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Research paper

The consequence of the chemical composition of HPMC in matrix tablets on the release behaviour of model drug substances having different solubility

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ABSTRACT

This study investigates the effect of the chemical heterogeneity of hydroxypropyl methylcellulose (HPMC) on the release of model drug substances from hydrophilic matrix tablets. The hypothesis was that the release of drug substances could be influenced by possible interactions with HPMC batches having different chemical heterogeneity. The cloud point of the most heterogeneous batch was more affected by the model drug substances, methylparaben and butylparaben, and most by butylparaben with the lowest solubility. The different clouding behaviour was explained by the heterogeneously substituted batches being more associative and the more lipophilic butylparaben being able to interact more efficiently with the hydrophobic HPMC transient crosslinks that formed. Interestingly, tablet compositions of the heterogeneously substituted HPMC batches released the more soluble methylparaben at lower rates than butylparaben. The explanation is that the hydrophobic HPMC interactions with butylparaben made the gel of the tablet less hydrated and more fragile and therefore more affected by erosional stresses. In contrast, drug release from compositions consisting of the more homogeneously substituted batches was affected to a minor extent by the drugs and was very robust within the experimental variations. The present study thus reveals that there can be variability in drug release depending on the lipophilicity of the drug and the substituent heterogeneity of the HPMC used.

1. Introduction

Polymeric materials such as cellulose derivatives have been widely used to modify drug release from solid dosage forms [1]. One example is the hydrophilic matrix tablet, which is formed of a well-mixed composite of a hydrophilic polymer, additives and the drug substance. The drug release from hydrophilic matrices is considered to be controlled among other things by the dissolution of the polymer and the obtained concentrated polymer solution formed around the tablet, also called the gel layer. This can be explained by the gel layer being expected to act both as a protective barrier to water ingress and simultaneously, as a diffusional/erosional barrier for the release of the drug [2]. To achieve a sustained drug release, it is therefore important that the polymer has the ability to rapidly hydrate and quickly form a coherent gel with sufficient mechanical integrity [1,3,4]. Furthermore, to be able to obtain predictable drug release rates and robust formulations, it is important to know and control the functional-related characteristics, FRCs, of the polymer.

Hydroxypropyl methylcellulose (HPMC) is one of the most frequently used carrier materials in hydrophilic matrix tablets [1,5–8]. The water transport into the tablet and its ability to hydrate has been studied via parameters such as particle size [9–12] and compression force [10,13]. However, the chemical structure of HPMC obviously also affects the hydration rate and the gel layer properties; hence, drug release from matrices composed of HPMC has been shown to depend on the molecular weight [14–17] and the degree of substitution [1,18]. These FRCs are known to influence the degree of swelling and the erosion rate of the gel, and it is expected that polymers with higher molecular weights are eroded from the gel layer surface at lower rates [14–17]. Cellulose, which is the origin of HPMC, is not soluble in water because of its crystalline structure. Incorporating hydrophobic substituents such as methoxyl (MeO) groups and hydroxypropoxy (HPO) groups will disrupt the crystalline structure, however, and HPMC becomes water soluble within a certain degree of substitution. This means that both the presence and the degree of substitution play a role in the solubility of the HPMC chain and hence, has shown to influence the swelling of the matrix tablet [1].

Another factor related to the hydration of HPMC is the phase behaviour, where decreased solubility at an increase temperature is observed. At a gradual increase in temperature, HPMC will eventually phase separate. The temperature at which HPMC phase

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separates is affected by the chemical composition, where for example HPMC samples with an increased degree of substitution would phase separate at lower temperatures [19]. In addition, polymer hydration can further be suppressed by other water-soluble compounds competing for the available water or as a result of interactions between the polymer and additives. Suppressed hydration can thus occur in the gel of the matrix tablets; and hence, the effects of drugs and additives on the matrix behaviour have been studied [20,21]. Furthermore, as extended release tablets are designed to remain in the gastro-intestinal tract over a prolonged period, studies have been carried out on the effects of salts [4,22,23] and dietary sugars [24] on drug release.

Although it is known that the substituent heterogeneity of cellulose derivatives influences both the solubility [25,26] and the phase behaviour [27], only a few studies have evaluated substituent heterogeneity as an FRC for matrix tablets [28–30]. This can partly be explained by the absence of reliable means to characterise the substituent heterogeneity. However, Viriden et al. showed that more heterogeneously substituted HPMC batches of the 2208 grade eroded at lower rates from pure polymer tablets [30]. It was later shown that the heterogeneous substituent pattern facilitated an amphiphilic behaviour of the polymer chain, where the highly substituted regions interacted and formed reversible gel-like structures in the gel of the matrix tablet [28]. These increased the viscosity of the solution and decreased the rate of erosion from the tablets. In a more recent study, the release of methylparaben was investigated in matrix tablets composed of batches with different substituent heterogeneity; it was found that the different compositions had different release rates and release mechanisms [29]. However, the gel of the more heterogeneously substituted batches appeared to be less robust to both the amount of drug added to the tablet and to the different paddle speeds used in the USP bath. It can thus be questioned whether the drug substance can influence its own release due to the possible interactions that might occur owing to the chemical structure of the drug and the HPMC used.

It has not been studied what effect the chemical structure of HPMC has on the release of drugs with various solubility. It would be highly relevant to study this since it might lead to a more predictable and rapid development of hydrophilic matrix tablets. The hypothesis in the present study is therefore that the drug could interact differently with HPMC having different chemical heterogeneity and that the drug solubility influences the drug-polymer interaction and hence, also affects the release behaviour from hydrophilic matrix tablets. Two model drug substances, methylparaben and butylparaben, were used to study the hypothesis because of their different solubilities and hence, their disparate possibility to interact with the various chemical structures of the HPMC. Furthermore, four commercial HPMC batches of the same substituent and viscosity grade (2208) (100 cps) were selected as gelling agents in the matrix tablets. These batches were chosen since they are of a standard selection of the pharmaceutical grade. However, the substituent heterogeneity has been characterised, and the batches have a substituent heterogeneity that is significantly different from each other.

2. Materials and methods

2.1. Materials

Four HPMC batches of the same substituent grade (USP 2208) and viscosity grade (100 cps) were used in this study as gelling agents in hydrophilic matrix tablets. These batches were supplied by Shin-Etsu (Shin-Etsu Chemical Co., Ltd., Tokyo, Japan) and Dow (Dow Chemical Co., USA) and are commercially denoted 90SH100 and K100LV, respectively.

Methylparaben and butylparaben were both purchased from Sigma–Aldrich Chemie (GmbH, Switzerland) and used as received. HPMC 6 cps (Pharmacoat 606) was used in a suspension of butylparaben and was purchased from Shin-Etsu (Shin-Etsu Chemical Co., Ltd., Tokyo, Japan).

2.2. Cloud point

The phase behaviour of the HPMC solutions was determined by light transmission on a Mettler Toledo FP90 central Processor, Mettler FB81C MBC combined with IPClab software (Switzerland). The temperature was raised by 1 °C/min. The measurements were made in 1, 5 and 10% (w/w) polymer solutions (phosphate buffer, $I = 0.1$, pH = 6.8). Methylparaben and butylparaben were added to the HPMC solutions to a concentration of 1.1 mM, which was the measured saturation concentration of the less soluble butylparaben in phosphate buffer ($I = 0.1$, pH = 6.8). The solubility was measured using a Spectra max Plus (Molecular Devices, Sunnyvale, CA, USA). The concentration was calculated using a standard calibration curve and the wavelength used was 258 nm. The light transmittance through the polymer solutions was normalised to 100% at the starting temperature. The tabulated values are the temperature at 96% transmittance. The reported average values are based on two measurements.

