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SUSTAINED RELEASE FROM PRECIROL® (GLYCEROL PALMITO-STEARATE) MATRIX. EFFECT OF MANNITOL AND HYDROXYPROPYL METHYLCELLULOSE ON THE RELEASE OF THEOPHYLLINE.

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ABSTRACT

The release of theophylline embedded in a Precirol® (glycerol palmitostearate) matrix containing varying amounts of mannitol and/or hydroxypropyl methylcellulose 4000 (HPMC) was studied. The results indicated that HPMC or mannitol when incorporated alone, the drug release followed the diffusion-controlled matrix model where the quantity of drug released was proportional to the square root of time. The release rate was found to increase with increase in the amount of HPMC or mannitol in the matrix. When both mannitol and HPMC were incorporated in the matrix, the mechanism of release changed from the Higuchi model to a first-order release. A linear relationship was found between the fraction of HPMC or mannitol in the matrix and the rate constant. An optimum

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combination of Precirol®, mannitol and HPMC was found for a 12 hour theophylline sustained release preparation.

INTRODUCTION

The matrix system is one of the choices to achieve a sustained drug release from a dosage form. However, for the drug to be released from the planar surface having a granular matrix, the dissolution fluid has to enter the drug-matrix phase through pores, cracks and intergranular spaces, and dissolve the drug. The drug is thought to dissolve slowly into the permeating fluid phase and to diffuse from the system along the cracks and capillary channels filled with extracting solvent[1]. It has been observed that the release rate of the drug from a matrix system depends upon the type of matrix, amount of drug incorporated in the matrix, solubility of drug used, matrix additives and solvent system used[2].

The release of a drug from a wax matrix has been improved by incorporating soluble surfactants[3], povidone[4] and microcrystalline cellulose[5], which produce a wetting action by displacing the air present in the pores of the matrix, and after dissolving in the dissolution medium, open new channels in the matrix for the penetration of the dissolution medium.

The purpose of this study was a) to prepare sustained release tablets of theophylline using Precirol® (glycerol palmito-stearate) as matrix base, b) to incorporate mannitol and HPMC

(hydroxypropyl methylcellulose-4000), and to observe the influence of these two agents on the release of theophylline from the Precirol® matrix base, c) to elucidate the mechanism of release from this system, d) to determine the optimum combination of Precirol®, mannitol and HPMC to have a release of theophylline in the range of 25-40 percent by 2 hours, 40-60 percent by 4 hours and 70-90 percent by 8 hours for the 12 hour sustained release preparation, and e) to determine a relationship between fraction of mannitol or HPMC in the matrix and release rate constant.

Precirol® has been used previously for the preparation of sustained release dosage forms for proxyphylline[6] and salicylate[7].

MATERIALS AND METHODS

Material

Precirol®[a], mannitol[b] and HPMC-4000[c] were of pharmaceutical grade. Theophylline anhydrous[d] was of USP XX grade.

Tablet Preparation

The formulations of different experimental tablets are given in Table 1. There were three groups of experimental tablets. All the groups had Precirol® (150 mg) and anhydrous theophylline (150

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[a]Gattefossé Corporation, Hawthorne, New York, U.S.A.
[b]Matheson Coleman and Bell, Norwood, Ohio, U.S.A.
[c]Fisher Scientific Company, Fair Lawn, New Jersey, U.S.A.
[d]Merell-Dow Pharmaceutical, Inc., Cincinnati, Ohio, U.S.A.

TABLE 1

Composition of Experimental Tablets

Formulation	Theophylline (mg)	Precirol® (mg)	Mannitol (mg)	HPMC (mg)
P	150	150	-	-
Group I				
PM 15	150	150	45	-
PM 30	150	150	90	-
PM 45	150	150	35	-
Group II				
PH 2.5	150	150	-	7.5
PH 5	150	150	-	15
PH 10	150	150	-	30
Group III				
PMH 5	150	150	90	15
PMH 10	150	150	90	30
PMH 15	150	150	90	45
PMH 20	150	150	90	60

mg) in common (P). Group I, PM 15, PM 30 and PM 45 had 15, 30 and 45 percent of mannitol. Group II, PH 2.5, PH 5 and PH 10 had 2.5, 5 and 10 percent of HPMC. Group III had Precirol® (150 mg), theophylline (150 mg) and mannitol (30 %) in common and varying amounts of HPMC. Thus PMH 5, PMH 10, PMH 15 and PMH 20 had 5, 10, 15 and 20 % HPMC.

