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The effect of substitution pattern of HPMC on polymer release from matrix tablets

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ABSTRACT

The purpose of this study was to gain further understanding of how the substituent heterogeneity of hydroxypropyl methylcellulose, HPMC, affects the polymer release from hydrophilic matrix tablets. The hypothesis was that the heterogeneous substituent pattern facilitated hydrophobic interactions that increased the viscosity and therefore affected the release rate to a major extent. Polymer tablets were prepared from three heterogeneously substituted HPMC batches of the same substituent (2208) and viscosity (100 cps) grade. To elucidate the hypothesis, fractions of both the dissolved polymer and the tablet residue were collected from the dissolution bath and further characterised. The extensive characterisation showed that, although the dissolved bath fraction and the tablet residue had a similar average degree of substitution, the residue was more heterogeneously substituted. It was further revealed that the heterogeneous substituent pattern of the tablet residue facilitated the formation of soluble gel-like components already at room temperature, which increased the viscosity. The viscosity increased by 150% at temperatures correlated to the dissolution bath, and it was thus concluded that the gel-like components grew in size with temperature. Finally, much lower release rates were obtained by tablets composed of the residue compared to tablets composed of the bath fraction, which clarified the hypothesis.

1. Introduction

One way to achieve an oral extended release formulation is by mixing the drug substance and the additives with a hydrophilic polymer and compressing this into a matrix tablet. The dissolution process of the solid matrix tablet is usually described by two moving boundaries that arise and disappear during different stages of the process (Colombo et al., 2000). The first boundary is established after the solution has entered the tablet and the dry polymer has transitioned into a highly concentrated polymer solution, which in this context is referred to as a gel. The first boundary can thus be found between the solid material and the gel layer, while the second boundary separates the gel layer from the diluted surrounding solution. The polymer concentration at the gel/solution border is referred to as the critical concentration, c_{crit} (Ju et al., 1995; Körner, 2006; Ueberreiter and Asmussen, 1962). This concentration is assumed to correspond to the lowest concentration at which the polymer chains can withstand the surrounding shear forces without being released. Depending on what polymer is used, c_{crit} varies and hence also the gel layer's thickness and the dissolution rate of the tablet. Because the release rate of the drug is determined either by its diffusion through the gel layer or by the polymer erosion, it is important to find and understand the functional related characteristics of the polymer being used.

Hydroxypropyl methylcellulose, HPMC, is a common matrix former in hydrophilic matrix tablets. HPMC is a cellulose derivative, consisting of a backbone of cellulose with methoxylic and hydroxypropoxylic moieties substituted onto the glucose units. The solution properties of HPMC can be altered by changing the molar mass and/or the degree of substitution and thus in the case of pharmaceutically approved HPMC, there are different substituent and viscosity grades commercially available (Kibbe, 2000; Pharmacopoeia, 2008; USP29-NF24, 2008). For a linear polymer, c_{crit} is related to the molecular weight (Ueberreiter and Asmussen, 1962), where a higher molecular weight is expected to give a lower c_{crit}. The average molecular weight is related to the viscosity, and c_{crit} can therefore be controlled by using different viscosity grades. However, the solution properties of HPMC are also affected by the degree of substitution. Hence, to obtain the desirable gel layer thickness and release rate, both the molecular weight and the degree of substitution must carefully be balanced. However, control of the release rate by a proper selection of grades has not always been achieved, and batch-to-batch variations within grades have been reported (Dahl et al., 1990; Viriden et al., 2009a). This to some extent be explained by the broad specifications for commercial grades, allowing rather large variability in parameters such as

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the viscosity and the degree of substitution (Pharmacopoeia, 2008; USP29-NF24, 2008). Furthermore, chemical data given by the specifications are average and do not cover variations in the distributions of either the molar mass or the degree of substitution.

