DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY, 13(3), 449-472 (1987)

RELEASE OF THEOPHYLLINE FROM ETHYL CELLULOSE MICROCAPSULES ALONE AND IN CONJUNCTION WITH FAT EMBEDDED (PRECIROL®) GRANULES AND HYDROXYPROPYL METHYLCELLULOSE

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ABSTRACT

Microcapsules of theophylline with ethyl cellulose were prepared by coacervation technique using Cabosil® (silicon dioxide) as separant. Tablets were prepared from microcapsules, microcapsules + theophylline fat embedded granules, and microcapsules and hydroxypropyl methylcellulose 4000 (HPMC). Theophylline release was studied in vitro by the rotating basket method. Prolonged release of theophylline was observed from microcapsules with no drug dumping. The release from microcapsules was of first-order whereas that from all the tablet formulations was diffusion controlled according to the Higuchi model. Good correla-

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tion was found between release rate and core:wall ratio for all the systems. Decrease in hardness of tablets made from microcapsules alone decreased the release rate, indicating damage of microcapsules during compression. The tablets compressed from fat embedded granules, microcapsules with fat embedded granules, and microcapsules with HPMC gave a desired release for a 24 hour sustained release preparation.

INTRODUCTION

Theophylline prolonged release dosage forms have been developed to avoid the problem associated with high plasma level fluctuations and the frequency of administration, since the upper and lower limits of effective therapeutic blood levels of theophylline are narrow, i.e., 20 mcg/ml and 10 mcg/ml, respectively[1]. Benita and Donbrow[2] prepared ethyl cellulose-walled theophylline microcapsules as sustained release dosage form. They used polyisobutylene as a protective colloid, which prevented aggregation of microcapsules and resulted in individually film-coated core particles. However, the dissolution data showed that 60 and 100 percent of theophylline was released within 25 minutes when 8 and 9 percent polyisobutylene respectively was used as protective colloid. The core:wall ratio was 1:1 and the ethyl cellulose grade was 100 cps in that study.

The release of the drug from the microcapsules occurs by permeation of drug through the coating membrane, however defects such as pores or cracks in the membrane will act as parallel pathways

for drug release[3]. Vidmar et al.[4] and Deasy et al.[5] have shown that these defects are common in ethyl cellulose microcapsules and can be corrected by using waxy sealants.

Jalsenjak et al.[6] gave detailed appraisal of the coacervation technique involved in coating of phenobarbitol sodium using ethyl cellulose and cyclohexane. They reported that the technique gave a partly aggregated product. Drug release was rapid and diffusion-controlled with more than 75 percent released in 1 hour, confirming the poor capacity of this coating polymer. Nixon et al.[7] tabletted phenobarbital sodium microcapsules which showed much slower in vitro release rate. The tablets did not disintegrate during the dissolution.

Film fillers such as talc, aluminum silicate and silicon dioxide have been used frequently in order to prevent aggregation during pan coating. Rowe[8] recommended use of talc to lessen coalescence during preparation of microcapsules by coacervation technique involving nonaqueous vehicles.

The release of drug from hydrophobic films like ethyl cellulose can be increased by addition of hydrophilic film formers such as hydroxypropyl cellulose[9]. The increase in release was ascribed to be due to the formation of swollen hydrated channels. The release of drug from tabletted wax matrix can be enhanced by incorporation of surfactants[10], povidone[11], microcrystalline cellulose[12], hydroxypropyl methylcellulose and mannitol[13].

Thermal analytical profiles have been used to detect drug-

excipient interactions. In the presence of interactions, the thermograms of the physical mixture of drug and excipient show appearance of one or more new peaks or the disappearance of one or more peaks corresponding to those of components[14].

In the present investigation theophylline was encapsulated with ethyl cellulose by coacervation technique using Cabosil® as separant and the rate of cooling was slowed in order to obtain uniform coating of the drug with ethyl cellulose. The release characteristics of theophylline from microcapsules, from tablets of varying hardness compressed from microcapsules, from tablets compressed from microcapsules with theophylline fat (Precirol®) embedded granules, and microcapsules with HPMC were observed. The goal was to achieve a 20-40 percent release of theophylline by 3 hours, 40-60 percent by 8 hours and 70-90 percent by 14 hours for a 24 hours sustained release preparation. The mechanism of release was evaluated by goodness of fit method[16] and the compatibility of theophylline with Precirol® was studied using differential scanning calorimetry.

MATERIALS AND METHODS

Material

Ethyl cellulose[a] (10 cps), Cabosil®[b], Precirol®[c] and

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[a]Ethocel®, Dow Chemical Company, Midland, Michigan.

[b]Cabot Corporation, Boston, Massachusetts.

[c]Gattefossé Corporation, Elmsford, New York.

HPMC-4000[d] were of pharmaceutical grade. Theophylline anhydrous[e] was of USP XX grade.

