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Model drug release from matrix tablets composed of HPMC with different substituent heterogeneity

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ABSTRACT

The release of a model drug substance, methylparaben, was studied in matrix tablets composed of hydroxypropyl methylcellulose (HPMC) batches of the USP 2208 grade that had different chemical compositions. It was found that chemically heterogeneous HPMC batches with longer sections of low substituted regions and lower hydroxypropoxy content facilitated the formation of reversible gel structures at a temperature as low as 37 °C. Most importantly, these structures were shown to affect the release of the drug from matrix tablets, where the drug release decreased with increased heterogeneity and a difference in T80 values of 7 h was observed between the compositions. This could be explained by the much lower erosion rate of the heterogeneous HPMC batches, which decreased the drug release rate and also released the drug with a more diffusion based release mechanism compared to the less heterogeneous batches. It can therefore be concluded that the drug release from matrix tablets is very sensitive to variations in the chemical heterogeneity of HPMC.

1. Introduction

The improvement in patient compliance that is experienced with long acting dosage forms has contributed to the development of hydrophilic matrix tablets. These tablets are achieved by compressing a well mixed composite of a hydrophilic polymer and the drug substance into a tablet (Lapidus and Lordi, 1968). The sustained release is achieved by the dissolution of the polymer that starts when the tablet comes into contact with water. The polymer eventually forms a concentrated polymer solution around the tablet that is referred to as a gel. This gel-layer acts simultaneously as a protective barrier to water ingress and a diffusional/erosional barrier for the drug release (Colombo et al., 1996). The ability of the polymer to rapidly hydrate and quickly form a coherent gel with sufficient mechanical integrity is closely connected to the chemical and physico-chemical properties of the polymer. Thus, to be able to predict the dissolution rate of the polymer and hence the drug release rate it is extremely important to know the properties of the polymer that affect the functionality of the matrix tablets.

Hydroxypropyl methylcellulose (HPMC) is a traditional gel former in hydrophilic matrix tablets. The release of a drug from matrixes composed of HPMC has been shown to depend on the degree of substitution (Alderman, 1984; Bonferoni et al., 1995) and the molecular weight (Gao et al., 1996; Ju et al., 1995; Kavanagh and Corrigan, 2004; Reynolds et al., 1998). The degree of substitution renders the solubility of the chain in aqueous solutions and thus influences the swelling of the matrix tablet (Alderman, 1984). The swelling and the dissolution rate are also affected by the molecular weight, where it is expected that batches with a higher molecular weight are eroded from the matrix at lower release rates (Gao et al., 1996; Ju et al., 1995; Kavanagh and Corrigan, 2004; Reynolds et al., 1998). A proper selection of grades has not always fulfilled the requirements for the products, however, and there have hence been batch-to-batch variations in matrix performance (Dahl et al., 1990; Viriden et al., 2009b). This can be explained to some extent by the broad specification limits that allow a rather large variability in substituent content, where for example Dahl et al. (1990) showed how the release of naproxen decreased with a decreased hydroxypropoxylic (HPO) content in the same HPMC grade. They stated that further work is needed to fully characterise the solubility behaviour of the various chemically substituted HPMC samples in order to understand their behaviour in matrix tablets. Nevertheless, it has not always been possible to explain the behaviour of the polymers by the average degree of substitution, and attention has instead been directed to the influence of the substituent pattern, which has been shown to affect the physico-chemical properties of cellulose derivatives (Haque and Morris, 1993; Haque et al., 1993; Hirrien et al., 1996; Neely, 1963; Schagerlof et al., 2006; Takahashi et al., 1987; Viriden et al., 2009a,b).

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The solubility of cellulose derivatives such as methylcellulose (MC) and HPMC is dependent on the degree of substitution and the substituent pattern. This can be explained by the native cellulose being insoluble due to its crystalline structure; thus substituents that disrupt the crystalline structure are introduced to increase the solubility. However, the substituents increase the hydrophobicity of the chain and highly substituted regions of methoxylic groups (MeO) are thereby able to interact. Because of these hydrophobic interactions, it is generally accepted that MC and HPMC form a reversible gel upon heating (Sarkar, 1979). However, it has been shown that gelation of MC can be prevented by a homogeneous substituent pattern, and that gelation occurs mainly in samples with amphiphilic behaviour where the hydrophobic interactions act as crosslinkings (Takahashi et al., 1987). Furthermore, for HPMC, the HPO groups prevent aggregation for steric (Neely, 1963) and entropic reasons (Haque et al., 1993) and thus HPMC is expected to gel at considerably higher temperatures as compared to MC (Sarkar, 1979). This has been shown to depend on the distribution along the chain; however, where heterogeneously substituted HPMC batches already formed reversible gel structures at room temperature (Viriden et al., 2010).

Although it can be seen that the solubility of HPMC is dependent on both the content of the substituents and their distribution, it has been difficult to characterise the substituent pattern. This partly depends on the lack of sensitive and selective analytical tools to characterise the complex chemical structure. One tool available for distinguishing between structural differences is the use of cellulose degrading enzymes, which efficiently hydrolyse (1 → 4)β-D-glucosidic linkages in cellulose (Karlsson et al., 2002a; Melander, 2006; Richardson and Gorton, 2003; Schagerlöf, 2006). These enzymes are hindered by the substituents along the polymer chain, and thus hydrolysis will selectively occur in regions with few or no substituents. It follows from this that batches that are degraded by the same enzyme will allow a relative comparison in heterogeneity. Thus information about chemical heterogeneity can be obtained using sensitive analytical tools in combination with enzymatic hydrolysis (Karlsson et al., 2002a; Melander, 2006; Richardson and Gorton, 2003; Schagerlöf, 2006; Viriden et al., 2009b).