Another parameter of HPMC that recently was found to be an important characteristic for matrix tablets was the substituent pattern (Viriden et al., 2009a). In that study Viriden et al. related the polymer release from pure polymer tablets composed of seven HPMC batches of the same substituent (USP 2208) and viscosity (100 cps) grade, to the chemistry of the HPMC batches. It was shown that the polymer release rates correlated to the substituent distribution analysed by enzymatic hydrolysis, where the most heterogeneously substituted batches obtained the lowest release rates. This former study indicated that the differences in the substituent pattern of HPMC affected the interactions between the polymer chains in the solution and that these interactions altered the c_{crit} and thus the release rates. Although the study elucidated the influence of the substituent pattern on the release rate, more studies are needed to clarify the underlying mechanism behind the particularly slow dissolution of the heterogeneously substituted batches. For this purpose, the intriguing question must be addressed of whether the proposed polymer interactions affecting c_{crit} are due to hydrophobic interactions between highly substituted regions of different chains or whether the effect on the dissolution rate is obtained as a consequence of insoluble aggregates of partly crystalline structure. Therefore, in the present study, both dissolved and undissolved tablet material was collected from the dissolution bath and further analysed with respect to size, degree of substitution, substituent pattern and solution properties.

2. Materials and methods

2.1. Materials

Three HPMC batches of the same substituent grade (USP 2208) and viscosity grade (100 cps) were supplied by Shin-Etsu (Metolose 90SH100 from Shin-Etsu Chemical Co., Ltd. Tokyo, Japan) and Dow (Dow Chemical Co., USA) under the trade names 90SH100 and K100LV, respectively.

2.2. Desalting of the fractionated bath material

The bath fractions collected were dialyzed against deionised water in a Spectra/Por dialysis membrane (with a molar mass cut-off at 10 kDa) for 24 h. The samples were then freeze dried (VirTis Advantage xL, USA) before the upcoming measurements.

2.3. Molar mass and radius of gyration

The molar mass was analysed using 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 Corp., 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). This instrument set-up makes it possible to determine the molar mass and the radius of gyration at each eluted fraction, which provides a distribution of the molar mass and the radius as well as different averages of these two (Wyatt, 1993).

The sample concentration was 0.4 mg/ml or 0.5 mg/ml in 10 mM NaCl, and the dry polymer was diluted in mobile phase for 48 h before analysed. 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 10 mM NaCl with 0.02% NaN_3 and the volume of the injected sample was 100 μl. The same system set-up was used to examine the solubility of the compact conformations, where the temperature of the mobile phase and the column was set to 5 °C and 37 °C, respectively. The reported average molar weights are an average of three repeated analyses. The software used to process the data was Astra 4.90.07 (Wyatt Technology, Santa Barbara, CA, USA).

2.4. Degree of substitution

The degree of substitution was determined in acetylated samples with proton Nuclear Magnetic Resonance (^{1}H NMR). The samples were aceylated by dissolving 75 mg of each of the polymer samples in 2.25 ml acetic anhydride and 0.75 ml pyridine. The solutions were heated to 90 °C under stirring for 6 h and then dialyzed against deionised water in a Spectra/Por dialysis membrane (with a molar mass cut-off at 10 kDa) for 24 h. The samples were dried before being dissolved in deuterated chloroform (0.8 mg/ml). The ^{1}H NMR measurements were carried out in a Varian 600 MHz Inova instrument operating at 14.09 T. The NMR instrument was equipped with a 5 mm Nalorac triple resonance probe. The ^{1}H NMR measurement was carried out using a flip angle of 45° with an acquisition time of 4 s and a delay time of 10 s. The spectral width was at least between −3.5 and 10.4 ppm with reference to the solvent peak of CDCl3 (7.26 ppm), and 16 transients were obtained for each sample. A line broadening factor of 0.3 Hz was used. The delay time between the pulse and the acquisition was optimised to give a zero first-order phase shift. The spectra were collected using oversampling with AnalogPlus as the digital filter. All spectra were recorded at 50 °C. The weight percentage of methoxyl (MeO) groups and hydroxypropoxy (HPO) groups were calculated according to the following formula:

$$\mathrm{MeO\%} = \frac{(31 \cdot \mathrm{DS} \cdot 100)}{(58 \cdot \mathrm{MS} + 162 + 14 \cdot \mathrm{DS})},$$
$$\mathrm{HPO\%} = \frac{(75 \cdot \mathrm{MS} \cdot 100)}{(58 \cdot \mathrm{MS} + 162 + 14 \cdot \mathrm{DS})} \quad (1)$$

where DS, degree of substitution, and MS, molar substitution, are achieved through the spectra according to a slight modification of the methods described by Andersson et al. (2003) and Fitzpatrick et al. (2006).