Theophylline was incorporated into Precirol® by the fusion method. Precirol® was melted on a water bath maintained at 70°C, theophylline powder was added to the melted mass under stirring

and continued stirring for 10 minutes. The melted mixture was poured onto an ice cold glass slab and left aside for 10 minutes. The solid mass was then passed through an oscillator granulator[1] having a sieve size of 1 mm. Mannitol, HPMC were added to the granules by the tumbling method. The granules were compressed on a single punch tabletting machine[2] to flat, bevelled tablets of 11 mm diameter and 5.2 kp hardness[3].

Dissolution Studies

Three dissolution studies were performed on each type of experimental tablets by the rotating basket method[4]. The dissolution medium (900 ml water) was maintained at 37 ± 1 °C and the basket was rotated at 50 rpm. The samples (5 ml) were collected at 5, 15, 30, 45, 60 and 90 minutes and there after at 2, 3, 4, 5, 6, 7 and 8 hours. The volume of sample withdrawn was immediately replaced by water maintained at 37°C. The samples were filtered, diluted with water and analyzed by a Perkin-Elmer spectrophotometer[5] at 274 nm. Drug concentrations in the sample solutions were calculated from a standard curve.

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[1]Oscillator granulator, Type FGS, Model No. 24995, Erweka Apparatebau, Heusenstamm, West Germany
[2]Tableting machine, Model EK-0, Emil Korsch Maschinenfabrik, Berlin, West Germany
[3]Heberlein Hardness Tester, Model 2E/106, Heberlein & Co., Zürich, Switzerland
[4]Dissolution test apparatus, Model T-1044-20X, Van-Kel Industries, Clatham, New Jersey
[5]Perkin-Elemer Double Beam Spectrophotometer, Ser. No. 44733-9, Tokyo, Japan

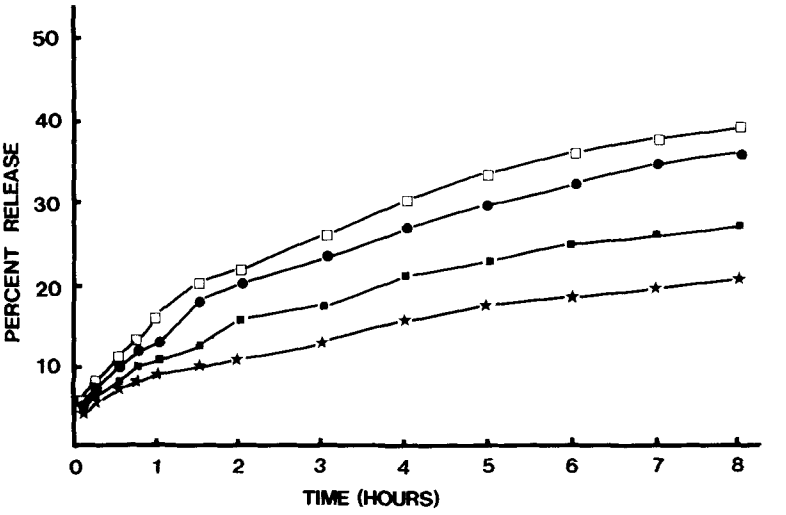

FIGURE 1

Theophylline release from Precirol® matrix tablets containing various percentages of mannitol. Symbols: P - ★-, PM 15 - ■ -, PM 30 - ● - and PM 45 - □ -.

RESULTS AND DISCUSSION

The cumulative amounts of theophylline released versus time for the three groups of tablets are shown in Fig. 1, 2 and 3. The Precirol® matrix base formulation P (Fig. 1), released only 20 % of drug in 8 hours. When 15, 30 and 45 percent mannitol were incorporated into the Precirol® matrix the amount released increased from 20 % for the Precirol® matrix to 26.5, 35.5 and 38.5 percent, respectively (Fig. 1). HPMC showed even better results than mannitol (Fig. 2) as in low concentrations of 2.5, 5 and 10 percent it increased the amount released in 8 hours from 20 % for Precirol® matrix to 31, 37 and 55 percent, respectively.

