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Effects of polymer particle size, compaction pressure and hydrophilic polymers on drug release from matrices containing ethylcellulose

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Abstract

The release of propranolol hydrochloride from matrices containing ethylcellulose 7 or 10 cP at different polymer contents and different pressures were examined. As the polymer content of the matrices increased, the release rate of the drug decreased, whereas the release exponents remained almost unchanged, indicating that the polymer content did not affect the release mechanism. As the particle size of either ethylcellulose increased, the release rates increased, indicating that penetration of water into the matrices was facilitated when coarser particle size fractions were used and the release exponents correspondingly increased. The highest value, $n = 0.88$, was obtained for ethylcellulose 10 cP with the 425–355 μm fraction. Compaction pressures up to 39.4 MNm^{-2} affected release rates whereas, compression pressure from 78.7 to 393.7 MNm^{-2} did not further modify the release rate. As the proportion of HPMC or NaCMC in admixture with ethylcellulose increased, the release rates gradually increased. Admixture of HPMC with ethylcellulose did not change the release exponent whereas a wide range of release exponent from matrices containing NaCMC: ethylcellulose was obtained. Differential scanning calorimetry was used to quantify the water uptake processes. Wafers containing ethylcellulose: HPMC displayed an approximate 39% of uptake after 5 min of contact with water, compared with values of 32 and 7% for HPMC and ethylcellulose, respectively, at the same time, indicating that wafers containing 1:1 HPMC:ethylcellulose were able to absorb more water than HPMC K4M at the commencement of the water uptake.

Keywords: Ethylcellulose; Hydroxypropylmethylcellulose; Sodium carboxymethylcellulose; Propranolol hydrochloride; Matrix tablets; Dissolution; Differential scanning calorimetry

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1. Introduction

Ethylcellulose (EC) is an inert, hydrophobic polymer and its properties such as lack of toxicity, stability during storage (Dubernet et al., 1990) and good compressibility (Upadrashta et al., 1993) make it suitable for sustained release matrices. Ethylcellulose is widely used to control the dissolution rate of drugs from sustained-release products in, for example, film-coated tablets (Porter, 1989; Narisawa et al., 1994) and microencapsulated dosage forms (Deasy et al., 1980). It has also been used as a matrix in the preparation of both water-soluble and sparingly water-soluble drugs using the solid dispersion technique (Shaikh et al., 1987a,b).

Gurny et al. (1982) reported that when porous hydrophobic polymeric drug-delivery systems are placed in contact with an appropriate dissolution medium, the release of the drug to the medium must be preceded by drug dissolution in the water-filled pores and by diffusion through the water-filled channels. The geometry and structure of the pore network are important to this drug release process. Upadrashta et al. (1993) using different grades of ethylcellulose, reported that the release of either theophylline or indomethacin from tablets followed a combined diffusion and erosion model. Its use in sustained release matrices has, however, not been thoroughly investigated.

In swelling systems, e.g. containing hydroxypropylmethylcellulose (HPMC) or sodium carboxymethylcellulose (NaCMC), the release of a solute is controlled by one or more of the following processes: the transport of solvent into the polymer matrix, swelling of the associated polymers, diffusion of the solute through the swollen polymer and erosion of the swollen polymer (Ranga Rao and Padmalatha Devi, 1988). Since ethylcellulose is a hydrophobic polymer and cannot swell in a manner similar to HPMC or NaCMC, it was considered that admixture of HPMC or NaCMC with ethylcellulose could change the permeability of the matrix (Porter, 1989) and consequently modify the release rate or, in the case of NaCMC, interact with propranolol hydrochloride (Dabbagh et al., 1993; Ford and Mitchell, 1995b).

The purpose of this study was to investigate the applications of ethylcellulose, as a potential carrier for the preparation of prolonged release formulations using propranolol hydrochloride as a model drug. The effects of drug: polymer ratio, viscosity grades and compaction pressure on drug release and also the replacement of ethylcellulose by hydrophilic polymers such as HPMC or NaCMC were investigated. Additionally, the water uptake of ethylcellulose on its own or admixture with HPMC, was investigated by Differential Scanning Calorimetry in an attempt to quantify the dissolution processes.

2. Materials and methods

2.1. Materials

Two grades of ethylcellulose were used: ethylcellulose 7 cP (Ethocel STD 7 PREM) and ethylcellulose 10 cP (Ethocel STD 10 PREM) were manufactured by Dow Chemicals (USA). Both grades of ethylcellulose were sieved to produce fractions of < 125 μm, 150–250 μm, 250–355 μm, and 355–425 μm. Hydroxypropylmethylcellulose type 2208 (Methocel™ K4M) was manufactured by Dow Chemicals (USA). Sodium carboxymethylcellulose type Blanose 7H4XF, supplied by Aqualon (France). Propranolol hydrochloride B.P. (particle size < 125 μm) and magnesium stearate (B.D.H., UK) were also used.