2.3. Solubility measurements

The solubility of butylparaben in the different HPMC solutions was not measured by conventional methods since it was preferred not to centrifuge, filtrate or dilute the solutions. Therefore, instead of measuring the concentration of dissolved butylparaben, the number of undissolved particles was examined by means of focused beam reflectance measurements (FBRM) (Lasentec®, model S400Q, Mettler Toledo, USA). The FBRM uses a focused beam of laser light that scans in a circular path. The light scattered back from the particle towards the probe is used to measure the chord length of a given particle, which can be used to obtain the particle size [31,32]. The newly developed methodology was that a suspension of BP would gradually be added to the HPMC solutions, and the particles would dissolve at concentrations below the solubility limit. However, as the concentration increased above the solubility of butylparaben, the added particles would not dissolve and hence, would be detectable by the FBRM. The measurements were performed by placing the FBRM probe in a beaker with 1%, 2% or 3% (w/w) HPMC solutions (phosphate buffer, $I = 0.1$, pH = 6.8). The beaker with the HPMC solution was placed in a heating bath (Tempette TE-8D, Techne, UK) (37 °C) for 30 min prior to and during measurements. The duration of the measurement for each value was set to 20 s. During the measurements, stirring was performed with an impeller (3 cm) at a speed of 400 rpm. Predetermined volumes of a suspension of butylparaben were gradually added to the HPMC solutions. The measurements were performed for at least 15 min at each concentration after which the number of BP particles was registered and averaged over 5 min. The solubility equilibriums have not been established; however, measurements performed over a 12-h period have been made without observing changes in particle counts. The number of counts at each BP concentration was normalised to the number of counts in pure HPMC solutions. The results presented in the present study are based on the number of counts in the particle size range of 1–30 μm.

The added suspension of butylparaben consisted of 10% (w/w) butylparaben and 1% (w/w) HPMC 6 cps in phosphate buffer ($I = 0.1$, pH = 6.8). The suspension had been exposed to ultrasound (Vibra Cell, 750 Watt Ultrasonic Processor, Sonics & Materials, Inc., USA) in order to decrease the particle size of butylparaben. The particle size of butylparaben in the suspension was measured

using a laser diffractometer (Malvern mastersizer 2000, Malvern Instrument Ltd., Worcestershire, UK), and the average particle size was 26 μm.

2.4. Tabletting

A single punch tabletting machine (Kilian SP300, Kilian & Co., GmbH, Germany) was equipped with 10-mm flat-faced punches. The compression force was 10 ± 0.5 kN, and the powder for each tablet was preweighed using a Mettler Toledo AX205 Delta Range to get a tablet weight of about 300 ± 5 mg. The parabens were blended with the polymer powder with a pestle and mortar for 5 min.

2.5. Drug and polymer release

The drug and polymer release from dissolving tablets was measured using a USP dissolution apparatus (Dissolutest, Prolabo, France) equipped with a standard USP II paddle. The paddle speed was set to 50 rpm or 100 rpm. The tablets were fixed in baskets (2.5 cm × 2.5 cm × 1 cm and with a mesh size of 2.5 mm × 2.5 mm), which were placed 1 cm above the paddle and 3 cm from the centre of the paddle. The release medium, 900 ml, was phosphate buffer (I = 0.1, pH = 6.8), and the temperature was 37 °C. Aliquots of 1.5 ml were removed from the release medium at different predetermined times using a Varian VK8000 fraction collector (North Carolina, USA) and the amount of drug and polymer released from two tablets were analysed and averaged.

The concentration of the parabens at each sample time was measured using a Spectra max Plus (Molecular Devices, Sunnyvale, CA, USA). The concentration was calculated using a standard calibration curve, and the wavelengths used were for methylparaben and butylparaben 255 nm and 258 nm, respectively.

The polymer concentration in the release medium was determined using exclusion chromatography with dual multi-angle light scattering and refractive index detection (SEC-MALS/RI). The column was a TSK gel GMPW$_{XL}$, 7.8 mm ID ∗ 30.0 cm L, with a particle size of 13 μm (TOSOH corporation, Japan). The refractometer was an Optilab rEX, (Wyatt Technology, Santa Barbara, CA, USA) and the MALS instrument was a DAWN® EOS™ (Wyatt Technology, Santa Barbara, CA, USA). The analyses were performed at room temperature using a flow rate of 0.5 ml/min. The refractive index increment (dn/dc) used was 0.136 ml/g. The mobile phase was 0.1 M phosphate buffer (I = 0.1, pH 6.8) with 0.02% NaN_3, and the volume of the injected sample was 100 μl. The software used to process the data was Astra 4.90.07 (Wyatt Technology, Santa Barbara, CA, USA).

The total amount of either drug or polymer released at each time was determined as:

$$\%\ \text{Released} = \left(\frac{c_n \times (V_0 - V_s(n-1)) + V_s \sum_{n=0}^{n-1} c_n}{x} \right) \times 100 \qquad (1)$$

where c_n is the concentration in the sample n, V_0 is the initial volume in the beaker and V_s is the sample volume. x is the weight of the total amount of polymer in the dry tablet or the weight of the total drug dose.

3. Results and discussion

3.1. Chemical properties of the HPMC

The hypothesis set in the present study was that drug molecules with varying solubility would interact differently with HPMC, having different chemical heterogeneity. Thus, the four HPMC batches used in the present study as gelling agents in the tablets were of the same commercial pharmaceutical substituent (2208) and viscosity (100 cps) grade. However, these batches had been thoroughly characterised in previous studies, and the chemical heterogeneity differed between the batches (Table 1) [30]. As can be seen in Table 1, two levels of both HPO and MeO content were selected. Batches A and B had a HPO content of 11% and a MeO content of 23%, while batches C and D had a HPO and a MeO content of around 7% and 25%, respectively (Table 1). Furthermore, the substituent heterogeneity along the polymer chain had been characterised with a selective cellulose degrading enzyme. An enzyme–substrate complex needs to form for the enzyme to hydrolyse, which requires that the polymer is unsubstituted over a certain number of glucose units [33] This means that polymer samples with more frequently occurring unsubstituted regions would liberate more glucose after being hydrolysed by the enzyme; hence, a comparison can be made between the substitution patterns of the different batches [30,33,34]. The results after hydrolysis with endoglucanases from *Trichoderma longibrachiatum* showed that batch A released the least amount of glucose and hence, was the least heterogeneously substituted batch followed by batches B, C and D (Table 1). Furthermore, to exclude the influence of the molecular weight on the release rates, the batches had similar average molecular weights and polydispersity index, P.I. (Table 1).

3.2. Screening of possible interactions between the parabens and the HPMC in solution

3.2.1. The effect of parabens on cloud point temperatures

The phase behaviour of HPMC is known to affect the performance of hydrophilic matrix tablets [4,20–24], and it is therefore of interest to investigate what effect additives and drug substances have on the phase behaviour of the HPMC batches. At temperature increase, HPMC loses water of hydration [35], which eventually leads to phase separation of the HPMC into one polymer-rich phase and one polymer-depleted phase. The polymer-rich phase will scatter light, and hence, the process can be followed by measuring the transmittance of light through the HPMC solution. The temperature at which the turbidity reached 96% transmittance is referred to in the present study as the cloud point temperature (CP) and was obtained for the different HPMC batches at three concentrations, with and without parabens (Table 2). In pure HPMC solutions (1% (w/w)), the more homogeneously substituted HPMC batches obtained a CP of approximately 60 °C, and the more

Table 1
Chemical characteristics of the HPMC batches.

Sample	% HPO[a]	% MeO[a]	% (w/w) Glucose released[a,b,c]	Mw[a,c] (10^4 g/mol)	P.I. [a,c]
Batch A	10.9	23.4	0.3(0.1)	14.1(0.3)	2.8(0.6)
Batch B	10.9	23.3	0.9(0.1)	12.4(0.1)	2.8(0.5)
Batch C	6.6	24.1	1.2(0.1)	9.1(0.0)	1.9(0.2)
Batch D	7.0	24.6	1.4(0.1)	10.4(0.2)	2.2(0.3)

[a] Data obtained by Viriden et al. [30].
[b] Glucose released after hydrolysis with endoglucanase from *Trichoderma longibrachiatum*.
[c] The results given are mean values and corresponding standard deviations in parentheses (n = 3).

