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Research paper

Effect of anionic polymers on the release of propranolol hydrochloride from matrix tablets

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Abstract

Anionic polymers, namely Eudragit S, Eudragit L 100-55, and sodium carboxymethylcellulose, were incorporated into hydroxypropylmethylcellulose (HPMC K100M) to modify the drug release from HPMC matrices. The effects of changing the ratio of HPMC to anionic polymers were examined in water and in media with different pH. The dissolution profiles were compared according to release rates. The interaction between propranolol hydrochloride and anionic polymers was confirmed using the UV difference spectra method. The drug release was controlled with the type of anionic polymer and the interaction between propranolol hydrochloride and anionic polymers. The HPMC–anionic polymer ratio also influenced the drug release. The matrix containing HPMC–Eudragit L 100-55 (1:1 ratio) produced pH-independent extended-release tablets in water, 0.1 N HCl, and pH 6.8 phosphate buffer. © 2001 Elsevier Science B.V. All rights reserved.

Keywords: Hydroxypropylmethylcellulose; Methacrylic acid copolymers; Sodium carboxymethylcellulose; Matrix tablets; pH-independent release

1. Introduction

Matrix systems appear to be a very attractive approach from the economic as well as from the process development and scale-up points of view in controlled-release systems [1,2]. Hydroxypropylmethylcellulose (HPMC) is used frequently as a rate-controlling polymer in matrix tablets. HPMC offers the advantages of being non-toxic and relatively inexpensive; it can be compressed directly into matrices and is available in different chemical substitution and hydration rates and viscosity grades [2–4].

HPMC tablets hydrate upon contact with water and a rate-controlling gel layer forms around the solid inner core. The drug release in soluble drugs is controlled by the rate of diffusion through such a gel and in poorly water-soluble drugs, by a combination of diffusion and gel erosion [5–7].

It is known that the HPMC dissolution rate is also the dominant process in drug release from matrices and that the dissolution rate of HPMC depends on the matrix shape, dimensions, and the type of dissolution medium and polymer [8–10]. Pham and Lee [11] found that polymer dissolution played a more important role in regulating drug release for low-viscosity grades of HPMC.

The drug release from HPMC matrix tablets has also been modified for various purposes through the addition of anionic surfactants, polymers, and ion exchange resins [12]. The effect of surfactants and polymeric excipients on drug release from HPMC matrices has been investigated by Feely and Davis [13,14]. It has been found that the retarding effect of ionic surfactants on drug release from HPMC matrices is dependent on a drug–surfactant ionic interaction [13]. It is also reported that non-ionic polymers did not alter drug release significantly; however, ionic polymers were capable of retarding the release of oppositely charged molecules, but the effect was found to be small [14]. Baveja et al. [15] used blends of HPMC and sodium carboxymethylcellulose (NaCMC) to achieve a zero-order release of propranolol. Dabbagh et al. [16] reported that the use of HPMC or NaCMC alone could not provide a zero-order release of propranolol hydrochloride and this was achieved only from matrices containing the combination of NaCMC–HPMC. Strubel et al. [17] reported that the addition of hydroxypropylmethylcellulose acetate succinate (HPMCAS, an enteric polymer) to HPMC-based matrix tablets failed to achieve a pH-independent release of a weakly basic drug.

The anionic polymers used in this study are used widely in various pharmaceutical applications. NaCMC is one of the dominant hydrophilic carriers used in matrix tablets. Eudragit L 100-55 and Eudragit S are FDA-approved coating polymers that are used widely in the pharmaceutical

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industry. The objective of the present study was to investigate how HPMC, anionic polymers, and their combinations affect the dissolution rate of propranolol hydrochloride from matrices and to study the effect of pH and dissolution media on the release of propranolol hydrochloride from HPMC–anionic polymer matrices.

2. Materials and methods

2.1. Materials

The following chemicals were obtained from commercial suppliers and used as received: propranolol hydrochloride (Wyckoff Chemical Co., Inc., MI, USA), HPMC type 2208 (Methocel® K100M Premium Grade, The Dow Chemical Company, Midland, MI, USA), methacrylic acid copolymers (Eudragit L 100-55, Eudragit S, Rohm Pharma, USA), sodium carboxymethyl cellulose (NaCMC, Sigma, USA), silicified microcrystalline cellulose (Prosolv SMCC 90) (Mendell, Patterson, NY, USA), magnesium stearate (Mallinckrodt Speciality Chemicals Co., St. Louis, MO, USA).

2.2. Tablet preparation

The tablets were made up of 160 mg of propranolol hydrochloride, 160 mg polymer, Prosolv SMCC 90 as filler, and 1% magnesium stearate as lubricant. The ratios of polymer used were 0:1, 1:3, 1:1, 3:1 or 1:0 HPMC–anionic polymers (Eudragit L 100-55, Eudragit S, and NaCMC). Mixing was carried out in a laboratory model turbula mixer and the blends were compressed using an instrumented Manesty D3B tablet press at 8.9 kN compression force. The total tablet weight was 400 mg. Table 1 lists the propranolol hydrochloride tablet formulations used in this study.

