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CONTROLLED RELEASE KINETICS OF CAPTOPRIL FROM TABLETED MICROCAPSULES

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ABSTRACT

Different viscosity grades ethylcellulose coated captopril microcapsules were prepared using temperature induced coacervation method from cyclohexane containing 2% Tween 80. Microcapsules were compressed directly into tablets. In vitro dissolution was carried out in 0.1N HCl at 37°C using the rotating basket method. Release from tablets of all the batches was extensively prolonged in comparison to the respective microcapsules. The longest time for 70% drug release was shown by microcapsules (55min) and tablets (378 min) of the batch E-2. Release rate

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constants, correlation, determination and regression coefficients were calculated for the first-order, zero-order and Higuchi's equations. The best fit of release kinetics with the highest correlation and determination coefficients was achieved with the first-order followed by Higuchi's plot.

INTRODUCTION

Captopril is an angiotensin-converting enzyme inhibitor used in the treatment of hypertension (1).It is freely water soluble and has an elimination half-life after oral dose of 1.7 h (2). Various methods are available to formulate water soluble drugs into sustained release dosage forms by retarding their dissolution rates (3). Microencapsulation is one method used to control drug release and hence, prolong therapeutic activity (4). In order to develop an oral sustained release formulation of captopril using microencapsulation techniques in our laboratory, we have studied the effect of non-ionic surfactants for an efficient microencapsulation of the drug with ethylcellulose by temperature induced coacervation from cyclohexane. 2% Tween 80 was found to be the most suitable for microencapsulation and controlling the drug release (5). Hence, 2% Tween 80 was added to the cyclohexane to produce microcapsules of the drug with different viscosity grades of ethylcellulose.

The most frequently used dosage forms for microencapsulated products have been suspension, gel and hard gelatin capsule (6). Only a few investigations of tablet formulations from microcapsules have

been reported (7). Therefore, the purpose of this investigation was to compress the respective batches of microcapsules into their tablets and study the release kinetics of the drug from them.

MATERIALS

Captopril was obtained from E.R. Squibb & Sons Inc., USA, and sieved through 120 um mesh before use. Ethylcellulose type N-10 (9 c.p.; ethoxyl content: 47.9%), N-50 (41 c.p.; ethoxyl content: 47.9%) and N-100 (93 c.p.; ethoxyl content: 47.7%) were received from Hercules, Dellaware, USA. Ethylcellulose (300 c.p.; ethoxyl content: 48%) was obtained from Aldrich Chemical, Wisconsin, USA. Cyclohexane and Tween 80 were procured from BDH Chemicals Ltd, England, and Sigma, respectively.

METHODS

Preparation of Microcapsules - 4 g of ethylcellulose was dissolved by refluxing for 30 min at 80°C in 200 ml cyclohexane containing 2% absolute alcohol and 2% Tween 80 on a hot plate magnetic stirrer (Nuova II, Medical Supplies Ltd., New Zealand). 2 g of captopril was dispersed in the solution and stirred for 10 min at 500 rev/min. The system was allowed to cool slowly while stirring for further 30 min at 350 rev/min, then finally immersed in an ice-water mixture while the stirring was maintained for further 1 h. Microcapsules were separated by decanting, washed three times each with 100 ml n-hexane, then

filtered and dried in the air. E-1, E-2, E-3 and E-4 batches of microcapsules were prepared using 9, 41, 93 and 300 c.p. viscosity grades of ethylcellulose as a coating material, respectively. The dried samples were sieved and microcapsules retained between 500 um - 850 um sieves (mean diameter 675 um) were used for further studies.

Scanning Electron Microscopy (SEM) - SEM was carried out by the method of Florence and Jenkins (8) using a Siemens Autoscan Instrument (ETEC Corporation, Hayward, California). Microcapsules were fixed onto a thin adhesive strip attached to aluminium specimen stub. The samples were coated using an E 5000 ESM Coater under a high vacuum, 0.2 torr, high voltage, 1.2 kV, and 40 mA.

