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EFFECTS OF BLENDING A NONIONIC AND AN ANIONIC CELLULOSE ETHER POLYMER ON DRUG RELEASE FROM HYDROPHILIC MATRIX CAPSULES

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ABSTRACT

Blends of hydroxyethylcellulose (HEC) and sodium carboxymethylcellulose (NaCMC) were used to achieve zero order release of chlorpheniramine maleate (CM) from hydrophilic matrix capsules. Dynamic swelling / erosion and response surface measurements were made to provide an insight into the drug release behavior. The drug to total polymer and the HEC to NaCMC ratio influences the rate of drug release. NaCMC appears to influence water uptake and erosion of the matrix mixture. The factors by which zero-order drug release is achieved may include synchronization of the rates of water uptake and polymer erosion even though a constant diffusional pathlength may not be maintained. The combined mixture factorial design presented in this study allows for the characterization and optimization of the drug release profiles.

INTRODUCTION

Hydrophilic matrix capsules were originally introduced as controlled release floating systems for prolonging the gastric residence time [1]. Research efforts in this area have focused on the effects of polymer type, microenvironment pH control and formulation variables on drug release [2-5]. Drug release from a hydrophilic matrix tablet or capsule is a result of several coupled mass transport phenomena. During the initial contact of hydrophilic tablets with the dissolution media, surface drug dissolution occurs as well as the surface pores become filled with the media and the drug is released by dissolution and diffusion through the pores. In addition, polymer-solvent interactions cause relaxation and swelling leading to gel formation. Eventually,

drug release from a swollen hydrophilic matrix occurs by diffusion through the gel layer countercurrently to the incoming dissolution fluid and by erosion of the swollen matrix. In the case of hydrophilic capsules, the gelatin shell may modify this behavior by allowing the polymer to gel prior to its own dissolution.

Several different approaches have been suggested to modify the typical square root of time release from hydrophilic matrices to obtain a constant rate or a zero order drug order release profile [6-13]. Of these, the simplest method is to modify the rates of water uptake and subsequent polymer erosion by blending nonionic cellulose ethers with an anionic cellulose ether, such as, sodium carboxymethyl cellulose (NaCMC) [14]. Although NaCMC suffers from the drawback of being insoluble in media of pH less than 3 [14], it provides us with a model system to study this concept. The polymer blending concept, reported for hydrophilic matrix tablets, may also be viable for hydrophilic matrix capsules but needs to be studied and verified. In addition, the information reported on hydrophilic matrix tablets has been generated by the usual "one factor at a time" approach which does not give a complete picture of the system behavior. The purpose of this investigation was to apply the polymer blending approach to hydrophilic matrix capsules using a combined mixture factorial design. Specifically, the effects of drug to total polymer ratio (D/P) and the nonionic (hydroxyethylcellulose, HEC) to anionic polymer (NaCMC) ratio (P1/P2) on the *in vitro* release of a model drug, chlorpheniramine maleate (CM) was investigated. A combined mixture factorial design [15] was adopted for this study because it allows for the variation for all three components in a systematic fashion and provides for a reduction in formulation variables from three to two. In addition, dynamic swelling and water uptake studies were conducted to give further insight into the mechanism of release.

MATERIALS AND METHODS

Hydroxyethylcellulose (250 HHX, HEC) was obtained from the Aqualon Co., (Wilmington, DE). Sodium carboxymethylcellulose, (degree of substitution 0.7, degree of polymerization 3,200, NaCMC), was purchased from Scientific Polymer Products, Inc. (Ontario, NY). Theophylline (TH) and chlorpheniramine maleate (CM) were purchased from Sigma Chemical Company (St. Louis, MO). Hard gelatin capsules, size No. 2, were obtained from Eli Lilly & Co. (Indianapolis, IN).

Experimental design

A combined mixture-factorial design was used in this investigation [15], the three mixture components were CM, HEC, and NaCMC. In all formulations, each individual component of the mixture was treated in terms of its mass fraction and conforms to the following constraint:

$$\sum_{i=1}^{3} f_i = 1.0 \qquad (1)$$

where f_1 is the mass fraction of CM, f_2 is the mass fraction of HEC, and f_3 is the mass fraction of NaCMC in the mixture. The variables of interest in this system were the drug to total polymer ratio (X_1) and the HEC to NaCMC ratio (X_2) giving:

$$X_1 = \frac{f_1}{f_2 + f_3} \quad (2)$$

and

$$X_2 = \frac{f_2}{f_3} \quad (3)$$

Variables X_1 and X_2 were coded as follows:

$$CODED\ LEVEL\ (X_2) = \frac{X_2 - 2}{1} \quad (4)$$

(drug to total polymer ratio) and

$$CODED\ LEVEL\ (X_1) = \frac{X_1 - 0.5}{0.25} \quad (5)$$

(HEC to NaCMC ratio).