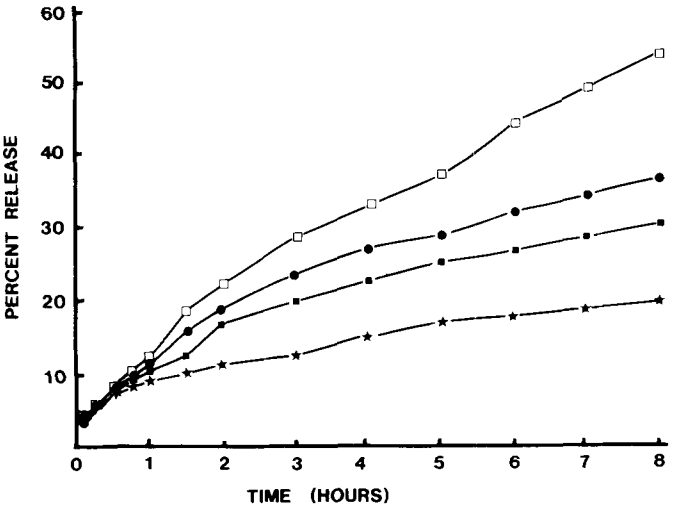

FIGURE 2

Theophylline release from Precirol® matrix tablets containing various percentages of HPMC. Symbols: P - ★ -, PH 2.5 - ■ -, PH 5 - ● - and PH 10 - □ -.

Any further increase in HPMC amount in the matrix did not further increase the total amount of theophylline released in 8 hours. Hence, 10 percent HPMC was regarded as the maximum amount to be effective to increase the release for this system. The PH 10 formulation which released 55 percent of theophylline in 8 hours is considered a promising formulation for a 24 hour sustained release preparation and will be evaluated further.

The main objective was to have a release in the range of 25-40 percent by 2 hours, 40-60 percent by 4 hours and 70-90 percent by 8 hours for the 12 hour sustained release preparation. As mannitol and HPMC, when incorporated alone, could not achieve this

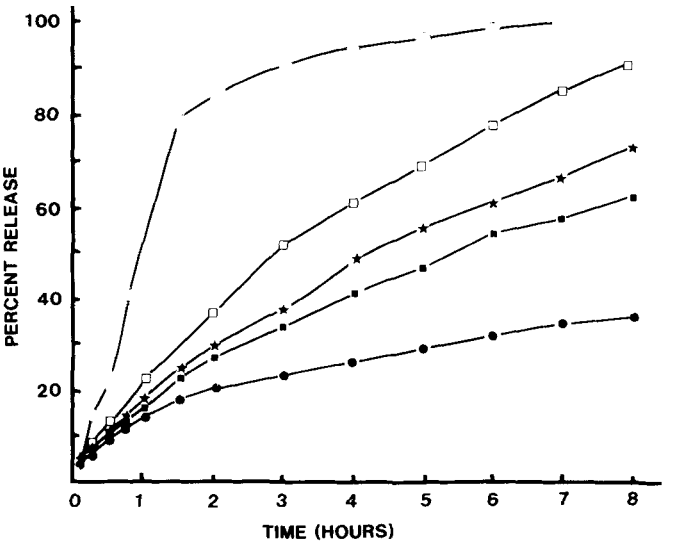

FIGURE 3

Theophylline release from Precirol® matrix tablets containing 30 percent of mannitol and varying percentages of HPMC. Symbols: PM 30 - ● -, PMH 5 - ○ -, PMH 10 - □ -, PMH 15 - ★ - and PMH 20 - ■ -.

objective, it was decided to study the release pattern after incorporating both, mannitol and HPMC, into the Precirol® matrix. Among the Group I experimental tablets, PM 30 formulation was considered to be better than PM 15 and PM 45, when the amount of mannitol incorporated and percentage of theophylline released after 8 hours was compared. Hence it was decided to keep the amount of mannitol (30 percent) constant in the Precirol® matrix and vary the amount of HPMC. The cumulative amounts of theophylline released from Group III experimental tablets are shown in Fig. 3.