In a previous study by Viriden et al. (2009b) different batches of the pharmaceutical 2208 grade were hydrolysed by an endoglucanase and rather large differences in heterogeneity were found. More importantly, the heterogeneity correlated to the polymer release from hydrophilic matrix tablets, where the more heterogeneously substituted polymers were released at a lower rate. The hypothesis was that the heterogeneous substituent pattern facilitated an amphiphilic behaviour of the polymer chain, where the highly substituted regions interacted and formed gel-like structures in the gel of the matrix tablet (Viriden et al., 2010). These increased the viscosity of the solution and decreased the erosion rate of the polymer from matrix tablets. However, to strengthen the hypothesis of amphiphilic behaviour the samples must be hydrolysed with a more selective enzyme that is hindered by the substituents over longer segments of the chain. Furthermore, if these amphiphilic structures were to be found, it would be of great pharmaceutical interest to study what influence a small molecule, such as a drug substance, has on the reversible gel structure in the matrix. It would be essential then to evaluate the drug release from matrix tablets composed of HPMC batches with different chemical heterogeneity. For this reason, the release of a model drug substance, methylparaben, was studied in tablets composed of four HPMC batches of the USP 2208 grade having different degrees of substitution and substituent heterogeneity. In addition, the four HPMC batches were hydrolysed by a more selective endoglucanase from *Trichoderma reesei* in order to investigate the hypothesis that the heterogeneously substituted batches had an amphiphilic structure.

2. Materials and methods

2.1. Materials

Four HPMC batches of the same substituent grade (USP 2208) and viscosity grade (100 cPs) were used. 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 was purchased from Sigma–Aldrich Chemie (GmbH, Switzerland) and used as received.

2.2. Enzymatic hydrolysis

An endoglucanase, Cel45Acore, from *T. reesei* was used and purified as described by Karlsson et al. (2002b). In addition, β-glucosidase from *Aspergillus niger* (Megazyme, Bray, Ireland) was used. The β-glucosidase solution was desalted by diluting 300 μl of enzyme solution with 3 ml of deionised water in an Amicon Ultra centrifugal device (10 kDa molecular weight cut-off, Millipore, Cork, Ireland). After dilution, the system was concentrated by centrifugation (Heraus Varifuge F, Hettich Laborationinstrument AB, Sweden) at 2000 rpm for 35 min. The procedure was followed for a total of three times and the enzyme concentration was measured using a Spectra max Plus (Molecular Devices, Sunnyvale, CA, USA). The concentration was calculated using a standard calibration curve at a wavelength of 280 nm.

For enzymatic hydrolysis, each HPMC was dissolved in water to a concentration of 10 g/L. The Cel45Acore was added to a concentration of 1 μM and the hydrolysis continued for 72 h at room temperature as described by Schagerlof et al. (2006). The samples were stored at 4 °C until 1 U/ml β-glucosidase was added to the already hydrolysed samples. The samples were then further incubated for 24 h at 37 °C. The temperature was increased to 85 °C for 5 min to end the hydrolysis.

Glucose released after enzymatic hydrolysis was detected by high-performance anion-exchange chromatography with pulsed amperometric detection (HPAEC-PAD) from Dionex (Sunnyvale, CA, USA). The HPAEC-PAD system consisted of a GS50 gradient pump, a CarboPac PA-100 guard- and analytical column, and an ED50 electrochemical detector. The injection volume was 20 μl. Elution of the components in the hydrolysate mixture was carried out at a flow rate of 1.0 ml/min using a gradient program with deionised water and 150 mM NaOH for 30 min. The software used for data processing was Chromeleon 6.40 (Dionex, Sunnyvale, CA, USA).

2.3. Viscosity

Flow curves were recorded for the selected samples by an Anton Paar Physica MCR 500 rheometer (Germany) equipped with a double gap cylinder with an external and internal radius of 13.33 and 12.33 mm, respectively. HPMC solutions of 5% (w/w) and 10% (w/w) were prepared in phosphate buffer (I = 0.1, pH = 6.8). The flow curves were obtained by increasing the shear rate in a logarithmic manner from 0.1 to 100 s^{-1}. The measuring point duration was decreased logarithmically from 20 to 0.5 s. The flow curves were recorded at 37 °C and the solutions were allowed to equilibrate at the same temperature for 1 h before measurements. The average values reported are based on two measurements.

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 was preweighed for each tablet using a Mettler Toledo AX205 Delta Range to get a tablet weight of about 300 ± 1 mg. The methylparaben was blended with the polymer powder with a pestle and mortar for 5 min to obtain a well mixed composition before tabletting.

2.5. Polymer and drug release

The release of the drug and the HPMC from the dissolving tablets was carried out in a USP dissolution apparatus (Dissolutest, Prolabo, France) equipped with a standard USP II paddle. The paddle speed was set to 50 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) 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 was analysed and averaged.

The polymer concentration in the release medium was determined by size 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 made 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 solubility of methylparaben at 22 °C in the phosphate buffer used was measured and found to 2.9 mg/ml. The concentration of methylparaben at each sample time was measured using a Spectra max Plus (Molecular Devices, Sunnyvale, CA, USA). The concentration of methylparaben was calculated using a standard calibration curve at a wavelength of 255 nm.

The 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 either the weight of the polymer or the weight of the total drug dose in the tablet.

Table 1
Polymer characteristics of the four HPMC batches[a].

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

[a] Data obtained by Viriden et al. (2009b).
[b] The results given are mean values and corresponding standard deviations in parentheses (n = 3).
[c] RSD of 0.02 according to an in-house validation.

3. Results and discussion

3.1. Chemical properties of HPMC

The aim of the present study was to evaluate how the chemical heterogeneity of HPMC affected the release of the drug from matrix tablets. Thus four HPMC batches (A–D) of the same pharmaceutical substituent and viscosity (100 cPs) grade were selected according to the differences that were characterised in the degree of substitution, molecular weight and substituent heterogeneity (Table 1) (Viriden et al., 2009b). As can be seen in Table 1, the batches had average molecular weights of the same magnitude with similar distributions, giving a comparable polydispersity index (P.I.). To evaluate the effect of the substituent heterogeneity within a grade, two levels of both the HPO and the MeO content were selected. As can be seen in Table 1, 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). The specification limits for a 2208 grade are 19–24% (w/w) for MeO and 4–12% (w/w) for HPO (Pharmacopoeia, 2006; USP29-NF24, 2003). Thus, with the exception of the 25% MeO characterised in batch D, the average substitution was within the specification limits. However, the experimental substitution data were systematically larger than that reported by the suppliers, which may be a result of the use of different analytical methods (Andersson et al., 2003).

