consisting of theophylline, dried molasses, and hydroxypropylmethyl cellulose was prepared by the process of direct compression. The release mechanism was shown to be by diffusion control. However, first-order kinetics also appeared to describe the release process.

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The release rate constant in various media was in the rank order of intestinal fluid > gastric fluid > distilled water, and was found to be independent of both tablet hardness and drug concentration. Experimental formulations compared well with commercial products, and met the USP proposed standards for controlled release products.

INTRODUCTION

The release pattern of a drug may differ substantially among products based on barrier coating, either of beads or whole tablets, insoluble matrix, eroding matrix or hydrophilic gel matrix (1-3). The release mechanism of many sustained release products can be described by the Higuchi equation (4):

$$Q_t = \frac{D \quad C_s}{\tau} (2A - C_s) t^{1/2} \qquad (1)$$

where:

Q_t = mass of drug released at time, t, per unit exposed surface

A = initial mass of drug present in the matrix per unit volume

C_s = solubility of the drug in the dissolution fluid

D = diffusion coefficient of the drug in the dissolution fluid

ε = porosity of the matrix

τ = tortuosity factor for the capillary system of the matrix

Although the above equation is based on release from a single surface, it may be used to describe diffusion-controlled release from all surface tablets. According to Eq. 1, a plot of the amount of drug released against the square root of time will be linear. On the assumption that the exposed surface area of a tablet decreases exponentially with time, Wagner (5) suggested that drug release from most slow-release tablets could be described by apparent first order kinetics, thus:

$$C_t = C_o e^{-k_1 t} \qquad (2)$$

where:

k_1 = first order release constant

C_o = initial amount of drug

C_t = amount of drug remaining in the matrix at time, t

Simplifying and taking the logarithm of Eq. 2 yields:

$$\text{Log } C_t = \log C_o - \frac{k_1 t}{2.303} \qquad (3)$$

Hence, a plot of the logarithm of the amount of drug

remaining against time will be linear, if sink conditions are operative.

Many factors are known to affect the release characteristics of a drug from sustained release preparations, among which are shape of tablet, drug solubility in the dissolution fluid, pH of dissolution fluid, porosity and tortuosity of the matrix, and drug concentration (6-10).

It was therefore the purpose of this study to investigate the release mechanism from this system, and to determine the effect, if any, of such factors as tablet hardness, dissolution fluid pH, and drug concentration on the release characteristics. Finally, a comparative dissolution study was conducted to assess the system's performance against commercial sustained release products.

EXPERIMENTAL

Effect of Dissolution Fluid pH

Formulations containing 12.50, 15.0, 20.0 and 28.57% of hydroxypropyl methylcellulose (HPMC) (Methocel F4M, Dow Chemical USA, Midland, Michigan) and dried molasses (Mola-Tab, Specialty Products Division, Ingredient Technology Corporation, Pennsauken, New

Jersey) were prepared as previously reported (11). Drug release studies of each of the formulations were performed in stimulated gastric fluid (pH 1.2), simulated intestinal fluid (pH 7.5), and distilled water, respectively, as previously described (11).

Effect of a Change-Over from Gastric to Intestinal Fluid

A drug release study of a tablet formulation containing 20% HPMC, 42.86% theophylline, and 37.86% dried molasses was performed in gastric fluid for a period of 1.5 hours (representing an average residence time in the stomach), after which the gastric fluid was completely replaced with intestinal fluid, and the release study continued in this fluid.

Effect of Tablet Hardness

A tablet formulation containing 20.0% HPMC, 42.86% theophylline and 37.86% dried molasses was compressed to hardness levels of approximately 5.0, 8.0 and 10.0 kp. Theophylline release study was performed in intestinal fluid using the procedure previously described.

Effect of Drug Concentration

The effect of varying the concentration of theophylline in tablet was investigated using tablets containing 100.0, 200.0 and 300.0 mg of theophylline. In each case, the ratio of HPMC to dried molasses was kept constant.

Comparative Release Study

For evaluation and comparison purposes, release studies were performed on two commercial sustained release products: Theo-dur^{R} 200 mg (Key Pharmaceuticals, Florida), and Uniphyllin Unicontin 200 mg (Napp Laboratories, Ltd., Watford, England) under identical conditions as described for experimental formulations.

The experimental formulation A consisted of 15.0% HPMC, 28.59% theophylline (or 200 mg theophylline) and 56.41% dried molasses. The corresponding levels for experimental formulation B were 20,0, 28.59 and 51.41%, respectively. Both formulations were compressed to a hardness of about 8 kp.