Preparation of Microcapsules

In a 2 liter three-necked flask, fitted with stirrer[1] and reflux condenser, 1500 ml of cyclohexane was placed. The flask was immersed into a water bath. While the temperature in the bath was at 60°C, and maintaining a stirring rate of 300 rpm, 14 grams of ethyl cellulose was dissolved in cyclohexane and the temperature raised to 78°C. The appropriate amount of theophylline and 0.5 percent Cabosil® (W/W of theophylline and ethyl cellulose) was dispersed in 100 ml cyclohexane and added. Successive small portions of cyclohexane were used for the complete transfer of drug to the flask to make the final volume to 1700 ml. The quantity of drug used varied according to the desired core:wall ratios. For 1:1, 2:1 and 4:1 core:wall ratios 14, 28 and 56 grams of theophylline was used. The temperature was maintained at 78°C for one hour with continuous stirring, then the system was allowed to slowly cool as shown below:

70°C, 300 rpm, 10 minutes
↓
60°C, 300 rpm, 10 minutes
↓
50°C, 300 rpm, 20 minutes
↓
40°C, with Cabosil® addition

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[d]Fisher Scientific Company, Fair Lawn, New Jersey.

[e]Merrell-Dow Pharmaceuticals, Inc., Cincinnati, Ohio.

[1]Fisher stedi-speed stirrer, Model 12, Lexington, Massachusetts.

When the temperature dropped to 37°C, the entire system was cooled to 20°C by circulating cold water and maintaining agitation (300 rpm). The microcapsules were filtered, washed with ice cold cyclohexane and dried in hot air for 30 minutes.

Preparation of Theophylline Fat Embedment

Precirol® (20 percent w/w of theophylline) was dissolved in isopropanol (40 percent w/w of theophylline), added to theophylline and kneaded to form a dough mass. The dough mass was passed through 0.1 mm sieve and dried at 30°C.

Preparation of Tablets

The formulations of the experimental tablets and their hardness[2] are given in Table 1. Microcapsules, fat embedded granules, or HPMC were mixed by the tumbling method and then compressed[3] into biconvex tablets having 9 mm diameter. There were five groups of tablets. All the groups had 100 mg of anhydrous theophylline. Group I and II tablets were compressed from microcapsules of different core:wall ratios having 5 kp and 2 kp hardness, respectively. Group III tablets were prepared by compressing a physical mixture of ethyl cellulose and theophylline to 5 kp hardness.

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[2]Heberlein hardness tester, Model 2E/106, Heberlein & Co., Zürich, Switzerland.

[3]Tabletting machine, Model EK-0, Emil Korsch Maschinenfabrik, Berlin, W. Germany.

Group IV tablets are a combination of 50 mg of theophylline embedded in fat and 50 mg of theophylline as microcapsules. Thus FM_1, FM_2 and FM_4 contain fat embedded granules and microcapsules of 1:1, 2:1 and 4:1 core:wall ratios, respectively. Formulation F are tablets compressed from theophylline fat embedded granules only.

TABLE 1

Composition of Experimental Tablets

Formulation	Theophylline	Ethyl cellulose	Precirol®	HPMC	Hardness [kp]
Group I (Microcapsules)					
M_1T-5	100	100	-	-	5
M_2T-5	100	50	-	-	5
M_4T-5	100	25	-	-	5
Group II (Microcapsules)					
M_1T-2	100	100	-	-	2
M_2T-2	100	50	-	-	2
M_4T-2	100	25	-	-	2
Group III (Physical mixture)					
PM_4T	100	25	-	-	5
Group IV (Microcapsules + theophylline fat embedment)					
F	100	-	20	-	5
FM_1	100	100	10	-	5
FM_2	100	50	10	-	5
FM_4	100	25	10	-	5
Group V (Microcapsules + HPMC)					
HM_1T	100	100	-	20	2
HM_2T	100	50	-	15	2
HM_4	100	25	-	12.5	2

Group V tablets contain microcapsules of different core:wall ratio with 10 percent HPMC (W/W of microcapsules). Thus HM_1T, HM_2T and HM_4T contain microcapsules with 1:1, 2:1 and 4:1 core: wall ratio and HPMC.

Dissolution Studies

The dissolution of theophylline from each formulation was studied in triplicate by the rotating basket method[4]. The dissolution medium (900 ml water) was maintained at 37 ± 1°C and the basket rotated at 50 rpm. Samples (5 ml) were collected at 10, 30, 45, 60 and 90 minutes and thereafter at 2, 3, 4, 5, 6, 7, 8, 10, 12 and 14 hours. The volume of sample (5 ml) withdrawn was replaced by water maintained at 37°C. The samples were filtered, diluted with water and analyzed spectrophotometrically[5] at 274 nm. Drug concentration in each sample solution was calculated from a standard curve.

Thermal Analysis

Accurately weighed samples of theophylline, Precirol® and theophylline-Precirol® physical mixture were analyzed using a Perkin-Elmer DSC-2C instrument[6].

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[4]Dissolution test apparatus, Model T-1044-20X, Van-kel Industries, Clatham, New Jersey.

[5]Perkin-Elmer double beam spectrophotometer, Ser. No. 44733-9, Tokyo, Japan.

[6]Differential scanning calorimeter, Model DSC-2C, Perkin-Elmer, Norwalk, Connecticut.