3.2. Chemical heterogeneity of HPMC

HPMC can be regarded as a highly polydisperse material where the distribution of both the molecular weight and the substituents must be considered in order to predict and understand the behaviour of the polymer as a matrix former. A relative comparison of the substituent heterogeneity along the polymer chain was obtained in the former study by the means of an endoglucanase from *T. longibrachiatum* (Viriden et al., 2009b). The enzyme must form an enzyme–substrate complex with the polymer chain to hydrolyse and to do that, the HPMC needs to be unsubstituted over a certain number of glucose units (Schagerlöf, 2006). This means that batches with more frequently occurring unsubstituted regions would liberate more glucose after being hydrolysed by the enzyme. As seen in Table 2, the amount of glucose released after hydrolysis with *T. longibrachiatum* increased from batch A

Table 2
Percentage (w/w) glucose released after enzymatic hydrolysis.

Sample	Glucose released after hydrolysis with endoglucanase from *Trichoderma reesei* and β-glucosidase from *Aspergillus niger*[a]	Glucose released after hydrolysis with endoglucanase from. *Trichoderma longibrachiatum*[a,b]
A	0.4(0.0)	0.3(0.1)
B	1.2(0.0)	0.9(0.1)
C	1.3(0.0)	1.2(0.1)
D	1.5(0.1)	1.4(0.1)

[a] The results given are mean values and corresponding standard deviations are in parentheses (n = 3).
[b] Data obtained by Viriden et al. (2009b).

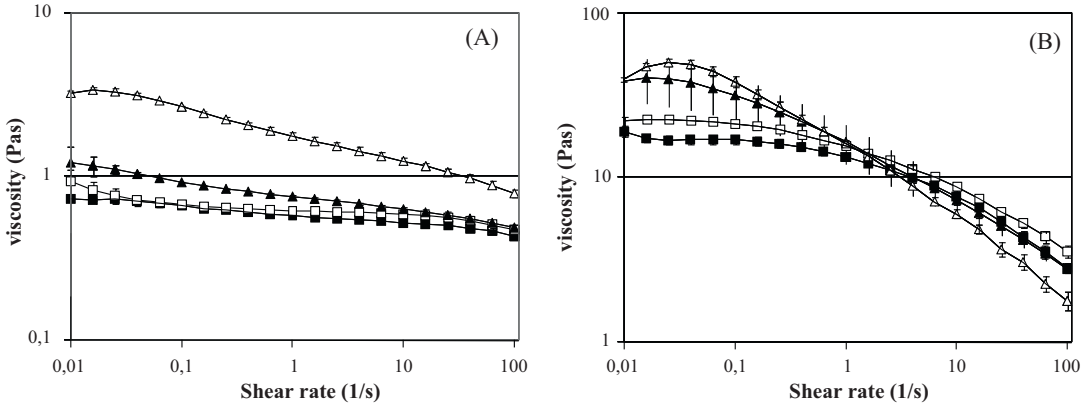

Fig. 1. Flow curves obtained at 37 °C. (A) 5% (w/w) HPMC solutions and (B) 10% (w/w) HPMC solutions. (■) Batch A, (□) Batch B, (▲) Batch C and (△) Batch D. The symbols denote the calculated average value from two measurements and the error bars show the deviation from the mean value.

to batch D, and hence the substituent heterogeneity increased in the same order. The hypothesis in the former study was that the most heterogeneously substituted polymers were more block-like in their chemical structure and hence took on an amphiphilic character, where hydrophobic interactions between the highly substituted regions facilitated the formation of reversible gel-like structures in the matrix tablet (Viriden et al., 2009b). To support the proposed hypothesis and simultaneously gain more information about the chemical differences along the polymer backbone, the present study used a more selective endoglucanase from *T. reese*. This enzyme has been shown to be hindered to a greater extent by the substituents and longer low substituted regions are therefore needed to form the enzyme–substrate complex (Karlsson et al., 2002a; Schagerlöf, 2006). Furthermore, to account for a larger amount of the hydrolysed product, β-glucosidase, an exo-enzyme that efficiently degrades larger oligosaccharides presumably released after the enzymatic hydrolysis was also added. The results of the enzymatic hydrolysis showed that batch A released the smallest amount of glucose from the enzymes followed by batches B, C and D (Table 2). The relative order between the batches in terms of glucose released was the same as obtained in the earlier study, although it can be seen that the differences between batch A and B became greater (Table 2). This can be explained to a certain extent by the fact that a larger amount of the hydrolysed product was accounted for. However, it also shows that additional information can be obtained by using enzymes with different selectivity. Thus, according to the result of the present study, longer low substituted regions were more frequent in batch B compared to batch A. (Tables 1 and 2). Moreover, the longer low substituted regions were about the same in batch C as in batch B but increased even more in batch D. Flow curves were obtained to investigate whether the differences between the batches affected the solution behaviour.

3.3. Effect of chemical heterogeneity on viscosity

Flow curves were obtained at 37 °C in 5% (w/w) and 10% (w/w) solutions after equilibration for 1 h at the same temperature. At 5% (w/w), the viscosity increased in the order batch A ≈ B < C < D throughout the shear rate interval. It was also found that the viscosity of batch D was three times as high as the viscosity of batches A and B at a shear rate of 1^{-1} s (Fig. 1). For a linear polymer without other interactions apart from entanglements the viscosity is expected to increase with increased molecular weight (De Gennes, 1979). In this study batches A and B had the highest average molecular weights, and it could thus be seen that the molecular weight did not correlate to the differences observed in viscosity. However, the viscosity increased with increased chemical heterogeneity, and the most heterogeneously substituted batch D demonstrated the highest viscosity (Fig. 1 and Table 2). It can further be seen that the solution of batch D was more shear thinning than the other batches, which is an indication of the existence of hydrophobic interactions in the solution (Silva et al., 2008). This was even more evident at 10% (w/w) solutions where the higher viscosities of both batches C and D decreased at lower shear rates (Fig. 1).