Preparation of Tablets - Tablets were prepared by diretly compressing 250 mg of microcapsules in a Manesty F-3 type single punch tablet machine. A 12 mm dia flat punch and die set was used to compress microcapsules into tablets at a constant compression pressure of 40 units.

Assay of Total Drug Content - Triplicate 0.250 g samples of microcapsules or one tablet were placed in a mortar and thoroughly triturated. The drug was extracted using 250 ml of 0.1N HCl contained in a 300 ml Erlenmayer flask. After thoroughly rinsing all equipment, the total mixture was filtered through a Buchner funnel fitted with a sintered glass filter (G-3). The solution was transferred into 500 ml volumetric flask and the volume was made upto the mark with 0.1N HCl.

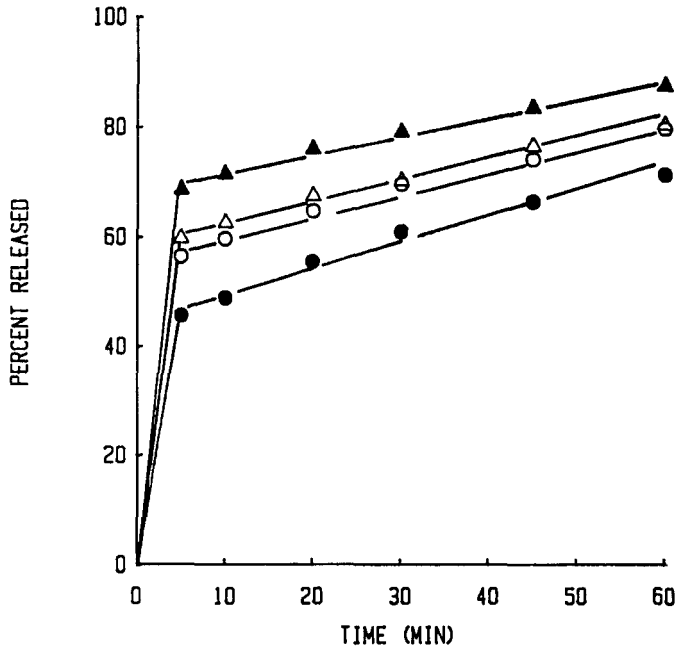

FIGURE 1

In Vitro Release of Captopril in 0.1 N HCl from Microcapsules.
Key: (○) E-1; (●) E-2; (△) E-3; (▲) E-4.

The drug was assayed spectrophotometrically at 214 nm using a Shimadzu UV-240 double beam Spectrophotometer.

In vitro Release - A Hanson Dissolution Test Station Model QC 72 RLB (Hanson Research Corporation, Northridge, California) consisting of the drive assembly with six spindles and a drive motor mounted on a Easi-Lift stand set on a vibration-free base was used for in vitro dissolution rate measurements. The digital readout speed control was set at 100±1 rev/min. Six one litre round-bottom glass dissolution flasks each containing 900 ml of 0.1N HCl dissolution fluid were