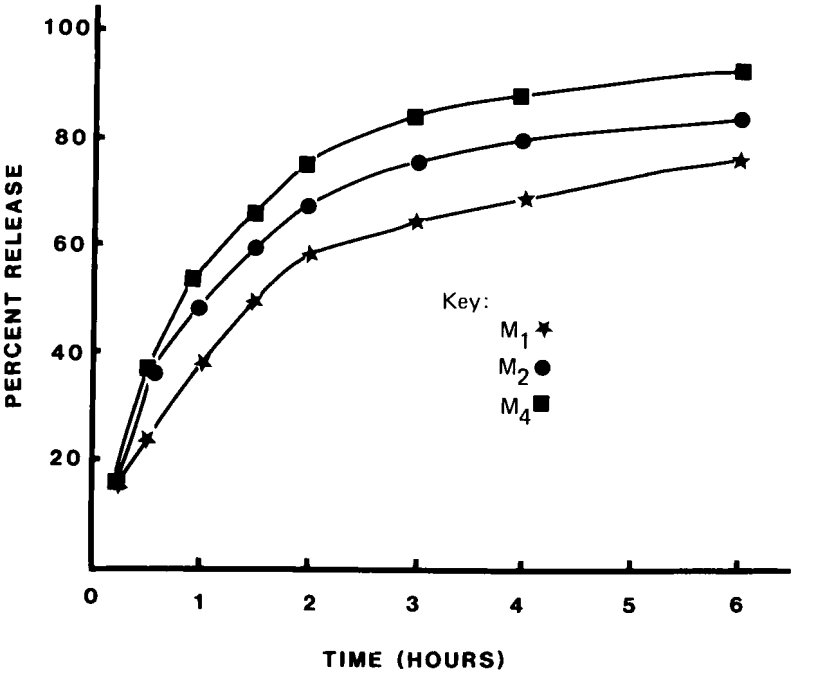

FIGURE 1

Theophylline release from microcapsules having different core:wall ratios.

RESULTS AND DISCUSSION

The release of theophylline from microcapsules of different core:wall ratios is shown in Fig. 1. The microcapsules with core:wall ratios 1:1, 2:1 and 4:1 released 76, 84 and 92 percent of drug in 6 hours. The release of theophylline was prolonged and no drug dumping (60-80 %) was observed within 30 minutes which is generally seen with sparingly and readily soluble drugs when encapsulated with ethyl cellulose by coacervation technique. This may be because in the present technique the rate of cooling is

controlled in order to have uniform deposition of the coating material on the core. This might have prevented the formation of cracks and pores in the ethyl cellulose film which is the regular cause for 60-80 % of drug release within one hour[5].

It has been reported that the inclusion of insoluble pigments or other fillers in the film will delay drug permeability, either by adsorbing it onto the extensive surface of these particles and/or by increasing the effective diffusional path length as the penetrant is forced to pass around these impermeable inclusions in the films. This effect was observed by Porter and Ridgway[15] for cellulose aceatate pathalate film formulation containing red iron oxide pigments. The inclusion of Cabosil® in the film may be delaying the release by these mechanisms.

In order to investigate the mechanism of release, the percent release versus time profile was evaluated for goodness of fit by the REG 8 computer program. The details of the use of this statistical technique are given by Bamba et al.[16]. The release of theophylline through the microcapsules (Table 2) could be fitted to first-order and Higuchi[17] square-root equations as the correlation coefficients (R^2) were similar and the F test could not differentiate between the two mechanisms. It is well known that the Higuchi porous penetration and first-order release can be differentiated by a plot of $\frac{dA}{dt}$ as function of $\frac{1}{Q}$ or Q, were $\frac{dA}{dt}$ is release rate and Q is the amount released. Table 3 shows that the data could be fitted well to the $\frac{dA}{dt}$ versus Q plot as the correla-

Table 2: Comparison of Fits of Data Using Least Square Equation

Formulation	1 First-order		2 Square-root		3 Cube-root		F-test	
	R^2	$\frac{(Resd)^2}{n-2}$	R^2	$\frac{(Resd)^2}{n-2}$	R^2	$\frac{(Resd)^2}{n-2}$	(1-2)	(3-2)
(Microcapsules)								
M_1	0.9222	56.55	0.9391	35.185	0.8875	70.7	not signif.	25%
M_2	0.8998	99.128	0.8972	68.07	0.8498	118.0	not signif.	25%
M_4	0.9277	100	0.8877	94.39	0.866	175.91	not signif.	25%
(Microcapsule tablets)								
M_1 T-2	0.9575	6.758	0.9951	0.710	0.9480	7.901	1%	1%
M_2 T-2	0.9549	6.111	0.9939	0.750	0.9461	6.972	1%	1%
M_4 T-2	0.9647	12.548	0.9919	2.218	0.9499	15.697	1%	1%
M_1 T-5	0.9635	8.065	0.9984	0.290	0.9513	9.804	1%	1%
M_2 T-5	0.9610	8.152	0.9943	1.219	0.9526	10.306	1%	1%
M_4 T-5	0.9600	14.026	0.9922	2.86	0.9429	19.569	1%	1%
(Physical mixture tablet)								
PM_4 T	0.8773	899.0	0.9994	11.031	0.9176	227	1%	1%
(Microcapsules + theophylline fat embedment tablets)								
F	0.9951	5.249	0.9988	0.608	0.9842	10.9	1%	1%
FM_1	0.9811	4.606	0.9994	0.111	0.9726	6.07	1%	1%
FM_2	0.9874	4.7	0.9996	0.093	0.9788	6.99	1%	1%
FM_4	0.9743	13.24	0.9816	7.189	0.96105	11.2	25%	25%
(Microcapsules + HPMC tablets)								
HM_1 T	0.9942	6.39	0.9965	2.21	0.9842	14.223	5%	1%
HM_2 T	0.9899	11.50	0.9938	3.53	0.9780	18.96	5%	1%
HM_4 T	0.9870	14.01	0.9902	5.95	0.9752	23.80	10%	1%