2.5. Acid hydrolysis

Acid hydrolysis was performed in the samples using trifluoroacetic acid (2 M). The solutions (10 mg/ml) were hydrolysed for 16 h with stirring and heating (100 °C). The acid was then evaporated over 8–10 h using N_2. The hydrolysed products were dissolved in 3 ml of water, and 30 μl were removed for further water dilution to a total volume of 2 ml (0.05 mg/ml). Released glucose was detected using 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 0.8 ml/min using a gradient programme with 150 mM NaOH and 500 mM NaOAc prepared in 150 mM NaOH.

2.6. Enzymatic hydrolysis

Enzymatic degradation was carried out in the batches to compare the homogeneity of the substituent groups across the polymer backbone. The samples were dissolved in 5 mM NAOAc (pH 5.0) to a concentration of 1 mg/ml. 20 U of an endoglucanase enzyme

(EGII from *Trichoderma longibrachiatum*) from Megazyme (Bray, Ireland) were added to 2 ml of HPMC solution, and the hydrolysis was carried out in a shaking water bath at 37 °C for 48 h. The amount of glucose units released was detected in the HPAEC-PAD system described above.

2.7. Cloud point

The phase behaviour of the polymer solutions was determined by light transmission in a Mettler Toledo FP90 Central Processor, Mettler FB81C MBC combined with the IPClab software (Switzerland). The measurements were made in phosphate buffer ($I = 0.1$, pH 6.5) in 1% (w/w) polymer solutions, and the temperature was raised by 1 °C/min. The light transmittance through the polymer solutions was normalised to 100% at the starting temperature. To characterize the clouding behaviour of the polymers, two different temperatures (cloud point temperatures) were determined, CP50 and CP96, which refer to the temperatures at which the transmittance decreased to 50% and 96%, respectively. The reported average values are based on three measurements.

2.8. Rheology

Flow curves were recorded for the selected samples using an Anton Paar Physica MCR 500 rheometer (Germany) equipped with a double gap cylinder with external and internal radius of 13.33 and 12.33 mm, respectively. HPMC solutions of 5% (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 both 23 and 37 °C and the solutions were allowed to equilibrium at respective temperature for 1 h before measurements. The reported average values are based on three measurements.

2.9. Tabletting

A single punch tabletting machine (Kilian SP300, Kilian&Co GmbH, Germany) was equipped with 12 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 315 ± 1 mg.

2.10. Polymer release

The release of the polymer 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. The tablets were fixed in baskets (2.5 cm × 2.5 cm × 1 cm, 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 polymer released from two tablets was analysed and averaged.

The polymer concentrations in the release medium were determined using the SEC–MALS/RI procedure as described above, except that the mobile phase was 0.1 M phosphate buffer ($I = 0.1$, pH 6.8) with 0.02% NaN_3.

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

$$\%\text{Released} = \left(\frac{c_n \times (V_0 - V_s(n-1)) + V_s \sum_{n=0}^{n-1} C_n}{w_{tb1}} \right) \times 100 \qquad (2)$$

where c_n is the concentration in the sample n, V_0 is the initial volume in the beaker, V_s is the sample volume and w_{tbl} is the weight of the dry tablet.

3. Results and discussion

The substituent pattern of HPMC has previously shown to affect the dissolution rate of pure polymer tablets, where the dissolution rate decreased with increased heterogeneity (Viriden et al., 2009a). Polymer tablets of the analysed grade (USP 2208, 100 cps) are normally found to be totally dissolved within 10–30 h dependent on the shear rate applied (Dahl et al., 1990; Körner, 2006; Tajarobi et al., 2009; Viriden et al., 2009a). However, the most heterogeneously substituted polymer batches were not totally dissolved within 150 h and thus a dramatic batch-to-batch variation was demonstrated (Viriden et al., 2009a). Furthermore, the former study revealed after an analysis with a SEC/MALS-RI instrument, that the heterogeneously substituted batches contained a few percentages of components that had a more compact conformation in solution. The hypothesis was that they were formed as a result of the heterogeneous substituent pattern and affected the c_{crit} at the gel/solution border, and hence contributed to the exceptionally slow polymer release. However, it was questioned whether that small amount of compact components could affect the dissolution rate to that extent.