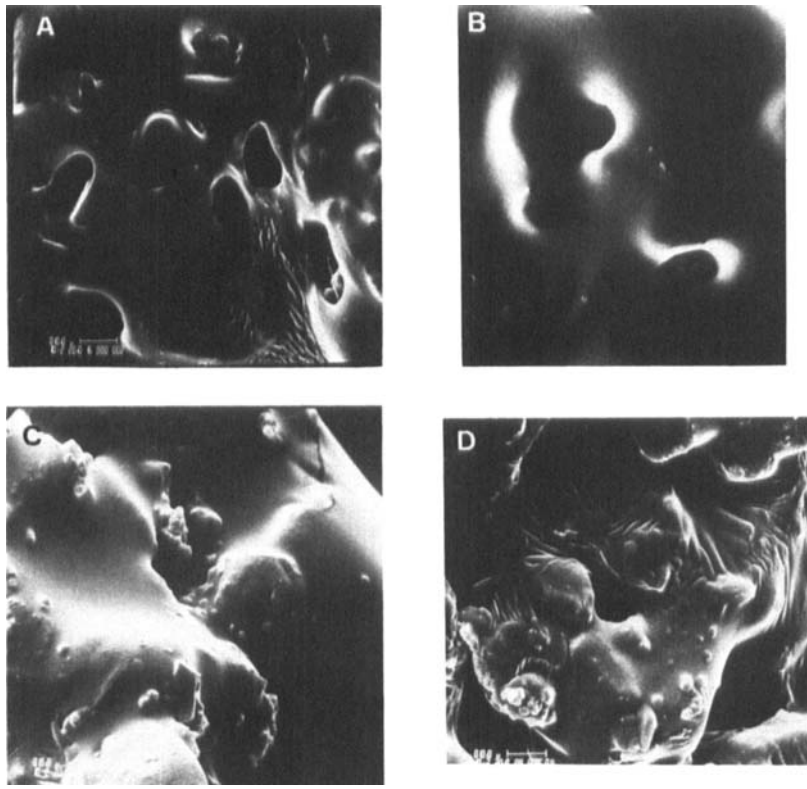

FIGURE 2

Scanning Electron Micrographs of Microcapsules prepared with different viscosity grades of Ethylcellulose.
A: E-1; B: E-2; C: E-3; D: E-4; (Magnification: x 1000)

equilibrated at 37±1°C in a water bath controlled by an independent heater-circulator model 6454. The six basket-shaft assemblies conformed to both USP and BP specifications. Cylindrical stainless wire baskets, 36 x 20 mm, 40 mesh (0.254 diameter) containing 100 mg microcapsules or one tablet were set 2.5 cm from the base of the flask. Each basket contained a vent to allow any entrapped air to escape.

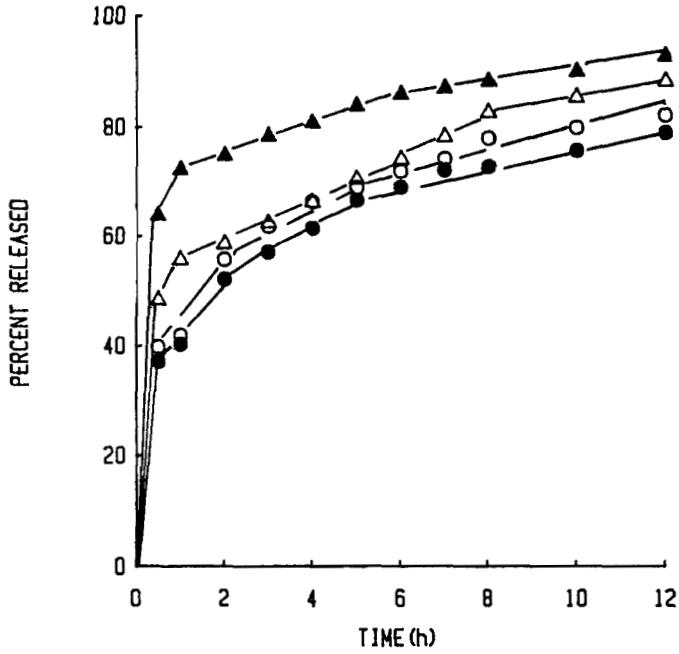

FIGURE 3

In Vitro Dissolution of Captopril in 0.1 N HCl from Tableted Microcapsules. (Symbol representation same as in Fig. 1).