2.2. Tablet preparation

Flat-faced tablets, 12.7 mm diameter, were directly compressed using a Manesty F3 single punch tableting machine (Manesty Machines, UK) for pressures up to 213.7 MNm^{-2}. In order to avoid damage to the press, tablets made at higher pressures were compressed using a compaction simulator (ESH Testing, Brierly Hill, UK). Compaction was accomplished by direct compression of blends containing 160 mg propranolol hydrochloride, ethylcellulose 7 cP or ethylcellulose 10 cP and 0.75% w/w magnesium stearate. The blends were made using a tumbler

mixer and a mixing time of 15 min and tablets were prepared to quantify the following variables:

(1) The effects of propranolol hydrochloride:ethylcellulose ratio.Tablets contained 95, 140 or 285 mg ethylcellulose 7 cP (< 125 μm) and were compressed at 181.1 MNm^{-2}.

(2) The effects of particle size of ethylcellulose. Tablets contained 285 mg of the different particle size fractions of the two grades of ethylcellulose and were compressed at 181.1 MNm^{-2}.

(3) The effects of compaction pressures. Tablets contained 285 mg ethylcellulose 7 cP (< 125 μm) and were compressed at 7.8, 39.4, 78.7, 118.1, 181.1, 213.7, 315.0 or 393.7 MNm^{-2}.

(4) Ethylcellulose-polymer blends. Tablets containing either HPMC: ethylcellulose or NaCMC: ethylcellulose were made containing 285 mg of HPMC: ethylcellulose 7 cP < 125 μm or NaCMC (Blanose): ethylcellulose 7 cP < 125 μm at the ratios 1:3, 1:1 or 3:1 compressed at 181.1 MNm^{-2}.

2.3. Dissolution studies

Dissolution was determined using a Pharmatest (GmbH, Germany) dissolution tester and a Hewlett Packard HP8452A Diode Array spectrophotometer. The USP XXII (Apparatus 1) was used, rotating at 100 rev min^{-1}, in 1000 ml distilled water maintained at 37°C. Propranolol hydrochloride was monitored at 288 nm. The mean of six tablets was used to characterise the drug release for each of the formulations.

2.4. Analyses of drug release

In order to investigate the mode of drug release from matrices, the data corresponding to 5 to 80% release were fitted to Eqs. (1) and (2) (Ford et al., 1991).

$$Q = K_1(t - l)^n \quad (1)$$

$$Q = K_2 t^{1/2} + C \quad (2)$$

In Eq. (1), Q is the percent of drug released at time t, K_1 is a dissolution rate constant, l is a lag time and n is the release exponent. In equation 2, K_2 (% $min^{-1/2}$) is the root time release rate constant and C is a constant. The value of n gives an indication of the release mechanism. For instance $n = 0.5$ for square root of time kinetics and $n = 1.0$ for zero-order release (Ford et al., 1991).

2.5. Porosity determination

The porosities of the matrices were calculated using Eq. (3) (Narisawa et al., 1994).

$$\varepsilon = (1 - P_r/P_t) \times 100 \quad (3)$$

where ε = porosity of matrix, P_r = the apparent density of the compact at any given pressure and P_t = the true density of blended powder (mixed powder before compression).

P_t of the matrix powder was determined using an Air Comparison Pycnometer (Model 930, Beckman Instruments, UK). The mean of three determinations of the powder for each batch was used for the true density of powder. The dimensions of the tablets were measured using a screw-gauge micrometer (Moore and Wright, Sheffield) and used to calculate the tablet volume in order to determine P_r for each tablet. The mean of six determinations was used for the determination of the porosity of matrices at each compaction pressure.

2.6. Water uptake of ethylcellulose, hydroxypropylmethylcellulose and their mixture

Approximately 10 mg samples of ethylcellulose 7 cP (< 125 μm), HPMC K4M or 1:1 HPMC: ethylcellulose 7 cP powders were manually compressed into wafers of 6.35 mm diameter, using flat-faced punches and die and a Manesty F3 single punch tableting machine. The methods of Ford and Mitchell (1995b) were adopted to test the wafers.