Table 2
Cloud point temperatures of HPMC solutions with and without parabens.[a,b]

Solutions of HPMC with and without parabens	Cloud point[c] 1% (w/w) HPMC	Cloud point[c] 5% (w/w) HPMC	Cloud point[c] 10% (w/w) HPMC
Batch A	59.8(0.1)	58.6(0.1)	57.0(0.2)
Batch A and MP	59.4(0.2)	58.1(0.2)	56.8(0.1)
Batch A and BP	58.2(0.0)	57.0(0.1)	54.5(0.5)
Batch B	60.6(0.2)	59.2(0.2)	55.9(0.3)
Batch B and MP	59.8(0.2)	58.5(0.1)	55.9(0.2)
Batch B and BP	58.7(0.2)	57.6(0.0)	55.1(0.5)
Batch C	63.6(0.8)	56.3(0.2)	46.4(0.3)
Batch C and MP	62.6(0.6)	55.4(0.5)	47.4(0.3)
Batch C and BP	63.0(0.6)	53.9(0.6)	44.8(0.5)
Batch D	66.3(0.1)	54.0(0.4)	47.1(0.2)
Batch D and MP	65.5(0.2)	53.9(0.4)	44.5(0.4)
Batch D and BP	65.0(0.4)	52.4(0.4)	41.5(0.8)

[a] Calculated average value from two measurements (x_1 and x_2) and the deviation from the mean values ($(x_1 - x_2)/2$) in parentheses.
[b] Methylparaben (MP)and butylparaben (BP) were added to the HPMC solutions (A–D) to the concentration of 1.1 mM.
[c] Obtained at 96% transmittance.

heterogeneously substituted batches, C and D, exhibited a CP at 64 and 66 °C, respectively. The differences may be explained by the somewhat higher total degree of substitution of batches A and B, which has been seen to decrease the CP of the HPMC [36]. However, when the HPMC concentration was increased to 5% and 10% (w/w), the relative order between the samples changed. The CP of batches A and B in10% solutions decreased by 3 and 5 °C, respectively, whereas the CP of batches C and D decreased by 17 and 19 °C. This suggests that the more heterogeneously substituted batches were more associative. Hence, a significantly decreased CP was obtained at higher polymer concentrations, and thus, a different concentration dependency was found compared to the more homogeneously substituted polymers. This pronounced concentration dependency of heterogeneously substituted HPMC batches was seen in a former study [27]. There it was concluded that the amphiphilic character of the polymers influenced metastable associations, and thus, reversible polymer structures were formed at lower temperatures than expected. The same seems to apply to the results in the present study, where the CP decreased more with increased heterogeneity.

It is known that parabens are able to interact with non-ionic macromolecules such as surfactants [37–39], where for example the phenolic hydroxyl group has been shown to interact with the oxygen in the ether groups of polyethylene glycol [38]. It is therefore possible that the parabens could interact with the HPMC chains differently dependent on the substituent heterogeneity. In addition, the two parabens might affect the cloud point to different extent, and hence, to elucidate the hypothesis the parabens were added to the solutions. The addition of MP hardly affected the CP of batches A, B and C, and it can be seen in Table 2 that the CP was not affected by even a single degree. About the same affect was seen in solutions of batch D, apart from the 10% solution where the CP decreased by 2.5 °C. The addition of BP decreased the CP of all batches slightly more than MP, with the exception of batch D, which obtained a CP of more than 5° below that obtained without parabens (Table 2). These results, thus, indicate that at the same concentration, BP affected the hydration of the polymers more than MP, which is in line with other studies [37,39]. In addition, the slightly greater effect the parabens showed on CP of batch D at the higher HPMC concentration might indicate that the heterogeneity of the substituent pattern influenced the interactions between the HPMC and the parabens. However, the effect was not as apparent for batch C having a slightly lower heterogeneity in terms of released glucose amount. To elucidate the hypothesis further, a different method allowing higher amounts of BP was utilised.

3.2.2. The effect the chemical structure of HPMC on the solubility of butylparaben

If a heterogeneous substituent pattern would facilitate interactions with BP, a higher amount of BP might be able to dissolve in solutions of the more heterogeneously substituted batches C and D compared to as in batch A and B. Thus, solubility measurements were performed with an FBRM method as described in Section 2.3. This method determines the amount of undissolved BP particles and thus, indirectly the solubility of BP in the HPMC solutions. Predetermined volumes of a 10% (w/w) suspension of BP were added to 1, 2 and 3% (w/w) HPMC solutions. For clarity, the number of particles, referred to as counts, as a function of BP concentration in 1, 2 and 3% (w/w) HPMC solutions is shown for only two HPMC batches, A and C (Fig. 1). In general, it can be seen that the number of counts was low until a certain limit was reached; there the number of particle counts increased dramatically with increased BP concentration (Fig. 1). The increase in counts occurred at higher BP concentrations at an increased HPMC concentration. This shows that fewer BP particles were detected in the presence of higher amounts of HPMC, which indicates that HPMC increased the solubility of BP. Consequently, the increased solubility indicates that BP interacted with HPMC and that the interactions were facilitated by an increased HPMC concentration. As also indicated in Fig. 1, the solubility of BP was differently affected by the increase in the

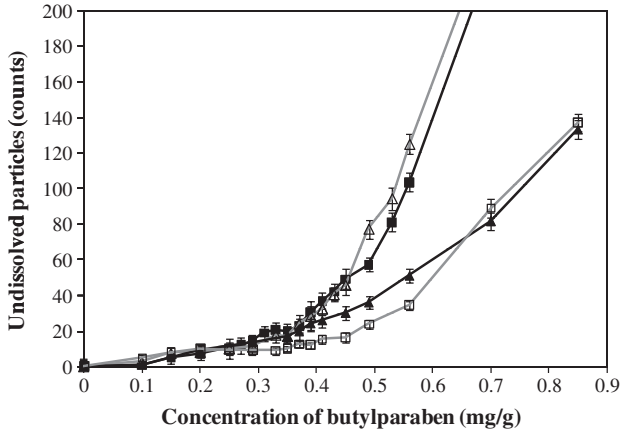

Fig. 1. Number of undissolved particles of butylparaben at 37 °C in: (●) 1% (w/w) HPMC solutions of batch A, (○) 1% (w/w) HPMC solutions of batch C, (▲) 2% (w/w) HPMC solutions of batch A, (△) 2% (w/w) HPMC solutions of batch C, (□) 3% (w/w) HPMC solutions of batch A and (■) 3% (w/w) HPMC solutions of batch C.

HPMC concentration in the different batches, where a greater improvement in solubility could be seen by increasing the concentration of the more heterogeneously substituted batch C compared to batch A.