2.3. Solubility determination

The solubility measurement of propranolol hydrochloride at pH 1.2, 6.8, and in water was investigated by adding an excess of drug to the solvents at 37°C. After equilibrium was reached, the drug concentration in the supernatant was determined spectrophotometrically at 288 nm.

Table 1
Propranolol hydrochloride extended-release tablets

Formulations	HPMC–anionic polymer ratio (%)				
	(1:0)	(3:1)	(1:1)	(1:3)	(0:1)
Propranolol HCl	40	40	40	40	40
HPMC K100M	40	30	20	10	–
Eudragit S–Eudragit L 100-55–NaCMC	–	10	20	30	40
Prosolv SMCC 90M	19	19	19	19	19
Mg stearate	1	1	1	1	1

2.4. Dissolution tests

The dissolution behavior of propranolol hydrochloride was recorded continuously using a fully automated dissolution apparatus. The USP XXIV rotating paddle method was used at 100 rpm, in 900 ml of deionized water, 0.1 M HCl or pH 6.8 phosphate buffer maintained at 37°C. The mean of three determinations was used to calculate the drug release from the matrix tablets. The samples were withdrawn at predetermined time intervals, filtered, and assayed spectrophotometrically at 288 nm.

2.5. Drug–anionic polymer interaction study

The interaction between drug (P) and anionic polymers (AP) is an equilibrium reaction which, assuming 1:1 complexation, may be presented as:

$$P + AP \overset{K}{\leftrightarrow} P\text{–}AP \tag{1}$$

where P–AP is the complex with a binding constant K. The weakly basic propranolol hydrochloride and anionic polymer binding constants were determined by UV difference spectroscopy [18]. UV difference experiments were performed using a Beckman spectrophotometer and a 1 cm quartz cell. The solution prepared for analysis was 0.1 mM propranolol hydrochloride in water. The range of anionic polymer concentrations was from 0.0 to 0.20 mM. The study of the drug–anionic polymer interaction was performed at a controlled pH of 6.8. All solutions and mixtures were scanned from 200 to 400 nm as triplicates. In UV difference spectroscopy, the absorbance spectrum of an unbound drug was measured and subtracted from its spectra at several polymer concentrations. The calculated absorbance differences of all propranolol hydrochloride–anionic polymer mixtures from 200 to 350 nm were overlain. The binding constant of the propranolol hydrochloride–anionic polymer complex is then obtained from the Scatchard plot based on the following equation:

$$\frac{\Delta A}{C} = K\Delta A + \text{const.} \tag{2}$$

where K is the binding constant, ΔA the absorbance difference, C the ligand concentration and const. = binding constant $K \times$ mass balance $S \times$ molar absorptivity difference $\Delta\varepsilon$.

2.6. Kinetics and mechanism of drug release

To investigate the mechanism of drug release and to compare the release profile differences among these matrix formulations, the percent drug released versus time profiles were used. Data corresponding to 5–60% release were fitted using the equation proposed by Ritger and Peppas [19]:

$$M_t/M_\infty = kt^n \tag{3}$$

where M_t/M_∞ is the fraction of drug released at time t, k the kinetic constant, and n the release exponent that charac-

terizes the mechanism of drug release. For matrix tablets, an n value of ~0.5 indicates diffusion control and an n value of ~1.0 indicates erosion control. Intermediate values suggest that diffusion and erosion contribute to the overall release mechanism.

3. Results and discussion

3.1. Effect of pH of dissolution media

Propranolol hydrochloride has the characteristics of a weakly basic drug; therefore, it shows a pH-dependent solubility in the pH range of the gastrointestinal tract. The solubility is found to be 225 mg/ml at pH 1.2, 130 mg/ml at pH 6.8, and 360 mg/ml in water.

It is observed that propranolol hydrochloride gave pH-dependent release from HPMC-based matrix formulations due to its pH-dependent solubility (Fig. 1). Propranolol hydrochloride release is faster in water and 0.1 N HCl compared to that in a phosphate buffer. After 14 h, 83 and 69% of the drug were released in water and 0.1 N HCl, respectively, whereas only 53% was released in the phosphate buffer. Although conventional hydrogel formulations such as those based on high-viscosity HPMCs are known to deliver the drug at a constant rate independent of, in relation to the hydration, gel viscosity, and relative permeability of the dosage form, the rate of drug release is related directly to the solubility of the drug [20]. In our study, it is observed that the pH–solubility profile of propranolol hydrochloride caused the drug release mechanism in high-viscosity HPMC matrix tablets to differ in acid and phosphate buffers.

3.2. Release of propranolol hydrochloride from HPMC matrices containing Eudragit L 100-55, Eudragit S, and NaCMC in water

Fig. 2 shows the release profiles of propranolol hydrochloride from matrices containing HPMC, Eudragit S, and their combinations in water. The propranolol hydrochloride release increased as the proportion of Eudragit S increased in the HPMC–Eudragit S blend. It is observed that the amount of HPMC played a dominant role, affecting the drug release in these mixtures. The release rate increased from 23.3 ± 0.46 to 39.6 ± 3.0% $h^{-1/2}$ as the HPMC content decreased. The release-rate data from matrices containing only Eudragit S were not calculated because of the fast release of the drug (Table 2).