The wafers and the aluminium sample pans (Perkin-Elmer, 6.35 mm diameter) were separately and accurately weighed. Approximately 10 mg double distilled water (approximately equivalent to the wafer weight) was placed in the pan and the wafer placed on it. A loosely fitting aluminium lid (6.35 mm diameter, Perkin-Elmer) was placed on top of the wafer to prevent water loss by evaporation. The pans were left unsealed and were kept at

room temperature for 1, 5, 15 or 30 min. Samples were reweighed immediately before testing to adjust for water lost by evaporation. After storage for the prescribed time, the samples were placed into the sample compartment of a Perkin-Elmer DSC-7 differential scanning calorimeter which was maintained at 20°C and wafers were immediately chilled to −30°C at −10°C min^{-1} using liquid nitrogen. Samples were scanned from −30°C to 20°C at 5°C min^{-1} and the enthalpy of fusion of unbound ice measured. The mean of at least three determinations were used to calculate the water uptake for each type of wafers at each time interval. The quantity of bound water was then calculated from the difference between the weight of water in the pan and the amount of unbound water equivalent to the observed enthalpy of fusion (Ford and Mitchell, 1995b).

3. Results and discussion

3.1. Effect of propranolol hydrochloride:ethylcellulose 7 cP ratio on drug release

Fig. 1 shows the effect of drug:ethylcellulose ratio on the release of propranolol hydrochloride. The release kinetics from matrices composed of varying amounts of ethylcellulose were analyzed using Eqs. (1) and (2) as shown in Table 1. It can be observed that as the polymer fraction increased, the release rate of the drug decreased (value of K_2 in Table 1) whereas the release exponents remained almost unchanged. The value of n around 0.5 indicates diffusion release mechanisms (Ritger and Peppas, 1987). It is clearly seen that the polymer content between 95 and 285 mg did not affect the release mechanism. Negative values of C indicate a burst release of drug and high positive values imply a delay to release. The data in Table 1 indicate that matrices containing 95 mg ethylcellulose 7 cP had a burst release while matrices containing 285 mg polymer did not.

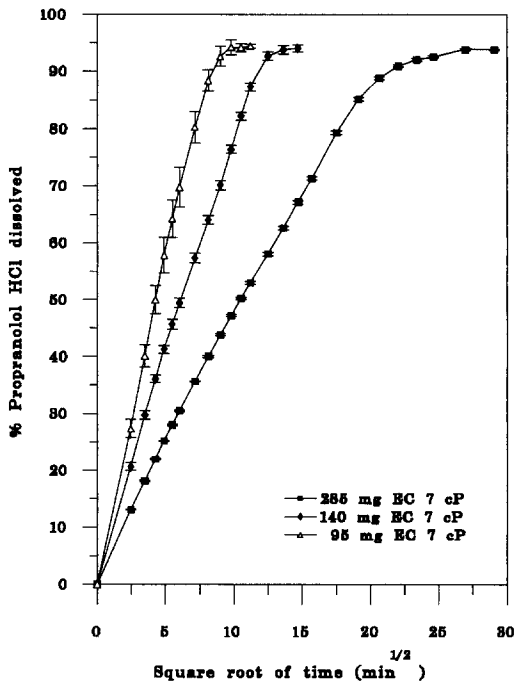

Fig. 1. The effect of ethylcellulose 7 cP content on the release of propranolol hydrochloride from matrices containing 160 mg propranolol hydrochloride and 95, 140 or 285 mg ethylcellulose 7 cP. Results are the means ± S.D. of six determinations.

Table 1
Effect of polymer content of ethylcellulose 7 cP on the dissolution constants from tablets containing 160 mg propranolol hydrochloride and different amount of ethylcellulose 7 cP

Ethylcellulose 7 cP content (mg)	Equation 1			Equation 2	
	K_1 (% min^{-n})	n	l (min)	K_2 (% $min^{-1/2}$)	C (%)
95	11.4	0.49	0.95	12.48 ± 0.72	−5.46
140	9.7	0.46	1.24	7.98 ± 0.15	−0.26
285	6.3	0.44	0.82	4.53 ± 0.03	3.95

K_1, n, l, K_2 and C are parameters described in Eqs. (1) and (2).

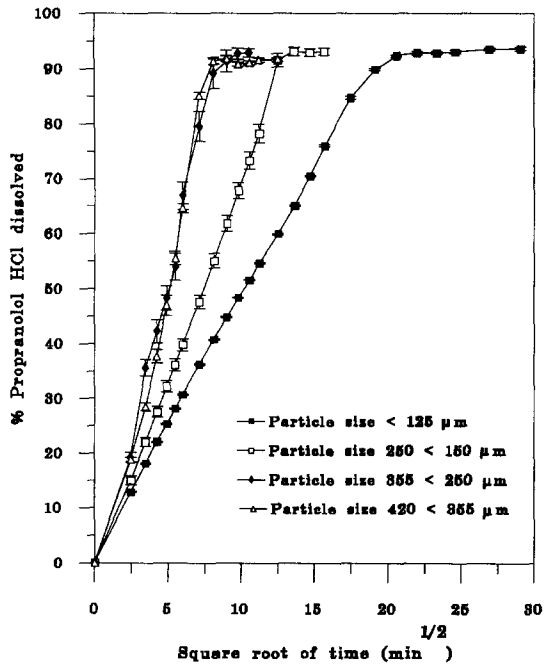

Fig. 2. The effect of particle size of ethylcellulose 10 cP on the release of propranolol hydrochloride from matrices containing 160 mg propranolol hydrochloride and 285 mg ethylcellulose 10 cP. Results are the means ± S.D. of six determinations.

