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RELATIONSHIPS BETWEEN DRUG DISSOLUTION PROFILE AND GELLING AGENT VISCOSITY IN TABLETS PREPARED WITH HYDROXYPROPYLMETHYLCELLULOSE (HPMC) AND SODIUM CARBOXYMETHYLCELLULOSE (NaCMC) MIXTURES

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ABSTRACT

Two varieties of HPMC, two varieties of NaCMC and various HPMC/NaCMC mixtures were characterized with the aim of providing a sound basis for the selection of appropriate mixtures to use as gelling agents in controlled-release tablets for hydrosoluble drugs. For both HPMC and NaCMC, one variety was of high and the other of low nominal viscosity. We also investigated possible relationships between the rheological properties of HPMC/NaCMC mixtures and atenolol release from tablets prepared with such mixtures. The mean molecular weights of each polymer variety were estimated on the basis of determination of their intrinsic viscosities in aqueous dispersions. Rotational viscosimetry of 2% aqueous dispersions of the polymers and polymer mixtures revealed rheological synergism in some mixtures. Drug dissolution trials were carried out in water and 0.1 N HCl. Dissolution medium, gelling agent composition and proportion of gelling agent in the tablet all affected dissolution profiles. Fitting of Korsmeyer et al.'s equation to the data for dissolution in water indicated zero-order dissolution kinetics for all formulations. For tablets prepared with the most viscous HPMC variety, 8-hour dissolution efficiency was closely correlated with the apparent viscosity (shear rate 0.5 s^{-1}) of the aqueous dispersion of the polymer mixture used as gelling agent. Assays of tablet erosion rates indicated that the erosion mechanism may contribute to the observed zero-order dissolution kinetics, but that other factors are probably also involved.

INTRODUCTION

Mixtures of hydroxypropylmethylcellulose (HPMC) and sodium carboxymethylcellulose (NaCMC) have proved very suitable as gelling agents for matrix tablets, particularly when constant rates of release of a hydrosoluble drug are required (1)(2)(3). Zero-order dissolution profiles for hydrosoluble drugs are not generally obtained with gelling agents comprising nonionic ethers alone, and there has been considerable debate as to why such profiles occur when the gelling agent is an HPMC/NaCMC mixture. Feely and Davis (4) suggested that zero-order profiles arise because of interactions between ionized drug molecules and polar groups on the NaCMC. By mixing HPMC and NaCMC in the appropriate proportions, Ranga Rao et al. (5)(6)(7) obtained matrices from which drug release showed zero-order kinetics, and suggested that this might be attributable to the rate of advance of the swelling front being similar to the rate of erosion. In tablets prepared with such mixtures, the distance over which drug molecules must diffuse to reach the tablet surface will remain roughly constant throughout the release process, thus leading to constant release rates even when the tablet has been heavily eroded. Bonferoni et al. (8) have suggested that the zero-order dissolution profiles observed in some HPMC/NaCMC formulations may be related to the rheological synergism reported between polymers of these types.

In the work reported here, we determined the rheological properties of two varieties of HPMC, two varieties of NaCMC and various HPMC/NaCMC mixtures, with the aim of providing a sound basis for selection of the most suitable polymers and mixing proportions for the preparation of gelling agents. We also investigated possible causes of the zero-order drug dissolution kinetics typically observed in tablets prepared with HPMC/NaCMC gelling agents. For these experiments, erosion rates and drug release profiles were determined for tablets prepared with a series of HPMC/NaCMC mixtures. Atenolol was used as the model hydrosoluble drug. Particular attention was paid to possible effects of the rheological properties of the HPMC/NaCMC mixture on drug release profile.

MATERIALS AND METHODS

Drugs and Excipients

Atenolol BP (J. Escuder, Spain, lot 005); HPMC with nominal viscosity of 100 cP (Methocel K100LV, Colorcon, Spain, lot 88031321); HPMC with nominal viscosity of 100,000 cP (Methocel K100M, Colorcon, Spain, lot 87071902); NaCMC with nominal viscosity of 400 - 800 cP (NaCMC I, Sigma Chemicals, Spain, lot 71H0397); NaCMC with nominal viscosity of 1000 cP (NaCMC II, J. Escuder, Spain, lot 012) lactose USP/BP (C. Barcia, Spain, lot 872); magnesium stearate USP/BP (C. Barcia, Spain, lot 832).

Estimation of Intrinsic Viscosities and Molecular Weights of the Cellulose Ethers

Intrinsic viscosity was determined in aqueous dispersions of polymers at a range of low concentrations. The dispersions of HPMC were obtained by dilution of a stock dispersion containing 2% polymer w/w, prepared by a modification of the USP XXII procedure as follows. HPMC was added to distilled water in a 250 ml beaker and stirred with a propeller mixer (Janke & Kankel RW 20 DZM; Staufen, Germany) at 500 rpm for 5 min then 1000 rpm for 55 min (at 80°C for the first 10 min, on ice for the remaining 50 min). The dispersion (weight 200 g) was then centrifuged at 1800 rpm for 30 min at 4°C (Kontron TGA-6; Zurich, Switzerland) to remove air bubbles introduced during stirring. The dispersions of NaCMC were obtained in the same way with the following exceptions: a) the stock dispersion was diluted in 0.1M NaCl, not distilled water, b) stirring was at 500 rpm for 5 min then 1500 rpm for 55 min and c) temperature was maintained at 20°C throughout the process.