The dissolution of propranolol hydrochloride from HPMC–NaCMC matrices was complex. The blends of 3:1 and 1:1 HPMC–NaCMC gave a slower drug release compared to the formulation that contains only HPMC (Fig. 3). The release rates were found to be 19.1 ± 0.28 and 17.7 ± 1.73% $h^{-1/2}$, respectively. The diffusional release of a soluble drug such as propranolol hydrochloride may be controlled primarily by the gel viscosity. The addition of NaCMC to a non-ionic cellulose like HPMC increases the viscosity. This was attributed to the strong hydrogen bonding between the carboxyl groups on NaCMC and the hydroxyl groups on HPMC, leading to strong cross-linking between the two polymers [21]. So the blends of HPMC–NACMC in ratios 3:1 and 1:1 result in the increase in the viscosity of the gel layer, which retards drug diffusion from the tablet. This decrease in release rate was probably related partially to the formation of a complex between the cationic drug (propranolol hydrochloride) and

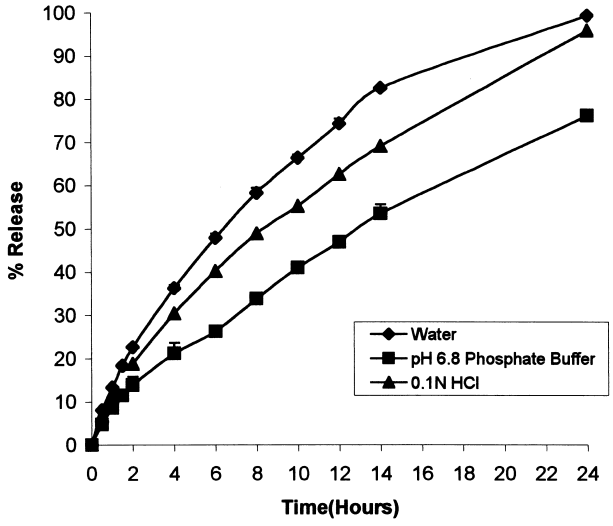

Fig. 1. The propranolol hydrochloride release from the HPMC matrix in different media.

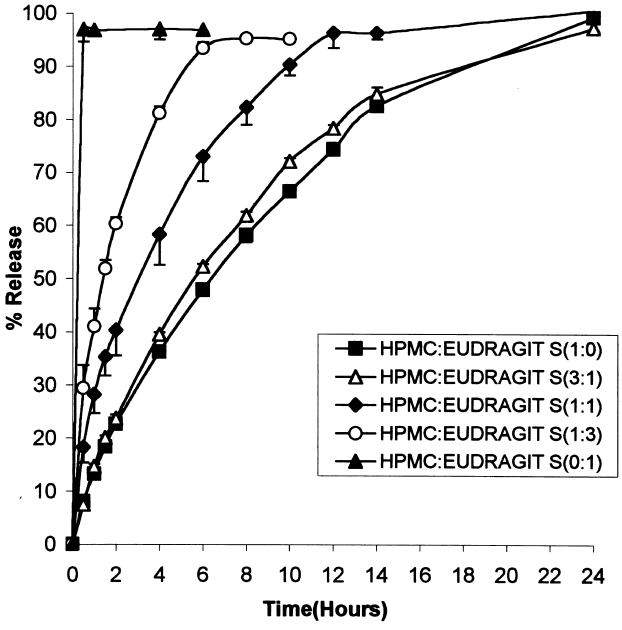

Fig. 2. The effect of HPMC, Eudragit S, and their blends on propranolol hydrochloride release in water.

Table 2
Release rates (% $h^{-1/2}$), K, and release exponent (n) values of propranolol hydrochloride from matrices calculated from data equivalent to 5–60% drug release in water[a]

HPMC–anionic polymer ratio	HPMC–Eudragit S			HPMC–Eudragit L 100-55			HPMC–NaCMC		
	Release rate	K	n	Release rate	K	n	Release rate	K	n
1:0	23.3 ± 0.46	1.44	0.698	23.3 ± 0.46	1.44	0.698	23.3 ± 0.46	1.44	0.698
3:1	26.1 ± 0.38	1.43	0.695	25.9 ± 0.21	1.43	0.636	19.1 ± 0.28	1.55	0.636
1:1	30.7 ± 2.00	0.751	0.554	24.4 ± 2.22	1.18	0.526	17.7 ± 1.73	1.33	0.526
1:3	39.6 ± 3.00	0.561	0.385	26.6 ± 3.26	–	–	–	–	–
0:1	–	–	–	–	–	–	–	–	–

[a] Results are the means ± SD of three determinations.

the anionic NaCMC. A similar result was also reported by Dabbagh et al. [16]. Matrices containing 1:3 and 0:1 HPMC–NaCMC showed a fast release of propranolol hydrochloride because of disintegration. More than 80% of the drug in the matrices was released during the initial 5 min of contact with dissolution media. The rapid erosion of the matrices may be due to the higher solubility of NaCMC compared to HPMC. Hussain et al. [22] reported that the presence of the ionized carboxylic acid groups in NaCMC was responsible for the rapid dissolution of NaCMC matrices. Therefore, the release rates from the blends of 1:3 and 0:1 HPMC–NaCMC were not calculated because of the fast release of propranolol hydrochloride from the matrices (Table 2).