TABLE 3

Comparison of Parameters of Linearity Obtained from Plots of Release Rate Against the Reciprocal of Amount (1/Q) and Amount of Drug Released (Q) from Microcapsules

Formulation	Correlation coefficients of plots of release rate dA/dt	
	Versus 1/Q	Versus Q
M_1	0.8411	0.9638
M_2	0.9342	0.9757
M_4	0.9430	0.9720

tion coefficient was better, hence we may conclude that the microcapsules released the drug by first-order.

Both first-order and square root mechanisms have been observed from ethyl cellulose microcapsules prepared by coacervation technique in the presence and absence of protective colloids[2]. Generally, the drug release from clusters of microcapsules formed by aggregation of individual microcapsules follows the Higuchi porous penetration model, whereas the individually film-coated core particles follow first-order release[2] if the core forms an unsaturated solution inside the microcapsule. The microcapsules in the present study gave a complex release pattern which could not be definitely distinguished between first-order and square-

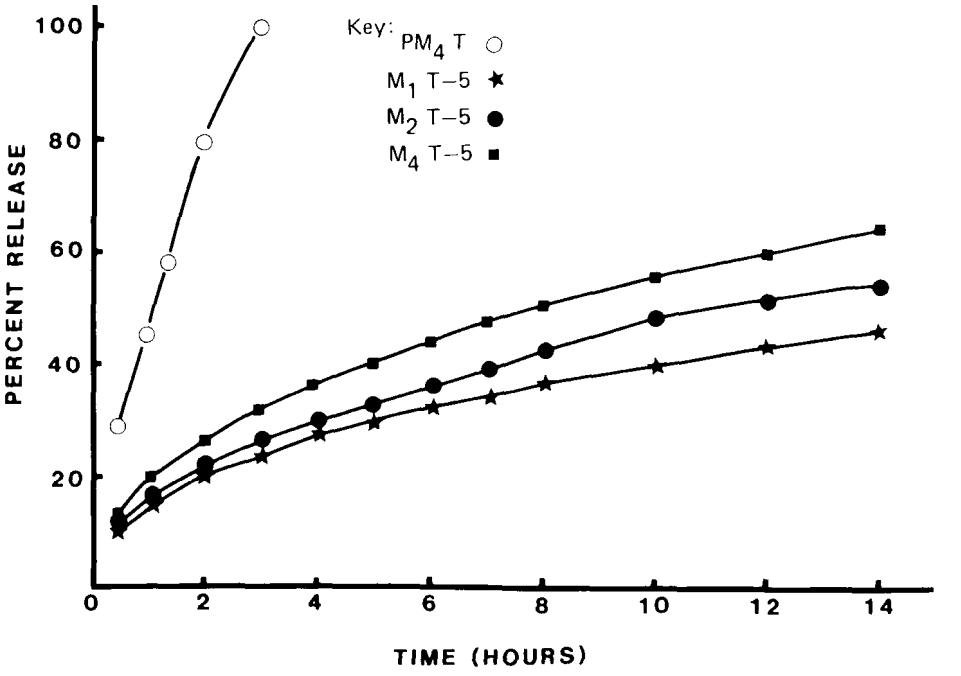

FIGURE 2

Theophylline release from microcapsule tablets of different core:wall ratios and tablets of a physical mixture of theophylline and ethyl cellulose.

root mechanism because the microcapsule formed were mixture of both individually coated particles and aggregates.

The release of theophylline from microcapsule tablets and tablets of physical mixture is given in Fig. 2. The tablets having core:wall ratios of 1:1 (M_1T-5), 2:1 (M_2T-5) and 4:1 (M_4T-5) released 48, 54 and 65 percent of theophylline within 14 hours. The tablets prepared from physical mixture PM_4T released 100 percent of drug within 3 hours indicating that the