It is generally accepted that HPMC and MC possess the property of forming a reversible gel with increasing temperature (Sarkar, 1979). However, gelation has been shown to be closely connected to the heterogeneity of the substituents (Viriden et al., 2010; Haque and Morris, 1993; Takahashi et al., 1987), where for example Takahashi et al. showed that gelation occurred only for samples with amphiphilic behaviour where the hydrophobic interactions acted as crosslinkings (Takahashi et al., 1987). However, regardless of the substituent heterogeneity, the HPO group has been shown to prevent and increase the thermal gelation temperature (Haque et al., 1993; Neely, 1963). This might explain the comparable flow curves of batches A and B, where the larger amount of HPO groups seemed to decrease the effect of the substituent heterogeneity on thermal gelation. Thus, even though batch B was more heterogeneously substituted than batch A, the thermal gelation temperature of batch B did not decrease to 37 °C, and hence the flow curves of batches A and B were similar. Although none of the HPMC batches used were exceptionally low substituted, the HPO content of batches C and D was lower than that of batch B. This would have increased the possibility of frequently occurring segments that are able to hydrophobically interact if the distribution of the glucose units and the MeO groups favoured such behaviour. Consequently, the more heterogeneously substituted batches C and D also seemed to facilitate reversible gel-like structures at the low temperature of 37 °C, which increased the viscosity and made the solutions more shear thinning. These types of gel-like structures have been shown to affect the erosion rate of the polymer in matrix tablets (Viriden et al., 2010). To our knowledge, however, it has not been investigated whether the differences in chemical heterogeneity also affect the drug release. Hence release studies were carried out with tablets composed of the four HPMC batches.

3.4. Matrix performance

To study whether the polymer heterogeneity affects the drug release, tablet compositions with the addition of the slightly soluble

Table 3
T50 and T80 of methylparaben and the HPMC batches used at two paddle speeds[a].

	T50, 50 rpm	T80, 50 rpm	T50, 100 rpm	T80, 100 rpm
MP release from compositions of				
Batch A	5.3(0.2)	11.5(0.2)	4.1(0.1)	8.4(0.1)
Batch B	5.0(0.1)	10.8(0.0)	3.8(0.1)	7.7(0.1)
Batch C	6.4(0.2)	16.5(0.2)	5.5(0.3)	12.5(0.5)
Batch D	7.4(0.1)	17.4(0.4)	6.9(0.0)	14.4(0.1)
Polymer release from MP compositions of				
Batch A	7.9(0.4)	14.1(0.8)	5.2(0.2)	9.3(0.3)
Batch B	7.5(0.1)	13.2(0.1)	4.8(0.1)	8.6(0.3)
Batch C	25.3(1.3)	36.2(2.1)	11.8(1.0)	17.9(1.2)
Batch D	25.7(0.9)	35.7(0.2)	13.5(0.4)	18.7(0.5)
Polymer release from tablets of 100% polymer				
Batch A	7.4(0.1)	12.6(0.1)	5.4(0.1)	9.2(0.1)
Batch B	7.5(0.3)	13.4(0.3)	5.2(0.2)	9.0(0.2)
Batch C	26.7(0.0)	44.0(0.2)	11.8(0.4)	18.7(0.4)
Batch D	28.3(1.3)	46.3(3.4)	17.0(0.1)	23.7(0.1)

[a] Calculated value from two tablets and the deviation from the mean value is in parentheses.

methylparaben (MP) were investigated. This was done by analysing both the MP release and the erosion rate of the polymer. To evaluate the effect of MP on the polymer erosion, pure polymer tablets were also analysed as a comparison. The release data were studied with a modified USP method where the tablets were fixed in baskets. Here, the release rates were examined at two different paddle speeds, 50 and 100 rpm. The time at which 50% (T50) and 80% (T80) were released was measured to quantify the different release rates of MP and the HPMC (Table 3).

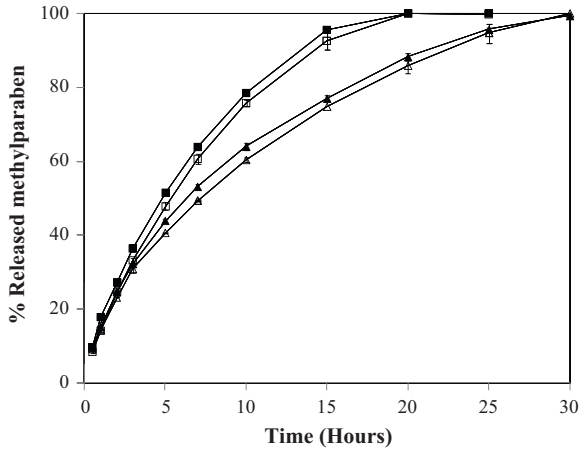

Fig. 2. Release profiles of methylparaben obtain in a modified USP II apparatus at the paddle speed of 50 rpm. The release of methylparaben was achieved from tablets composed of the four different HPMC batches: (■) Batch A, (□) Batch B, (▲) Batch C and (△) Batch D. The symbols denote the calculated average value from two tablets and the error bars show the deviation from the mean value.

3.4.1. Effect of polymer heterogeneity on the release of methylparaben at 50 rpm

The release profiles of MP from the tablets composed of the different HPMC batches are shown in Fig. 2. Almost no difference was first seen between the four MP profiles. After 3 h, however, tablets of batch A and B released MP at a much higher rate and hence the total dose of MP was released 10 h later from tablets composed of