RESULTS AND DISCUSSION

Release Mechanism

In order to explore the mechanism of drug release from this system, the experimental data were treated on

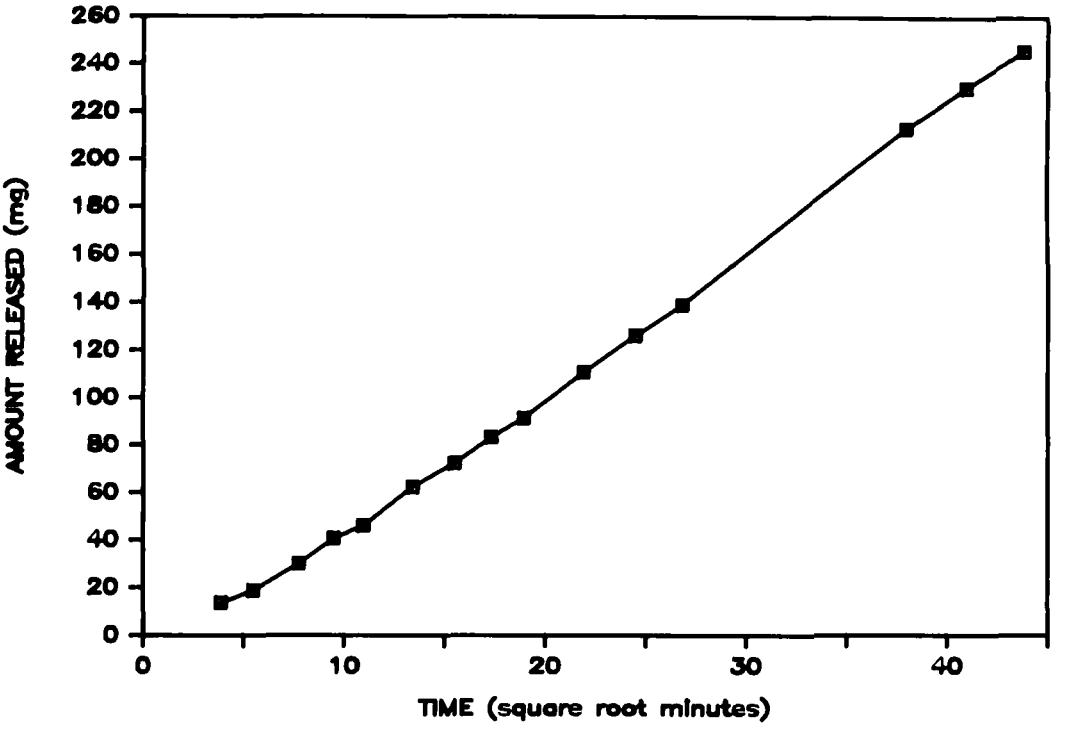

Figure 1

A Plot of Amount of Drug Released Against the Square Root of Time. Dissolution Medium: Distilled Water. HPMC Concentration: 15.0%.

the basis of the diffusion controlled model (Eq. 1), and first order kinetics model (Eq. 3).

Figure 1 shows a linear square root of time plot, thus indicating that the release of the drug is by the diffusion controlled mechanism.

Interestingly, the data also yielded a straight line when the log of the amount of drug remaining in the matrix was plotted as a function of time, as predicted by first order kinetics (Eq. 3). Figure 2

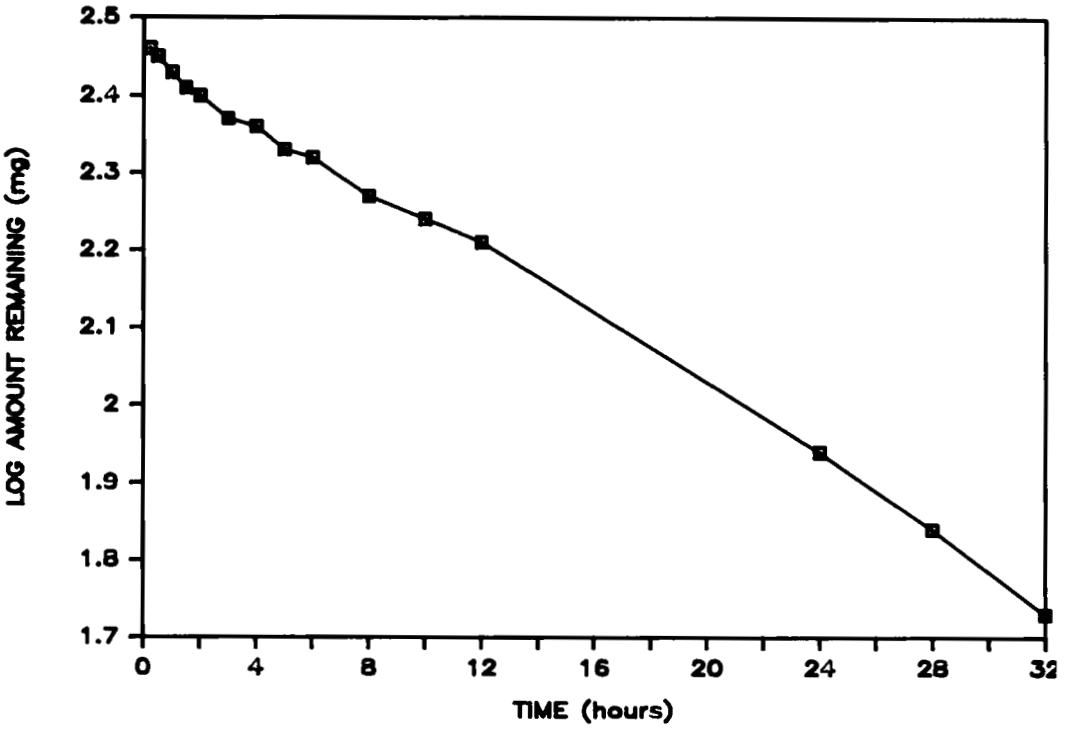

Figure 2

A Plot of the Log of Amount of Drug Remaining Against Time. Dissolution Medium: Distilled Water. HPMC Concentration: 15.0%.