The drug release profiles in water were found to be almost similar to the blends of HPMC–Eudragit L 100-55 except for the formulation that contained only Eudragit L 100-55 (Fig. 4). The drug release rates remained almost the same as the HPMC ratio decreased in the formulations. The release rate was faster in matrices containing only Eudragit L 100-55 and it released 60% of the drug during the first 2 h (Table 2). Even on reducing the amount of high-molecular-weight HPMC in the formulations the drug release rates were found to be similar; however, the percent release decreased at 24 h in water. The propranolol hydrochloride release from the blends of 1:0, 3:1, 1:1, 1:3 and 0:1 HPMC–Eudragit L 100-55 was found to be 100, 97, 92.4, 87.7, and 74.5%, respectively, at 24 h. The retarding effect was probably caused by the interaction of the cationic propranolol hydrochloride with the anionic polymer in the dissolution medium. The 74.5% release value was reached in water in the matrices containing HPMC–Eudragit L 100-55 (0:1), since there were no counterions in the medium to replace the drug ions from the drug–anionic polymer complex.

Table 2 shows the K and n values in matrices containing different ratios of HPMC–anionic polymers, calculated from the range of 5–60% drug release and based on Eq. (3). For most formulations, the value of the release exponent (n) was between 0.5 and 1, indicating both a diffusional release and an erosion mechanism [20]. The n values were not calculated in matrices containing 0:1 HPMC–anionic

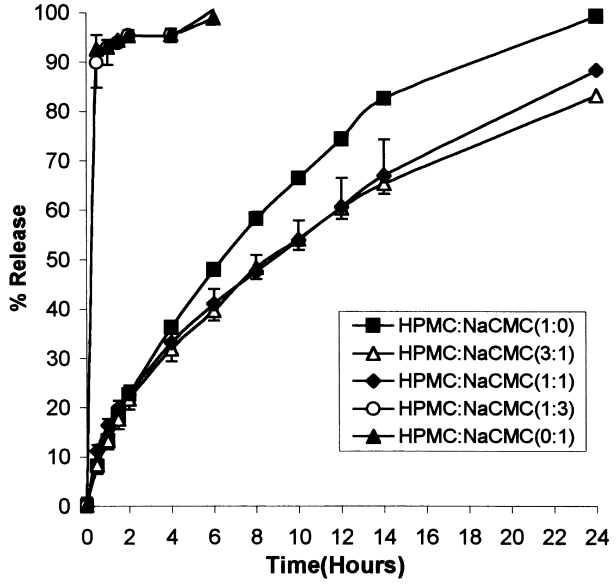

Fig. 3. The effect of HPMC, NaCMC, and their blends on propranolol hydrochloride release in water.

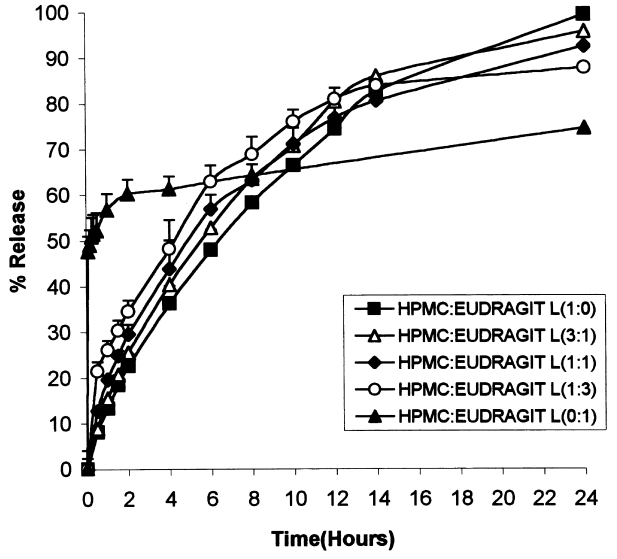

Fig. 4. The effect of HPMC, Eudragit L 100-55, and their blends on propranolol hydrochloride release in water.

polymer because propranolol hydrochloride was released very quickly.

3.3. Release of propranolol hydrochloride from HPMC matrices containing Eudragit L 100-55, Eudragit S, and NaCMC in media with different pH

The matrices containing different HPMC–anionic polymer ratios were also tested in 0.1 N HCl and in a phosphate buffer to evaluate the effect of media with different pH (Figs. 5–7). Fig. 5a and b shows that the drug release in 0.1 N HCl from HPMC tablets containing Eudragit S was faster than the release in pH 6.8, indicating that the addition of anionic polymer did not promote the same mechanism of drug release in acidic and basic media, and thereby giving pH-independent release. The HPMC amount in the matrices played an important role in both acidic and basic media. The decrease in release rate in pH 6.8 was probably related partially to the drug solubility and it was considered that release in both media was controlled by the diffusion and erosion of the tablet matrix (Tables 3 and 4).