The same behaviour as was explained above was seen for all batches; thus, the number of particle counts increased in 1% (w/w) HPMC solutions at a concentration of about 0.25 mg/g in all four batches (Fig. 2a). Increasing the concentration to 3% (w/w), however, a greater difference could be seen between the batches (Fig. 2b). The differences were first noticeable at about 0.4 mg/g of BP, where the amount of undissolved BP particles in solutions of batch A and B increased more pronounced compared

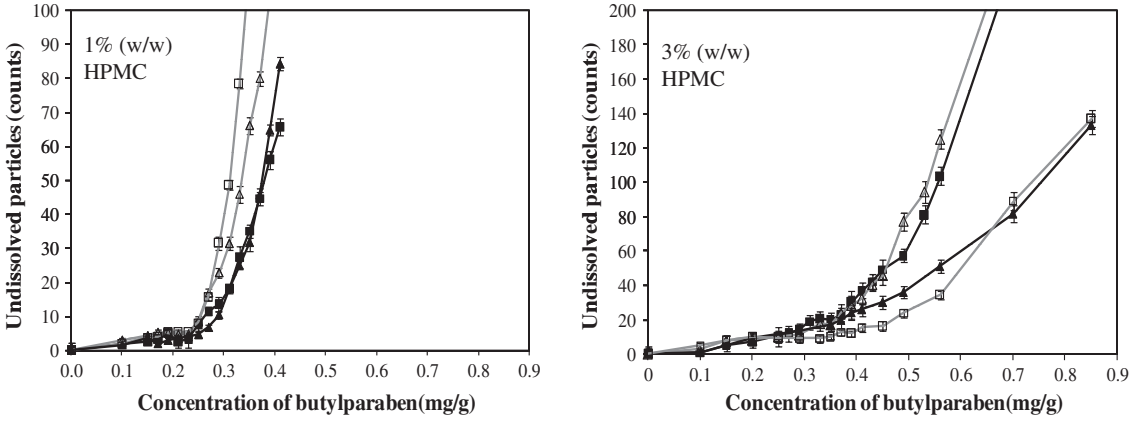

Fig. 2. Number of undissolved particles of butylparaben at different concentrations in HPMC solutions: Top figure represents 1% (w/w) HPMC solutions and bottom figure 3% (w/w) HPMC solutions. (■) batch A, (Δ) batch B, (□) batch C and (▲) batch D. The symbols denote the calculated average value, and the error bars show the deviation from the mean value.

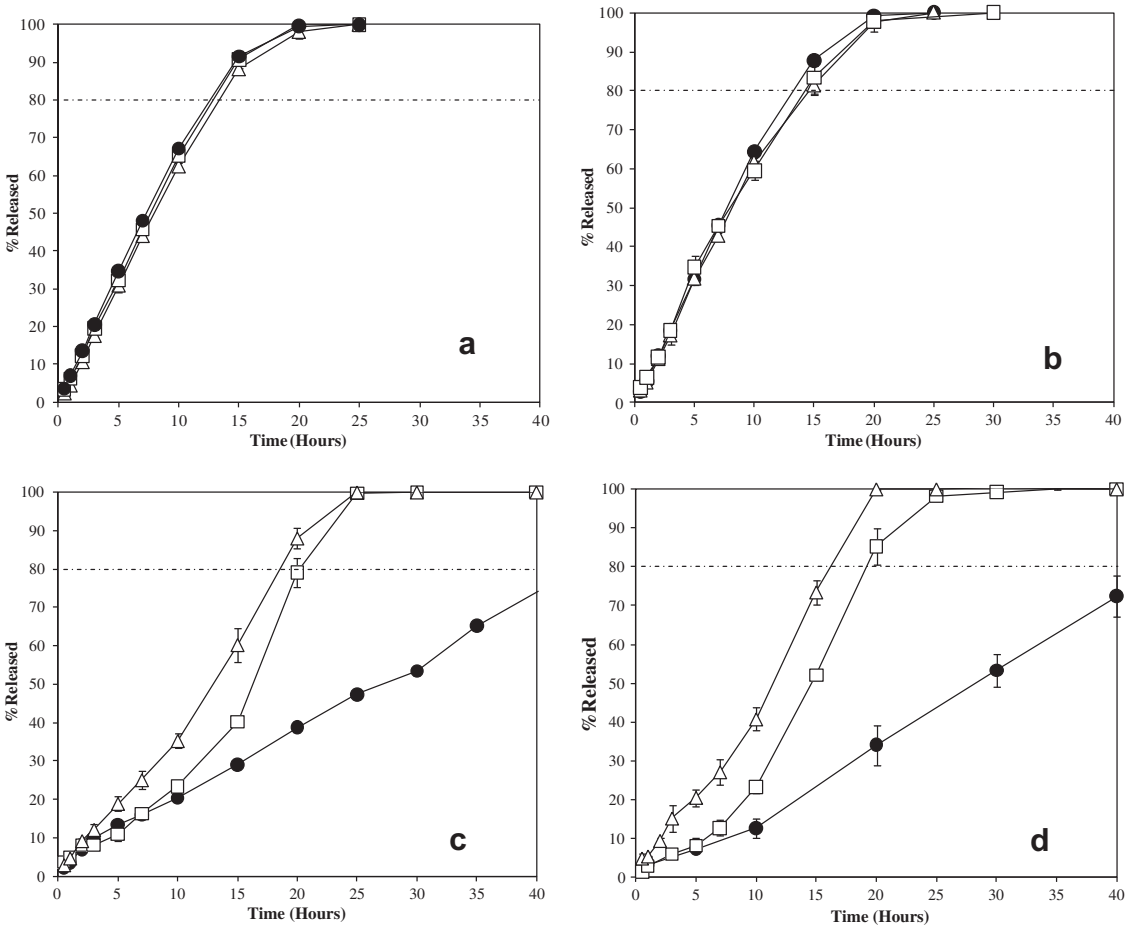

Fig. 3. Release profiles obtained from matrix tablets with and without an addition of 5% butylparaben, at the paddle speed of 50 rpm. (△) release of butylparaben, (□) erosion of HPMC from compositions with butylparaben and (●) erosion of HPMC from pure polymer tablets. (a–d) Represent the four different HPMC batches A–D, respectively. The symbols denote the calculated average value of two tablets, and the error bars show the deviation from the mean value.

to as for batches C and D. The reason for this could be that the equilibrium was different in the four batches or that the interactions between BP and HPMC had features of being cooperative. Meaning that, a dissolved BP molecule interacts more easily with HPMC if there already are HPMC–BP interactions, when compared to systems without such interactions. Thus, either way, the results indicate that BP was able to interact differently with the four HPMC batches having different substituent heterogeneity and to greater extent with the heterogeneously substituted batches at higher concentrations. This might be explained by the increased

Table 3
Times at which MP and BP were released from compositions at two paddle speeds.[a,b]

	T_{50} (h), 50 rpm	T_{80} (h), 50 rpm	T_{50} (h), 100 rpm	T_{80} (h), 100 rpm
Compositions of 5% BP and:				
Batch A	7.9(0.1)	13.4(0.1)	5.1(0.2)	8.9(0.3)
Batch B	8.1(0.1)	14.7(0.5)	5.0(0.0)	8.5(0.0)
Batch C	12.9(0.5)	18.6(0.6)	7.2(0.1)	11.2(0.4)
Batch D	11.4(0.5)	16.4(0.3)	6.7(0.2)	9.8(0.2)
Compositions of 10% BP and:				
Batch A	9.3(0.4)	14.4(0.2)	5.3(0.0)	9.0(0.2)
Batch B	8.9(0.2)	13.9(0.1)	5.9(0.1)	9.3(0.1)
Batch C	8.7(0.2)	13.1(0.2)	4.8(0.1)	7.6(0.1)
Batch D	5.2(0.2)	8.3(0.1)	3.5(0.1)	5.4(0.1)
Compositions of 10% MP and:				
Batch A	6.7(0.1)	13.7(0.1)	4.7(0.0)	9.3(0.0)
Batch B	5.1(0.2)	10.8(0.3)	4.2(0.1)	8.2(0.1)
Batch C	7.5(0.1)	18.4(0.0)	5.6(0.1)	12.2(0.1)
Batch D	9.0(0.1)	20.8(0.9)	7.4(0.1)	14.1(0.3)

[a] Times at which 50% (T_{50}) and 80% (T_{80}) of methylparaben (MP) and butylparaben (BP) were released from compositions of the four HPMC batches (A–D) at the paddle speed of 50 and 100 rpm.
[b] The value presented is the calculated average value from two tablets (x_1 and x_2) and the deviation from the mean values ($(x_1 - x_2)/2$) in parentheses.