illustrates the release profiles when plotted in this manner. All the formulations in all of the dissolution fluids gave similar release patterns. Table I gives the comparison between the linearizations of release rate data by the two models. The diffusion equation gave consistently higher values for the correlation coefficient than did the first order equation; however, since both models are acceptably linear, a more

TABLE I

COMPARISON BETWEEN LINEARIZATIONS OF RELEASE RATE DATA BY DIFFUSION AND FIRST-ORDER TREATMENTS

Release Mechanism	HPMC Conc. (%)	Dissolution Fluid	Slope	Intercept	Correlation Coefficient
Diffusion	15.00	Distilled Water	5.957±0.083	-17.930	0.999
	20.00	pH 1.2	6.244±0.181	-19.423	0.999
Controlled	28.57	pH 7.5	6.604±0.311	-21.767	0.997
First-Order	15.00	Distilled Water	0.022±0.035	2.455	0.999
	20.00	pH 1.2	0.025±0.108	2.455	0.998
	28.57	pH 7.5	0.027±0.213	2.475	0.994

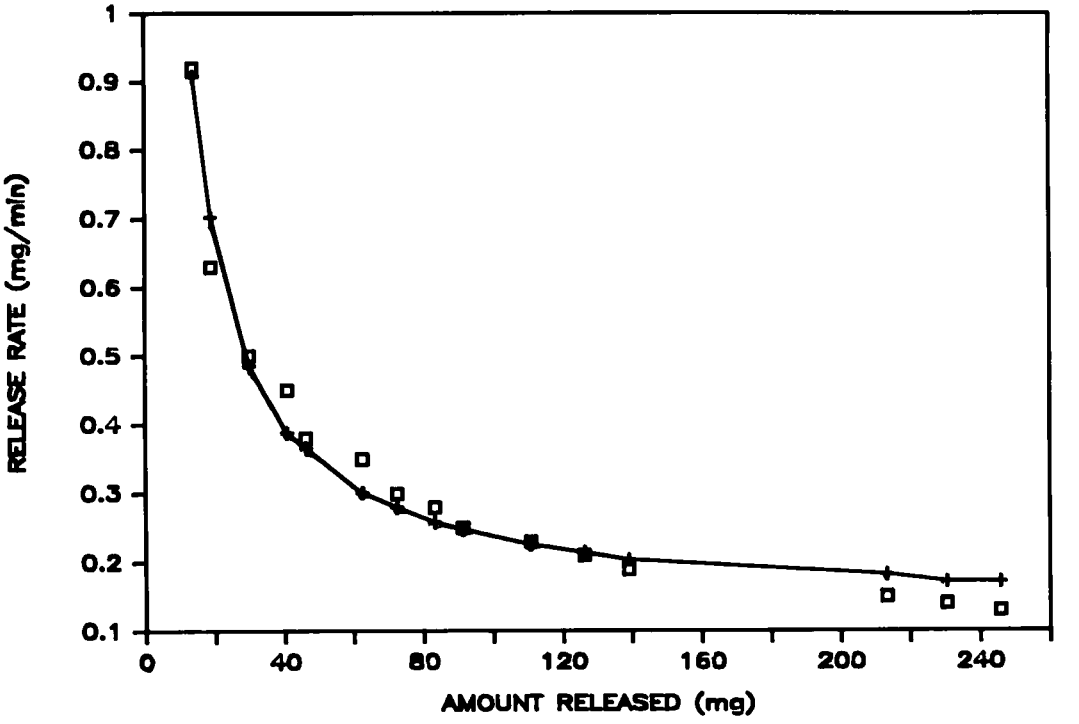

Figure 3A

A Plot of the Rate of Drug Released Against the Amount of Drug Released. Dissolution Medium: Distilled Water. HPMC Concentration: 15.0%.

discriminating test, reported by Schwartz et al (12), was utilized to distinguish between the two mechanisms. The relative validity of the test was obtained by using the differential forms of the rate equations (Eqs. 1,3).

For diffusion controlled, the rate $\frac{dQ'}{}$ is proportional to the reciprocal, $1/Q'$, where Q' is the total amount of drug released at a given time