The actual and the coded variable values are listed in Table 1. The experimental data was used to estimate the coefficients of a polynomial equation relating the response variables to the independent variables, X_1 and X_2. The additional points $(\pm\sqrt{2},\pm\sqrt{2})$ were added to completely cover the design space.

Preparation and evaluation of dosage forms

The powders were passed through an 80 mesh screen, mixed, and hand filled into hard gelatin capsules. In order to assess the interaction between CM and NaCMC, TH was substituted for CM in a series of experiments. The powder content of each capsule remained fairly constant, weighing approximately 275 mg. The dissolution studies (n=3) were performed using the USP XXII paddle apparatus at a rotation speed of 50 rpm at 37 °C in 900 ml distilled water. Due to the inherent buoyancy of this system, a stainless steel #10 mesh screen was placed above the capsule to keep it submerged. The CM and TH concentrations were determined by U.V. spectrophotometry at λ_{max} of 261 nm and 274 nm respectively.

Swelling and water uptake studies

Dynamic swelling and erosion studies were performed only on the following systems: CM:NaCMC (1:3), CM:HEC:NaCMC (1:1.5:1.5), and CM:HEC (1:3). The filled capsules were subjected to the dissolution test as described earlier. After a predetermined time interval, based on earlier drug release studies, the capsules were removed from the vessels, a sample of dissolution fluid was taken to estimate the amount of drug released, and the capsules were weighed to determine the wet weight. Each capsule was subsequently dried in a forced convection oven at 60 °C until a constant weight was reached. The amount of polymer remaining in the matrix was calculated as the difference between the dry weight and the amount of drug remaining

TABLE 1. Summary of Experimental Results

Form. No.	X_1	X_2	D/P[a]	P1/P2[b]	n	$T_{0.5}$
1	-1	-1	0.25	1	0.94 (0.04)	7.97 (0.20)
2	0	-1	0.50	1	0.87 (0.03)	8.04 (0.53)
3	1	-1	0.75	1	0.71 (0.03)	6.46 (0.23)
4	-1	0	0.25	2	0.70 (0.04)	10.5 (0.16)
5	0	0	0.50	2	0.68 (0.01)	6.86 (0.46)
6	1	0	0.75	2	0.63 (0.05)	5.73 (0.22)
7	-1	1	0.25	3	0.71 (0.01)	6.37 (0.22)
8	0	1	0.50	3	0.58 (0.01)	5.25 (0.26)
9	1	1	0.75	3	0.54 (0.01)	4.58 (0.11)
10	$-\sqrt{2}$	0	0.15	2	0.84 (0.03)	9.66 (0.43)
11	0	$-\sqrt{2}$	0.50	0.59	0.91 (0.04)	6.73 (0.22)
12	0	$\sqrt{2}$	0.50	3.41	0.61 (0.01)	5.87 (0.42)
13	$\sqrt{2}$	0	0.85	2	0.60 (0.03)	4.70 (0.51)
14	$-\sqrt{2}$	$-\sqrt{2}$	0.15	0.59	1.07 (0.07)	6.80 (0.07)
15	$\sqrt{2}$	$-\sqrt{2}$	0.85	0.59	0.87 (0.01)	6.29 (0.19)
16	$-\sqrt{2}$	$\sqrt{2}$	0.15	3.41	0.75 (0.01)	6.18 (0.29)
17	$\sqrt{2}$	$\sqrt{2}$	0.85	3.41	0.58 (0.04)	4.21 (0.19)

[a]Drug to polymer ratio
[b]HEC to NaCMC ratio

in the matrix (estimated spectrophotometrically). The amount of water uptake was expressed as the difference between the wet weight and the dry weight. This procedure was repeated with different sets of capsules for each corresponding preselected time-points.