It was observed that PMH 5 which has 5 percent of HPMC, released 80 percent of the drug in 90 minutes. In this formulation the tablet disintegrated within 30 minutes and it was not an intact matrix system anymore. However, this was not observed in the PMH 10, PMH 15 and PHM 20 experimental tablets which had 10, 15 and 20 percent of HPMC, respectively. It was found in Group III experimental tablets that increasing the amount of HPMC in the Precirol® - mannitol matrix the amount released in 8 hours decreased, which was in contrast to the Group II experimental tablets in which, when HPMC was incorporated alone, an increase in amount of HPMC in Precirol® matrix increased the percent released in 8 hours. The physical examination of the Group II tablets during dissolution study showed erosion of the matrix, which might be due to swelling of HPMC. The Group III tablets showed no erosion, however there was a swelling and formation of gel. Thus, when HPMC was used alone in an optimum amount the increase in amount of theophylline released was due to erosion of the matrix but when used in combination with mannitol, it formed a gel mass and as the amount of HPMC in the (Group III) tablets increased, there was an increase in viscosity of the gel and thus decrease in release of theophylline.

The PMH 10 and PMH 15 formulations gave desired release (Fig. 3) to be promising for a 12 hour sustained release preparation which will be evaluated further in vivo.

Bamba and coworkers[8] have proposed a goodness of fit method to determine the mechanism of release from a system. They pro-

posed the following mechanisms which may be rate-determining in the release of drug from a system. They are a) the permeation of water, b) the gelation rate, c) the diffusion rate of the drug in the gel, d) the dissolution rate of the drug in the penetrating water and e) the Higuchi porous penetration.

If the release pattern from the system is governed by a, b or c processes then it is a first-order release and Eq. 1 should be applicable. If the release is depicted by process d, then it follows the cube root law and Eq. 2 should be applicable, and if it is governed by porous penetration then the Higuchi square root law should apply (Eq. 3).

$$\ln W = - k_f t + i \qquad (1)$$

$$\sqrt[3]{100} - \sqrt[3]{W} = k_c t \qquad (2)$$

$$100 - W = k_d \sqrt{t} \qquad (3)$$

where, W is the percentage of drug undissolved at time t (min), k_f is the first-order dissolution rate constant (min^{-1}), i is the intercept of the log-linear plot of the type in Eq. 1, k_c is the cube root dissolution rate constant ($mg/min^{1/3}$) and k_d is the Higuchi constant ($mg/min^{1/2}$).

The cumulative amount dissolved versus time data was evaluated by a computer program for the goodness of fit for these three equations and the residuals and correlation coefficients were determined which are given in Table 2.

TABLE 2

Comparison of Fits of Data Using Least Square Equation

Formulation	1 First-order R^2	1 First-order $\frac{\Sigma(Resd)^2}{n-2}$	2 Square root R^2	2 Square root $\frac{\Sigma(Resd)^2}{n-2}$	3 Cube root R^2	3 Cube root $\frac{\Sigma(Resd)^2}{n-2}$	F-test (1-2)	F-test (3-2)
P	0.931	6.304	0.978	1.997	0.927	6.62	1 %	1 %
Group I								
PM 15	0.956	8.263	0.994	0.883	0.951	8.997	1 %	1 %
PM 30	0.956	13.872	0.993	2.037	0.949	15.57	0.05 %	0.05 %
PM 45	0.958	13.563	0.990	3.36	0.952	15.82	5 %	0.05 %
Group II								
PH 2.5	0.967	10.029	0.995	1.29	0.961	11.52	<1 %	<1 %
PH 5	0.958	17.940	0.991	3.52	0.950	20.80	<1 %	<1 %
PH 10	0.987	12.230	0.987	9.617	0.982	15.59	(NS)	25 %
Group III							(2-1)	(3-1)
PMH 5	0.9776	22.100	0.861	44.5	0.931	35.7	5 %	25 %
PMH 10	0.998	2.961	0.991	15.90	0.993	12.58	<1 %	5 %
PMH 15	0.996	5.091	0.99	15.79	0.994	8.49	<1 %	NS
PMH 20	0.992	6.480	0.984	16.04	0.991	8.09	5 %	NS