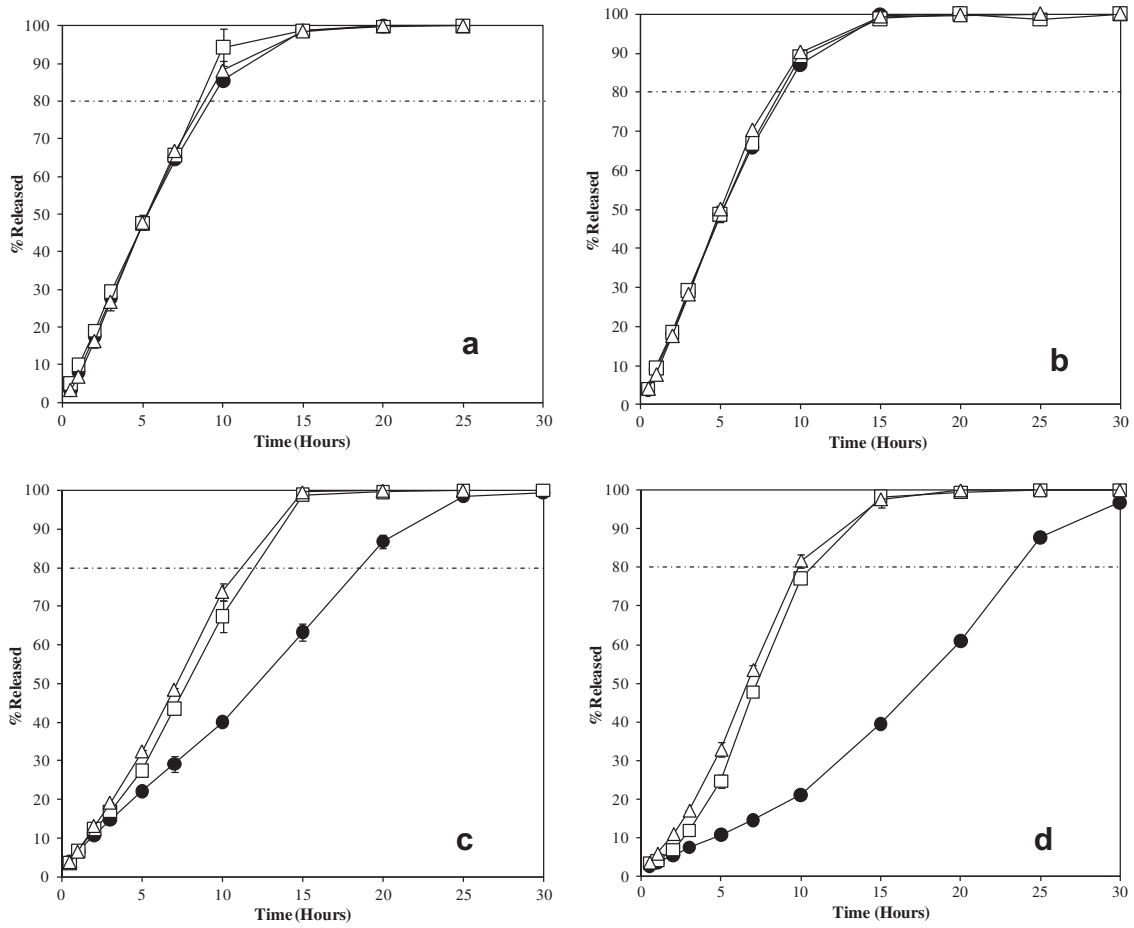

Fig. 4. Release profiles obtained from matrix tablets with and without an addition of 5% butylparaben, at the paddle speed of 100 rpm. (△) release of butylparaben, (□) erosion of HPMC from compositions with butylparaben and (●) erosion of HPMC from pure polymer tablets. (a–d) Represent the four different HPMC batches A–D, respectively. The symbols denote the calculated average value of two tablets, and the error bars show the deviation from the mean value.

amount of unsubstituted glucose units able to interact with BP or that BP interacted hydrophobically with the hydrophobic transient crosslinks presumably formed by the more heterogeneously substituted batches. From a pharmaceutical point of view, one must ask whether these interactions affect the drug release behaviour of hydrophilic matrix tablets. Hence, release studies were performed on matrix tablets.

3.3. Matrix performance

3.3.1. The influence of polymer heterogeneity on the release of butylparaben

Release studies performed on tablet compositions with and without 5% (w/w) BP at the paddle speed of 50 rpm are illustrated in Fig. 3a–d. To quantify the different release rates of BP, the time at which 50% (T_{50}) and 80% (T_{80}) were released was determined (Table 3). The erosion of HPMC from the different compositions was also measured, and an indication of the release mechanism of BP could be obtained by comparing the release profile of BP with the erosion rate of HPMC. At 50 rpm, the T_{50} values of BP from the different compositions were 7.9, 8.1, 12.9 and 11.4 h and the T_{80} values were 13.4, 14.7, 18.6 and 16.4 h from compositions of batch A, B, C and D, respectively (Table 3). The different compositions clearly released BP at different rates, and a batch-to-batch variation of 5 h in T_{50} and T_{80} values was obtained. However, the release of BP was quite similar from compositions of batches A and B. This can be seen both by the similar T_{50} and T_{80} values and the release behaviour (Fig. 3a and b, Table 3). As illustrated in Fig. 3a and b, the erosion rate of the polymers from batches A and B was parallel and close to the release profile of BP. Since the polymer and BP were released at about the same rate, this indicates that BP was mainly released by an erosion controlled release mechanism from both compositions (Table 3, Fig. 3a and b). In addition, the erosion rate of the polymer from pure polymer tablets was the same as the erosion rate from compositions with the addition of BP. It can thus be concluded that the addition of BP did not noticeably affect the polymer erosion of these batches.

At 50 rpm, the compositions of batches C and D released BP at lower rates than batches A and B (Fig. 3a–d). The release profile of BP was also faster compared to the erosion rate of both batch C and D, and a stronger contribution of diffusion to the release mechanism could be seen from these compositions. However, even though BP was released at lower rates, the polymer erosion of batches C and D was affected more by the addition of the drug to the matrix, and batch D was more affected than batch C. This can be seen from that the erosion rate of the polymer from the drug compositions followed the erosion rate of the pure polymer systems during the first 5 h. The polymer erosion rate from the drug compositions then increased rapidly and dual erosion rates were obtained (Fig. 3c and d). The dual erosion rate of the polymer consequently affected the release mechanism of BP. The diffusional contribution was thus initially larger, whereas the BP-release rate was quite parallel to the erosion of the polymer during the latter stage of the release process, and it seems as though the