The effect of the pH of the dissolution medium on the release from HPMC–NaCMC is shown in Fig. 6a and b. Propranolol hydrochloride release from HPMC–NaCMC matrices into 0.1 N HCl and pH 6.8 also confirmed a sensitivity to changes in pH. Matrices containing 1:3 and 0:1 HPMC–NaCMC showed a fast release of propranolol hydrochloride due to the higher solubility of NaCMC at 0.1 N HCl and pH 6.8. The drug release rate of HPMC–NaCMC (1:1 and 3:1 ratios) in 0.1 N HCl was faster than in the pH 6.8 phosphate buffer, indicating the non-ionization of carboxyl groups of NaCMC in 0.1 N HCl; therefore, the drug was not bound to the anionic polymer (Fig. 6a). The retardation in the drug release in the pH 6.8 phosphate buffer could be explained by the ionization of the carboxyl groups and the drug binding to the anionic polymer (Fig. 6b).

The drug release rates were found to be almost the same for the different blends of HPMC–Eudragit L 100-55 in 0.1 N HCl (Fig. 7a, Table 4). However, in the phosphate buffer of pH 6.8, the drug release increased in the matrices of

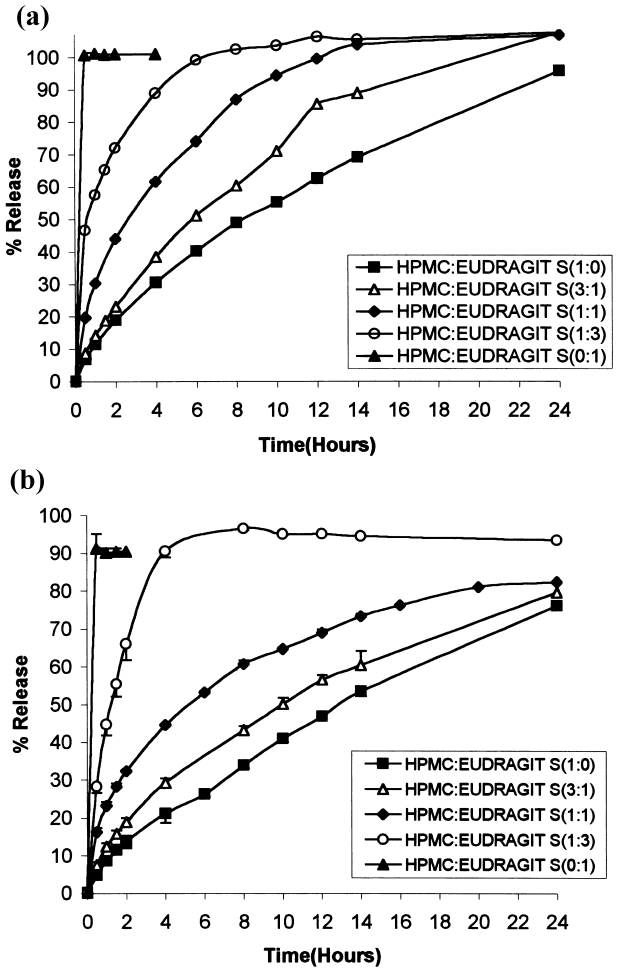

Fig. 5. The effect of HPMC, Eudragit S, and their blends on propranolol hydrochloride release in (a) 0.1 N HCl and (b) pH 6.8 phosphate buffer.

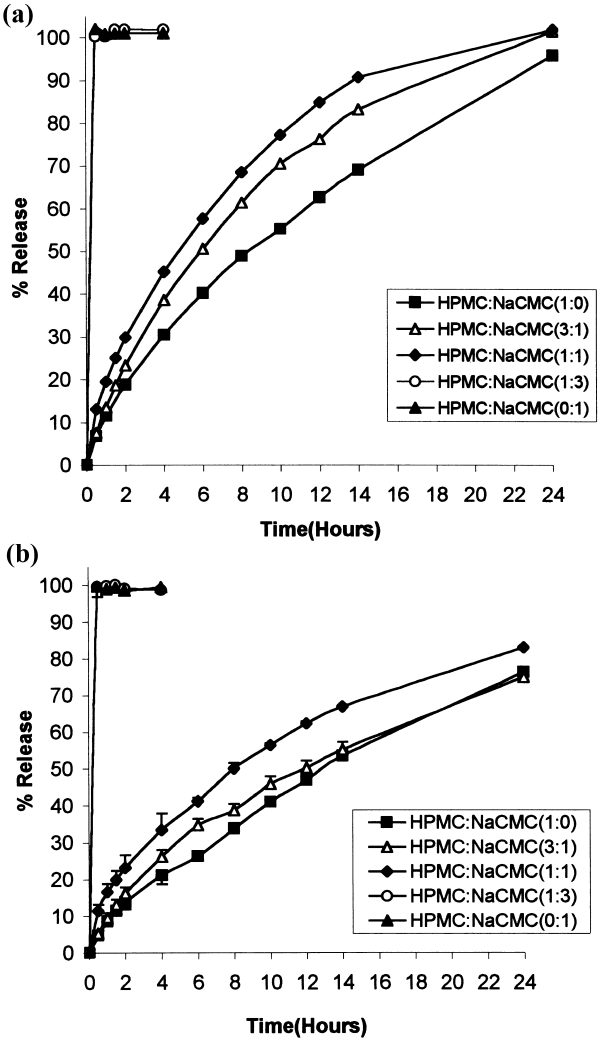

Fig. 6. The effect of HPMC, NaCMC, and their blends on propranolol hydrochloride release in (a) 0.1 N HCl and (b) pH 6.8 phosphate buffer.