Data analysis

The drug release data, up to 70% drug release, was fitted by nonlinear regression (PC NONLIN, Statistical Consultants, Lexington, KY) to the following equation [16]:

$$\frac{M_t}{M_\infty} = kt^n \qquad (6)$$

where n is the release exponent and k is the kinetic release rate constant. The $T_{0.5}$ (time for 50% drug release from the matrix) values were calculated from the experimental data by cubic spline interpolation (MATHCAD, Cambridge, MA). The relationship between the response variables, n and $T_{0.5}$, and X_1 and X_2 were approximated by polynomial equations (ECHIP, Hockessin, DE).

RESULTS AND DISCUSSION

The experimental results are summarized in Table I. The regression polynomials (Cox polynomials) used to approximate the response surface for n and $T_{0.5}$ were:

$$n = 0.657 - 0.064X_1 - 0.117X_2 + 0.02X_1^2 + 0.058X_2^2 + 0.007X_1X_2 - 0.005X_1X_2^2 - 0.005X_1^2X_2 \quad (r^2 = 0.921) \tag{7}$$

and

$$T_{0.5} = 7.51 - 1.66X_1 - 0.60X_2 - 0.09X_1^2 - 0.73X_2^2 - 0.14X_1X_2 + 0.70X_1^2X_2 + 0.12X_1X_2^2 \quad (r^2 = 0.864) \tag{8}$$

Contour plots for n and $T_{0.5}$ as a function of the drug to polymer ratio (D/P) and the HEC to NaCMC ratio (P1/P2) are shown in Figure 1 and Figure 2. At a fixed D/P, the release exponent decreases with an increase in P1/P2. Similarly at a fixed P1/P2, the release exponent was observed to decrease with an increase in D/P. Figure 1 clearly demonstrates that the release exponent was less than 0.6 in regions with high P1/P2 and D/P ratios indicating a diffusion controlled behavior. However, in the region of low D/P (D/P < -1.2) and low P1/P2 (P1/P2 < -0.6); the release exponent approaches 1. These formulations are characterized by a matrix that has low drug loading and significant NaCMC concentrations.

Regarding $T_{0.5}$, at low D/P (D/P < 0.5), $T_{0.5}$ increases, reaches a maximum, and subsequently declines as P1/P2 increases. This observation appears to be consistent with the fact that mixtures of HEC and CMC experience a synergistic increase in viscosity [16]. However, at higher D/P (D/P > 1.0), $T_{0.5}$ decreases with an increase in P1/P2. This could be attributed to the declining rate controlling influence of the polymer fraction with increased drug loading. Likewise, for a fixed P1/P2, $T_{0.5}$ decreases with an increase in the D/P indicating the reduction in the influence of the polymer fraction with increases in drug loading.

To validate the predictive ability of the polynomial equations, the composition of two different matrices yielding an exponent value of 1 and $T_{0.5}$ values of 7.5 and 8.0 hours were calculated and prepared as described earlier. The compositions of the matrices and the experimental results are given in Table 2. The close agreement between the calculated and experimental values shows the validity of this approach.

Swelling, erosion and water uptake studies

The values of the release exponent n, and $T_{0.5}$ of the three matrices containing CM, used in the swelling and water uptake studies are listed in Table 3. During the