For the Percirol® matrix P, Group I and Group II experimental tablets, Eq. 3 shows significantly better fitting than Eq. 1 and 2 by the F test. Thus it is observed that in Group I and II experimental tablets, when Mannitol or HPMC are incorporated alone the data fit to the Higuchi square root law, whereas when mannitol and HPMC both are incorporated into the system (Group III), it changes to a first-order release pattern according to Eq. 1 showing significantly better fitting than by equations 2 and 3 by the F test.

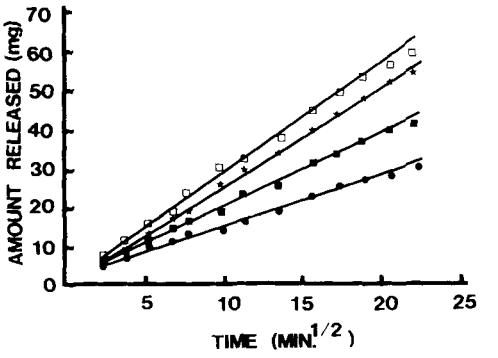

FIGURE 4

Cumulative amount of theophylline released versus square root of time plot for Percirol® matrix tablets containing varying percentages of mannitol. Symbols: P - ● -, PM 15 - ■ -, PM 30 - ★ - and PM 45 - □ -.

The square root of time plot for Group I experimental tablets is shown in Fig. 4. Linear fits were observed for the curves of all the three formulations in this group. The diffusion rate constants for these formulations were determined from the slopes of the linear square root plots and are given in Table 3. The increase in amount of mannitol in the Precirol® matrix increased the release rate, which may be due to higher solubility of mannitol, which dissolves and increases the number of pores in the matrix, making the dissolution medium to penetrate and come in contact with the drug in the matrix which dissolves in it and then diffuses out through the pores.

The square root plot for Group II - experimental tablets is shown in Fig. 5a and 5b. Although the linear fitting can be done

TABLE 3

Diffusion Release Rate Constant ($mg/min^{1/2}$) of Experimental Tablets.

Formulation	Diffusion release rate constant ($mg/min^{1/2}$) [mean ± S.D. (C.V.)]; n = 3
P	1.366 ± 0.03(4.5 %)
Group I	
PM 15	1.766 ± 0.142(8.06%)
PM 30	2.388 ± 0.163(6.87 %)
PM 45	2.632 ± 0.104(3.97 %)
Group II	
PH 2.5	2.169 ± 0.162(7.49 %)
PH 5	2.504 ± 0.423(16.91 %)
PH 10	3.994 ± 0.256(5.28 %)

for these formulations (Fig. 5a) it is observed that there are regions where there is a shift in linearity (Fig. 5b). In this system the tablets erode at certain intervals and expose new surfaces for the dissolution medium to penetrate and dissolve the drug in the matrix. This is observed at 60 - 80 minutes intervals for all the three formulations and in addition around 4.5 hours for PH 10 formulation (Fig. 5b). The diffusion rate constant, determined from the slopes of the linear fittings (Fig. 5a) for the Group II tablets is given in Table 3.

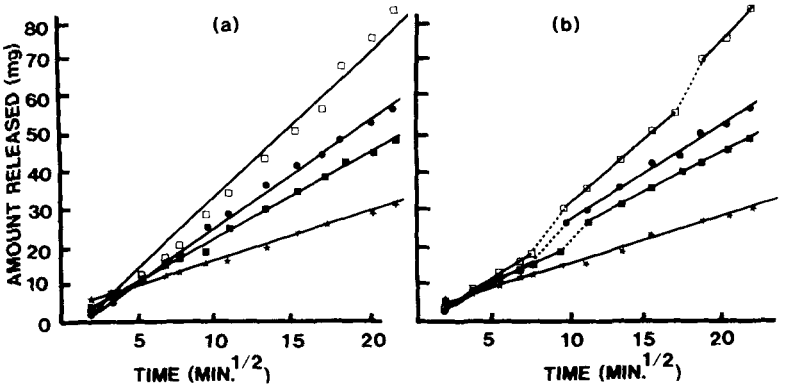

FIGURE 5

Cumulative amount of theophylline released versus square root of time plot for Precirol® matrix tablets containing varying percentages of HPMC. Symbols: P - ★ -, PH 2.5 - ■ -, PH 5 - ● - and PH 10 - □ -.