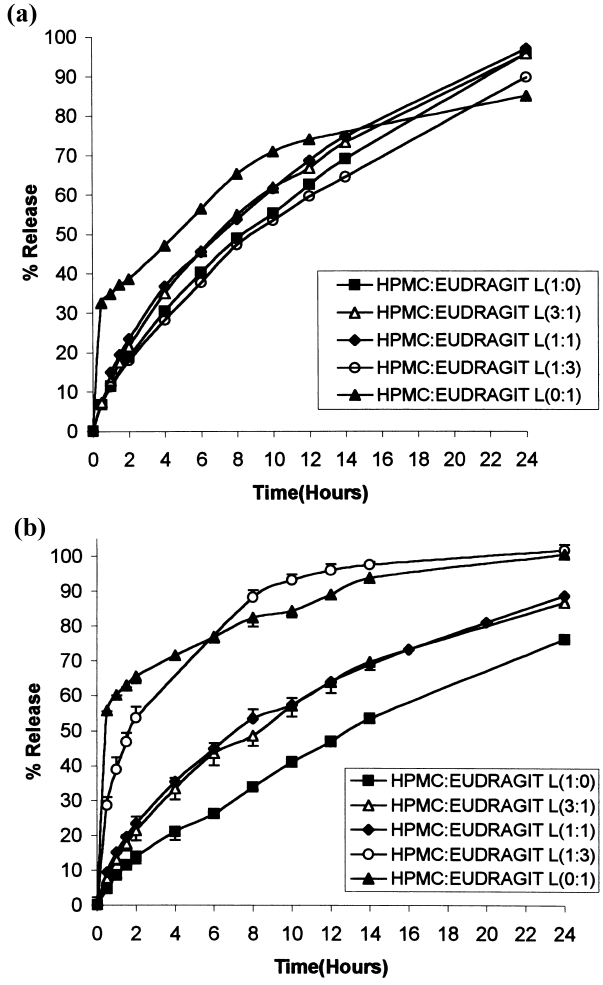

Fig. 7. The effect of HPMC, Eudragit L 100-55, and their blends on propranolol hydrochloride release in (a) 0.1 N HCl and (b) pH 6.8 phosphate buffer.

HPMC–Eudragit L 100-55 (1:3 and 0:1 ratios) due to the solubility of Eudragit L 100-55 at pH 5.5 (Fig. 7b). The effect of the pH of the dissolution medium on the release for the blend of HPMC–Eudragit L 100-55 (1:1 ratio) is shown in Fig. 8. The drug release rates were found to be very close to each other in 0.1 N HCl, pH 6.8 phosphate buffer, and water, suggesting the pH-independent release. In the phosphate buffer with pH 6.8, HPMC–Eudragit L 100-55 dissolves and thereby increases the permeability and rate of erosion of the tablets.

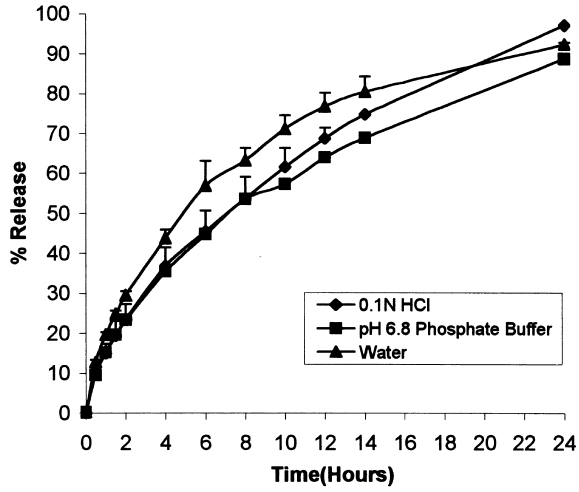

Fig. 8. Dissolution profile of HPMC K100M–Eudragit L 100-55 (1:1 ratio) in different media.

3.4. Interaction study between propranolol hydrochloride and anionic polymers by UV difference spectroscopy

Fig. 9 shows the resulting Scatchard plot from which the binding constant was obtained. The binding constant, *K*, was found to be 3785, 3819, and 6274 for propranolol hydrochloride–Eudragit S, –NaCMC, and –Eudragit L 100-55 complexation, respectively. It is observed that there is a considerable propranolol hydrochloride–anionic polymer interaction depending on the COOH groups of the anionic polymers. The rank order of the binding constant of propranolol hydrochloride to anionic polymers was Eudragit L 100-55 > NaCMC > Eudragit S. The ratio of the free carboxyl groups to the ester groups is an important parameter for the complex formation, which is approximately 1:1 in Eudragit L 100-55 and about 1:2 in Eudragit S. Dittgen et al. [23] also reported that the ion exchange capacity of Eudragit L 100-55 is around 6 mEquiv/g of polymer and

Table 3
Release rates (% $h^{-1/2}$), *K*, and release exponent (*n*) values of propranolol hydrochloride from matrices calculated from data equivalent to 5–60% drug release in phosphate buffer pH 6.8[a]