$$\frac{dQ'}{dt} = \frac{k^2}{2Q'} \qquad (4)$$

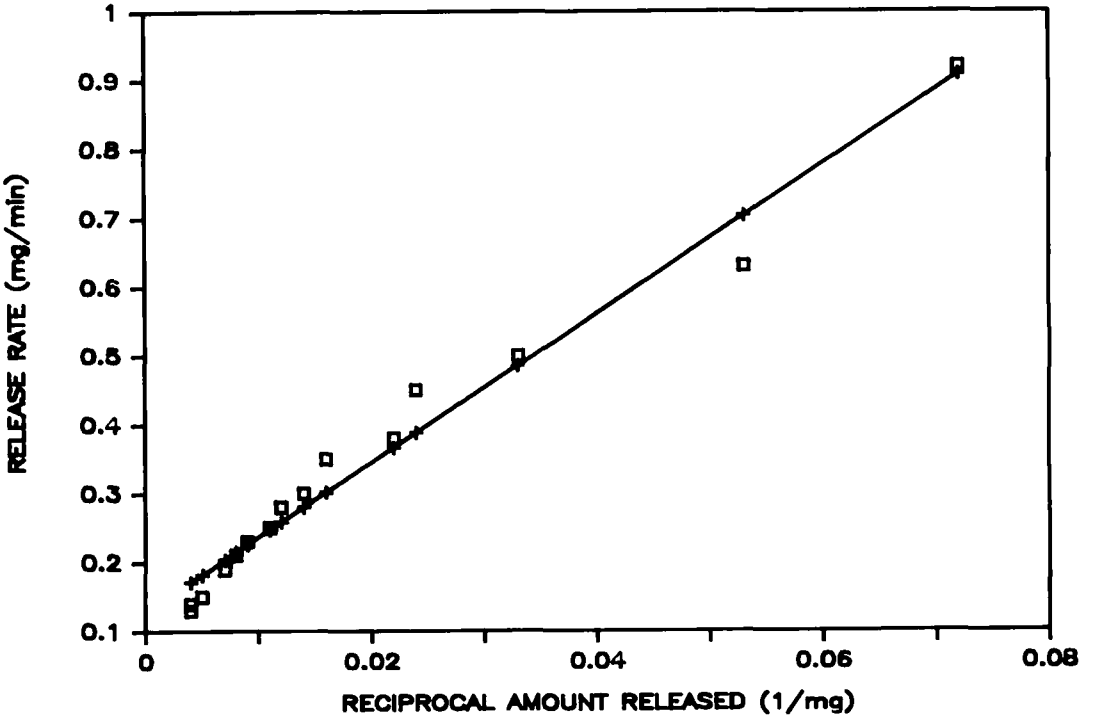

Figure 3B

A Plot of the Rate of Drug Released Against the Reciprocal Amount Released. Dissolution Medium: Distilled Water. HPMC Concentration: 15.0%.

and for first order, the rate is related directly to Q'

$$\frac{dQ'}{dt} = kA - kQ' \qquad (5)$$

When the rates were plotted as functions of 1/Q' and Q', respectively, linearity was obtained only in the former case. This is demonstrated in Figure 3, and indicates that the process is diffusion controlled and not first order.

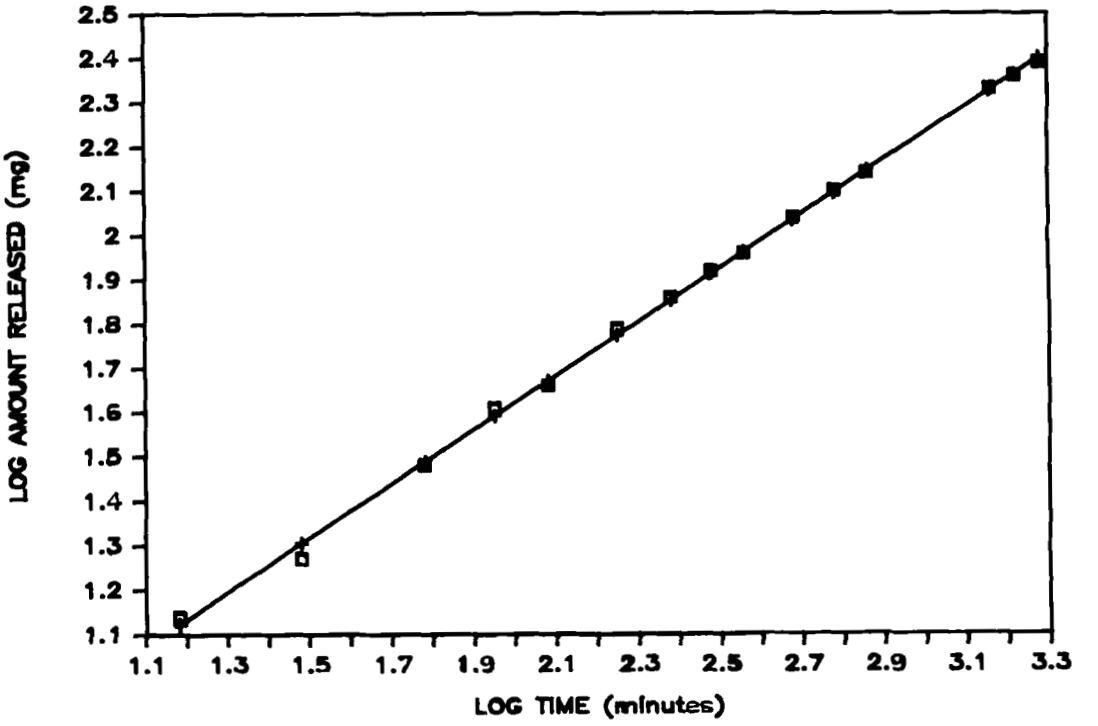

Figure 4

A Plot of the Log of the Amount of Drug Released Against the Log of Time. Dissolution Medium: Distilled Water. HPMC Concentration: 15.0%.