Viscosity was determined (six determinations per sample) with a Canon-Fenske viscometer (Afora, Ref. 5354/2; Barcelona, Spain) at 20°C (HPMC) or 25°C (NaCMC). Intrinsic viscosity was then estimated from the equation of Martin (9):

$$\log \eta_{SP}/C = \log [\eta] + k_M [\eta] C \quad \text{(Equation 1)}$$

where η_{sp} is specific viscosity, C is polymer concentration, $[\eta]$ is intrinsic viscosity and k_M a constant. This equation has been widely used in related studies of other cellulose ethers (10) (11).

Mean molecular weight was then estimated from intrinsic viscosity by the Mark-Houwink equation (12) (13):

$$[\eta] = k M^a \quad \text{(Equation 2)}$$

where M is mean molecular weight and k and a are constants assigned values of 0.88 and 3.39×10^{-4} for HPMC (14) and 0.91 and 1.23×10^{-5} for NaCMC (15).

Rheological Characterization of 2% Dispersions of Cellulose Ethers and HPMC-NaCMC Mixtures

Rheograms were obtained for 2% dispersions of the HPMC, NaCMC or HPMC-NaCMC mixtures with the aid of a Brookfield DVII rotational viscometer (Stoughton, MA, U.S.A.). Dispersions of HPMC K100LV (A), HPMC K100M (B), NaCMC I (C), NaCMC II (D), a 70:30 HPMC K100LV:NaCMC I mixture (Ac), a 30:70 HPMC K100LV:NaCMC I mixture (aC), a 70:30 HPMC K100LV:NaCMC II mixture (Ad), a 30:70 HPMC K100LV:NaCMC II mixture (aD), a 70:30 HPMC K100M:NaCMC I mixture (Bc), a 30:70 HPMC K100M:NaCMC I mixture (bC), a 70:30 HPMC K100M:NaCMC II mixture (Bd) and a 30:70 HPMC K100M:NaCMC II mixture (bD) were prepared in water and 0.1 N hydrochloric acid. The dispersions were maintained at rest at 20°C for 24 h prior to obtaining rheograms at 37°C (four replicates per dispersion type) for rotation velocities between 0.3 and 60 rpm. Apparent viscosities at a shear rate of 0.5 s^{-1} were estimated from the averaged rheograms for each dispersion type.

Preparation of Tablets

Atenolol tablets were made with every one of the HPMC-NaCMC mixtures listed above under a compression pressure of 88.4 or 141.5 MPa, with the gelling agent (i.e. the polymer mixture) making up 40% or 80% of total weight. The gelling agent was first dry-granulated in an Erweka AR400 apparatus (Heusenstamn, Germany). Atenolol/lactose (50:50) granulates were wet-granulated with an aqueous dispersion of the corresponding HPMC as binder. For each tablet type, the 0.25 - 0.5 mm fractions of the corresponding gelling agent and atenolol granulates were then mixed in the required proportion in a Turbula T2C mixer (Basel, Switzerland) at 30 rpm for 20 min and then, following addition of 0.5% magnesium stearate, for a further 5 min. Tablets (9 mm diameter for formulations with 40% gelling agent; 12 mm diameter for formulations with 80% gelling agent) were made in a Korsch-Eko excentric press (Berlin, Germany) fitted with a pressure transducer (16) and teflon-coated punches. Tablet weight was adjusted to obtain 50 mg of atenolol per tablet. The formulations are designated by the same symbols used to identify the gelling mixtures and two sub-indices, taking the values 1 or 2, the first corresponding to the proportion of gelling agent (40 and 80% respectively) and the second to the maximum pressure applied over the compression cycle (88.40 MPa and 141.50 respectively).