HPMC–anionic polymer ratio	HPMC–Eudragit S			HPMC–Eudragit L 100-55			HPMC–NaCMC		
	Release rate	*K*	*n*	Release rate	*K*	*n*	Release rate	*K*	*n*
1:0	15.5 ± 0.44	2.00	0.702	15.5 ± 0.44	2.00	0.702	15.5 ± 0.44	2.00	0.702
3:1	16.9 ± 1.08	1.61	0.619	19.0 ± 0.45	1.59	0.651	15.9 ± 0.67	1.77	0.708
1:1	18.3 ± 0.60	0.973	0.474	19.9 ± 0.32	1.52	0.524	18.2 ± 2.13	1.24	0.530
1:3	35.6 ± 2.10	0.416	0.611	27.5 ± 2.16	0.326	0.468	–	–	–
0:1	–	–	–	–	–	–	–	–	–

[a] Results are the means ± SD of three determinations.

Table 4
Release rates (% $h^{-1/2}$), K, and release exponent (n) values of propranolol hydrochloride from matrices calculated from data equivalent to 5–60% drug release in 0.1 N HCl[a]

HPMC–anionic polymer ratio	HPMC–Eudragit S			HPMC–Eudragit L 100-55			HPMC–NaCMC		
	Release rate	K	n	Release rate	K	n	Release rate	K	n
1:0	20.4 ± 0.24	1.71	0.698	20.4 ± 0.24	1.71	0.698	20.4 ± 0.24	1.71	0.698
3:1	23.5 ± 0.80	1.45	0.710	20.8 ± 1.25	1.58	0.711	23.0 ± 2.37	1.53	0.751
1:1	29.6 ± 1.60	0.629	0.809	21.5 ± 1.76	1.54	0.583	25.7 ± 0.81	1.24	0.598
1:3	38.8 ± 1.10	0.124	0.304	22.3 ± 0.16	1.68	0.683	–	–	–
0:1	–	–	–	19.4 ± 1.45	–	–	–	–	–

[a] Results are the means ± SD of three determinations.

3.5 mEquiv/g in the case of Eudragit S. Our results are also consistent with the finding that Eudragit S has the lowest binding constant compared to Eudragit L 100-55 and NaCMC.

NaCMC has a large molecular weight, so the interaction between propranolol hydrochloride and NaCMC is more complex than methacrylic acid copolymers. It is observed that NaCMC has a lower binding constant than Eudragit L 100-55. Tucker et al. [24] found that one propranolol cation would be bound to each carboxyl anion of NaCMC. Dabbagh et al. [16] reported that each sodium in NaCMC can potentially be replaced by a propranolol moiety but the number of sites of sodium that require replacement before precipitation is unknown, so it is difficult to create a model to describe the binding interaction between propranolol hydrochloride and NaCMC. In order to confirm the existence of this interaction between cationic drug and anionic polymers, investigations have to be pursued by using various physicochemical methods.

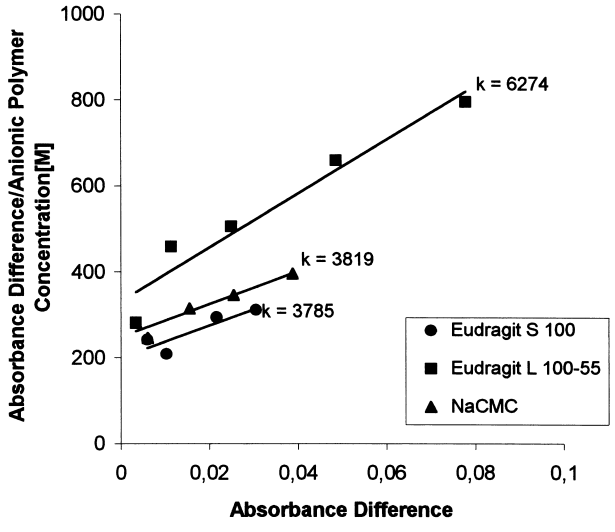

Fig. 9. Scatchard plot for propranolol hydrochloride–anionic polymer complexation resulting from the difference spectra.

4. Conclusions

The addition of anionic polymers to HPMC K100M matrices significantly modified the release of weakly basic propranolol hydrochloride. A complex between the propranolol hydrochloride and anionic polymers formed in the gel matrix and the type of anionic polymer affected the complex formation. The dissolution was, therefore, controlled by a combination of the interaction between propranolol hydrochloride and the anionic polymers and its influence on the dissolution/erosion of the matrix.

Blends of HPMC and Eudragit L 100-55 in 1:1 ratio succeeded in producing pH-independent extended-release tablets; however, the blends of HPMC and other anionic polymers (Eudragit L 100-55, Eudragit S, and NaCMC) in various other ratios did not produce pH-independent extended-release tablets in water, 0.1 N HCl, and phosphate buffer with pH 6.8.