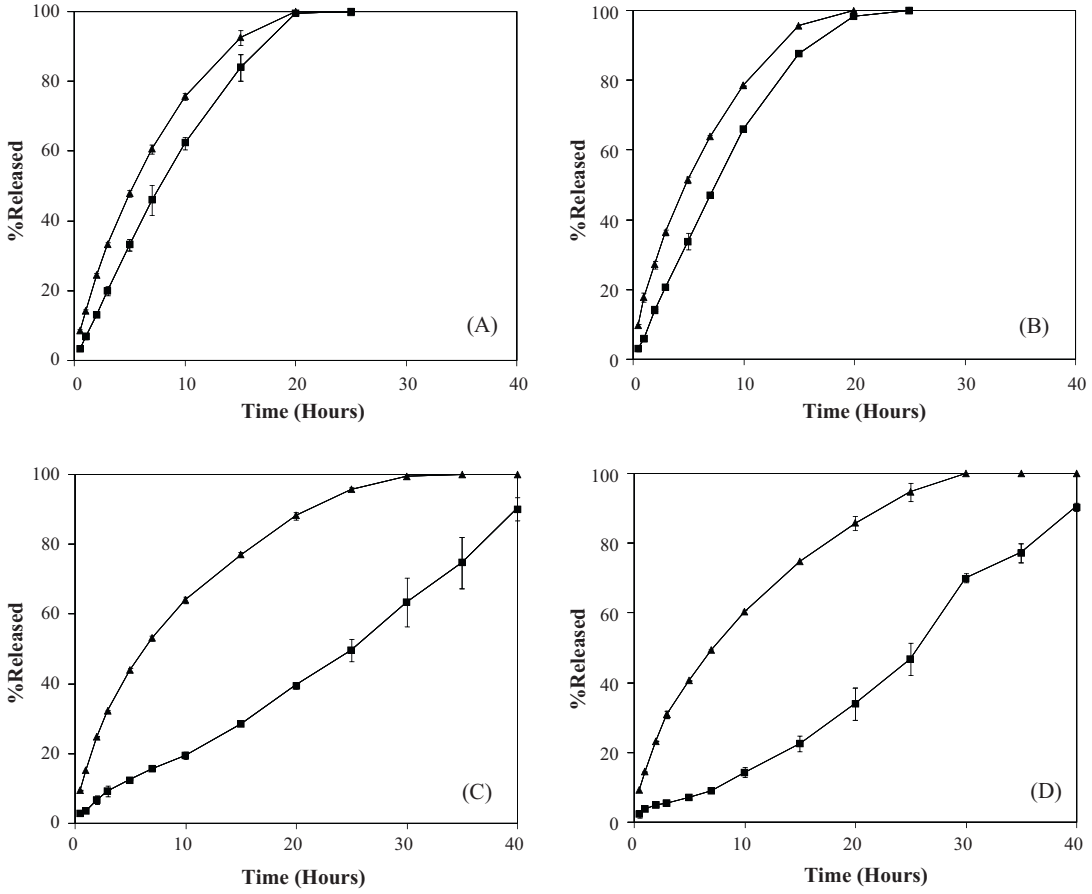

Fig. 3. Release profiles from tablet compositions of HPMC and 5% (w/w) methylparaben obtained in a modified USP II bath, at the paddle speed of 50 rpm: (▲) release of methylparaben and (■) polymer release. Figure (A)–(D) represents the four different HPMC batches. The symbols denote the calculated average value from two tablets and the error bars show the deviation from the mean value.

batch C and D (Fig. 2). The differences in the T80 values were thus quite large and were 11.5, 10.8, 16.5 and 17.4 h from tablets composed of batch A, B, C and D, respectively (Table 3). These results show that the release rate essentially decreased in compositions of the two most heterogeneously substituted batches and it is therefore clear that the chemical heterogeneity between batches of a pharmaceutical grade affects drug release.

The MP release profiles showed a noticeable curvature suggesting a diffusion based release mechanism in all four compositions. However, to gain further insight into the release mechanism of MP from compositions of the four different HPMC batches the MP release profiles were compared to the erosion rate of the polymer (Fig. 3A–D). The faster release of MP from compositions of batch A and B can be explained by Fig. 3A–D, where it is seen that the release profiles of MP and the polymer were quite close and parallel. This suggests that the diffusional contribution to the release mechanism from these compositions was limited and the erosional contribution of the polymer was noticeable. In contrast, the erosion rate of batches C and D was much lower, and it can be seen in Fig. 3C and D that 90% of MP had been released while only 50% of the polymer had been eroded from the tablets. This seems to be in line with the hypothesis that batches C and D formed reversible gel structures in the matrix tablets, which were less affected by the paddle speed and hence decreased the erosion rate of the polymer from the matrix. Consequently, compositions of batches C and D released MP with a greater diffusional contribution to the release mechanism.

3.4.2. *The effect of shear rate on the release of methylparaben*

The MP release profiles from all tablet compositions at 100 rpm are shown in Fig. 4. As seen at 50 rpm, the release profiles were fairly similar during the first hours while the differences became larger after about 3 h. Thus, large batch-to-batch variations were seen even at a higher paddle speed and the T80 values were 8.4, 7.7, 12.5 and 14.4 from tablets composed of batches A, B, C and D, respectively (Table 3). The release of MP was faster at 100 rpm in all four compositions compared to what was observed at 50 rpm; this can be seen from the lower T80 values; which decreased by 3.1, 3.1, 4.0 and 3.0 h in compositions of batches A–D,

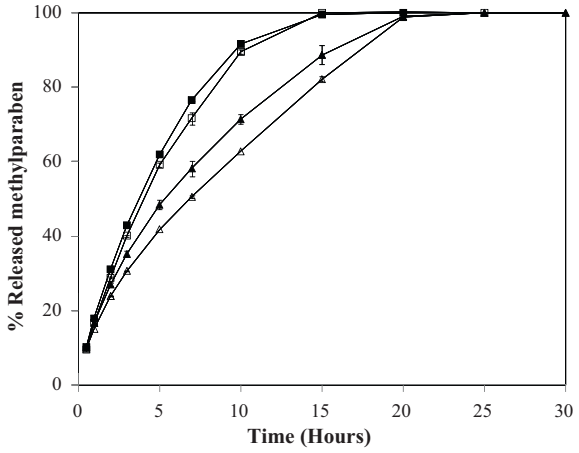

Fig. 4. Release profiles of methylparaben obtain in a modified USP II apparatus at the paddle speed of 100 rpm. The release of methylparaben was achieved from tablets composed of the four different HPMC batches: (■) Batch A, (□) Batch B, (▲) Batch C and (△) Batch D. The symbols denote the calculated average value from two tablets and the error bars show the deviation from the mean value.