A further evidence to confirm the diffusion process is provided by the use of the logarithmic form of the diffusion equation

$$\log Q = \log k + 1/2 \log t \qquad (6)$$

Equation 6 predicts that a plot of log Q versus log t must not only give a straight line, but must have a slope of 0.5. This is illustrated in Figure 4 with a

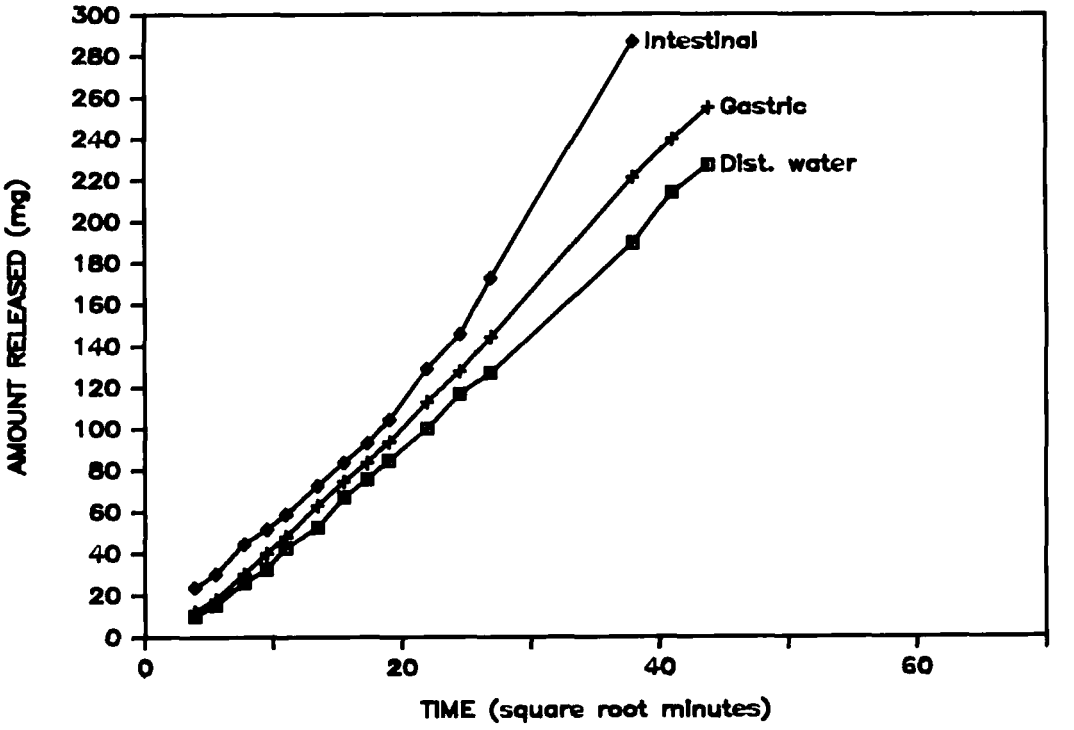

Figure 5

A Plot of the Amount of Drug Released Against the Square Root of Time Showing the Effect of pH of the Dissolution Medium. HPMC Concentration: 20.0%.

slope of 0.61, a value not markedly different from theoretical.

Effect of Dissolution Fluid pH

A representative plot showing the effect of dissolution fluid pH on the release rate is shown in Figure 5 with release rate constants of 7.336 $\pm$ 0.416,

6.244 ± 0.181 and 5.540 ± 0.138 $min^{-1/2}$ in intestinal fluid, gastric fluid and distilled water, respectively. Several authors (6,7,13-15) have shown that the dissolution fluid as well as the drug solubility affected drug release to different degrees. However, in this study, the solubility of theophylline in the dissolution fluids did not seem to affect the release rate since no marked difference in its solubility in these fluids was observed. Therefore, what appeared to have affected the release rate was attributed to the relative solubility of HPMC and/or ionic species present in these fluids.

At 12.50% HPMC, the release rate constants of 6.348 ± 0.203, 7.211 ± 0.098 and 24.661 ± 2.946 $min^{-1/2}$ were obtained in distilled water, gastric fluid and intestinal fluid, respectively. At 15.0% HPMC, the corresponding values were: 5.957 ± 0.083, 6.667 ± 0.343 and 12.545 ± 0.148 $min^{-1/2}$.

At much higher HPMC concentrations, when its solubility apparently approached equilibrium in these fluids, the differences in the release rate constants became smaller. For example, at 28.57% HPMC, the release rate constants in distilled water, gastric fluid and intestinal fluid were 5.356 ± 0.140, 5.953 ± 0.011 and 6.590 ± 0.311 $min^{-1/2}$, respectively.

Chloride and phosphate ions are known to cause dehydration of cellulose ethers (16) which could possibly result in more polymer-polymer interaction. This could disrupt the intermolecular bonding, and thus affect the gel network structure. During the release study in intestinal fluid, it was observed that, upon an immersion of tablets into fluid, a rapid "disintegration" of tablet surface into flocs of gellified material occurred within the first 30 minutes before a "stable" gel layer formed around the tablet. The phenomenon was less pronounced in gastric fluid, and unnoticeable in distilled water.