A mannual Dissoette precision dissolution sampling assembly, Model 27-6M-1-2, with both media replacement and dilution facilities was calibrated to dilute the equal volume of the sample withdrawn and to replace the same volume of the dissolution medium. Each sample probe with filter attachment was set level with the top of the rotating basket and 4 cm from the centre. 4 ml samples were removed at intervals and diluted with the same amount of the fresh dissolution fluid. Drug release was monitored by measuring the absorbance at 214 nm. The concentrations of the drug were determined from the standard calibration data for the drug in the dissolution fluid. An equal

TABLE 1

Time for 70% Drug Release from Microcapsules and Tableted Microcapsules

Batch	$T_{70\%}$ (min)	
	Microcapsules	Tableted Microcapsules
E-1	32.0	318.0
E-2	55.0	378.0
E-3	29.5	294.0
E-4	8.5	54.0

volume of fresh dissolution fluid maintained at 37 ± 1^{C} C was added to replace the sample volume used for analysis. Dissolution data were corrected for this dilution effect (9). Six samples from each batch of microcapsules/tablets were subjected to in vitro dissolution.

RESULTS AND DISCUSSION

Figure 1 shows the dissolution characteristics of microcapsules prepared with different grades of ethylcellulose. Microcapsules of the batch E-2 showed the least release among all the batches of microcapsules. SEM (Figure 2) reveals that the ethylcellulose of 41 c.p. viscosity grade (batch E-2) produced microcapsules with smaller

TABLE 2

Release Kinetics of the Drug from Microcapsules

Kinetics	Microcapsules			
	E-1	E-2	E-3	E-4
FIRST ORDER				
$K_1 \times 10^{-2}$	3.88	2.41	4.46	17.20
r	-1.000	-0.996	-1.000	-1.001
r^2	0.997	0.993	0.997	0.998
b	-0.008	-0.007	-0.005	-0.009
ZERO-ORDER				
$K_o \times 10^{1}$	0.219	0.127	0.237	0.824
r	0.993	0.988	0.994	0.992
r^2	0.986	0.977	0.988	0.984
b	0.416	0.469	0.375	0.337
HIGUCHI EQUATION				
$K_h \times 10^{1}$	1.270	0.930	1.400	2.800
r^2	0.998	0.999	0.997	0.999
r	0.997	0.998	0.994	0.999
b	4.214	4.780	3.795	3.424

TABLE 3

Release Kinetics of the Drug from Tableted Microcapsules

Kinetics	Tableted Microcapsules			
	E-1	E-2	E-3	E-4
FIRST-ORDER				
$K_1 \times 10^{-2}$	0.365	0.254	0.418	1.254
r	-0.976	-0.976	-0.997	-0.991
r^2	0.954	0.949	0.991	0.978
b	-0.046	-0.041	-0.056	-0.055
ZERO-ORDER				
$K_o \times 10^{1}$	0.022	0.019	0.024	0.129
r	0.925	0.932	0.978	0.935
r^2	0.856	0.869	0.957	0.874
b	3.631	3.550	3.452	2.207
HIGUCHI EQUATION				
$K_h \times 10^{1}$	0.051	0.047	0.056	0.101
r	0.974	0.976	0.991	0.982
r^2	0.948	0.953	0.983	0.964
b	16.958	15.242	14.343	9.788