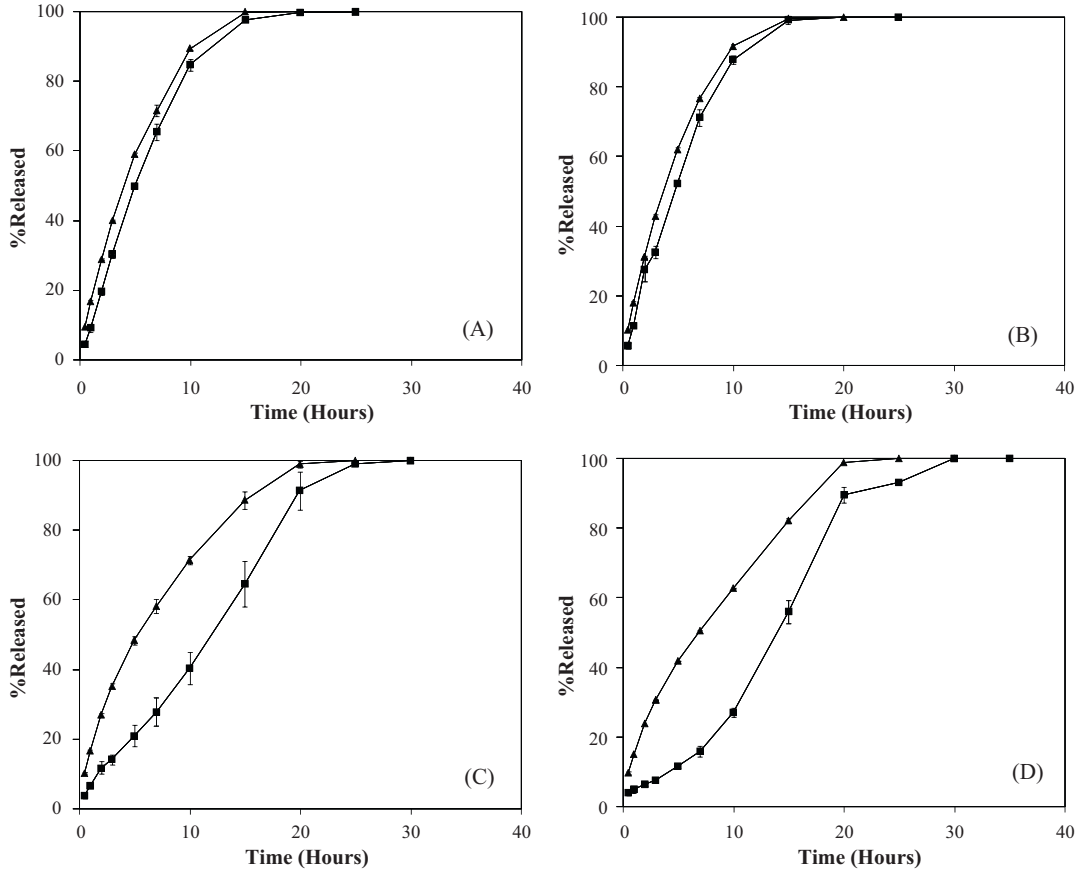

Fig. 5. Release profiles from tablet composed of HPMC and 5% (w/w) methylparaben obtained in a modified USP II bath, at the paddle speed of 100 rpm: (▲) release of methylparaben and (■) polymer release. Figure (A)–(D) represents the four different HPMC batches. The symbols denote the calculated average value from two tablets and the error bars show the deviation from the mean value.

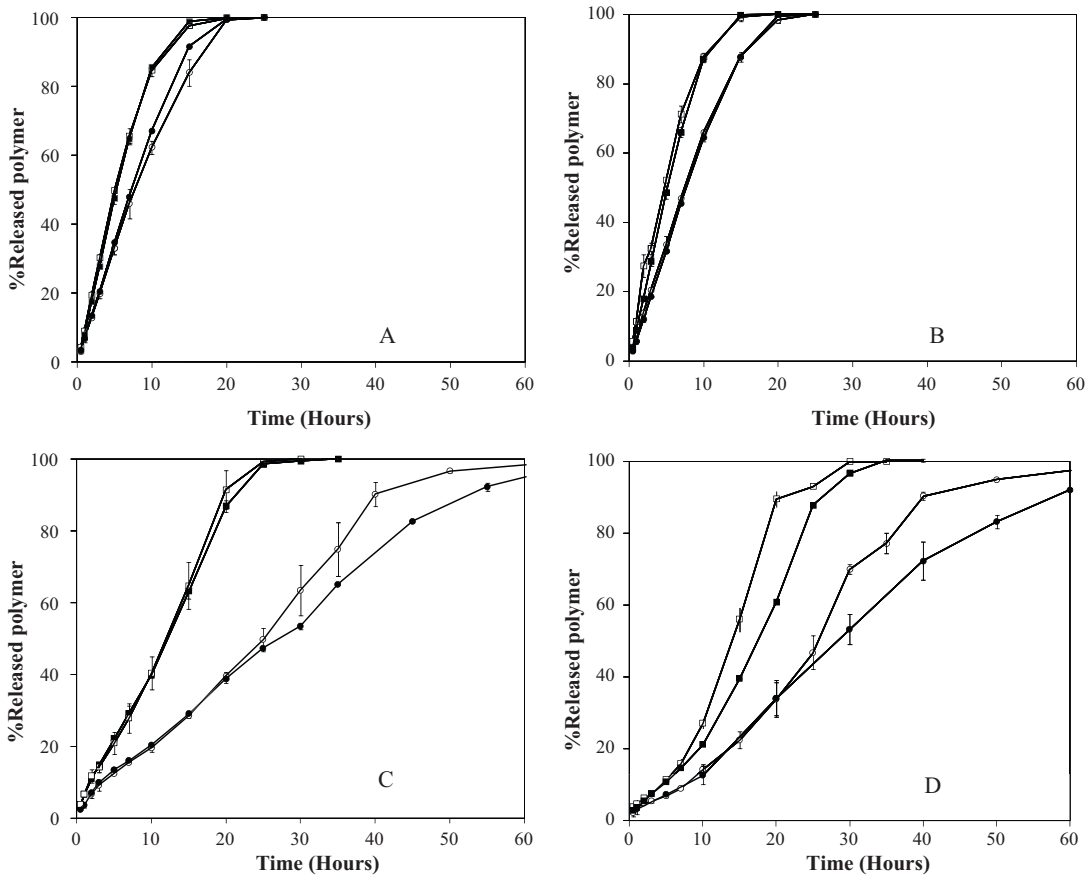

Fig. 6. Polymer release profiles obtained from matrix tablets with and without the addition of methylparaben. The results are obtained from a modified USP II apparatus and at two paddle speeds, 50 and 100 rpm. (□) Polymer release from tablet composed of HPMC and 5% (w/w) methylparaben at 100 rpm, (■) polymer release from pure polymer tablets at the paddle speed of 100 rpm, (○) polymer release from tablet composed of HPMC and 5% (w/w) methylparaben at 50 rpm and (●) polymer release from pure polymer tablets at the paddle speed of 50 rpm. Figure (A)–(D) represents the four different HPMC batches. The symbols denote the calculated average value from two tablets and the error bars show the deviation from the mean value.

respectively. These results indicate that the increase in the MP release rate was about the same in all compositions except in tablets composed of batch C, where the release rate of MP increased somewhat more.