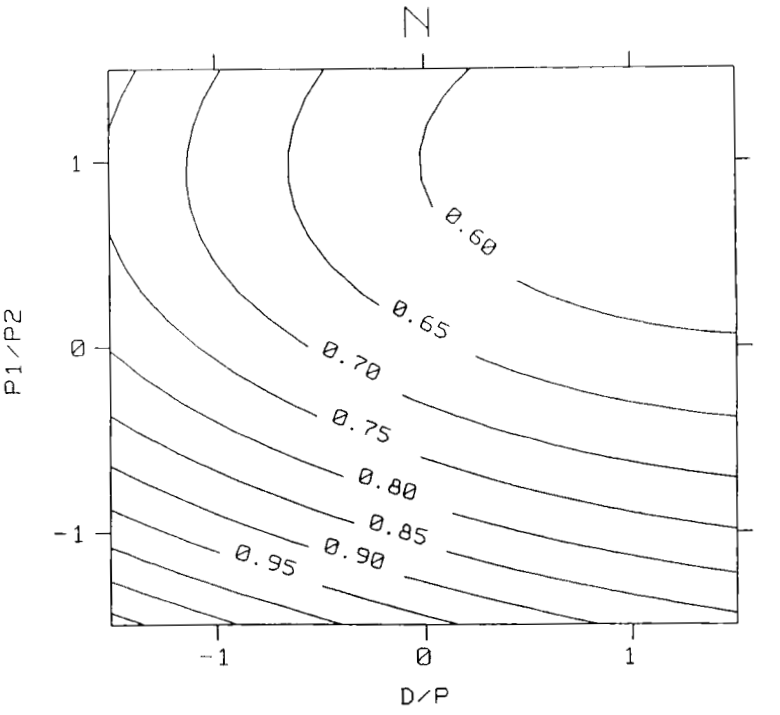

FIGURE 1
Release exponent (n) as a function of drug to total polymer and nonionic to anionic polymer ratio.

swelling studies, in addition to the drug release we monitored the water uptake (mg) and the polymer erosion (mg). The observed drug release profile during these experiments (symbols) correspond well with the drug release profiles obtained from previous experiments (lines, Figure 3). Figure 4 shows the time course of water uptake normalized to the weight of polymer remaining from the three systems. Initially, the rate of water uptake ($t \leq 1$ hr.) was quite similar for the three systems and appears to reflect the influence of the gelatin shell. The water uptake profiles by the three matrices appears to be similar to their drug release profiles (Figure 3). Curve fitting the water uptake data to a power equation similar to eqn. (6) gives exponent values of 1.22, 0.46, and 0.80 for NaCMC, HEC, and HEC+NaCMC mixture, respectively. The polymer erosion, expressed as the fraction of the total polymer initially present, as a function of time, is shown in Figure 5. The average polymer erosion rates (slopes from Figure 5) were 29, 3.7, and 7.1 percent per hour for NaCMC, HEC, and HEC +NaCMC, respectively. Significant time lags of 0.65, 1.8, and 0.4 hours were observed for matrices containing NaCMC, HEC, and the HEC+NaCMC mixture, respectively. The long lag time for HEC matrix may reflect the relatively slow rate of

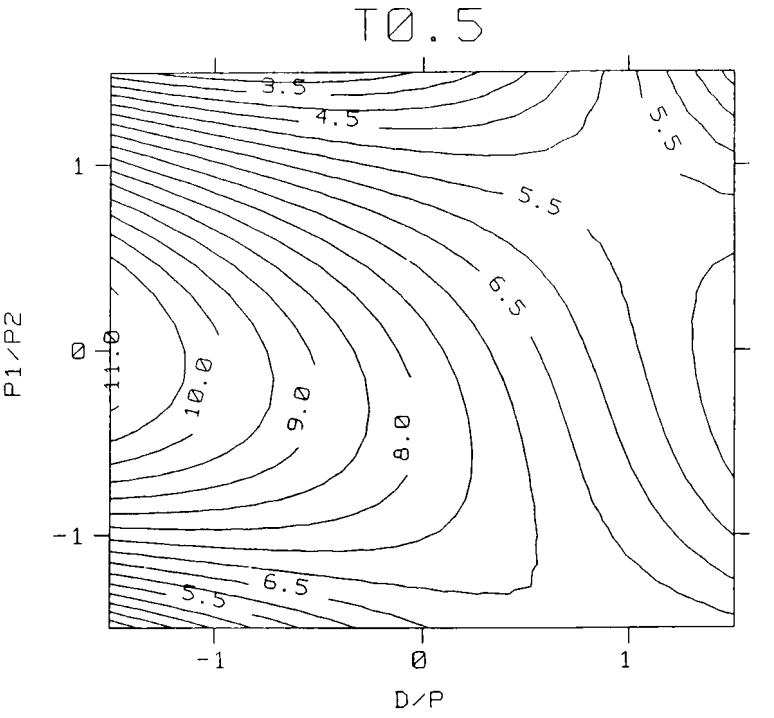

FIGURE 2
$T_{0.5}$ as a function of drug to total polymer ratio and nonionic to anionic polymer ratio.

TABLE 2: Formulations used to validate model predictions

Composition	Formulation 1		Formulation 2	
HEC	0.352		0.432	
NaCMC	0.462		0.440	
CM	0.186		0.128	
Parameters	Calculated	Observed*	Calculated	Observed*
$T_{0.5}$ (h)	7.5	7.8 ± 0.73	8.0	8.12 ± 0.79
n	1	1.04 ± 0.13	1	0.99 ± 0.08

* Mean ± S.D.