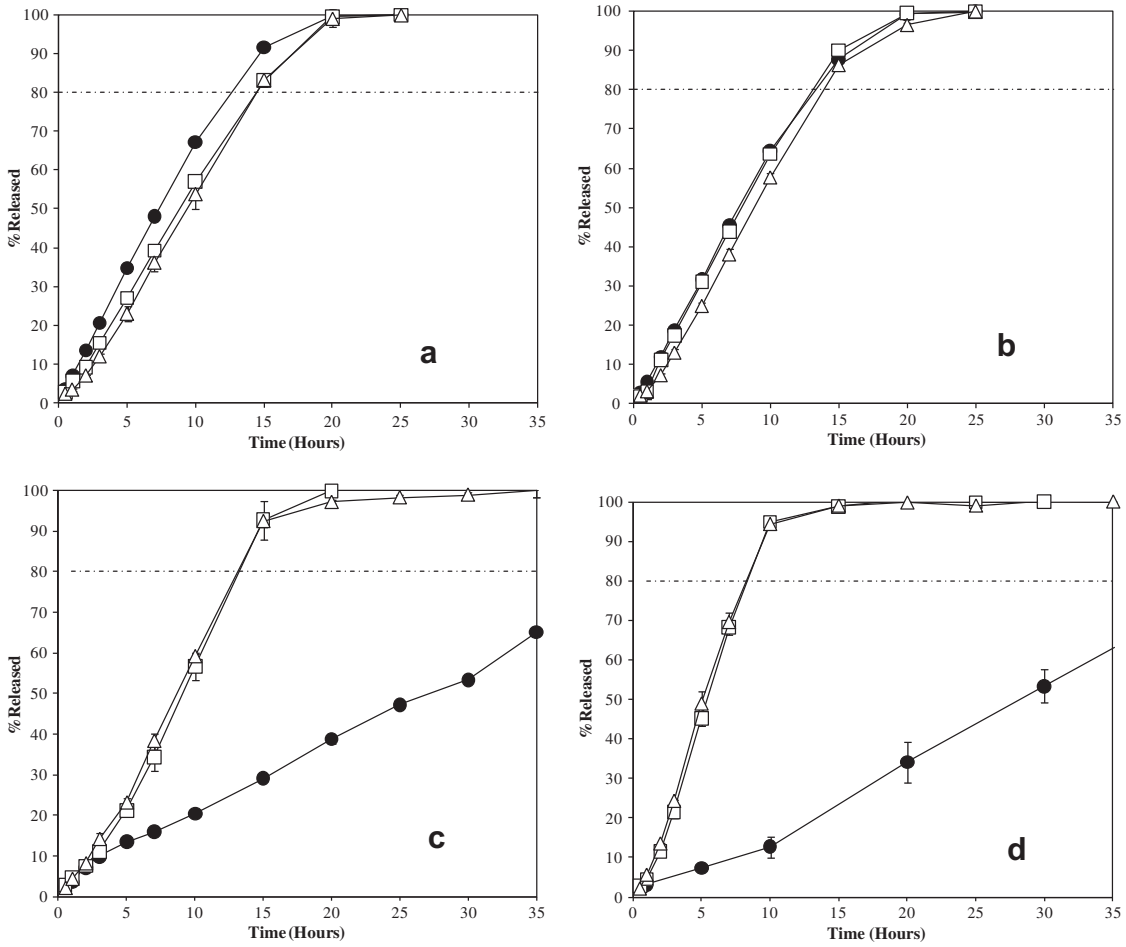

Fig. 5. Release profiles obtained from matrix tablets with and without an addition of 10% butylparaben, at the paddle speed of 50 rpm. (△) release of butylparaben, (□) erosion of HPMC from compositions with butylparaben and (●) erosion of HPMC from pure polymer tablets. (a–d) Represent the four different HPMC batches A–D, respectively. The symbols denote the calculated average value of two tablets, and the error bars show the deviation from the mean value.

contribution of erosion became the dominating factor in this stage (Fig. 3c and d).

The compositions of batches C and D were also affected to a greater extent by the increase in the paddle speed to 100 rpm (Fig. 4a–d). This can be seen in that the T_{80} values of BP decreased to 8.9, 8.5, 11.2 and 9.8 h from compositions of batches A, B, C and D, respectively (Table 3). The decrease in T_{80} values from all compositions can be explained by the increase in the erosion rates of the polymers (Fig. 4a–d). However, for the two most heterogeneously substituted batches C and D, which were most affected by the paddle speed, the greater erosion not only increased the release rate of BP but also changed the release mechanism to more of an erosion controlled release mechanism (Fig. 4c and d). The hypothesis in the present study was that the drug could interact differently with HPMC with different chemical heterogeneity and hence, affects the release behaviour in hydrophilic matrix tablets. It could be concluded from the cloud point and the solubility measurements that the more heterogeneously substituted batches were able to interact with BP to a higher extent than the more homogeneously substituted HPMC batches. This also seemed to affect the tablet compositions, where the addition of BP made the tablets of batch C and D more fragile and hence, more affected by the higher shear rate. Adding a higher load of BP and hence, increasing the concentration of BP in the matrix might then further reduce the ability of the heterogeneously substituted HPMC batches to hydrate. Thus, to elucidate the hypothesis, matrix tablets with an addition of 10% (w/w) BP were analysed in addition to the 5% compositions.

3.3.2. Influence of drug load – tablet compositions with the addition of butylparaben

With 10% BP in the compositions the relative position in the release rate changed completely and BP was released at a faster rate from compositions of batch D followed by compositions of batch C > B > A (Table 3, Fig. 5a–d). However, the higher BP load affected neither the release rate nor the release mechanism considerably from tablet compositions of batches A and B. This can be seen by comparing the T_{50} and the T_{80} values between the 5% and 10% BP compositions, where the differences were not even an hour (Table 3). The similarity in results of compositions of these more homogeneously substituted batches can be explained by the polymer erosion from these compositions being little affected by BP, and only a small decrease in the erosion rate was seen from batch A (Fig. 5a and b). In contrast, the two more heterogeneously substituted batches, C and D, were much affected by the higher drug load, and the T_{80} value of BP from batch D decreased by 12 h compared to the T_{80} value obtained from the 5% composition. The reason for the much faster release seems to be that the erosion rate of batches C and D increased tremendously from compositions with 10% BP, and it can be seen that tablets of batch D were completely eroded within ten hours, which is 60 h prior to tablets in which no BP was present. As already indicated, the gel layer function of