The log-linear plot for Group III experimental tablets which followed first-order release pattern is shown in Fig. 6 and the release rate constant determined from the slopes of these plots are given in Table 4. There was a change in the mechanism of release from the Higuchi porous penetration to first-order release in Group III tablets. This was due to the formation of a gel through which the dissolution medium had to diffuse into the matrix and dissolve the drug and then diffuse out of the gel material. The gel materials are generally found to follow first-order release[8].

A plot of fraction of agent F (mannitol or HPMC) versus the diffusion rate constant k_d, gave a linear relationship [Fig. 7 and 8], which follows Eq. 4.

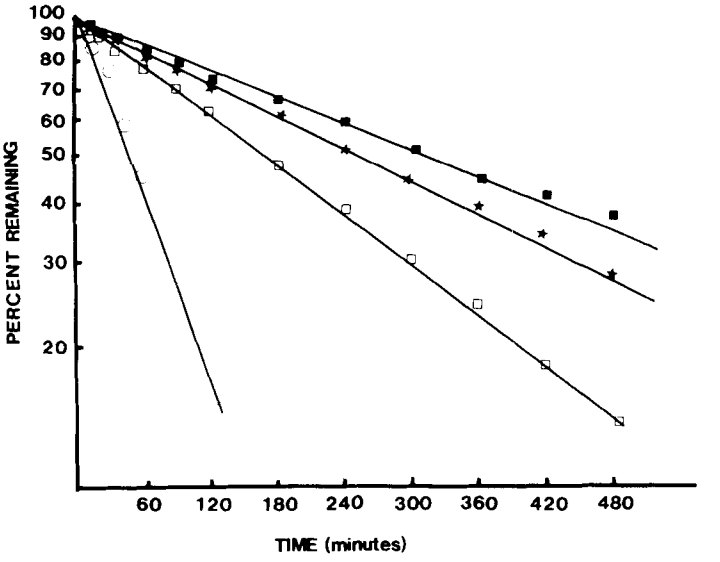

FIGURE 6

Percentage remaining to be released versus time plot for Precirol® matrix tablets containing 30 percent mannitol and varying percentages of HPMC. Symbols: PMH 5 - ○ -, PMH 10 - □ -, PMH 15 - ★ - and PMH 20 - ■ -.

TABLE 4

First-Order Release Rate Constant ($min^{-1} \times 10^{-2}$) of Experimental Tablets.

Formulation	First-order release rate constant ($min^{-1} \times 10^{-12}$) [mean ± S.D. (C.V.)]; n = 3
PMH 5	1.163 ± 0.0128(1.10 %)
PMH 10	0.344 ± 0.0078(2.29 %)
PMH 15	0.255 ± 0.0297(11.17 %)
PMH 20	0.1952 ± 0.0111(5.69 %)

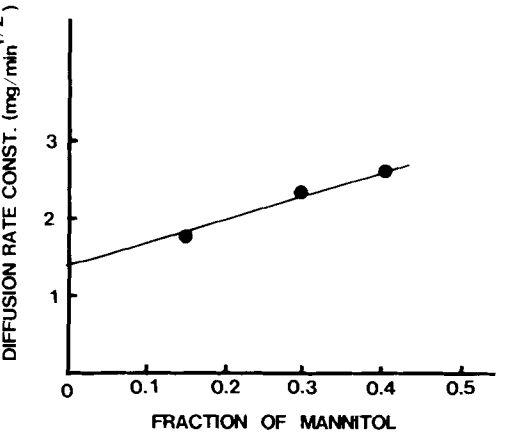

FIGURE 7

Relationship between diffusion rate constant and the fraction of mannitol.