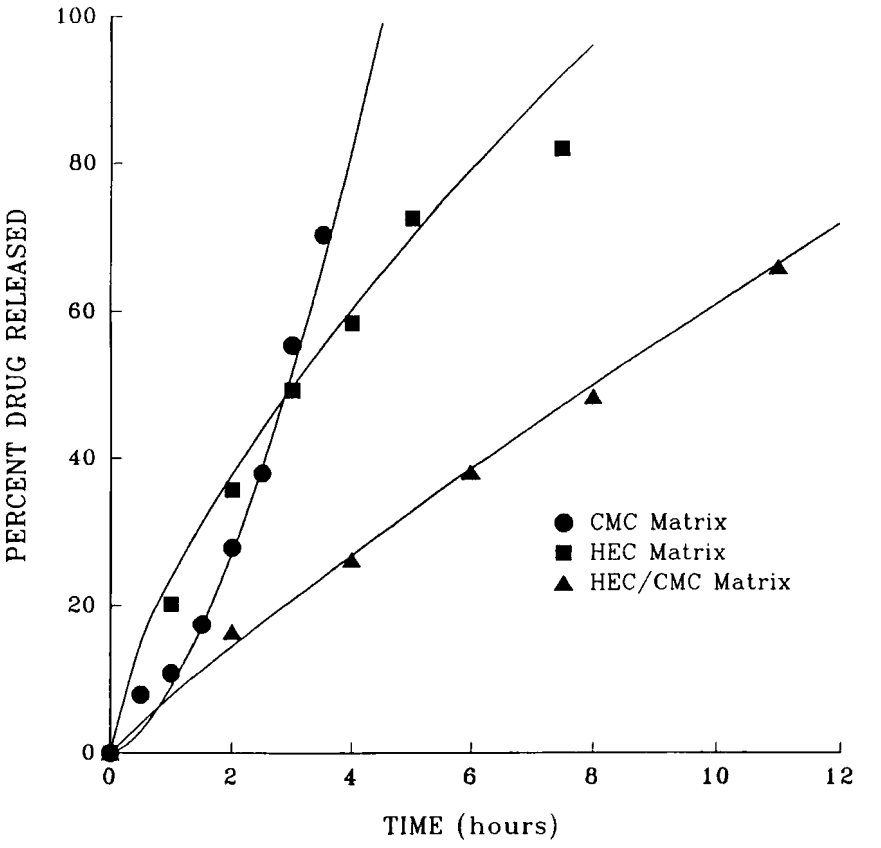

FIGURE 3
Drug release during dynamic swelling/erosion (symbols) and dissolution experiments (lines).

water uptake. The dimensional changes that occur during the drug release are shown in Figures 6 and 7. The diameter of the NaCMC matrix increased for about 1 hour, remained constant for an hour, and declined thereafter. This trend was also observed for the binary mixture, however, it maintained a fairly constant diameter for about 6 hours and then declined. The diameter of the HEC matrix continued to expand over most of the drug release period. It was observed that the decline in the capsule diameters coincided with the disappearance of the internal dry powder core. Since these matrices are weakly compacted powder cylinders, measurement of the core dimensions was not possible with the technique adopted in this study. The dimensional changes in the capsule length were more pronounced than the changes in the diameter. For the NaCMC containing matrices, a decline in the capsule length was observed towards the end of the release period. Swelling of cellulose fibers has been