Characterization of Tablets

Having confirmed that all tablet formulations met USP XXII requirements for uniformity of weight and drug content, tablets of each type were characterized as follows.

a) Tensile strength was calculated for each of six tablets from the equation (17):

$$TS = 2\,CS / (\pi\,D\,E) \qquad \text{(equation 3)}$$

where CS is the crushing strength determined in an Erweka TB24 apparatus (Heusenstamn, Germany), D denotes the diameter of the tablet and E is its thickness.

b) Friability was evaluated as percentage weight loss by 10 tablets after 15 min at 20 rpm in an Erweka TAP apparatus (Heusenstamn, Germany).

c) Total porosity was determined by mercury intrusion porosimetry (Micromeritics 9305; Norcross, USA). three tablets for each formulation, between 0.6 and 25,000 psi. The tablets were first degassed at 0.001 psi. Penetrometer of 3 ml capacity was used; the volume of sample was roughly 1/3 the capacity of the penetrometer.

d) Drug dissolution profiles were obtained for six tablets of each formulation using apparatus adapted to the specifications of method II described in the USP XXII ed.(Turu Grau; Barcelona, Spain). Tablets were held at the bottom of a beaker containing 900 ml of water or 0.1 N HCl as described by Pérez-Marcos et al. (18). The stirring rate was 150 rpm. Atenolol concentrations were determined by UV spectrophotometry at 274 nm for eigth hours. Dissolution profiles were characterized on the basis of dissolution eficiency over this period, DE (19).

Release kinetics were characterized by estimation of the parameters of Korsmeyer et al.'s equation (20):

$M_t/M = K_t t^n$ (equation 4)

where M_t/M is the fraction of drug dissolved at time t and the value of exponent n is conditioned by the mechanism ruling the process.

e) Erosion profiles in water, under the same conditions as for the dissolution assays, were obtained for the tablets prepared with each of the HPMC/NaCMC I mixtures and under 141.50 MPa pressure, following the procedure of Bonferoni et al. (8). Erosion (i.e. loss of polymer and other insoluble components) was estimated on the basis of weight loss by tablets following correction for atenolol and lactose losses. Lactose loss was determined on the basis of analyses with a Boehringer-Mannheim kit (product ref. 986119). Assay duration was in all cases adjusted to be approximately that required for complete dissolution of atenolol. Erosion was characterized on a zero-order model, with estimation of the rate constant K_E.

Statistical Analysis

For each proportion of gelling agent (40% or 80%), the effects of the other formulation factors - a) percentage of HPMC K100LV in the gelling agent (F_1) (30% or 70%), and b) maximum pressure applied during compression (F_2) (88.4 MPa or 141.5 MPa) - on dissolution profile (as characterized by DE) were investigated with the aid of stepwise multiple regression. The fitted equations were plotted as response surfaces. Kinetic models were fitted to the mean dissolution or erosion profiles for each formulation by linear regression.

RESULTS AND DISCUSSION

The information included in standard pharmacopaeas on the nominal viscosities and mean molecular weights of polymers such as HPMC and NaCMC is often imprecise and incomplete, particularly since these properties tend to vary considerably among brands. Clearly, this can lead to problems in manufacturing (21)(22).

Intrinsic viscosities (as determined by capillary viscometry) and estimated mean molecular weights of the four polymers studied are listed in Table 1. The molecular weights of the two HPMC varieties are very different, as expected given their extreme nominal viscosities (23). The molecular weights of the two NaCMC varieties (despite their similar nominal viscosities) likewise differ considerably, although both are close to the middle of the range reported by Stelzer and Klug (24) for commercially available varieties of this polymer.

Rheograms for 2% dispersions of each of the four polymers, in water or in 0.1 N HCl, are shown in Figure 1. All dispersions showed pseudoplastic behaviour. There are clear differences between HPMC K100LV and HPMC K100M, and between NaCMC I and NaCMC II. The apparent viscosities (shear rate 0.5 s^{-1}) of the HPMCs in 0.1 N HCl were markedly lower than in water (Table 2), as expected given that HCl is a poor solvent for nonionic cellulose ethers. For

TABLE 1. Results of determination of intrinsic viscosities and mean molecualr weights of the indicated polymers.

Polymer	[η] (dl g^{-1})	Molecular Weight
A	3.78	39737
B	14.98	190000
C	5.35	124940
D	6.83	163699

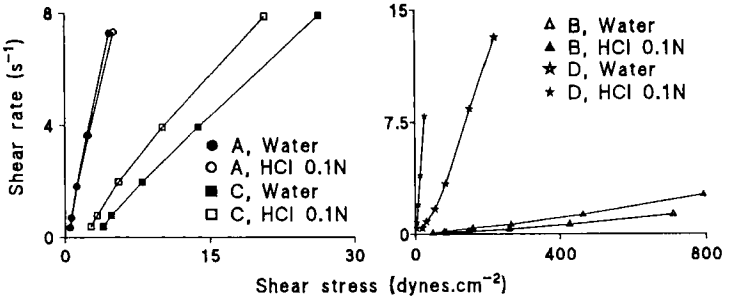

FIGURE 1
Rheograms of 2% dispersions of the polymers obtained by rotational viscometry at 37°C in water or HCl 0.1N.

TABLE 2. Apparent viscosities (shear rate 0.5 s^{-1}) of the polymer and polymer mixtures studied, in water and 0.1 N Hydrochloric Acid.