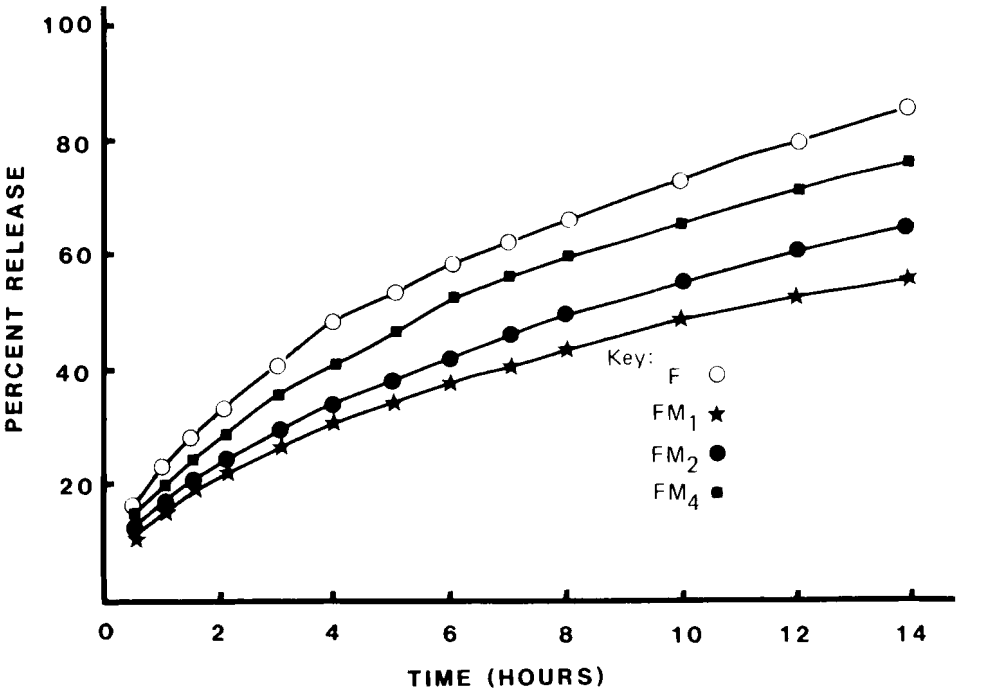

FIGURE 3

Theophylline release from tablets compressed from fat embedment granules and tablets compressed from fat embedment granules + microcapsules of different core:wall ratios.

theophylline encapsulated in ethyl cellulose is responsible for sustained release. However, none of these formulations gave a desired release suitable for a 24 hours sustained release preparation.

The release of theophylline from group IV tablets is shown in Fig. 3. Tablets with fat embedded granules (F) gave the maximum release and as the microcapsule core:wall ratios decreased the

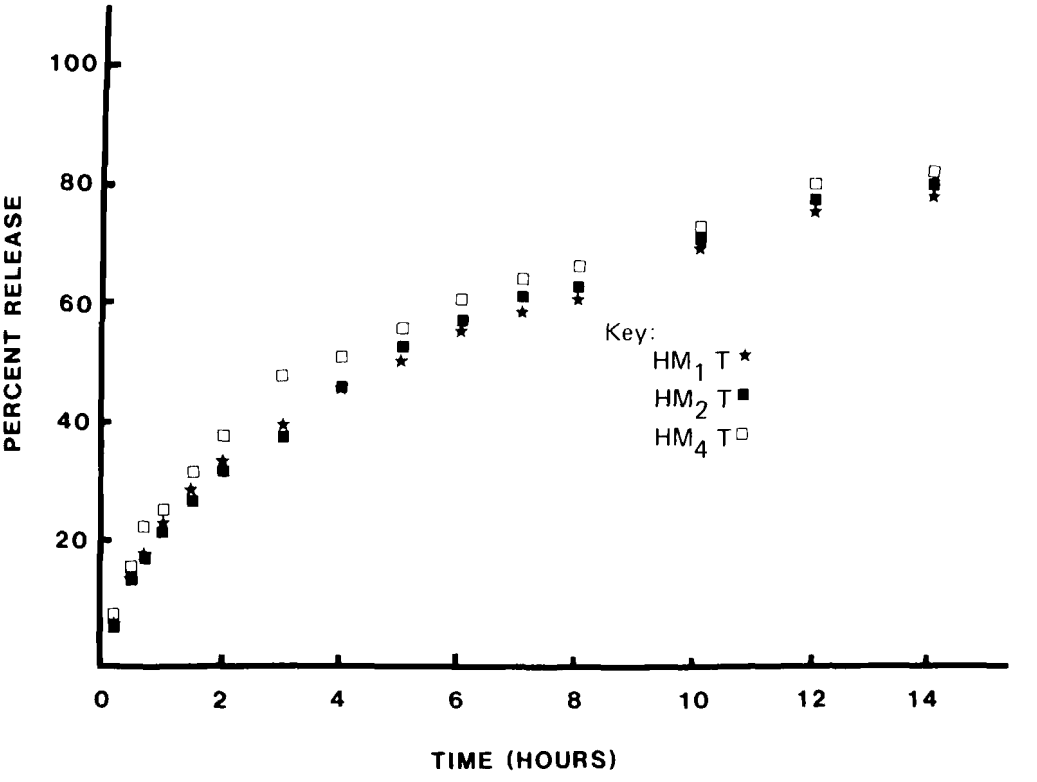

FIGURE 4

Theophylline release from microcapsule tablets of different core: wall ratios having 10 % HPMC 4000.

release decreased. The formulation F and FM_4 which released 85 and 75 percent of theophylline within 14 hours gave a desired release pattern to be promising for a 24 hour sustained release preparation which will be further evaluated *in vivo*.