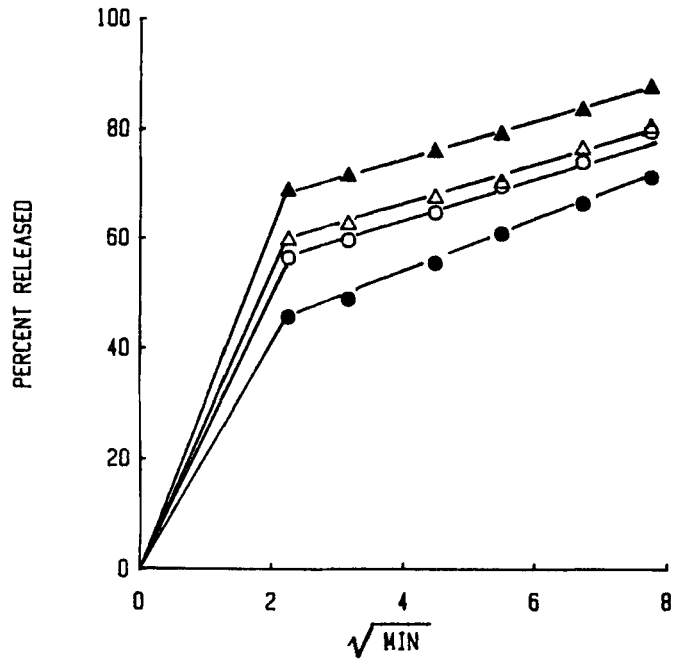

FIGURE 4

Higuchi's plots of the Released Captopril from Microcapsules in 0.1 N HCl. (Symbol representation same as in Fig. 1).

and fewer pores in comparison to the ethylcellulose of 9 c.p. (Batch E-1). However, 100 c.p. and 300 c.p. viscosity grades produced microcapsules with discontinuous and incomplete wall formation.

Batches of tablets were prepared from microcapsules to develop a sustained release solid oral dosage form. Microcapsules were compressed directly without any added excipients. In vitro release profiles of the drug from tablets were similar to those obtained from microcapsules but the rate of release was markedly prolonged (Figure 3). The longest time for 70% drug release was shown by microcapsules (55 min) and tablets (378 min) of the batch E-2 (Table 1).

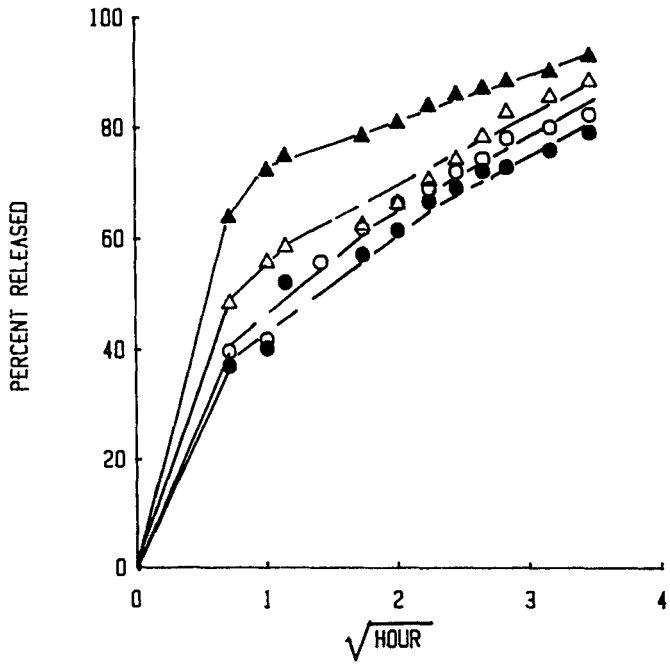

FIGURE 5

Higuchi's plots of the Released Captopril from Tableted Microcapsules in 0.1 N HCl. (Symbol representation same as in Fig 1).

Various equations and kinetic models are used to explain the in vitro release (10-14). Different kinetic equations were applied to interpret the release rate from microcapsules and their tablets. Release rate constants for the first-order (K_1), zero-order (Ko) and Higuchi's eqaution (K_h), as well as their correlation (r), determination (r^2) and regression (b) coefficients were calculated. These results are presented in Table 2 and 3. The best fit with the highest correlation and determination coefficients was achieved with the first order kinetics followed by Higuchi's equation. The results