Dispersion	Apparent viscosity (cps)	
	Water	HCl 0.1 N
A	132	122
B	72730	40160
C	610	906
D	4460	1952
Ac	715	204
aC	814	982
Ad	1302	162
aD	1925	1035
Bc	31775	24149
bC	6065	11200
Bd	46980	27750
bD	21190	19795

NaCMCs, no such clearcut relationship was observed: the apparent viscosity of NaCMC I in 0.1 N HCl was higher than in water, while the apparent viscosity of NaCMC II in 0.1 N HCl was lower than in water (Table 2). The two varieties of NaCMC are from different manufacturers, raising the possibility that this apparently anomalous result is due to differences in substitution pattern. The importance of ionization of carboxyl groups for the gelling process and the dependence of pK_a on substitution pattern (24)(25) provide support for this hypothesis.

As a basis for subsequent interpretation of drug release profiles, we investigated the rheological characteristics of aqueous dispersions of the polymer mixtures used as gelling agents. Again, all dispersions (whether in water or 0.1 N HCl) showed pseudoplastic behaviour (Figure 2). Rheograms for dispersions of HPMC K100M mixtures were very similar, regardless of the NaCMC variety used. However, rheograms for dispersions of HPMC K100LV mixtures differed considerably, depending on the NaCMC variety used.

The apparent viscosities (shear rate 0.5 s^{-1}) of most mixtures were as would be predicted assuming there to be no rheological interaction between components. Appreciable rheological synergism -as reported to be characteristic of mixtures of this type by Mannion et al. (26)- was only observed in dispersions of HPMC K100LV and NaCMC II in water. These results confirm the importance of the chain length and substitution pattern of the nonionic polymer in determining the extent to which a given nonionic/ionic polymer mixture will display rheological synergism (27)(28), and demonstrate that the choice of NaCMC variety is likely to have profound effects on the rheological characteristics of the dosage form.

The results of the tests carried out to characterize each tablet type are summarized in Table 3. Most formulations had acceptable mechanical characteristics. However, friability was rather high in tablets in which the gelling agent contained 70% NaCMC I or NaCMC II, particularly when the proportion of gelling agent in the tablet was 80%. Tablets made with 70% NaCMC likewise had low tensile strength, particularly when the lower maximum compression pressure (88.4 MPa) was used. The results of these tests also indicate that porosity is closely related with mechanical properties.

In view of the known influence of pH on the ionization and gelling of NaCMCs, dissolution profiles were obtained both in water and in 0.1 N HCl. For all formulations, release occurred more slowly in 0.1 N HCl than in water (Figure 3), despite the higher solubility of atenolol at low pH. This can probably be attributed to effects on the gel formation process (due to reduced ionization of carboxyl groups) in the acid medium. NaCMC variety had no appreciable effect on dissolution in 0.1 N HCl; in water, however, release from tablets made with NaCMC II was markedly slower (all else being equal) than from tablets made with the less viscous NaCMC I. Student's t-test indicated that, for all formulations, dissolution medium was a significant factor ($\alpha < 0.01$) in DE, confirming the above conclusions. Likewise, DE in water differed significantly ($\alpha < 0.05$)

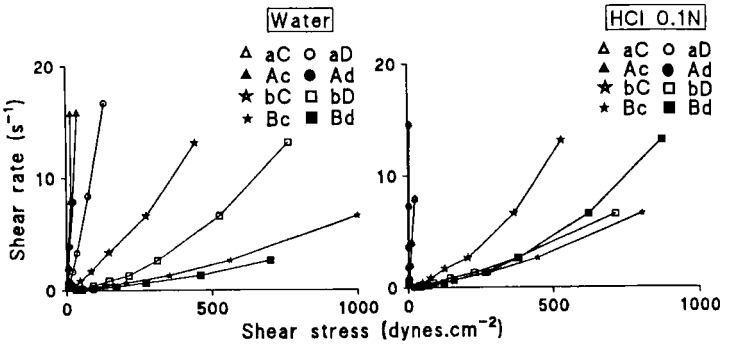

FIGURE 2
Rheograms of 2% dispersions of the polymer mixtures obtained by rotational viscometry at 37°C in water or HCl 0.1N.

between all pairs of formulations differing only in the variety of NaCMC (I or II) used.

Response surfaces illustrating this effects on DE of the controlled variables (proportion of gelling agent, maximum compression presure and percentage of HPMC in the gelling agent, for each dissolution medium and for each group of formulations studied, are shown in Figures 4 and 5 (the equations fitted using stepwise multiple linear regression are presented in Table 4). In water, the percentage of HPMC in the gelling agent has marked effects on DE; in tablets containing 80% gelling agent, maximum compression pressure also has an appreciable effect. In 0.1 N HCl, both variables have appreciable effects.

Release kinetics were characterized by fitting Korsmeyer et al.'s equation (20) to the dissolution data (Table 5). In water, the values of n for most formulations (regardless of the composition and proportion of gelling agent) are close to unity, indicating zero-order dissolution kinetics. In 0.1N HCl, however, the values of n for most formulations are close to 0.5, indicating a tendency towards Higuchi kinetics.