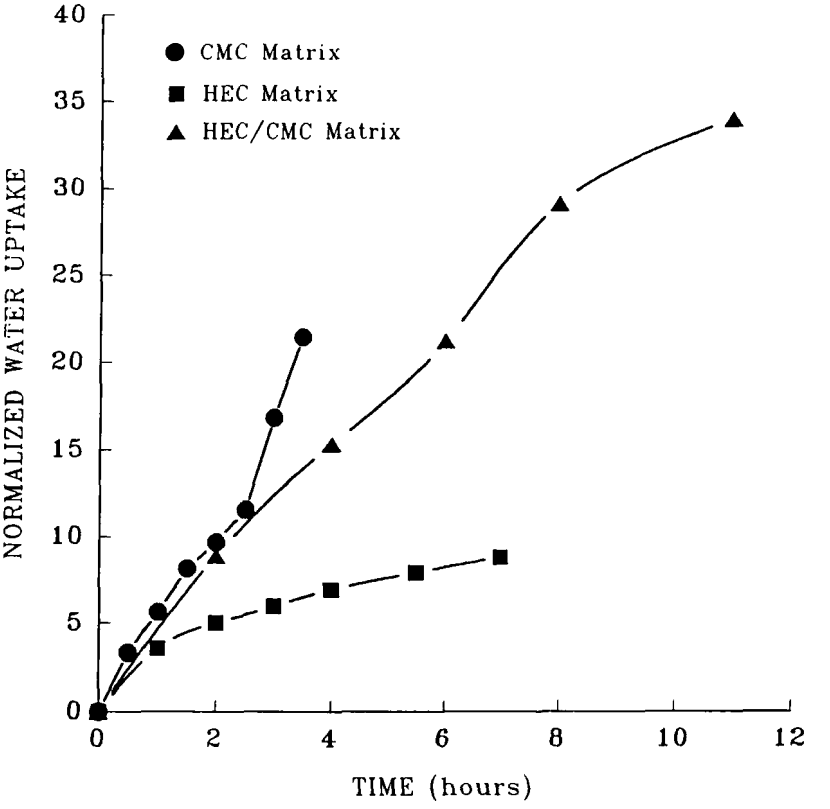

FIGURE 4
Water uptake (mg) normalized to the weight (mg) of polymer remaining in the matrix.

reported to occur mainly along the direction of fluid diffusion (radial); whereas the dominant tensile strength is in the axial direction [19]. This axially directed tensile stress could be a factor in the dramatic increase in the capsule length. These observations suggest that both swelling and erosion are factors important to drug release.

The linearizing effect of adding NaCMC to nonionic cellulose ether polymers has been suggested to be due to a constant diffusional pathlength resulting from the synchronization of the erosion and swelling fronts [13]. Since the rate of water uptake normalized to the amount of polymer remaining, tends to parallel the shape of the drug release profile, zero-order drug release occurs when these rates are synchronized. The rapid water uptake observed in the presence of NaCMC is due to the presence of ionized carboxylic acid groups [18]. As the fraction of NaCMC in the matrix increases, the number of ionizable carboxylic acid groups within the gel increases leading to an increase in ion-pair repulsion. This leads to an increase in the rate and