3.2. Effect of particle size and viscosity grades of ethylcellulose on drug release

The release profiles of propranolol hydrochloride from matrices containing 285 mg ethylcellulose 10 cP (Fig. 2) or ethylcellulose 7 cP (Fig. 3) of different particle sizes were generally linear for up to more than 80% drug release when plotted as a function of the square root of time. The release data, analyzed using Eqs. (1) and (2), are shown in Table 2 and Table 3. The matrix tablets which consisted of < 125 μm ethylcellulose showed the slowest release rates. As the particle size increased, the release rate increased (values of K_2 in Table 2 and 3). This may be due to the fact that the penetration of water into the matrices was facilitated when the coarser particle size fractions were used. As the particle size of both grades of ethylcellulose increased, the values of l (lag time) and C decreased, indicating a burst release of drug with the coarser particle sizes.

Although both ethylcellulose 10 cP and ethylcellulose 7 cP showed similar behaviour, matrices containing ethylcellulose 7 cP showed marginally slower release rates than matrices containing ethylcellulose 10 cP at equivalent particle size. The lowest release rate of $4.53 \pm 0.03\%$ $min^{-1/2}$ was obtained from matrices containing 285 mg ethylcellulose 7 cP compared with $4.84 \pm 0.07\%$ $min^{-1/2}$ from matrices containing ethylcellulose 10 cP. Similar results have been reported by Upadrashta et al. (1993) who, using ethylcellulose 10, 20, 45 and 100 cP, reported that a controlled release rate is achieved with lower viscosity grades of ethylcellulose.

The matrices containing < 125 μm ethylcellulose 7 cP remained intact during testing, whereas matrices consisting of coarser particles slowly disintegrated. As the particle size of each ethylcellulose increased, the release exponent (values of n) increased and the highest value, $n = 0.88$, was obtained for the 425–355 μm fraction of ethylcellulose 10 cP. The data indicate that, since the

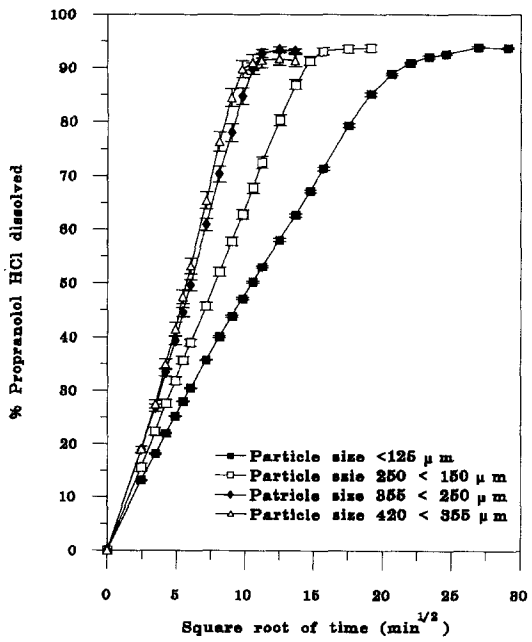

Fig. 3. The effect of particle size of ethylcellulose 7 cP on the release of propranolol hydrochloride from matrices containing 160 mg propranolol hydrochloride and 285 mg ethylcellulose 7 cP. Results are the means ± S.D. of six determinations.

Table 2
Effect of particle size of ethylcellulose 10 cP on the dissolution constants from tablets containing 160 mg propranolol hydrochloride and 285 mg ethylcellulose 10 cP

Particle size (μm)	Equation 1			Equation 2	
	K_1 (% min^{-n})	n	l (min)	K_2 (% min$^{-1/2}$)	C (%)
425–355	2.5	0.88	−3.78	11.91 ± 0.50	−19.80
355–250	4.9	0.66	−2.10	9.79 ± 0.61	−8.68
250–150	9.0	0.52	3.35	7.42 ± 0.06	−2.62
<125	5.5	0.47	−0.29	4.84 ± 0.07	2.27

K_1, n, l, K_2 and C are parameters described in Eqs. (1) and (2).

values of n were dependent on the particle size, as the particle size of ethylcellulose decreased the release became progressively controlled by diffusion. Although the value of n for the coarsest particle size fraction of ethylcellulose 10 cP is near that indicates of zero order release, the negative value of C indicates a burst release of drug before control of release was accomplished.