Several investigators (3)(5)(6)(7) have suggested that the consistency of the gel layer which forms following hydration of the tablet may have important effects on the type of drug release profile and on dissolution rate. Furthermore, it seems reasonable to suppose that the consistency of the gel layer may be related to the rheological characteristics of the gelling agent. We thus investigated whether DE in water is correlated with the apparent viscosity (shear rate 0.5 s^{-1}) of 2% aqueous dispersions of the gelling agent. For formulations containing HPMC K100M, there was a strong negative correlation between DE and apparent viscosity (in all cases, $r > 0.95$, $\alpha < 0.05$). For formulations containing HPMC K100LV, however, there was no correlation whatsoever between DE and

TABLE 3 . Mean results for tests characterizing tablets. Values in brackets are standard deviations.

Form.	Tensile Strength (N/cm^2)	Friability (%)	Porosity (%)	DE	
				Water	HCl 0.1N
aC_{11}	56.89 (6.83)	0.61	15.53 (0.50)	0.89 (0.03)	0.77 (0.01)
aC_{12}	83.19 (4.04)	0.02	13.48 (0.46)	0.89 (0.01)	0.74 (0.03)
Ac_{11}	91.78 (7.45)	0.12	13.78 (0.22)	0.83 (0.03)	0.81 (0.02)
Ac_{12}	124.64 (7.16)	0.13	11.34 (0.31)	0.85 (0.03)	0.67 (0.01)
aC_{21}	26.33 (1.44)	1.97	15.43 (0.48)	0.84 (0.03)	0.44 (0.02)
aC_{22}	38.78 (3.60)	1.08	20.48 (0.62)	0.78 (0.04)	0.41 (0.02)
Ac_{21}	67.54 (4.91)	0.44	16.76 (0.45)	0.69 (0.02)	0.36 (0.02)
Ac_{22}	100.87 (5.70)	0.27	13.12 (0.50)	0.69 (0.00)	0.52 (0.04)
aD_{11}	87.31 (3.84)	0.31	14.83 (0.62)	0.86 (0.02)	0.77 (0.02)
aD_{12}	130.44 (4.20)	0.27	11.69 (0.36)	0.83 (0.02)	0.74 (0.03)
Ad_{11}	121.54 (4.10)	0.32	11.71 (0.34)	0.76 (0.03)	0.76 (0.01)
Ad_{12}	142.61 (4.04)	0.20	10.33 (0.20)	0.78 (0.04)	0.76 (0.02)
aD_{21}	49.31 (1.10)	1.53	20.68 (0.44)	0.72 (0.02)	0.49 (0.02)
aD_{22}	74.37 (3.70)	0.98	18.04 (0.94)	0.72 (0.03)	0.50 (0.02)
Ad_{21}	102.90 (2.40)	0.43	17.19 (0.61)	0.60 (0.05)	0.59 (0.02)
Ad_{22}	144.86 (3.00)	0.31	12.88 (0.82)	0.55 (0.03)	0.43 (0.02)
bC_{11}	77.81 (5.08)	0.40	14.62 (1.10)	0.85 (0.02)	0.67 (0.02)
bC_{12}	110.76 (8.62)	0.25	12.32 (0.02)	0.84 (0.04)	0.60 (0.02)
Bc_{11}	108.97 (7.40)	0.32	14.03 (0.25)	0.67 (0.02)	0.63 (0.02)
Bc_{12}	133.98 (8.91)	0.18	10.94 (0.35)	0.67 (0.04)	0.59 (0.03)
bC_{21}	36.80 (4.54)	1.32	17.46 (0.68)	0.73 (0.03)	0.39 (0.03)
bC_{22}	62.13 (4.46)	0.89	14.00 (0.55)	0.74 (0.04)	0.40 (0.02)
Bc_{21}	104.15 (7.40)	0.37	15.82 (0.72)	0.44 (0.01)	0.37 (0.02)
Bc_{22}	137.49 (5.11)	0.26	13.86 (0.12)	0.39 (0.03)	0.38 (0.02)
bD_{11}	75.36 (4.26)	0.53	15.20 (0.11)	0.80 (0.02)	0.72 (0.03)
bD_{12}	112.31 (7.84)	0.34	12.42 (0.22)	0.75 (0.03)	0.73 (0.02)
Db_{11}	104.64 (5.82)	0.36	12.99 (0.31)	0.44 (0.02)	0.68 (0.02)
Db_{12}	140.33 (6.28)	0.47	10.50 (0.45)	0.45 (0.03)	0.63 (0.04)
bD_{21}	51.37 (6.65)	1.87	19.58 (0.66)	0.55 (0.03)	0.35 (0.02)
bD_{22}	83.00 (5.27)	0.84	17.40 (1.02)	0.50 (0.07)	0.41 (0.03)
Bd_{21}	91.22 (3.65)	0.74	17.65 (0.67)	0.24 (0.02)	0.37 (0.02)
Bd_{22}	115.07 (3.28)	0.55	15.20 (0.97)	0.26 (0.02)	0.38 (0.02)