In order to increase the release of theophylline from tablets compressed from microcapsules, 10 percent HPMC was incorporated into tablets as channeling agent. The release of theophylline from tablets in group V is shown in Fig. 4. All the three for-

mulations (HM_1, HM_2 and HM_4) gave the same amount of release although they had microcapsules of different core:wall ratios. However, all these tablet formulations differed from each other in their surface area, and as the tablets retained their shape and size throughout the dissolution study, the amount released was corrected for the surface area. The formulations HM_1, HM_2 and HM_4 which released 78-82 percent of drug within 14 hours gave a desired dissolution pattern to be promising for a 24 hour sustained release preparation to be evaluated *in vivo*.

The amount released *versus* time data for all tablet formulations was evaluated by a computer program for goodness of fit, the results of which are given in Table 2. All the tablet formulations followed Higuchi porous penetration model as the dissolution data fitted well to the square-root equation.

The plots of cumulative amount released per unit area *versus* square root of time for group I, II, IV and V tablets are shown in Fig. 5-7. The diffusion release rates for these formulations were determined from the slopes of their linear square root plots and are given in Table 4.

Increase in microcapsule core:wall ratios increased the diffusion release rate per unit area. Good correlation was found between core:wall ratios and the diffusion release rate constants (Table 4). This shows that the release of the drug in all the systems was controlled by the amount of ethyl cellulose in the microcapsules.

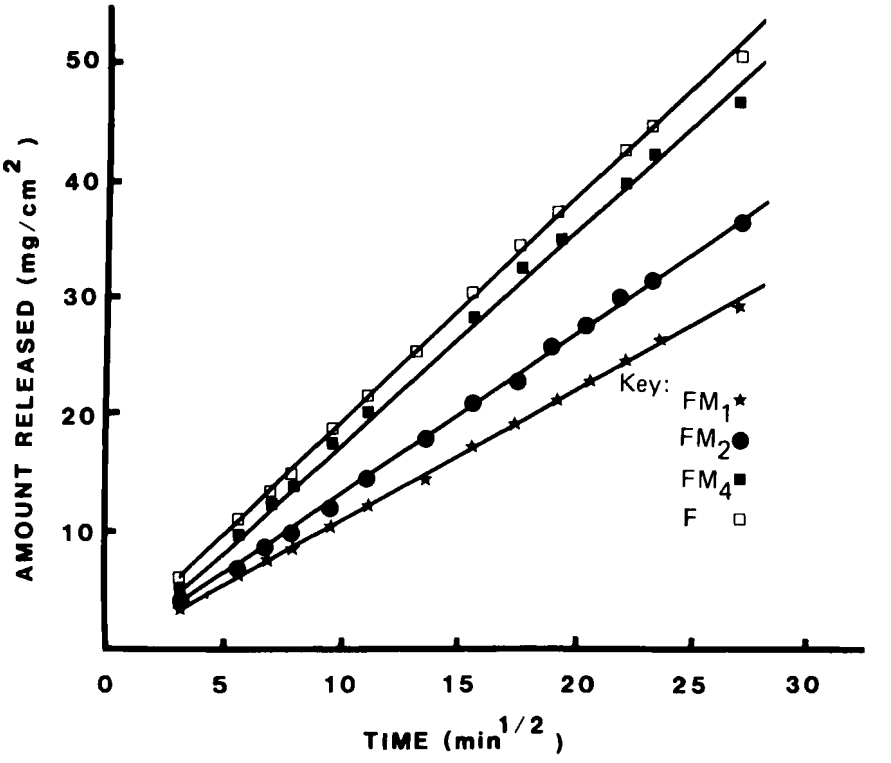

FIGURE 5

Amount of theophylline released per unit area versus square root of time plot for tablets compressed from fat embedment granules + microcapsules of different core:wall ratios.

A decrease in hardness from 5 kp to 2 kp of tablets prepared from microcapsules decreased the release rate (Table 4, Fig. 6). This indicates that at 5 kp hardness the microcapsules are damaged during compression to tablets and thus resulted in faster release. Similar findings were observed by Luzzi and coworker[18], who have shown that tablet hardness inversely affects drug release from