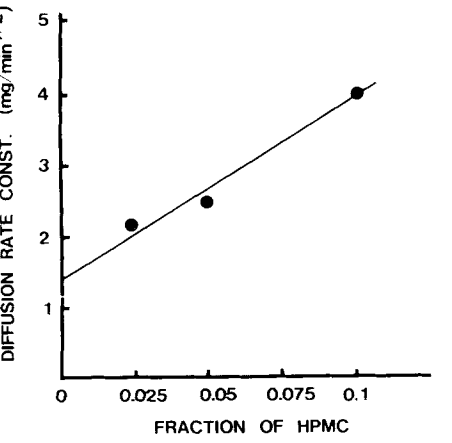

FIGURE 8

Relationship between diffusion rate constant and the fraction of HPMC.

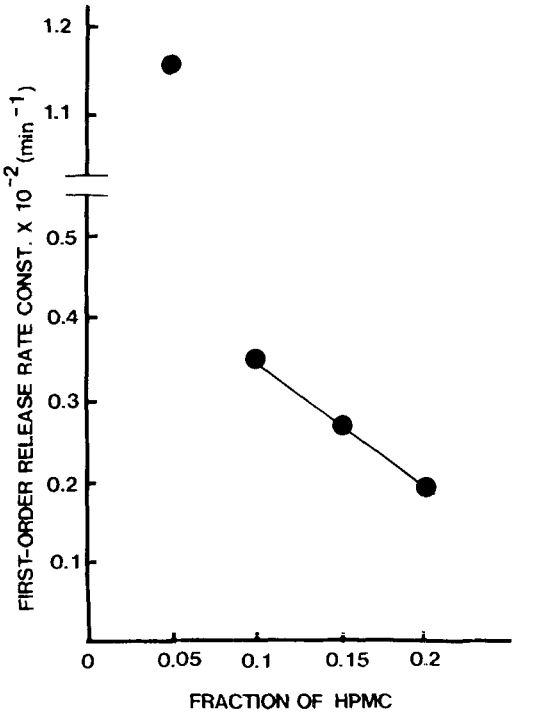

FIGURE 9

Relationship between first-order release rate constant and fraction of HPMC in Precirol® matrix tablets containing 30 percent mannitol.

$$k_d = kF + k_p \qquad (4)$$

where k is the constant specific for each drug concentration and k_p approximates the k_d in the pure Precirol® matrix system. Thus one can obtain a desired diffusion release rate by varying the fraction of mannitol or HPMC in this system.

The plot of fraction of HPMC versus first-order release rate constant k_f for Group III tablets, gave a linear relationship in

the region of 0.1 to 0.2 fraction of HPMC (Fig. 9). Thus by varying fraction HPMC in this system, one can obtain the desired release rate.

These studies indicate that the release of theophylline from a Precirol® matrix containing mannitol or HPMC, follows diffusion mechanism and the release can be approximated by varying the fraction of mannitol or HPMC. When both HPMC and mannitol are used the release changes to first-order and can be approximated by changing the fraction of HPMC. The proposed matrix system can be used for sustained release of other drugs.

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REFERENCES

1) T. Higuchi, J. Pharm. Sci., 52, 1145 (1963).

2) S.J. Desai, A.P. Simonelli and W.I. Higuchi, J. Pharm. Sci., 54, 1459 (1965).

3) A. Dakkuri, H.G. Schraeder and P.P. Deluca, J. Pharm. Sci., 67, 354 (1978).

4) A. Dakkuri, L.D. Bulter and P.P. Deluca, J. Pharm. Sci., 67, 357 (1978).

5) S. Said and H. Al-Shora, Int. J. Pharm., 6, 11 (1980).

6) W.A. Ritschel and G. Ritschel-Beurlin, Präparative Pharmazie, 4, 37 (1969).

7) J.L. Terrier, Gattefossé Report 1, 63 (1976).

8) M. Bamba, F. Puisieux, J.P. Marty and J.T. Carstensen. Int. J. Pharm., 2, 307 (1979).