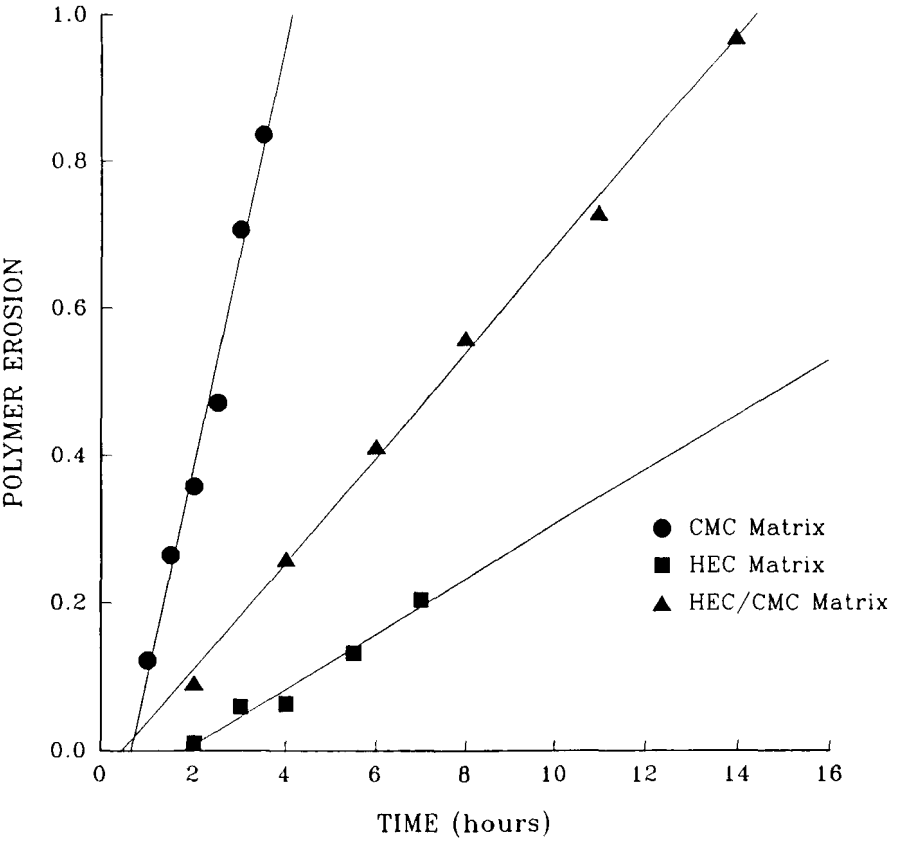

FIGURE 5
Fraction of polymer eroded as a function of time.

the extent of water uptake which may stretch the gel network such that the bonds responsible for gel structure are broken thereby initiating polymer erosion. Hence, as the rate and the extent of water uptake increases, so does the rate of polymer erosion. The ionic interaction between NaCMC and CM [19] may contribute to the drug release. The net effect of this interaction is likely to be a lowering in the release rate because of a decrease in the free drug concentration within the gel. This interaction may also serve to decrease the fraction of non associated ionizable carboxylic acid groups. As more drug is released, the fraction of free ionizable groups increases which may lead to an increase in the tendency for water uptake. As the tendency for water uptake increases, the diffusion coefficient within the gel is likely to respond to this change and increase. The effect of this interaction on the release exponent will depend upon the degree of association, the rates of free drug diffusion, and polymer erosion. As the degree of association increases, the exponent is likely to increase. A

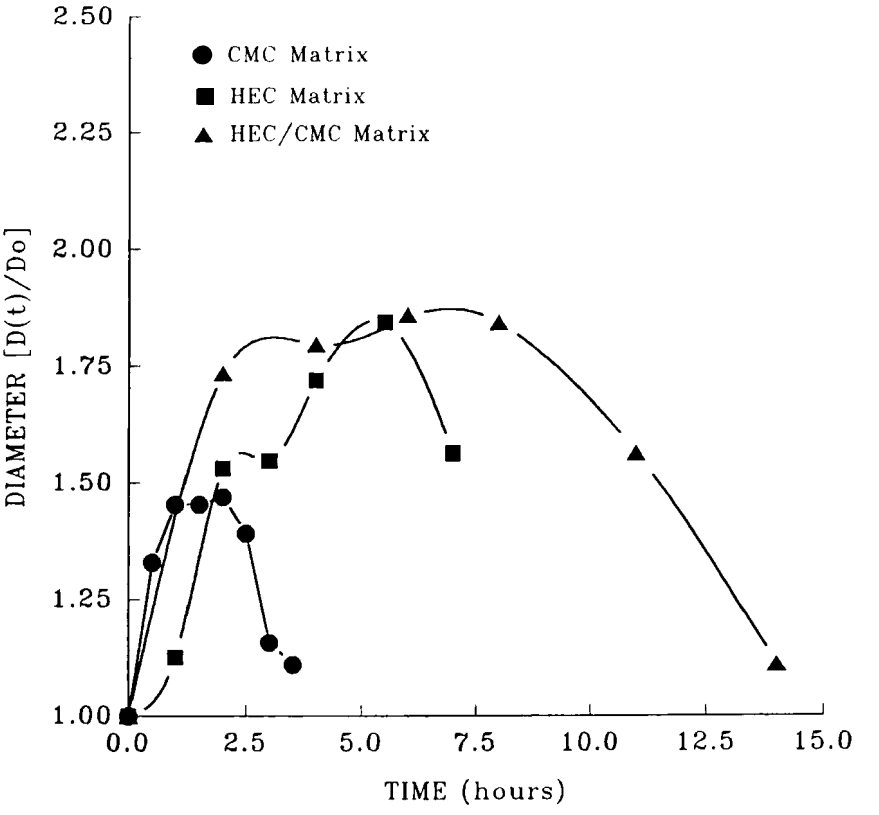

FIGURE 6
Normalized capsule diameter as a function of time.

drug with minimal or no association to NaCMC should have a lower release exponent from the NaCMC matrix. This was confirmed by substituting theophylline (TH) for CM in the same series of experiments.The release exponent n and $T_{0.5}$, observed for TH are given in Table 3.