The higher paddle speed might affect polymer erosion and hence also the MP release mechanism. A comparison of the release profiles of MP and the polymer shows that the release profiles from tablet compositions of batch A and B became more parallel and the polymer and MP were released at about the same rate (Fig. 5A and B). Accordingly, the faster polymer erosion contributed to a greater erosional contribution to the release mechanism from compositions of batch A and B at the increased paddle speed. A much slower polymer erosion was found by batch C and D, and the results were similar to those obtained at 50 rpm, and hence more than 90% of MP had been released while only 50% of the polymer had been eroded (Fig. 5C and D). The much lower erosion rate by batches C and D therefore explains the great contribution of diffusion to the MP release mechanism at both paddle speeds. As was seen at 50 rpm, the erosion rate of the polymer governed the release rate of MP and hence the much higher T50 and T80 values of batches C and D gave lower MP release rates from the same compositions (Table 3). However, even though batches C and D had a lower rate of erosion, it must be noted that these batches were more affected by the paddle speed. This can be seen by the increase in erosion rate at 100 rpm, and that the T80 values of the batches decreased by 4.8, 4.6, 18.3 and 17.0 h in batches A, B, C and D, respectively (Table 3). Further studies were made with pure polymer tablets to investigate the effect of MP on the polymer erosion.

3.4.3. Polymer release from pure polymer tablets

Polymer erosion from pure polymer tablets and compositions to which MP had been added are displayed in Fig. 6A–D. Two sets of profiles from batches A and B are shown, where the erosion rate of the polymer seems to depend only on the shear rate applied. Thus the erosion from pure polymer tablets was the same as the erosion rate from compositions to which MP had been added. Furthermore, as pointed out earlier, the difference between the erosion rates at the two paddle speeds were only minor, hence only a 5 h difference was observed between fully dissolved tablets at 50 rpm compared to at 100 rpm. In contrast, even without the addition of MP, tablets of batch C and D were much more affected by the applied shear rate and there was a time difference of 40 h between fully dissolved tablets at the two paddle speeds. Furthermore, a comparison of pure polymer systems with compositions to which MP had been added shows that the erosion rate of batches C and D was clearly affected by the addition of MP and that the polymer erosion increased from these tablets (Table 3). This was most obvious in compositions of batch D at the higher paddle speed where the erosion rate of the HPMC suddenly increased in comparison to the erosion rate from pure systems after about 7 h and dual erosion rates were obtained.

It has been illustrated that the erosion rate of the heterogeneously substituted batches was lower and more dependent on the shear rate as compared to the more homogeneous batches. This might be explained by the fact that the reversible gel structures formed in the matrix of the heterogeneously substituted batches were more resistant to lower shear rates, as indicated by the viscosity measurements. Thus, at lower shear rates, a less steep

polymer concentration gradient would be formed in the gel layer of the matrix tablet. However, at an increased paddle speed, the erosion front would have to move a larger distance to resist the increased shear, and this would then give fairly large differences in erosion rates between the two paddle speeds, as was observed in the present study. Moreover, there was an indication that the erosion rate of batches C and D was affected to a greater extent by the addition of MP to the tablets. The explanation here is that MP may have interfered with the formation of the reversible gel structure in the tablets. It has been shown that parabens has the ability to create hydrogen bonding between the hydrogen of the phenolic hydroxy group and the oxygen group in the ether groups of the polyoxyethylene chain (Blaug and Ahsan, 1961); thus it is likely that the parabens would also interact with the cellulose chain. Thus, the longer unsubstituted segments might have facilitated this bonding and, for this reason, the more heterogeneously substituted batches might have been able to interact to a greater extent. This would then have interfered with the reversible gel-like structures formed in the gel of the matrix tablets, which could have made the gel more susceptible to erosion and would explain the faster polymer release from these compositions. It is clear from the results of the present study that matrix tablets composed of HPMC batches of the same pharmaceutical grade with different substituent heterogeneities released MP at different rates and with different mechanisms. However, the present study also indicated that these batches were able to interact with MP to different extents, which might indicate that other drug molecules would be able to interact with the various chemical structures of HPMC and hence affect the release behaviour differently.

4. Conclusion

This is the first study that has shown how differences in substituent heterogeneity between HPMC batches of the same pharmaceutical grade affect drug release from hydrophilic matrix tablets. Batches with longer segments of low substituted regions and a lower HPO content facilitated reversible gel-like structures that decreased the polymer erosion in matrix tablets. This lower erosion rate then decreased the drug release rate and released the drug by a more diffusion based release mechanism. However, even though the most heterogeneously substituted batches decreased the rate of drug release, it was observed that the polymer erosion was more affected by the paddle speed and the drug content in the matrix. This indicates that the gel-like structures might affect the robustness of the gel layer function in matrix tablets. Thus, it can be concluded from the present study that extensive polymer characterisation is required to obtain predictable drug release rates from matrix tablets composed of HPMC batches.

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References

Alderman, D.A., 1984. A review of cellulose ethers in hydrophilic matrixes for oral controlled-release dosage forms. International Journal of Pharmaceutical Technology & Product Manufacture 5, 1–9.

Andersson, T., Richardsson, S., Ericksson, M., 2003. Determination of the hydroxypropoxy content in hydroxypropyl cellulose by ^{1}H NMR. Pharmeuropa.

Blaug, S., Ahsan, S., 1961. Interactions of parabens with nonionic macromolecules. Journal of Pharmaceutical Sciences 50, 441–443.