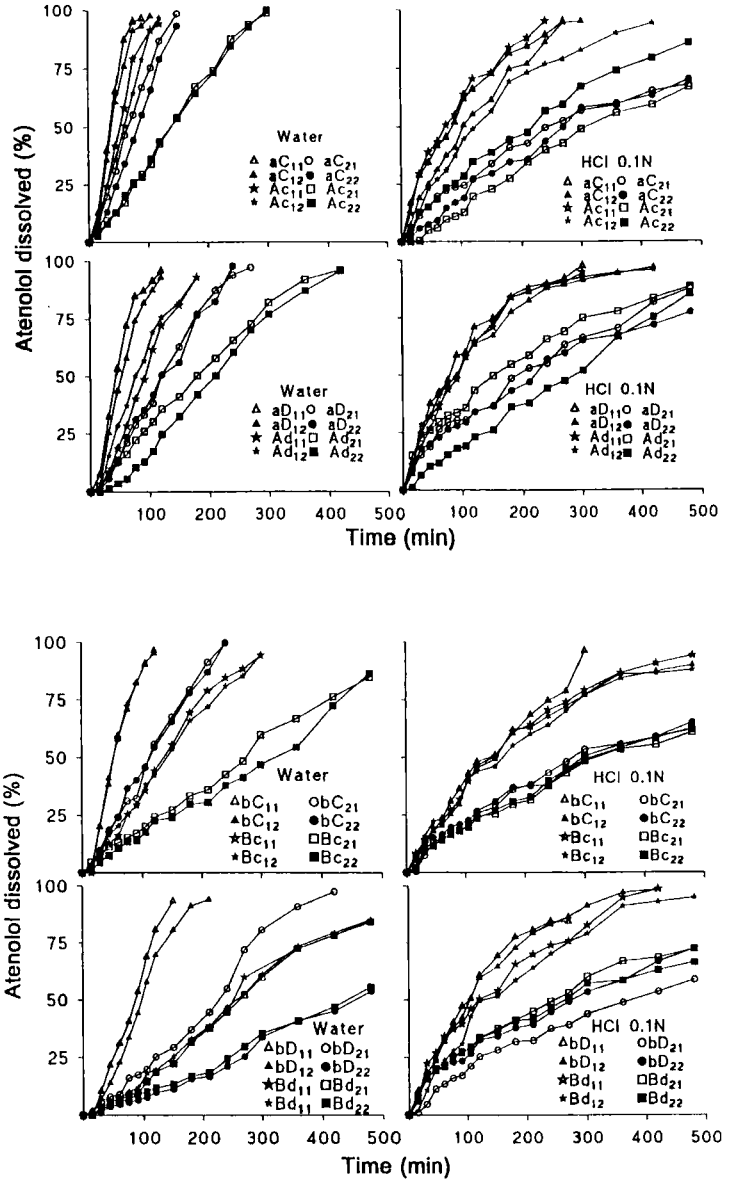

FIGURE 3
Mean dissolution curves of the indicated formulations.