3.3. Effect of compaction pressure on drug release

Fig. 4 shows the effect of compaction pressure on drug release from matrices containing 285 mg ethylcellulose 7 cP. The data obtained are presented in Table 4. The release from matrices compressed at 7.8 MNm^{-2} was very rapid. The dissolution profile from matrices made at 39.4 MNm^{-2} was biphasic. The rates were 5.62 ± 0.28% min$^{-1/2}$ for up to 30% release and subsequently 11.07 ± 0.41% min$^{-1/2}$ up to 80% release. The release rates of matrices compressed at between 78.7 and 393.7 MNm^{-2} were relatively unaffected by pressure.

As the compaction pressures initially increased, the porosities of matrices decreased, subsequently the release rates (value of K_2 in Table 4) decreased. The porosity of matrices made at pressures between 78.7 and 393.7 MNm^{-2} were similar and the values of release exponent (n) at this range of compaction pressure were also similar (between 0.43 and 0.46), whereas at 39.4 MNm^{-2} pressure the porosity and the value of n were high. Therefore, it could be suggested that the porosity of matrices affected the drug release mechanism. Stamm and Tritsch (1986) using ethylcellulose 20 cP, reported that matrices made with low crushing strengths had high porosity and gave quick release of metoclopramide hydrochloride whereas the release profiles of this drug were similar, but lower, from matrices made to higher crushing strengths. Higuchi (1963) showed that in the matrix type of delivery system, the porosity and degree of tortuosity in the capillaries influenced drug release rate and reported that the amount of drug per unit of matrix volume decreased with time as dissolution occurred. Similarly, Desai et al. (1965) reported that the release data from elastic matrices such as polyvinyl chloride were independent of the compression force which was attributed to a constancy of porosity within the matrix.

The release kinetics are also shown in Table 4. The values of n suggest that drug release became predominantly diffusional controlled as the compaction pressure increased. In Table 4 it may be observed that an increase in compaction pressure caused increase in the values of C or l. Therefore the burst release seen at low compaction pressures was suppressed at higher compaction pressures.

3.4. Effect of replacement of ethylcellulose by HPMC or NaCMC on drug release

Drug release profiles of tablets prepared from different ratios of HPMC K4M: ethylcellulose 7 cP are shown in Fig. 5 and the data obtained using Eqs. (1) and (2) are presented in Table 5. As the proportion of ethylcellulose in the matrix increased, the release rate increased from 2.7 ± 0.2% min$^{-1/2}$ (HPMC K4M alone) to 4.8 ± 0.1%

Table 3
Effect of particle size of ethylcellulose 7 cP on the dissolution constants from tablets containing 160 mg propranolol hydrochloride and 285 mg ethylcellulose 7 cP

Particle size (μm)	Equation 1			Equation 2	
	K_1 (% min^{-n})	n	l (min)	K_2 (% $min^{-1/2}$)	C (%)
425–355	6.4	0.59	−1.13	9.39 ± 0.24	−4.82
355–250	6.2	0.58	−0.76	8.67 ± 0.17	−4.91
250–150	6.6	0.50	0.24	6.43 ± 0.17	0.165
<125	6.3	0.44	0.82	4.53 ± 0.03	3.95

K_1, n, l, K_2 and C are parameters described in Eqs. (1) and (2).

$min^{-1/2}$ (ethylcellulose 7 cP alone). The values of n did not change when the matrices consisted of an admixture of the two polymers. This confirmed the findings of Ford et al. (1987) who investigated the effect of replacement HPMC by diluents and reported that replacement of portions of HPMC within the matrices by diluents increased the release rates of promethazine hydrochloride, irrespective of whether the diluents were water soluble or water insoluble.

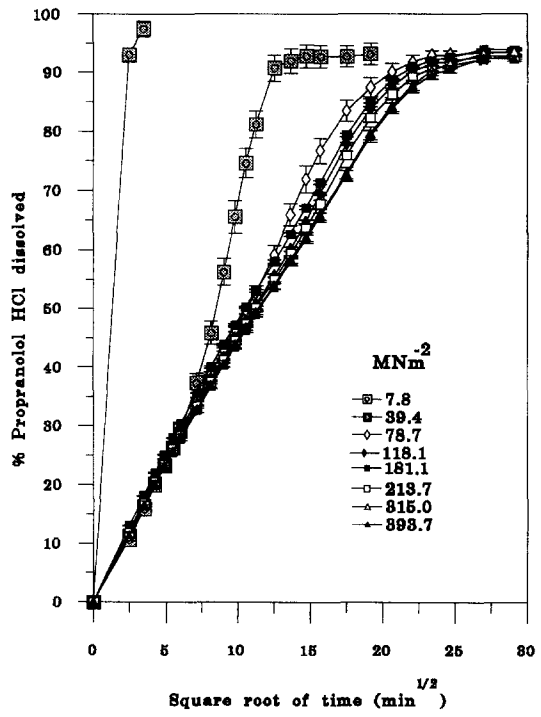

Fig. 4. The effect of compaction pressure (MNm^{-2}) on the release of propranolol hydrochloride from matrices containing 160 mg propranolol hydrochloride and 285 mg ethylcellulose 7 cP. Results are the means ± SD of six determinations.