Bonferoni, M.C., Rossi, S., Ferrari, F., Bertoni, M., Sinistri, R., Carmella, C., 1995. Characterization of three hydroxypropyl methyl cellulose substitution types. Rheological properties and dissolution behavior. European Journal of Pharmaceutics and Biopharmaceutics 41, 242–246.

Colombo, P., Bettini, R., Santi, P., De Ascentiis, A., Peppas, N.A., 1996. Analysis of the swelling and release mechanisms from drug delivery systems with emphasis on drug solubility and water transport. Journal of Controlled Release 39, 231–237.

Dahl, T.C., Calderwood, T., Bormeth, A., Trimble, K., Piepmeier, E., 1990. Influence of physico-chemical properties of hydroxypropyl methylcellulose on naproxen release from sustained release matrix tablets. Journal of Controlled Release 14, 1–10.

De Gennes, P.G., 1979. Scaling Concepts in Polymer Physics. Cornell Univ. Press, Ithaca, NY.

Gao, P., Skoug, J.W., Nixon, P.R., Ju, T.R., Stemm, N.L., Sung, K.-C., 1996. Swelling of hydroxypropyl methylcellulose matrix tablets. 2. Mechanistic study of the influence of formulation variables on matrix performance and drug release. Journal of Pharmaceutical Sciences 85, 732–740.

Haque, A., Morris, E.R., 1993. Thermogelation of methylcellulose. Part I. Molecular structures and processes. Carbohydrate Polymers 22, 161–173.

Haque, A., Richardson, R.K., Morris, E.R., Gidley, M.J., Caswell, D.C., 1993. Thermogelation of methylcellulose. Part II. Effect of hydroxypropyl substituents. Carbohydrate Polymers 22, 175–186.

Hirrien, M., Desbrieres, J., Rinaudo, M., 1996. Physical properties of methylcellulose in relation with the conditions for cellulose modification. Carbohydrate Polymers 31, 243–252.

Ju, R.T.C., Nixon, P.R., Patel, M.V., 1995. Drug release from hydrophilic matrices. 1. New scaling laws for predicting polymer and drug release based on the polymer disentanglement concentration and the diffusion layer. Journal of Pharmaceutical Sciences 84, 1455–1463.

Karlsson, J., Momcilovic, D., Wittgren, B., Schülein, M., Tjerneld, F., Brinkmalm, G., 2002a. Enzymatic degradation of carboxymethyl cellulose hydrolyzed by the endoglucanases Cel5A, Cel7B, and Cel45A from Humicola insolens and Cel7B, Cel12A and Cel45Acore from *Trichoderma reesei*. Biopolymers 63, 32–40.

Karlsson, J., Siika-Aho, M., Tenkanen, M., Tjerneld, F., 2002b. Enzymatic properties of the low molecular mass endoglucanases Cel12A (EG III) and Cel45A (EG V) of *Trichoderma reesei*. Journal of Biotechnology 99, 63–78.

Kavanagh, N., Corrigan, O.I., 2004. Swelling and erosion properties of hydroxypropylmethylcellulose (Hypromellose) matrices—influence of agitation rate and dissolution medium composition. International Journal of Pharmaceutics 279, 141–152.

Lapidus, H., Lordi, N.G., 1968. Drug release from compressed hydrophilic matrices. Journal of Pharmaceutical Sciences 57, 1292–1301.

Melander, C., 2006. New methods for enzyme hydrolysis, analysis, and characterization of modified cellulose. In: Analytical Chemistry. Lund University, Lund.

Neely, W.B., 1963. Solution properties of polysaccharides. IV. Molecular weight and aggregate formation in methylcellulose solutions. Journal of Polymer Science Part A 1, 311–320.

Pharmacopoeia, E. (Ed.), 2006. European Pharmacopoeia. Council of Europe, cop, Strasbourg.

Reynolds, T.D., Gehrke, S.H., Hussain, A.S., Shenouda, L.S., 1998. Polymer erosion and drug release characterization of hydroxypropyl methylcellulose matrices. Journal of Pharmaceutical Sciences 87, 1115–1123.

Richardson, S., Gorton, L., 2003. Characterisation of the substituent distribution in starch and cellulose derivatives. Analytica Chimica Acta 497, 27–65.

Sarkar, N., 1979. Thermal gelation properties of methyl and hydroxypropyl methylcellulose. Journal of Applied Polymer Science 24, 1073–1087.

Schagerlof, H., Johansson, M., Richardson, S., Brinkmalm, G., Wittgren, B., Tjerneld, F., 2006. Substituent distribution and clouding behavior of hydroxypropyl methylcellulose analyzed using enzymatic degradation. Biomacromolecules 7, 3474–3481.

Schagerlöf, H., 2006. Enzymatic Hydrolysis of Cellulose Derivatives. Active Site Studies and Polymer Characterisation. Department of Biochemistry, Lund University, Lund.

Silva, S.M.C., Pinto, F.V., Antunes, F.E., Miguel, M.G., Sousa, J.J.S., Pais, A.A.C.C., 2008. Aggregation and gelation in hydroxypropylmethyl cellulose aqueous solutions. Journal of Colloid and Interface Science 327, 333–340.

Takahashi, S.-I., Fujimoto, T., Miyamoto, T., Inagaki, H., 1987. Relationship between distribution of substituents and water solubility of O-methyl cellulose. Journal of Polymer Science Part A: Polymer Chemistry 25, 987–994.

USP29-NF24, U.S.P., 2003. United States Pharmacopeia.

Viriden, A., Larsson, A., Wittgren, B., 2010. The effect of substitution pattern of HPMC on polymer release from matrix tablets. International Journal of Pharmaceutics 389, 147–156.

Viriden, A., Wittgren, B., Andersson, T., Abrahmsen-Alami, S., Larsson, A., 2009a. Influence of substitution pattern on solution behavior of hydroxypropyl methylcellulose. Biomacromolecules 10, 522–529.

Viriden, A., Wittgren, B., Andersson, T., Larsson, A., 2009b. The effect of chemical heterogeneity of HPMC on polymer release from matrix tablets. European Journal of Pharmaceutical Sciences 36, 392–400.