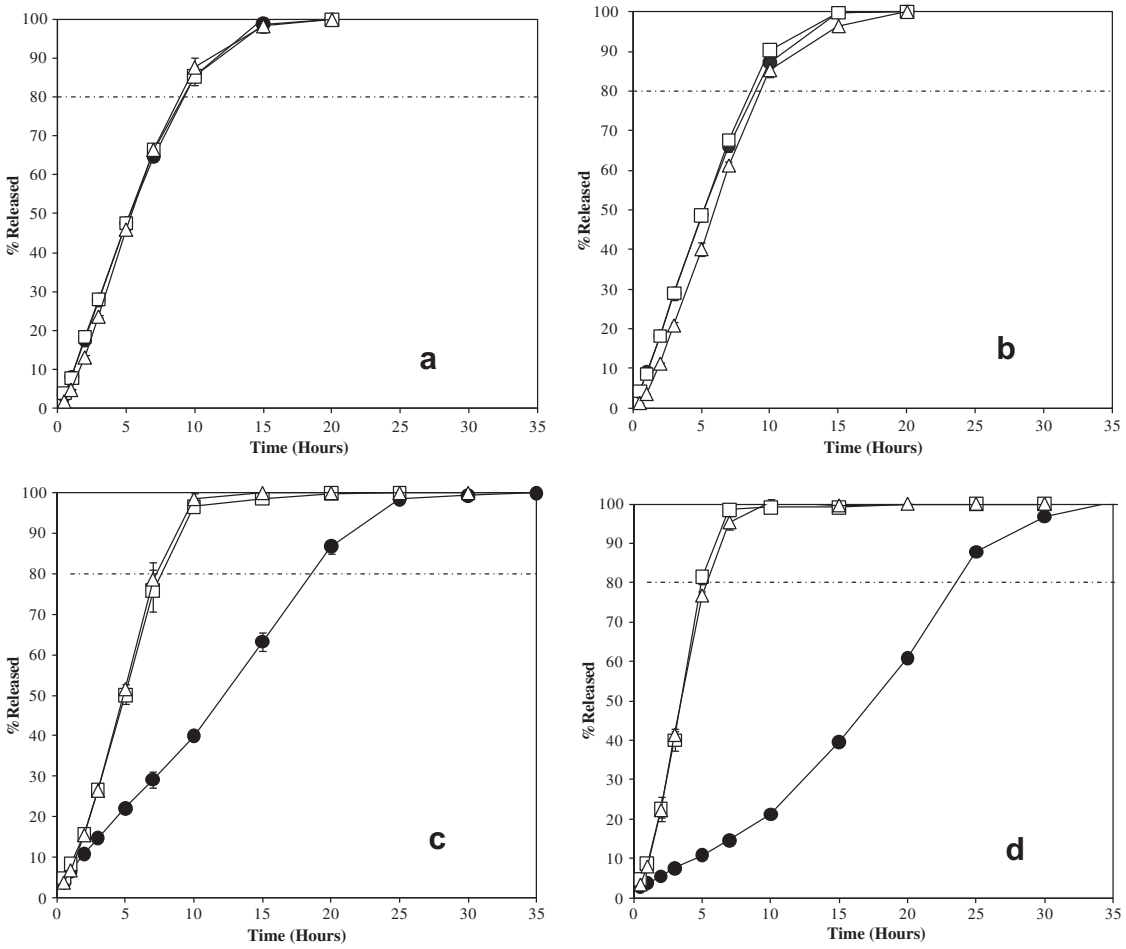

Fig. 6. Release profiles obtained from matrix tablets with and without an addition of 10% butylparaben, at the paddle speed of 100 rpm. (△) release of butylparaben, (□) erosion of HPMC from compositions with butylparaben and (●) erosion of HPMC from pure polymer tablets. (a–d) Represent the four different HPMC batches A–D, respectively. The symbols denote the calculated average value of two tablets, and the error bars show the deviation from the mean value.

batches C and D was very much affected by the BP and its ability to resist erosion forces therefore decreased; hence, the erosion rate of the HPMC increased rapidly (Fig. 5c and d).

The effect of a higher paddle speed, 100 rpm, on the release was similar to the results obtained for compositions with 5% BP. It can therefore be seen that the 10% compositions of batches A and B were less affected while the release rate from compositions of bathes C and D increased considerably; hence, these compositions were unable to release BP with an extended release (Table 3, Fig. 6a–d) The results suggest that the higher amount of BP interacting with the heterogeneously substituted batches made the HPMC unable to hydrate sufficiently, and their ability to achieve an extended release thus failed.

3.3.3. Influence of drug structure – tablet compositions with an addition of methylparaben

The hypothesis in the present study was that drug substances would interact differently with HPMC that has different substituent heterogeneity and that the drug substance would hence affect its own release rate. A more soluble, less lipophilic substance would presumably not interact with the hydrophobic HPMC associations made by the heterogeneously substituted batches to the same extent as BP and would therefore not affect the tablet compositions as much. To investigate the hypothesis further, compositions with 10% (w/w) MP were analysed at both 50 and 100 rpm. Release profiles with and without MP are shown in Fig. 7a–d. At 50 rpm, the T_{50} values were 6.7, 5.1, 7.5 and 9.0 h and the T_{80} values were 13.8, 10.8, 18.6 and 20.1 h from compositions of batches A, B, C and D, respectively (Table 3). As suggested, MP did not affect the compositions as much as BP did, and the MP release rates were considerably lower from compositions consisting of the more heterogeneously substituted batches. Furthermore, it can be seen in a comparison of the release profile of MP to the erosion rate of the polymer that the contribution of diffusion to the release mechanism was higher in all compositions compared to the mechanism by which BP was released. This can be explained by the higher solubility of MP; thus, a greater contribution of diffusion is expected from matrixes of the same size and shape [40].

In contrast to what could be predicted, MP, the model drug substance with the higher water solubility was released from compositions of batches C and D at lower rates when compared to the less soluble BP. This unexpected result seems to be in line with the proposed hypothesis, where MP interacted with the heterogeneously substituted HPMC batches to a lesser extent than BP, as was also indicated by the CP measurements. Consequently, MP did not affect the polymer erosion from matrix tablets as much as BP and batches C and D released MP in an extended way (Fig. 7c and d). At 100 rpm, the T_{50} and T_{80} values decreased from compositions of all four batches and, since the erosion rate of the polymers increased there was greater erosional contribution to the release mechanism (Table 3, Fig. 8). In addition, as already shown, the compositions of batches C and D were affected to a greater extent

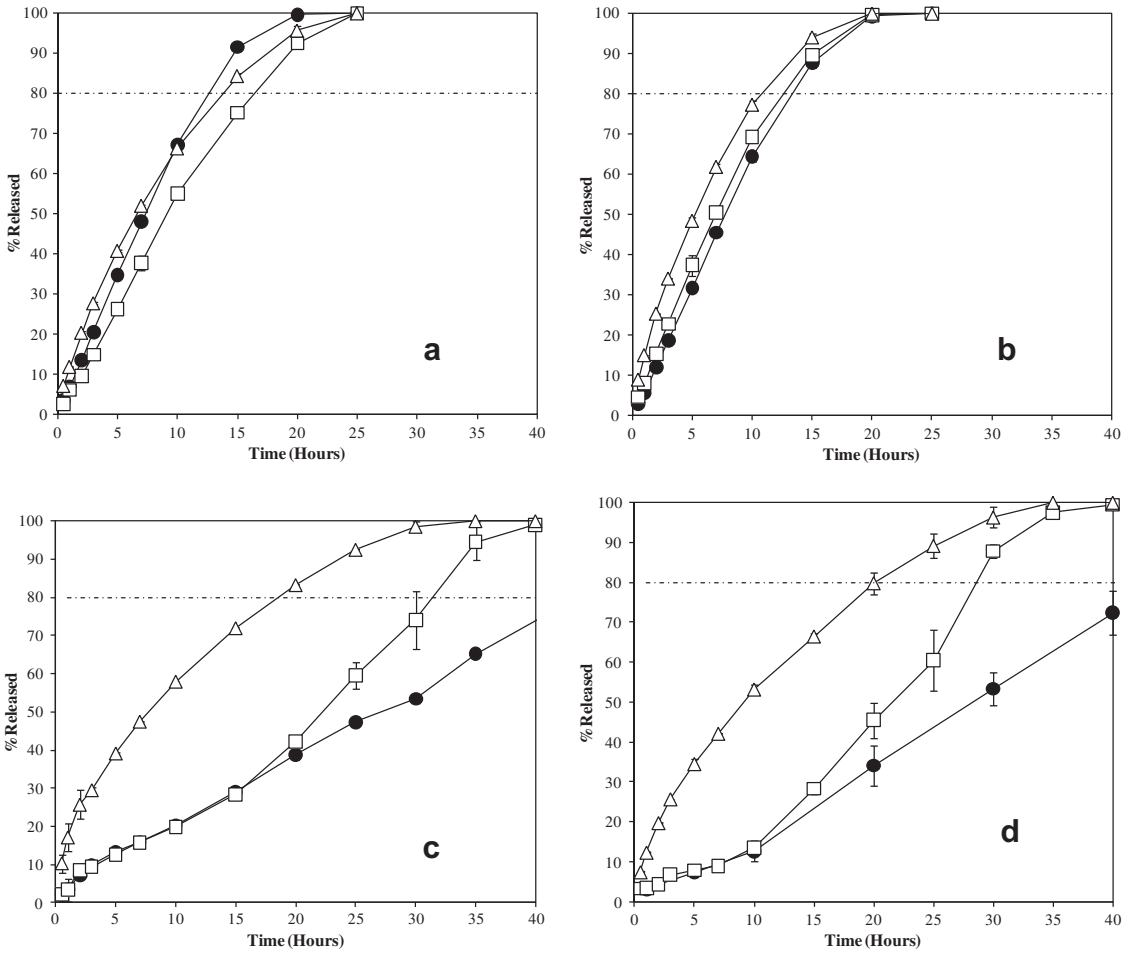

Fig. 7. Release profiles obtained from matrix tablets with and without an addition of 10% methylparaben, at the paddle speed of 50 rpm. (△) release of butylparaben, (□) erosion of HPMC from compositions with butylparaben and (●) erosion of HPMC from pure polymer tablets. (a–d) Represent the four different HPMC batches A–D, respectively. The symbols denote the calculated average value of two tablets, and the error bars show the deviation from the mean value.