Effect of Change-Over from Gastric to Intestinal Fluid

Table II shows the computed release rate constants obtained during the change-over from gastric to intestinal fluid. The release rate constants in distilled water, gastric fluid and intestinal fluid are also included for comparison purposes. The results showed that, at optimum HPMC concentration, there was no marked difference in the release rate constants, thus suggesting that, for this system, one may expect minimal or no effect on the release rate during a change over from gastric to intestinal fluid in a dissolution study. The result may also suggest no

TABLE II

COMPUTED RELEASE RATE CONSTANT (K_r): EFFECT OF A CHANGE-OVER FROM GASTRIC TO INTESTINAL FLUID

HPMC CONCENTRATION 20.0%

Dissolution Fluid	Release Rate Constant, K_r ($min^{-1/2}$)
Distilled Water	5.540 ± 0.138
Gastric Fluid pH 1.2	6.244 ± 0.181
Intestinal Fluid pH 7.5	7.336 ± 0.416
Change Over from Gastric to Intestinal Fluid after 1.5 hr	6.517 ± 0.155

significant difference in the release rate constant during the drug's transit in-vivo through the gastrointestinal tract.

Effect of Tablet Hardness

The effect of hardness on the release characteristics of theophylline is shown in Figure 6. The release rate constants were 7.376 ± 0.267, 7.553 ± 0.315 and 7.336 ± 0.416 $min^{-1/2}$, respectively,

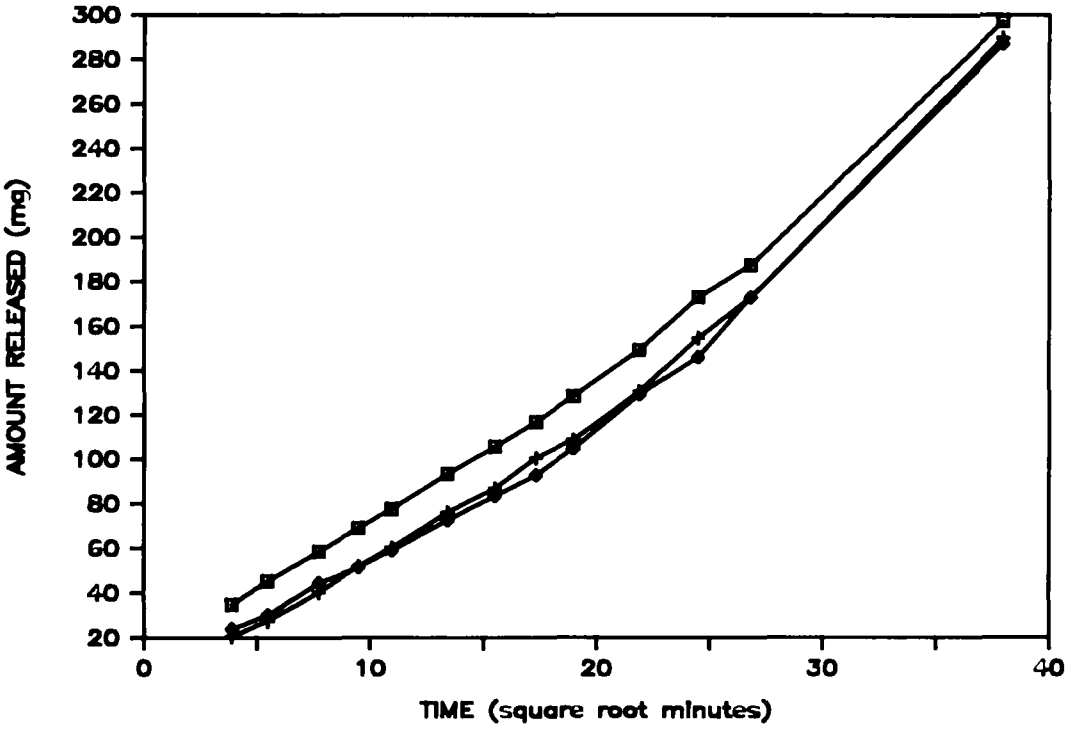

Figure 6

A Plot of the Amount of Drug Released Against the Square Root of Time Showing the Effect of Tablet Hardness. Dissolution Medium: Intestinal Fluid. HPMC Concentration: 20.0%. (Key: = 5.4 kp tablet hardness; = 8.2 kp tablet hardness; = 10.6 kp tablet hardness)

for hardness values of 5.42, 8.22 and 10.57 kp. No significant difference in the release rate constants was observed ($p < 0.05$).

The porosity and density of the tablets were not determined. From a theoretical standpoint, hardness measurements quantitatively reflect differences in density and porosity of the tablets. These could

possibly influence the rate of tablet dissolution by affecting the initial rate of penetration of dissolution fluid at the tablet surface. This, in turn, would affect the rate of formation of the gel barrier at the periphery. The result thus indicates that one can expect little or no change in release pattern as a result of alteration in tablet density and porosity of the system.