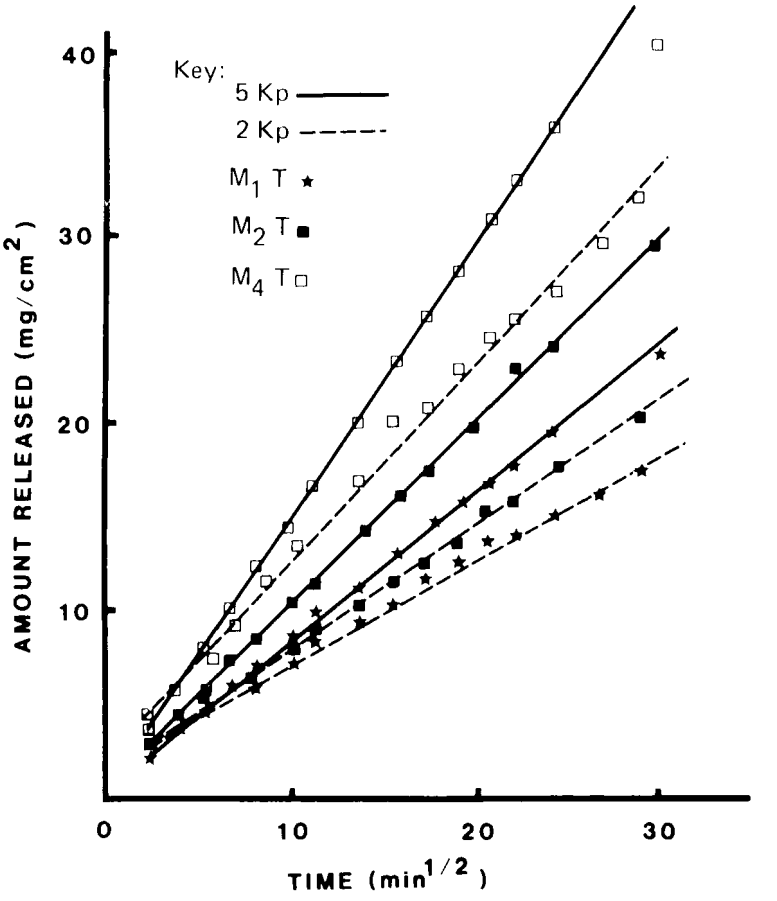

FIGURE 6

Amount of theophylline released per unit area versus square root of time plot for microcapsule tablets having 5 Kp and 2 Kp hardness.

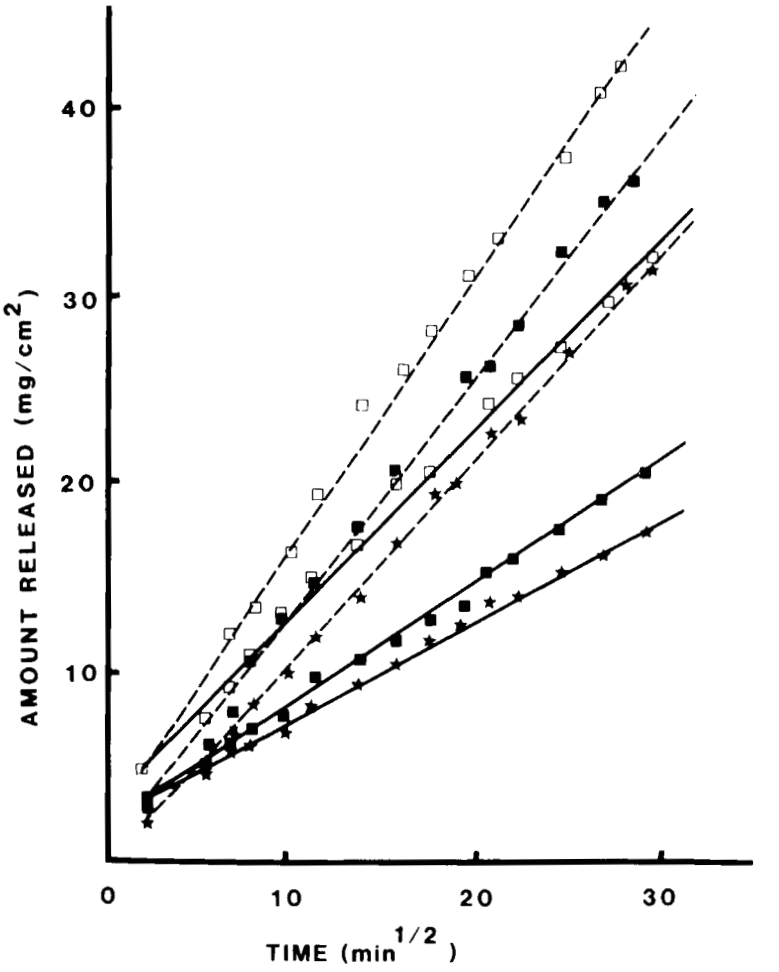

FIGURE 7

Effect of HPMC 4000 on the release of theophylline from microcapsule tablets of different core:wall ratios. Symbols: M_1T-2-★-, M_2T-2 -■-, M_4T-2 -□-, HM_1T --★--, HM_2T --■--, HM_4T --□- -.

TABLE 4

Diffusion Release Rate Constant ($mg/cm^2/min^{1/2}$), Hardness, and Correlation Coefficient of the Plot of core:wall ratio of Microcapsules and the Diffusion Release Rate Constant

Formulation	Hardness [kp]	Diffusion release rate Constant [$mg/cm^2/min^{1/2}$]	Correlation coefficient
M_1T-5	5	0.7915	
M_2T-5	5	1.0180	0.9996
M_4T-5	5	1.4236	
M_1T-2	2	0.5621	
M_2T-2	2	0.6637	0.9918
M_4T-2	2	1.0347	
F	5	1.932	
FM_1	5	1.1197	0.9918
FM_2	5	1.4179	
FM_4	5	1.7729	
HM_1T	2	1.1389	
HM_2T	2	1.3250	0.9878
HM_4	2	1.5359	

microcapsules. These findings indicate that hardness is an important factor to be considered when tablets are prepared from microcapsules of incompatible drugs.