The exponent value from matrix tablets containing ethylcellulose (0.44) indicates that the matrix exhibits mainly diffusional release mechanisms, whereas the exponent values from matrices containing various ratios of HPMC K4M: ethylcellulose (0.59–0.62) indicates a coupling of diffusion (case I) and polymer relaxation phenomena (case II). This fact indicates that the presence of HPMC encouraged erosion in the matrices.

Visually, the matrices containing ethylcellulose remained intact during the test and matrices containing HPMC alone swelled. When the matrix tablets consisted of 1:3 HPMC: ethylcellulose, they disintegrated slowly. This phenomenon could be due to the fact that when the proportion of ethylcellulose in the matrix is high, the hydrophilic particles in the matrix were separated from each other and formation of a protective gel layer around the matrix did not occur. As the proportion of HPMC in the matrices increased, the matrix remaining at the end of dissolution became larger.

Fig. 6 shows the data for NaCMC-ethylcellulose matrices. The data obtained by using Eqs. (1) and (2) (between 5–60% drug release) are presented in Table 5. Since the release data from matrices containing NaCMC alone or ratio 3:1 NaCMC: ethylcellulose did not fit to Eq. (1), they are omitted from Table 5. As the ethylcellulose portion in the matrices consisting of NaCMC: ethylcellulose increased, the release rates (K_2 in

Table 4
Effect of compaction pressure of ethylcellulose 7 cP on the dissolution constants from tablets containing 160 mg propranolol hydrochloride and 285 mg ethylcellulose 7 cP

Pressure MNm^{-2}	Porosity % ± S.D.	Equation 1			Equation 2	
		K_1 (% min^{-n})	n	l (min)	K_2 (% $min^{-1/2}$)	C (%)
7.8	37.1 ± 0.2	–[a]	–	–	–	–
39.4	17.9 ± 0.5	0.62	0.99	−13.8	8.15 ± 0.41	−15.50
78.7	14.2 ± 0.3	4.54	0.51	−1.6	4.89 ± 0.15	0.43
118.1	11.5 ± 0.6	5.40	0.46	−0.1	4.45 ± 0.06	2.92
181.1	11.4 ± 0.6	6.31	0.44	0.8	4.34 ± 0.03	3.95
213.7	9.9 ± 0.2	5.54	0.44	0.5	4.16 ± 0.04	3.04
315.0	13.3 ± 0.1	5.92	0.44	1.7	4.02 ± 0.06	3.47
393.7	13.5 ± 0.3	6.12	0.43	1.4	4.13 ± 0.05	3.48

K_1, n, l, K_2 and C are parameters described in Eqs. (1) and (2).
[a]No data due to very fast release.

Table 5) increased. When the proportion of polymers in the matrices was 1:3 NaCMC: ethylcellulose, a burst release was observed and more than 45% drug was released during the initial 6 min of the dissolution test. Since the proportion of NaCMC in the matrix was low and therefore its particles were separated by non-hydrophilic ethylcellulose particles, the formation of a protective layer by NaCMC (which occurs following water absorption at higher proportions of NaCMC) did not occur effectively. Consequently the drug was released rapidly. The interaction between propranolol hydrochloride and NaCMC (Ford et al., 1995a) is another controlling factor to the fast release.

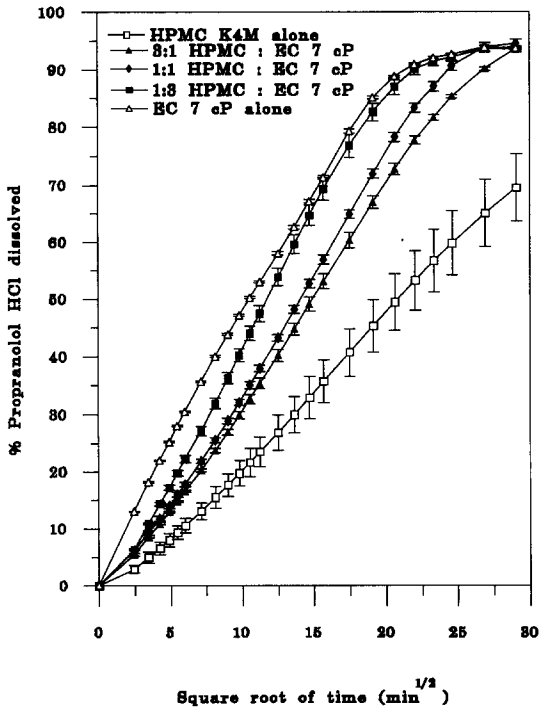

Fig. 5. The effect of HPMC K4M:ethylcellulose 7 cP ratio on propranolol hydrochloride release from matrices containing 160 mg propranolol hydrochloride and 285 mg total polymer. Results are the means ± S.D. of six determinations.