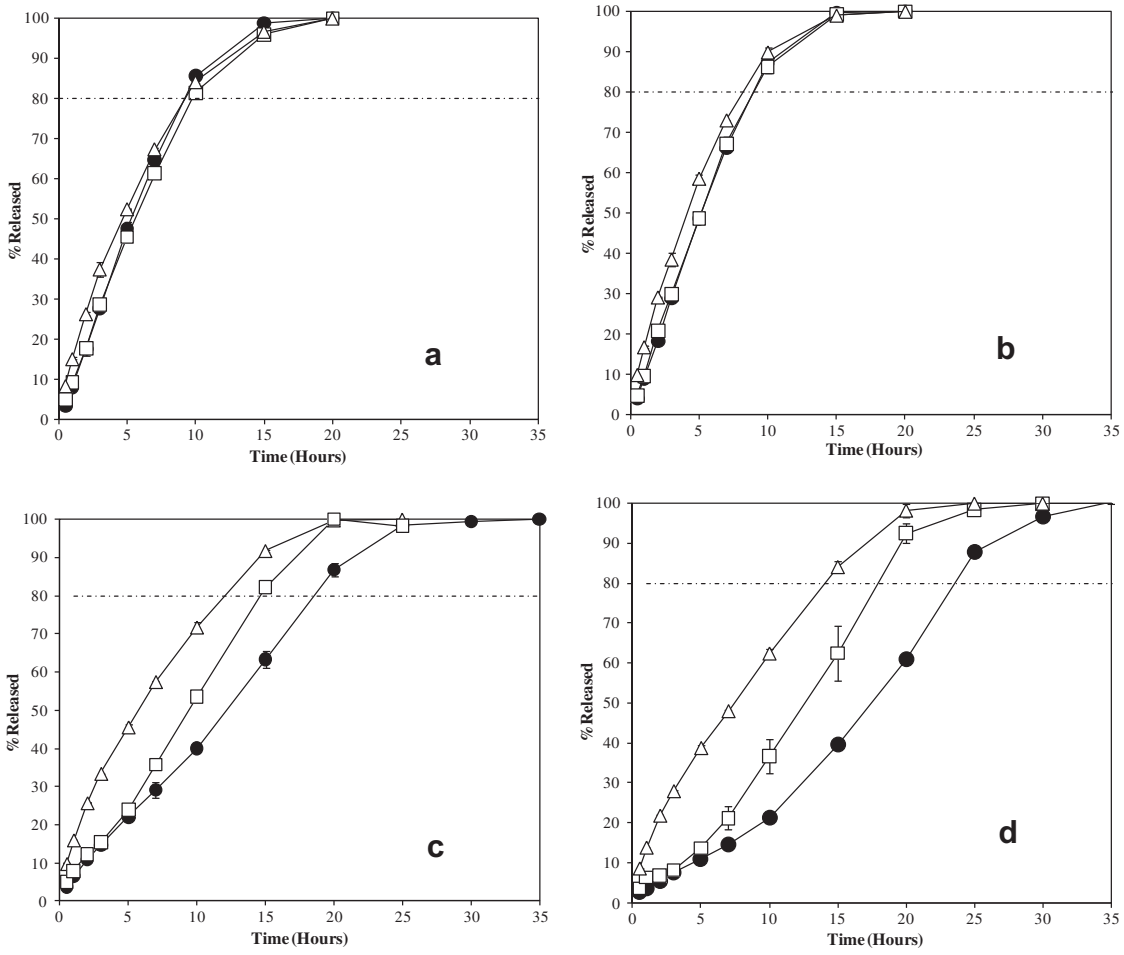

Fig. 8. Release profiles obtained from matrix tablets with and without an addition of 10% methylparaben, at the paddle speed of 100 rpm. (△) release of butylparaben, (□) erosion of HPMC from compositions with butylparaben and (●) erosion of HPMC from pure polymer tablets. (a–d) Represent the four different HPMC batches A–D, respectively. The symbols denote the calculated average value of two tablets, and the error bars show the deviation from the mean value.

by an increased paddle speed, and the polymer erosion rate from these compositions increased in comparison with the tablets without MP.

3.4. Relating matrix performance to chemical heterogeneity of HPMC

Rapid polymer hydration and the establishment of a coherent gel layer are important parameters for the performance of a hydrophilic matrix tablet [1,3,4]. CP, which is an indicator of the hydration of the polymer, showed that the heterogeneously substituted batches, C and D, were affected to a greater extent by an increase in the polymer concentration from 1 to 10% (w/w), and the CP decreased considerably with increased concentration. This more associative behaviour of batches C and D was shown in a previous study of heterogeneously substituted HPMC batches where gel-like structures were formed before the samples precipitated out of solution [27]. This was thought to depend on the amphiphilic character of the polymer chains, where more hydrophobic interactions between the chains could take place. It was further shown that the reversible gel-like structures were formed at very low concentrations and that the number increased with increased concentration. Thus, in the gel layer of the tablet, these interactions formed a coherent gel and decreased the erosion rate, as was observed in the present study [28]. However, in solutions of the more homogeneous batches A and B, the more homogeneous substituent pattern and perhaps the somewhat higher amount of HPO groups seemed to prevent hydrophobic interactions between chains, which might explain the less associative behaviour, as indicated by the concentration dependency of CP. Therefore, along the concentration gradient within the gel of the matrix, the amount of hydrophobic interactions between the chains would not increase in the same manner as in the gel of batches C and D. As a result, in the absence of parabens, the polymer erosion of batches A and B was faster than the erosion of batches C and D.

A small decreased solubility of the heterogeneously substituted batches C and D would disturb their metastable gelation phase and cause them to phase separate. This was indicated by the CP at the 10% HPMC solutions, where the addition of parabens caused the CP of the most heterogeneously substituted batch D to decrease the most. Consequently, in the matrix tablets the gel of the heterogeneously substituted batches became more fragile by the parabens and hence, also less able to resist the erosional stresses. Comparing the release to the structure of the parabens, it can be concluded that the addition of MP to the compositions did not affect the erosion rate of the polymer to the same extent as BP did. This might be explained by that BP was able to interact to greater extent with the heterogeneously substituted HPMC structures, as indicated by the solubility measurements, which further decreased the ability of the heterogeneously substituted batches to hydrate. As a result, the gel layer became less able to adapt to increased swelling and hence as was shown in the present study, the erosion rate increased.

The more homogeneous substituent pattern of batches A and B and thus the less associative behaviour of these batches seemed to cause fewer interactions with the parabens when compared to batches C and D; hence, the CP was less affected by the parabens and the solubility of BP was less affected by the higher concentration of batches A and B. For that reason, either BP or MP could affect the functionality of the gel. Neither did the small decrease in CP obtained by MP and BP jeopardise the hydration of the gel layer. Consequently, the erosion rate of the different tablet compositions with different drug loads was similar to compositions in absence of drug.

4. Conclusion

The interactions between BP and the heterogeneously substituted HPMC batches affected the ability of HPMC to hydrate. Thus, the gel of the matrix tablets became more fragile and less able to resist erosional stress. The compositions of these batches therefore released the less soluble BP at a faster rate than the more soluble MP. In contrast, the erosion rates of the more homogeneously substituted batches were very little affected by the amount of drug and the drug type and were very robust within the variations in this study. It can therefore be concluded that the substituent heterogeneity influenced the ability of the HPMC to be used as a gelling agent in hydrophilic matrix tablets. Thus, one factor that should be considered is how the drug interacts with the HPMC and that these interactions are affected by both the substituent heterogeneity and the drug structure. Consequently, formulating matrix compositions with drugs having various structures and solubilities requires an awareness of that the substituent heterogeneity of HPMC may determine whether the composition fails or will behave as an extended release formulation. It can therefore be concluded that the substituent heterogeneity should be regarded as an important functionally related characteristic of HPMC for drug release from matrix tablets.

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