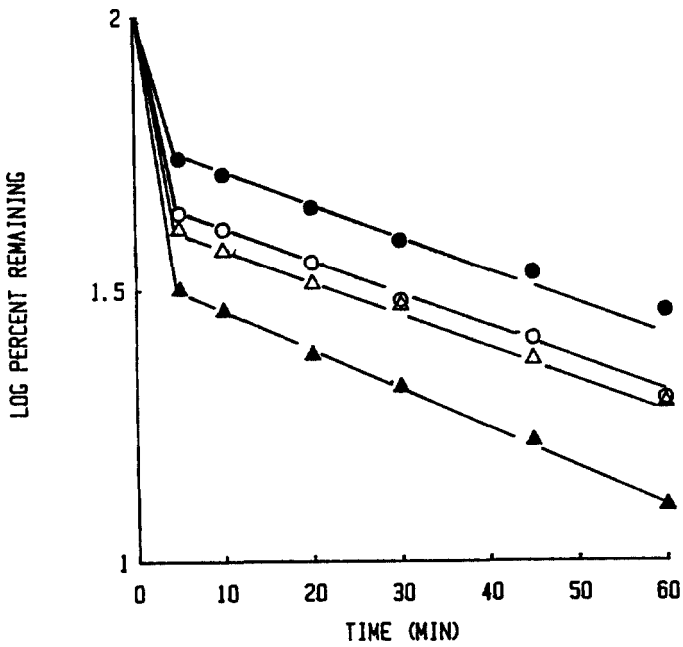

FIGURE 6

Log Percent Remaining versus Time plots of the Released Captopril from Microcapsules in 0.1 N HCl. (Symbol representation same as in Fig.1).

are in accordance with the work of Yalabik-Kas (15) for oxazepam microcapsules. Figures 4 and 5 present the Higuchi plot for microcapsules and their tablets, respectively. The biphasic release profiles were obtained as also evident from Wagner's plots (Figures 6 and 7). The first straight line gave larger slope and faster release rate than the second. The rapid initial release may provide a useful loading dose of the sustained release formulation. As the tablet remained intact during the dissolution study, the second phase corresponds to diffusion controlled release from a solid, inert,

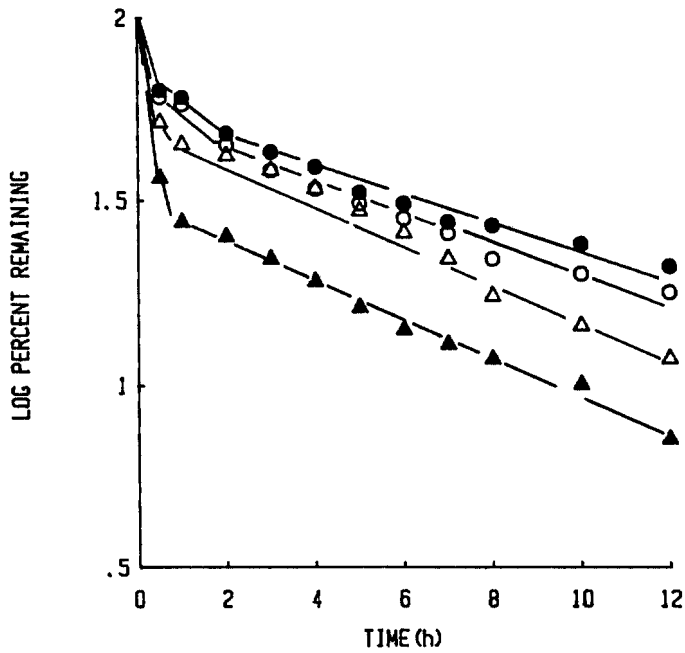

FIGURE 7

Log Percent Remaining versus Time plots of the Released Captopril from Tableted Microcapsules in 0.1 N HCl. (Symbol representation same as in Fig. 1).

non-biodegradable matrix which will provide the sustaining dose of the formulation.

CONCLUSIONS

Ethylcellulose coated microcapsules can be directly compressed into tablets. The in vitro release was studied in 0.1N HCl. The release was substantially delayed from tablets with respect to their microcapsules. Various kinetic models were applied to explain the release. The best fit with the highest correlation coefficient was achieved by the first-order equation.

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