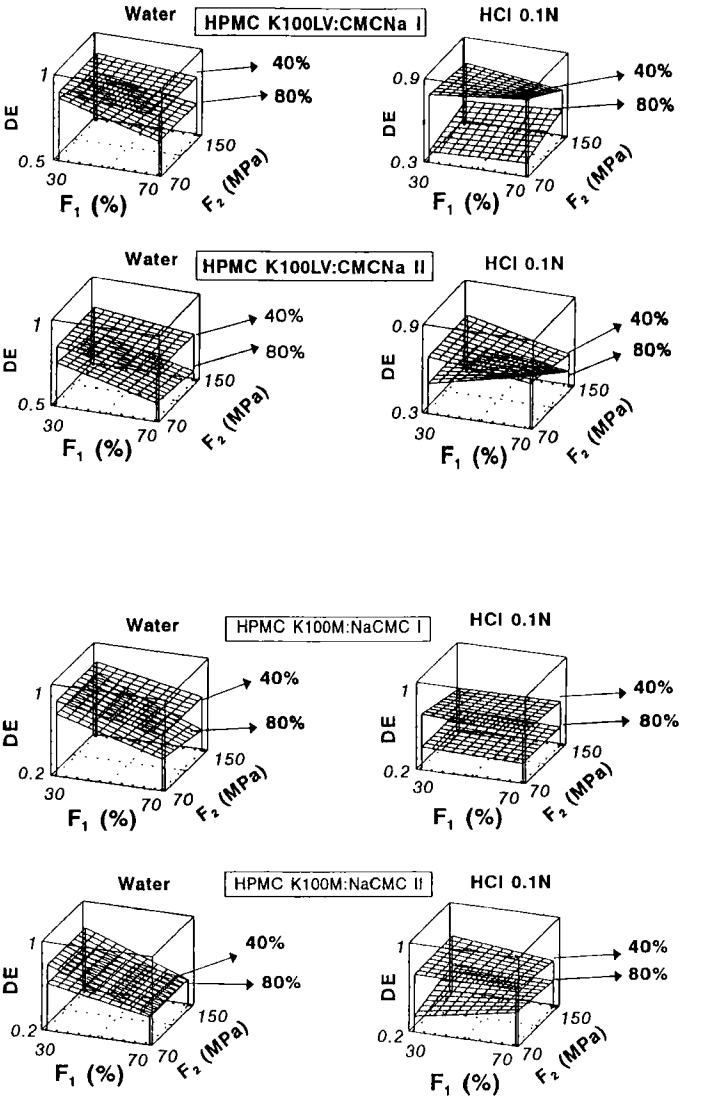

FIGURE 4
Response surfaces corresponding to the dissolution eficiency.

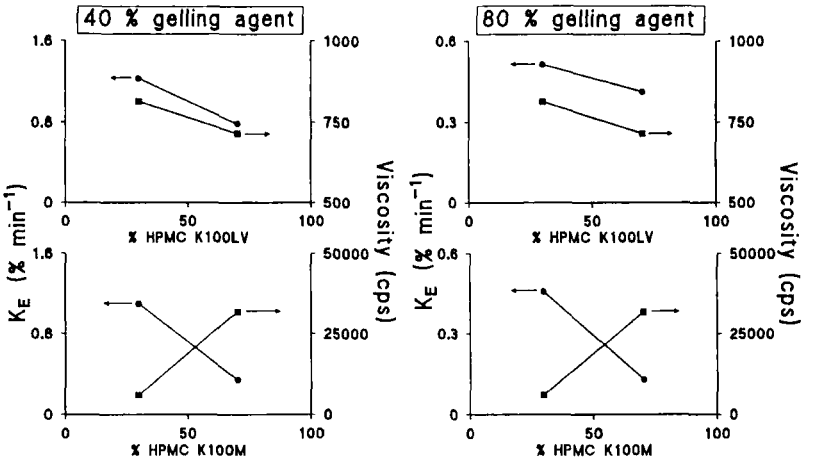

FIGURE 5

Relationship a) between apparent viscosity (shear rate 0.5 s-1) of aqueous dispersions of the polymer mixtures and percentage of HPMC in the gelling agent and b) between erosion rate constant KE and percentage of HPMC in the gelling agent.

apparent viscosity. For formulations containing HPMC K100LV, it is also of interest that (all else being equal) DE is highest when the ratio of HPMC to NaCMC is 30:70. Thus high proportions of NaCMC, despite conferring increased viscosity, lead to higher rather than lower release rates. This is probably attributable to the high hydrosolubility of NaCMC, and its consequent inability to form an adequate gel layer.

In order to further investigate the factors controlling release behaviour, we evaluated rates of erosion (K_E) for all tablet types containing NaCMC I. The differences in erosion rate between K100LV- and K100M-containing tablets are less pronounced than the differences in DE between these tablet types. For K100LV-containing tablets, however, the apparently anomalous relationship between viscosity and DE is reflected in a similar relationship between viscosity and K_E (Figure 6). Finally, comparison of the proportions of the atenolol released from tablets with the proportions of drug originally present in the fraction eroded by the same times, assuming erosion rate to be homogeneous over the surface of the tablet indicates that the last were higher. This implies that a significant proportion of NaCMC is rapidly eroded from the tablet, as a result of its high hydrosolubility, but that The matrix maintain their physical integrity.

TABLE 4 . Regression equations for the parameter dissolution efficiency.