The theophylline release exponent from the NaCMC matrix was significantly lower ($p < 0.05$) than that of CM from the same matrix. However, the release exponent of the HEC+NaCMC mixture was slightly higher, for theophylline compared to CM. The lower solubility of theophylline may contribute to the higher exponent observed for the HEC+NaCMC and the HEC matrix. It was also observed that theophylline containing NaCMC matrices eroded at a faster rate than the CM containing matrices which supports our explanation on the binding effect.

CONCLUSIONS

The linearizing effect of adding NaCMC to a nonionic cellulose ether polymer observed in the case of tablet matrices also occurs in the capsule system. The gelatin

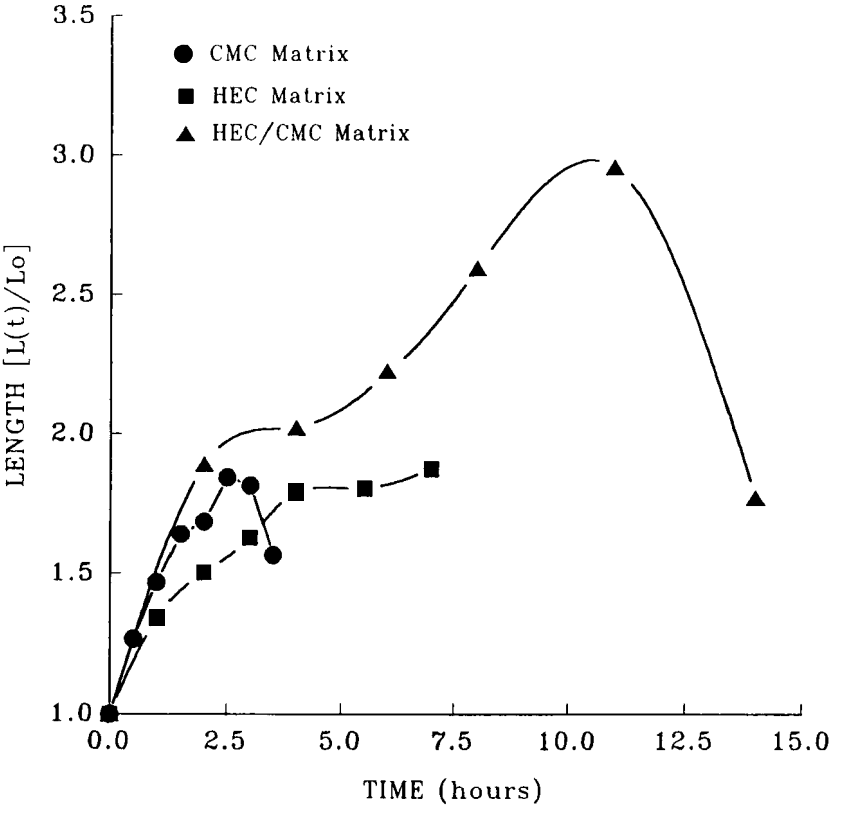

FIGURE 7
Normalized capsule length as a function of time.

TABLE 3: Release parameters of CM and TH matrices (CM matrices used in swelling and water uptake studies (Mean ± S.D.)).

Matrix	Chlorpheniramine maleate		Theophylline	
	$T_{0.5}$	n	$T_{0.5}$	n
NaCMC	3.0 ± 0.2	1.59 ± 0.06	2.0 ± 0.06	1.35 ± 0.03
HEC	3.1 ± 0.3	0.67 ± 0.05	4.0 ± 0.40	0.74 ± 0.04
HEC+NaCMC	7.8 ± 0.8	0.91 ± 0.04	4.2 ± 0.22	1.02 ± 0.04

shell was responsible for imparting the cylindrical shape to the powder plug, beyond this, it appears to have a minimal effect. The rate and extent of water uptake depends on the type of polymer and dictates in part the subsequent release profile. Polymer erosion and time dependent drug permeability are also a direct result of the extent and rate of water uptake. The response variables for the release profiles are related to both the drug to total polymer and nonionic to anionic polymer ratios. This relationship was well characterized by a combined mixture-factorial experimental design. To date, NaCMC is the only anionic polymer shown to linearize the release profile of water soluble drugs from polymer blends containing nonionic cellulose ethers. A drawback of using NaCMC is that it exhibits a pH dependent solubility. Further work is needed to make this system pH independent and will be the subject of future studies.

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