If, however, changes occur, they probably will appear during the initial phase of the dissolution period, and the shape of the release profile will not be markedly altered. Apparently, the high affinity of HPMC for aqueous solutions will overcome any deterring influence which an increased density or decreased porosity may tend to exert on the initial rate of fluid penetration into the tablet surface.

Effect of Drug Concentration

Plots of the amount of drug released versus the square root of time as a function of drug concentration, are shown in Figure 7. It was observed that the release rate increased as the concentration of drug was increased. It could be assumed that increasing the amount of theophylline in the tablet would result in a corresponding increase in porosity by

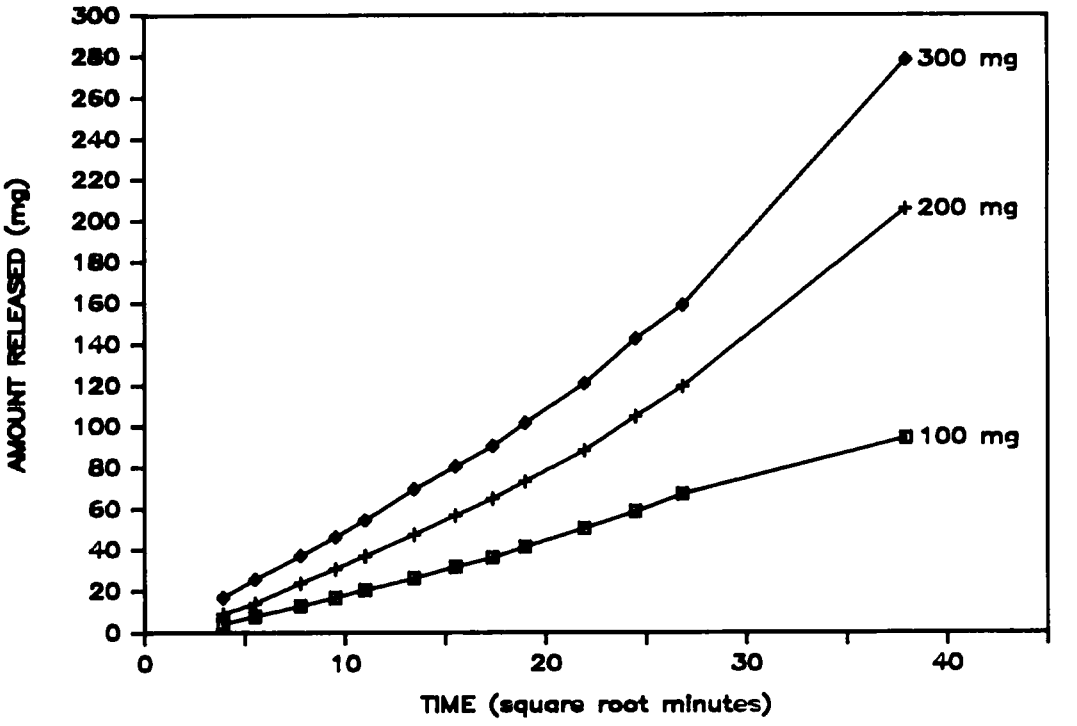

Figure 7

A Plot of the Amount of Drug Released Against the Square Root of Time Showing the Effect of Drug Concentration. Dissolution Medium: Intestinal Fluid.

the same factor but would not affect other variables. It is evident from the rate equation that the slope should also increase by the same factor. On examination of the results, the slope of the 200 mg tablet was 2.033 times that of the 100 mg tablet, and the 300 mg tablet was 2.663 times that of the 100 mg tablet. If the above assumptions were correct, the factor should have been 2 and 3 times, respectively.