In a more recent study, it was seen that the viscosity of solutions of heterogeneously substituted HPMC batches increased as the temperature was raised, and it was suggested that these batches formed reversible gel-like components before complete phase separation (Viriden et al., 2009b). These results indicate that the compact components found in the SEC/MALS-RI were microdomains of gel-like structures formed as a consequence of the heterogeneous substituent pattern already at very dilute solutions. Therefore, the hypothesis for the present study is that at higher polymer concentrations, like in the gel of the matrix tablets, a more coherent gel-like network would be formed, increasing the viscosity and thus decreasing the release rate to a major extent. An investigation of the proposed hypothesis would give a deeper mechanistic understanding of the release behaviour of heterogeneously substituted HPMC batches. Consequently, we wished to elucidate the influence of the components that have a compact conformation and also clarify the nature of these. Therefore, further characterisation studies were conducted on three heterogeneously substituted batches (A–C) (Table 1), which obtained a remarkably slow release in the former study (Viriden et al., 2009a).

3.1. Chemical characterisation

It was thought that the extreme dissolution times of more than 150 h might result in an enrichment of polymers that possess properties that are critical for the dissolution rate. Therefore, both the tablet residue and the dissolved bath material left in the dissolution bath after 100 h were collected and further characterised. After 100 h, there was approximately 20% (w/w) left of the tablets from batches A and C and 7% (w/w) left of the tablets from batch B (Table 1). To get a sufficient amount of material to characterise.

3.1.1. Molecular weight

HPMC is based on cellulose that has been processed to various chain lengths covering several orders of magnitude in molecular weight; thus all batches available on the market are quite polydisperse. The molecular weight distributions and the average molecular weight were characterized in the present study using SEC-MALS/RI. The molecular weight distributions of the original batches had a polydispersity index (P.I.) of approximately 2 (Table 1) and there were no signs of any bimodal distribution

Table 1
Polymer characteristics of the three HPMC batches and their bath and residue fractions.

Sample	% (w/w) of tablet residue (100 h)	M_w[a] ($\times 10^4$ (g/mol))	P.I.[a]	Cp[a] at 96% transmittance (°C)	Cp[a] at 50% transmittance (°C)	% MeO[b]	% HPO[b]	% (w/w) glucose (acid hydrolysis[c])	% (w/w) glucose (enzymatic hydrolysis[c])
A		10.4 (0.2)	2.2 (0.2)	66.3 (0.1)	79.7 (0.7)	24.6	7.0	8.4 (0.0)	1.4 (0.1)
Residue A	20	19.1 (0.2)		65.9 (0.0)	91.6 (1.2)	23.4	6.3	9.5 (0.0)	1.5 (0.0)
Bath A		8.8 (0.7)		65.8 (0.5)	73.0 (0.3)	24.4	6.9	7.5 (0.0)	1.0 (0.0)
B		9.1 (0.0)	1.9 (0.2)	63.6 (0.8)	77.9 (0.1)	24.1	6.6	8.9 (0.0)	1.2 (0.1)
Residue B	7	16.5 (0.2)		69.5 (0.1)	91.9 (0.6)	22.2	6.5	11.0 (0.0)	1.9 (0.1)
Bath B		9.0 (0.2)		59.1 (0.7)	74.0 (0.4)	24.4	6.9	8.2 (0.0)	1.2 (0.0)
C		10.2 (0.2)	1.9 (0.2)	67.4 (0.3)	78.6 (0.2)	24.0	7.4	8.6 (0.0)	1.4 (0.1)
Residue C	17	24.5 (0.4)		66.5 (0.3)	84.3 (0.4)	23.0	7.0	10.7 (0.0)	1.7 (0.0)
Bath C		8.9 (0.7)		64.1 (0.9)	74.4 (0.2)	24.0	7.4	8.0 (0.0)	1.0 (0.2)

[a] The results given are mean values and corresponding standard deviations are shown in parentheses (n = 3).
[b] RSD of 0.02 according to an in-house validation.
[c] The results given are mean values and corresponding deviations from the mean value are shown in parentheses (n = 2).

(Fig. 1). Analysis of the molecular weight distributions showed that the distributions of the residue and the dissolved bath material partly overlapped with the distribution of the original material. However, the distribution of the tablet residue from all three samples shifted towards higher molecular weights. As a result, the average molecular weight was almost twice as high for the tablet residue compared to both the original material and the dissolved tablet material (Table 1, Fig. 2). As a consequence of the higher average molecular weight of the tablet residue, the dissolved tablet material had a slightly lower average molecular weight than the original material (Table 1, Fig. 2).