Polymer mixture	Polymer proportion	Dissolution Medium		r	α
HPMCK100LV CMCNa I	40	Water	$DE = 0.93 - 1.26X10^{-3}F_1$	0.7028	<0.05
		HCl 0.1N	$DE = 0.66 + 5.30X10^{-3}F_1 + 8.94X10^{-4}F_2 - 5.00X10^{-5}F_1XF_2$	0.9335	<0.01
	80	Water	$DE = 1.10 - 5.7X10^{-3}F_1 - 1.72X10^{-3}F_2 + 2.30X10^{-5}F_1XF_2$	0.9432	<0.01
		HCl 0.1N	$DE = 0.29 + 8.72X10^{-4}F_1 + 7.26X10^{-6}F_1XF_2$	0.6542	<0.01
HPMCK100LV CMCNa II	40	Water	$DE = 0.89 - 1.70X10^{-3}F_1$	0.7494	<0.01
		HCl 0.1N	$DE = 0.66 + 9.53X10^{-4}F_1 - 2.7X10^{-5}F_1XF_2$	0.4409	<0.01
	80	Water	$DE = 0.89 - 3.6X10^{-3}F_1 - 5.6X10^{-4}F_2$	0.8983	<0.01
		HCl 0.1N	$DE = 0.20 + 9.40X10^{-3}F_1 + 2.44X10^{-3}F_2 - 7.83X10^{-5}F_1XF_2$	0.9398	<0.01
HPMCK100M CMCNa I	40	Water	$DE = 0.98 - 4.40X10^{-3}F_1$	0.9456	<0.01
		HCl 0.1N	$DE = 0.88 - 2.90X10^{-3}F_1 - 1.90X10^{-3}F_2 + 2.00X10^{-5}F_1XF_2$	0.8254	<0.01
	80	Water	$DE = 0.86 - 4.6X10^{-3}F_1 + 1.08X10^{-3}F_2 - 3.00X10^{-5}F_1XF_2$	0.9882	<0.01
		HCl 0.1N	$DE = 0.42 - 7.52X10^{-4}F_1$	0.5694	<0.01
HPMCK100M CMCNa II	40	Water	$DE = 1.03 - 8.14X10^{-3}F_1 - 2.20X10^{-6}F_1XF_2$	0.9867	<0.01
		HCl 0.1N	$DE = 0.65 + 1.50X10^{-3}F_1 + 9.5X10 - 4F_2 - 2.70X10^{-5}F_1XF_2$	0.8912	<0.01
	80	Water	$DE = 0.74 - 7.00X10^{-3}F_1$	0.9625	<0.01
		HCl 0.1N	$DE = -7.32X10^{-3} + 7.63X10^{-3}F_1 + 3.14X10^{-3}F_2 - 5.40X10^{-5}F_1XF_2$	0.7890	<0.01

TABLE 5. Values of the parameters of Korsmeyer et al's (1983) equation obtained by fitting the equation to the dissolution data for each formulation.

Formulation	Water			HCl 0.1N		
	K_k	n	r	K_k	n	r
aC_{11}	0.025	0.83	0.9644	0.044	0.55	0.9949
aC_{12}	0.026	0.79	0.9624	0.018	0.70	0.9954
Ac_{11}	0.012	0.92	0.9846	0.042	0.57	0.9922
Ac_{12}	0.0081	1.00	0.9963	0.022	0.63	0.9811
aC_{21}	0.0096	0.93	0.9941	0.014	0.64	0.9927
aC_{22}	0.0034	1.12	0.9973	0.0046	0.82	0.9895
Ac_{21}	0.0033	1.00	0.9958	0.0053	0.78	0.9778
Ac_{22}	0.0036	0.99	0.9975	0.010	0.71	0.9971
aD_{11}	0.030	0.74	0.9600	0.048	0.53	0.9822
aD_{12}	0.014	0.89	0.9757	0.045	0.52	0.9517
Ad_{11}	0.004	1.07	0.9869	0.044	0.54	0.9795
Ad_{12}	0.011	0.86	0.9869	0.063	0.47	0.9659
aD_{21}	0.0037	1.01	0.9900	0.016	0.64	0.9941
aD_{22}	0.0028	1.07	0.9943	0.019	0.60	0.9932
Ad_{21}	0.0055	0.86	0.9957	0.032	0.54	0.9947
Ad_{22}	0.0045	0.88	0.9734	0.023	0.60	0.9983
bC_{11}	0.0086	1.00	0.9813	0.0094	0.80	0.9945
bC_{12}	0.0097	0.97	0.9772	0.018	0.64	0.9806
Bc_{11}	0.0039	0.97	0.9892	0.020	0.63	0.9891
Bc_{12}	0.0048	0.93	0.9960	0.020	0.62	0.9878
bC_{21}	0.0036	1.03	0.9951	0.0088	0.70	0.9891
bC_{22}	0.0052	0.96	0.9966	0.0012	0.64	0.9973
Bc_{21}	0.0025	0.94	0.9971	0.0080	0.70	0.9943
Bc_{22}	0.0051	0.80	0.9743	0.0065	0.74	0.9944
bD_{11}	0.0019	1.25	0.9922	0.024	0.65	0.9844
bD_{12}	0.0041	1.03	0.9779	0.033	0.58	0.9826
Db_{11}	0.0029	0.82	0.9714	0.029	0.59	0.9955
Db_{12}	0.0042	0.85	0.9759	0.019	0.65	0.9852
bD_{21}	0.0048	0.88	0.9750	0.0075	0.71	0.9939
bD_{22}	0.0043	0.87	0.9777	0.016	0.61	0.9930
Bd_{21}	0.0047	0.84	0.9759	0.019	0.59	0.9966
Bd_{22}	0.0023	0.86	0.9616	0.024	0.54	0.9963

In conclusion, the results of this study indicate that drug release from tablets prepared with HMPC/NaCMC mixtures as gelling agent is a complex process governed not only by erosion rates but also by other factors which can be assumed to contribute to the observed zero-order kinetics.

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