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References

[1] C.G. Cameron, J.W. McGinity, Controlled release theophylline tablet formulations containing acrylic resins, II. Combination resin formulations, Drug Dev. Ind. Pharm. 13 (1987) 1409–1427.
[2] G.S. Rekhi, R.V. Nellore, A.S. Hussain, L.G. Tillman, H.J. Malinowski, L.L. Augsburger, Identification of critical formulation and processing variables for metoprolol tartrate extended-release (ER) matrix tablets, J. Controlled Release 59 (1999) 327–342.
[3] K. Mitchell, J.L. Ford, D.J. Armstrong, P.N.C. Elliot, C. Rostron, J.E. Hogan, The influence of substitution type on the performance of methylcellulose and hydroxypropylmethycellulose gels and matrices, Int. J. Pharm. 100 (1993) 143–154.
[4] B. Perez-Marcos, J.L. Ford, D.J. Amstrong, P.N.C. Elliott, C. Rostron, J.E. Hogan, Release of propranolol hydrochloride from matrix tablets

containing hydroxypropylmethycellulose K4M and Carbopol 974, Int. J. Pharm. 111 (1994) 251–259.
[5] K. Mitchell, J.L. Ford, D.J. Armstrong, P.N.C. Elliott, J.E. Hogan, C. Rostron, The influence of drugs on the properties of gels and swelling characteristics of matrices containing methylcellulose or hydroxypropylmethycellulose, Int. J. Pharm. 100 (1993) 165–173.
[6] I. Katzhendler, A. Hoffman, A. Goldbergern, M. Friedman, Modeling of drug release from erodible tablets, J. Pharm. Sci. 86 (1997) 110–115.
[7] P. Gao, P.R. Nixon, J.W. Skoug, Diffusion in HPMC gels, II. Prediction of drug release rates from hydrophilic matrix extended-release dosage forms, Pharm. Res. 12 (1995) 965–971.
[8] B. Narasimhan, N.A. Peppas, Disentanglement and reptation during dissolution of rubbery polymers, J. Polym. Sci., Polym. Phys. 34 (1996) 947–961.
[9] B. Narasimhan, N.A. Peppas, Molecular analysis of drug delivery systems controlled by dissolution of the polymer carrier, J. Pharm. Sci. 86 (3) (1997) 297–304.
[10] J. Siepmann, H. Kranz, R. Bodmeier, N.A. Peppas, HPMC-matrices for controlled drug delivery: a new model combining diffusion, swelling, and dissolution mechanisms and predicting the release kinetics, Pharm. Res. 16 (1999) 1748–1756.
[11] A.T. Pham, P.I. Lee, Probing the mechanism of drug release from hydroxypropylmethyl cellulose matrices, Pharm. Res. 11 (1994) 1379–1384.
[12] M. Sriwongjanya, R. Bodmeier, Effect of ion exchange resins on the drug release from matrix tablets, Eur. J. Pharm. Biopharm. 46 (1998) 321–327.
[13] L.C. Feely, S.S. Davis, Influence of surfactants on drug release from hydroxypropylmethylcellulose matrices, Int. J. Pharm. 41 (1988) 83–90.
[14] L.C. Feely, S.S. Davis, The influence of polymeric excipients on drug release from hydroxypropylmethylcellulose matrices, Int. J. Pharm. 44 (1988) 131–139.
[15] S.K. Baveja, K.V. Ranga Rao, K.P. Devi, Zero-order release hydrophilic matrix tablets of β-adrenergic blockers, Int. J. Pharm. 39 (1987) 39–45.
[16] M.A. Dabbagh, J.L. Ford, M.H. Rubinstein, J.E. Hogan, A.R. Rajabi-Siahboomi, Release of propranolol hydrochloride from matrix tablets containing sodium carboxymethycellulose, Pharm. Dev. Tech. 4 (1999) 313–324.
[17] A. Strubel, J. Siepmann, A. Dashevsky, R. Bodmeier, pH independent release of a weakly basic drug from water-insoluble and soluble matrix tablets, J. Controlled Release 67 (2000) 101–110.
[18] S.R. Gratz, A.M. Stalcup, Enantiomeric separations of terbutaline by CE with a sulfated β-cyclodextrin chiral selector: a quantitative binding study, Anal. Chem. 70 (1998) 5166–5171.
[19] P.L. Ritger, N.A. Peppas, A simple equation for description of solute release II: Fickian and anomalous release from swellable devices, J. Controlled Release 5 (1987) 37–42.
[20] P.L. Oren, W.M.K. Seidler, Sustained release matrix, US Patent 4,968,508, 1990.
[21] C.V. Walker, J.I. Wells, Rheological synergism between ionic and non-ionic cellulose gums, Int. J. Pharm. 11 (1982) 309–322.
[22] A.S. Hussain, R.D. Johnson, P. Shivanand, M.A. Zoglio, Effects of blending a non-ionic and an anionic cellulose ether polymer on drug release from hydrophilic matrix capsules, Drug Dev. Ind. Pharm. 20 (1994) 2645–2657.
[23] M. Dittgen, M. Durrani, K. Lehmann, Acrylic polymers. A review of pharmaceutical applications, STP Pharma Sci. 7 (1997) 403–437.
[24] I.G. Tucker, G.H. Ahmed, P.J. Stewart, The binding of propranolol hydrochloride to sodium carboxymethylcellulose, Aust. J. Hosp. Pharm. 18 (1988) 196–199.