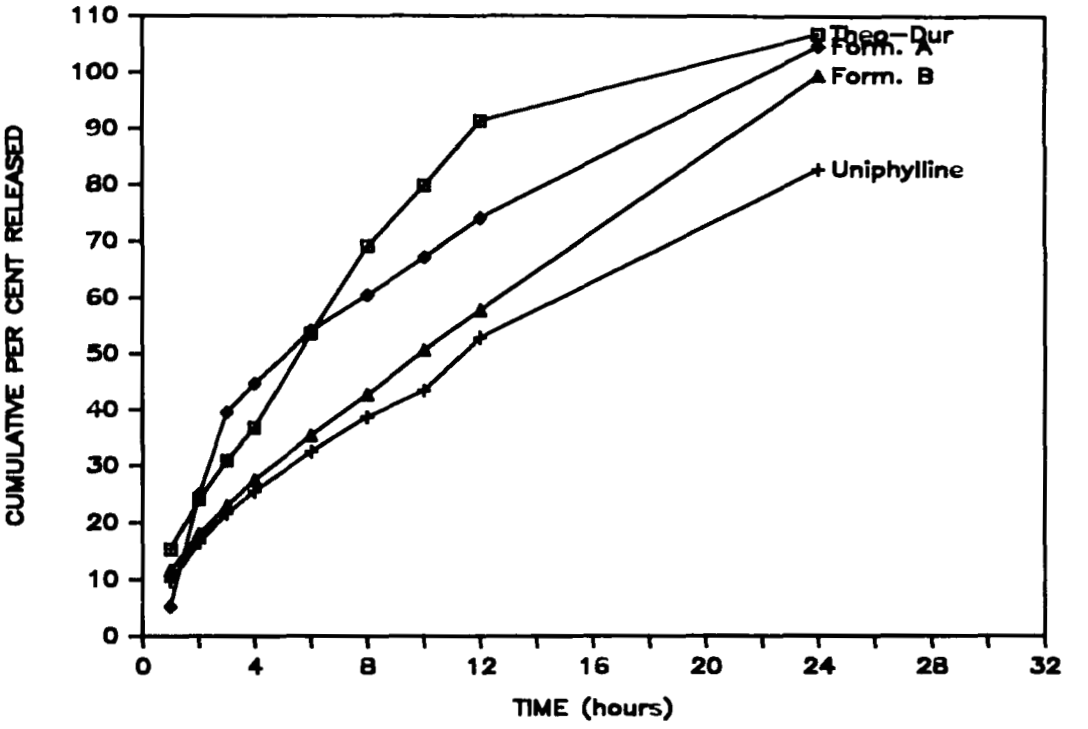

Figure 8

Comparative Release Profiles of Theophylline Formulations.

The results obtained were close to theoretical values, and the deviations may indicate that other factors in the equation were changing with the amount of theophylline, or that the porosity was not proportional to A (the initial amount of drug in matrix).

The release rate constants obtained were 2.779 ± 0.310, 2.659 ± 0.438 and 2.334 ± 0.384 $min^{-1/2}$ for 100, 200 and 300 mg tablets, respectively, and were

not significantly different ($p < 0.05$). The result indicates that the release rate constant is independent of drug concentration.

Comparative Release Study

The cumulative percent of theophylline dissolved at various times for Theo-dur^R, Uniphyllin^R, and the two experimental formulations is shown in Figure 8.

At 4 hours, the percent release for Theo-dur^R, Uniphyllin^R, formulations A and B were 36.81, 25.54, 44.73 and 27.50%, respectively. At 12 hours, the corresponding values were 91.43, 52.93, 74.20 and 57.84%. Except for Uniphyllin^R (with 82.72%), more than 90% of drug was released by the products in 24 hours.

All of the products displayed some type of sustained release characteristics, with Uniphyllin^R comparing with formulation A, and Theo-dur^R with formulation B. The formulations also met the USP proposed standards for sustained release preparations (17). At 6 hours, the percent released ranged from 31.19 to 43.01% (USP: 20-50%). At 12 hours, the range was 47.98 to 62.78% (USP: 45-75%) and at 24 hours more than 90% was released (USP: NLT 75%). These results, however, may not reflect in-vivo situations; but

provide additional information as to the usefulness of dissolution studies as compendial methods for determining product content, uniformity, rate and extent of drug release, and in the demonstration of differences among products of various manufacturers.

CONCLUSION

This study indicates that drug release from this system is by matrix diffusion controlled process. While release rate constant shows an inverse relationship with the concentration of HPMC, it is independent of both tablet hardness and drug concentration.

REFERENCES

1. C. Bogentoft and J. Sjogren. In D.D. Brenier (ed.). Towards Better Safety of Drugs and Pharmaceutical Products. Elsevier/North Holland Biomedical Press. Amsterdam. 1980. pp. 229-246.
2. B.E. Cabanna. In D.D. Brenier (ed.). Towards Better Safety of Drugs and Pharmaceutical Products. Elsevier/North Holland Biomedical Press. Amsterdam. 1980. pp. 301-322.
3. K. Marshall. In G.S. Banker and C.T. Rhodes (eds.). Modern Pharmaceutics. Marcel Dekker. New York. 1979. pp. 359-428.

4. T. Higuchi. J. Pharm. Sci. 52:1145-1149 (1963).

5. J.G. Wagner. J.Pharm.Sci. 58:1253-1257 (1969).

6. S.J. Desai, A.P. Simonelli, W.I. Higuchi. J. Pharm. Sci. 54:1459-1464 (1965).

7. R.J. Timko and N.G. Lordi. J. Pharm. Sci. 67:496-499 (1978).

8. A.A. Ghanem and H.M.H. Mahmoud. Pharm. Ind. 42:1307-1312 (1980).

9. J. Lazarus, M. Pagliery, L. Lachman. J. Pharm. Sci. 53:798-802 (1964).

10. E. Touitou and M. Donbrow. Int. J. Pharm. 11:355-364 (1982).

11. S.D. Uko-Nne, R.W. Mendes and S.S. Jambhekar. (Part I) Submitted to Drug Development and Industrial Pharmacy.

12. J.B. Schwartz, A.P. Simonelli and W.I. Higuchi. J. Pharm. Sci. 57:274-277 (1968).

13. N.H. Choulis and H. Papadopoulos. Pharmazie. 30:233-236 (1975).

14. S. Borodkin and F.E. Tucker. J. Pharm. Sci. 63:1359-1364 (1974).

15. S. Jambhekar and J. Cobby. J. Pharm. Sci. 74:991-994 (1985).

16. A.B. Savage. In N.M. Bikales and L. Segal (eds.). Cellulose and Cellulose Derivatives Volume V. Wiley-Interscience. USA. 1971. p. 796.

17. Pharm. Forum. 8(5):2383 (1982).