Incorporation of HPMC in the microcapsule tablets increased the release rate of theophylline (Table 4, Fig. 7). This increase in release rate is due to formation of swollen hydrated channels by HPMC through which the dissolution fluid can penetrate into the matrix, dissolve the drug and diffuse out. Similar findings were

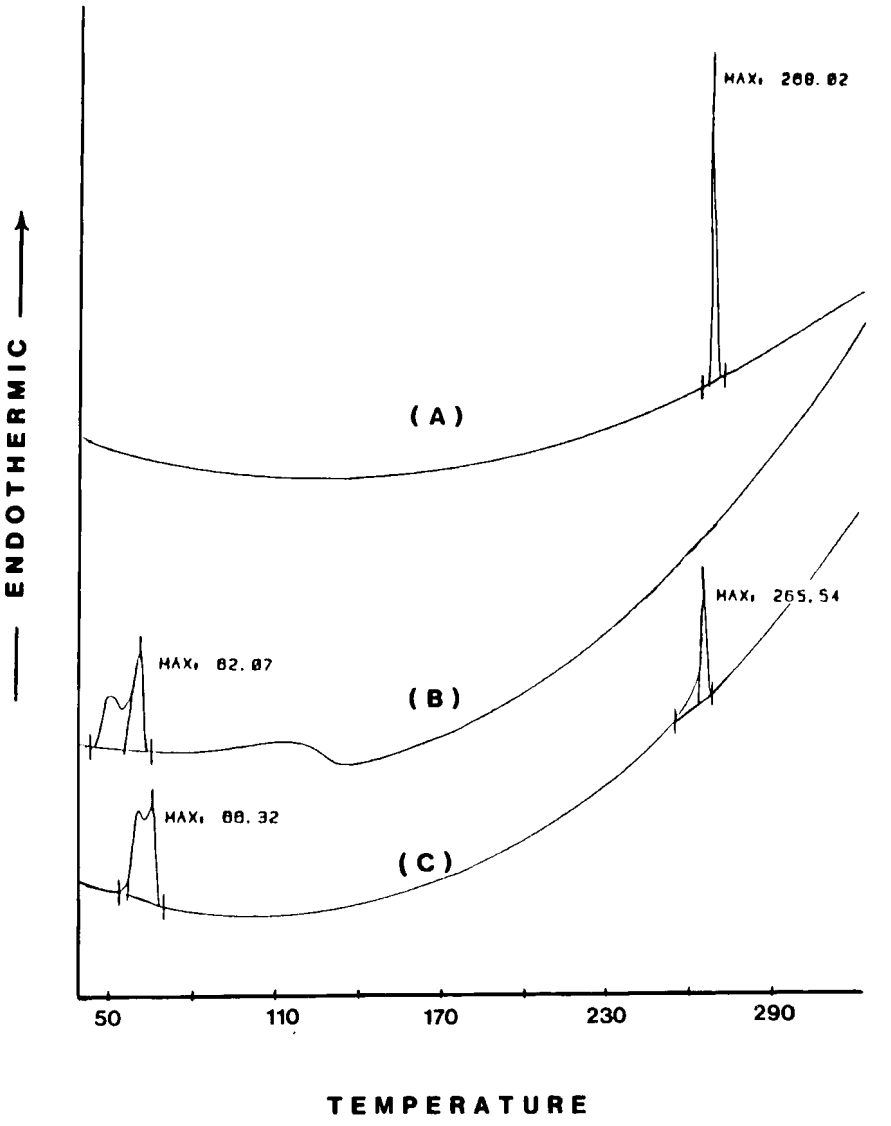

FIGURE 8

Differential scanning calorimetric thermograms of (A) theophylline, (B) Precirol® (C) physical mixture of theophylline and Precirol®.

observed when HPMC was incorporated in Precirol® matrix to enhance the release of theophylline[13].

The differential scanning calorimetry scan of theophylline, Precirol® and their (1:1 w/w) physical mixture is shown in Fig. 8. No change was observed in thermal analytical profiles indicating absence of any interaction between theophylline and Precirol®.

CONCLUSION

1. The present technique can be used to encapsulate drug with ethyl cellulose where prolonged release is desired.
2. The tablets compressed from fat embedded granules, microcapsules with fat embedded granules, and microcapsules with HPMC gave desired release to be a promising formulation for 24 hour sustained release preparations.
3. The microcapsules followed first-order release whereas when tabletted alone or with fat (Precirol®) embedded granules or HPMC followed the diffusion-controlled Higuchi models.
4. Hardness is an important parameter to be considered while compressing microcapsules.
5. Good correlation was found between release rate constants and core:wall ratios for all the formulations containing microcapsules.
6. Thermal analytical profiles showed absence of any interaction between theophylline and Precirol®.

ACKNOWLEDGEMENTS

The authors appreciate the assistance given by Dr. M.A. Zoglio, Mr. Kenneth Adams and Ms. Ruth Homan, in the use of REG-8

computer program and differential scanning calorimetry.

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