Matrices containing 3:1 NaCMC: ethylcellulose gave a release exponent value of 1.45 (Table 5). This value indicates super case-II transport. The reason for this value might be the high swelling nature of the polymer at this ratio (Ranga Rao et al., 1988; Bain et al., 1991).

3.5. Water uptake of ethylcellulose, HPMC and their mixtures

Fig. 7 shows typical DSC scans of water in contact with wafers containing ethylcellulose 7 cP (< 125 μm). The data of percent bound water are presented in Table 6. The amount of water taken up increased over the period of 30 min. After 5 min of contact with water, 7.4% of uptake had occurred. Typical data for water taken up by wafers containing 1:1 HPMC K4M: ethylcellulose are presented in Fig. 8 and Table 6. Approxi-

Table 5
The effect of HPMC K4M: ethylcellulose 7 cP or NaCMC Blanose: ethylcellulose 7 cP ratio on the dissolution constants from matrices containing 160 mg propranolol hydrochloride and 285 mg total polymer based on Eqs. (1) and (2). Results are the means ± S.D. of six determinations

Polymer	Ratio	Release rate ($min^{1/2}$ ± S.D.)	Equation 1			Equation 2	
			K_1 (% min^{-n})	n	l (min)	K_2 (% $min^{-1/2}$)	C (%)
HPMC:EC[a]	1:0	2.7 ± 0.2	1.42	0.59	5.39	2.64 ± 0.2	−5.47
	3:1	3.7 ± 0.1	1.88	0.61	−0.02	3.65 ± 0.1	−5.08
	1:1	3.9 ± 0.1	1.98	0.61	−0.50	3.86 ± 0.1	−4.93
	1:3	4.8 ± 0.1	2.76	0.59	1.84	4.76 ± 0.1	−6.11
NaCMC:EC	1:0	3.5 ± 0.1	–[b]	–[b]	–[b]	3.48 ± 0.1	−30.20
	3:1	4.0 ± 0.3	0.01	1.45	−40.00	4.05 ± 0.3	−25.80
	1:1	4.3 ± 0.1	0.45	0.86	9.19	4.38 ± 0.1	−18.40
	1:3	7.2 ± 0.2	–[b]	–[b]	–[b]	8.43 ± 0.2	7.85
EC	1:0	4.6 ± 0.0	6.30	0.44	0.82	4.53 ± 0.1	3.95

n, l and C are described in Eqs. (1) and (2).
[a]Ethylcellulose; K_1 (% min^{-n}); K_2 ($min^{-1/2}$).
[b]Data did not fit Eqs. (1) and (2).

mately 39% of uptake occurred after 5 min of contact of the wafers with water.

The results of Tukey's test from wafers containing ethylcellulose 7 cP suggest that at ($p < 0.05$), there was no significant difference between the enthalpies of pure water and the enthalpies of discs containing ethylcellulose after 1 min of contact with water indicating a weak ability of ethylcellulose to absorb water. There were significant differences between the percentage of bound water to discs containing ethylcellulose at 1, 5 and 15 min of contact with water. However, no significant increase in bound water was observed after 15 min indicating saturation of ethylcellulose. There were significant differences between the melting enthalpies of discs containing HPMC and ethylcellulose at all periods of time of contact with water.

The data in Table 6 indicate that discs containing 1:1 HPMC: ethylcellulose absorbed water similarly to HPMC K4M at 1 min, whereas they absorbed more water than HPMC at 5 min ($p < 0.05$, Tukey's test). The water uptake from discs containing the 1:1 mixture was more than anticipated. The expected amount of water taken up by these discs after 5 min of contact with water, was 19.8% (mean of values in Table 6) while the actual water uptake observed was about 39%. This suggests that water penetrated these wafers more easily than predicted from the data for the individual polymers. The ethylcellulose particles facilitated water uptake. Tukey's tests showed significant differences between discs containing HPMC or the 1:1 mixture at 15 or 30 min of contact with water ($p < 0.05$).

The endotherms of water in contact with ethylcellulose were sharp and there was no broadening in their scans (Fig. 7), whereas the endotherms from wafers containing 1:1 HPMC:ethylcellulose were broad (Fig. 8) which indicates an interaction between water and the HPMC. Generally the DSC peaks of water in contact with ethylcellulose were similar than those of water in contact with HPMC (Ford and Mitchell, 1995b). The data indicate more binding of water to HPMC due to reduced enthalpies and peak broadening.

4. Conclusion

The release rate of propranolol hydrochloride from matrices containing ethylcellulose can be modified using smaller particle sizes and a lower viscosity grade of ethylcellulose. The smaller par-

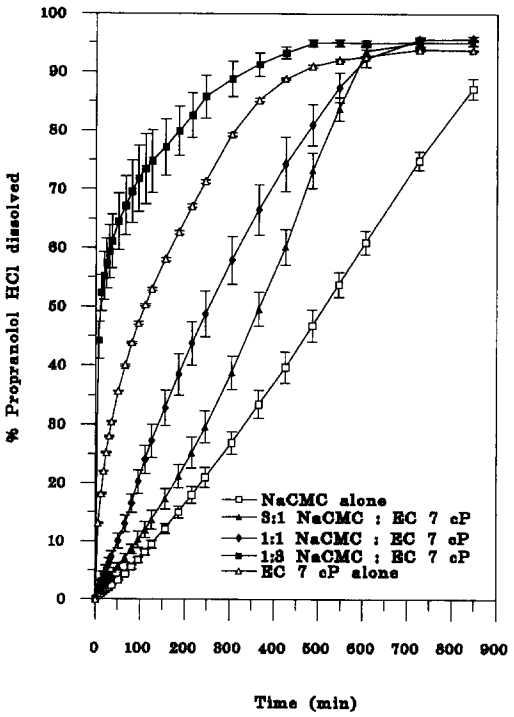

Fig. 6. The effect of NaCMC:ethylcellulose 7 cP ratio on propranolol hydrochloride release from matrices containing 160 mg propranolol hydrochloride and 285 mg total polymer. Results are the means ± S.D. of six determinations.

ticle size and the lowest viscosity grade of ethylcellulose gave the slowest release rate. In the matrices containing HPMC K4M:ethylcellulose, as the proportion of ethylcellulose increased the release rates gradually increased. Similar behaviour was seen for matrices containing NaCMC:ethylcellulose except when the portion of ethylcellulose was 75% where the burst release of propranolol hydrochloride occurred. Water bound to ethylcellulose was lower that water bound to the 1:1 mixture of ethylcellulose and HPMC. Ethylcellulose appeared to ease the penetration of water into the wafers containing 1:1 HPMC:ethylcellulose.

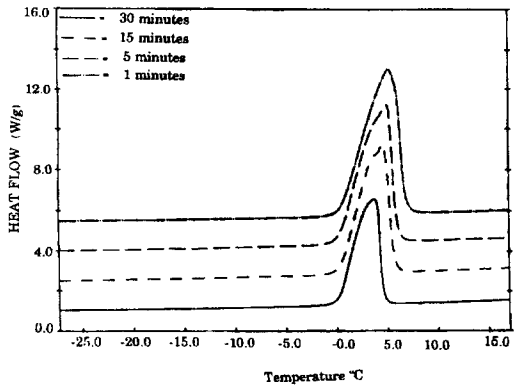

Fig. 7. DSC scans showing the melting endotherms of free water in contact with ethylcellulose 7 cP discs following storage at 1, 5, 15 or 30 min at ambient temperature.

Table 6
Effect of time on the percent of water bound by 10 mg discs containing HPMC K4M, ethylcellulose 7 cP or their 1:1 mixture (results are the means ± S.D. of three tests)

Time (min)	HPMC K4M	Ethylcellulose 7 cP	1:1 HPMC: EC
0	0	0	0
1	27.5 ± 2.3	3.4 ± 0.6	26.0 ± 1.3
5	32.2 ± 1.2	7.4 ± 1.6	39.1 ± 0.2
15	56.6 ± 0.4	12.5 ± 1.7	39.9 ± 1.2
30	63.6 ± 1.4	13.6 ± 1.7	51.2 ± 1.3

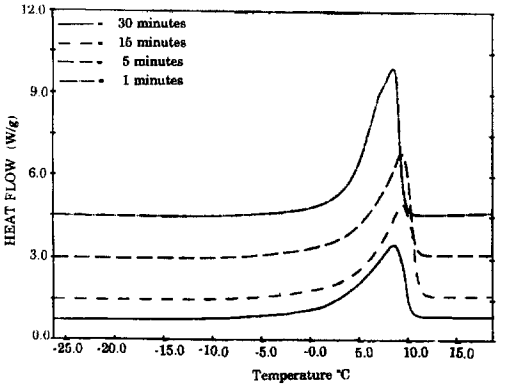

Fig. 8. DSC scans showing the melting endotherms of free water in contact with discs containing 1:1 HPMC K4M:ethylcellulose 7 cP following storage at 1, 5, 15 or 30 min at ambient temperature.

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