A few theoretical models assume that the polymer is released by diffusion through the gel layer and that this so-called reptation is the rate-limiting step in the dissolution process (Miller-chou and Koenig, 2003; Narasimhan and Peppas, 1997). Since shorter molecules have faster diffusion than longer chains, a fractionation due to size would be expected from a polydisperse sample. However, this was not found by Körner et al. after they mixed different viscosity grades (6 and 10,000 cps) of HPMC (USP 2910) in various combinations and pressed these into polymer tablets (Körner, 2006). They found that, even though the P.I. was more than three times higher than in the present study, the release rate was the same for both the high and low molecular weight chains in each formulation. Their interpretation was that the polymer components did not move significantly relative to each other during the transport to the erosion front and they therefore claimed that the water penetration into the tablet was the rate-limiting step. In contrast, there was fractionation due to size in the present study, even though the tablets were made from less polydisperse material. However, the relevant question is rather why these extremely low release rates were obtained, since it seems unlikely that this only was a result of the polymer size.

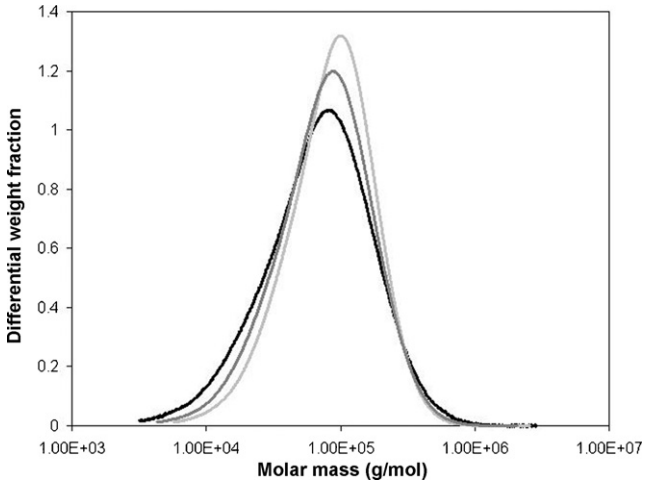

Fig. 1. Molecular weight distributions of the three original batches. Black: batch A; dark grey: batch B; light grey: batch C.

Another parameter known to affect the release rate of hydrophilic matrix tablets is the degree of substitution (Alderman, 1984; Bonferoni et al., 1995; Dahl et al., 1990; Velasco et al., 1998), where batches of the 2208 grade having a lower HPO content displayed lower release rates (Dahl et al., 1990). The polymer batches used for the present study were selected because they were found to be quite heterogeneously substituted, having more frequently occurring unsubstituted regions compared to four other HPMC batches of the same grade (Viriden et al., 2009a). The results obtained by the former study, does not distinguish in-between non-uniform substitution in between different chains or heterogeneous substitution pattern along the chain. Therefore, to elucidate how the substitution varied in-between the residue and the dissolved bath sample the fractions were further characterised.

3.1.2. Degree of substitution

The average degree of substitution was determined with ^{1}H NMR and the degree of substitution of the original batches were all quite similar, with a methoxylic (MeO) content of around 24% (w/w) and a hydroxypropoxylic (HPO) content of around 7% (w/w) (Table 1). These values reflected an approved USP 2208 grade where the amount of MeO groups was positioned in the upper region and the amount of HPO in the lower middle section. The bath and the residue fractions all had average values fairly similar to those of the original material, even though the tablet residue displayed somewhat lower average values in both the MeO and HPO content (Table 1). The extremely slow dissolution rates obtained for these batches cannot be explained by fractions having a different degree of substitution, neither of the MeO nor the HPO. Furthermore, since the fractions were almost equally substituted, the results did not reveal any non-uniform substitution within the batch, and thus the distributions of the substituents were further characterised.

3.1.3. Acid hydrolysis

A complete hydrolysis of the samples in 2 M THF with a subsequent analysis using an HPAEC-PAD system makes it possible to characterise the glucose units liberated from the sample. The amount of unsubstituted glucose units was characterised in this process, which provides an indication of how the substituents are distributed among the glucose units. It was reported in the previous study (Viriden et al., 2009a) that the amount of unsubstituted glucose units from the original batches was higher than expected, considering the substitution to be a random process. Even

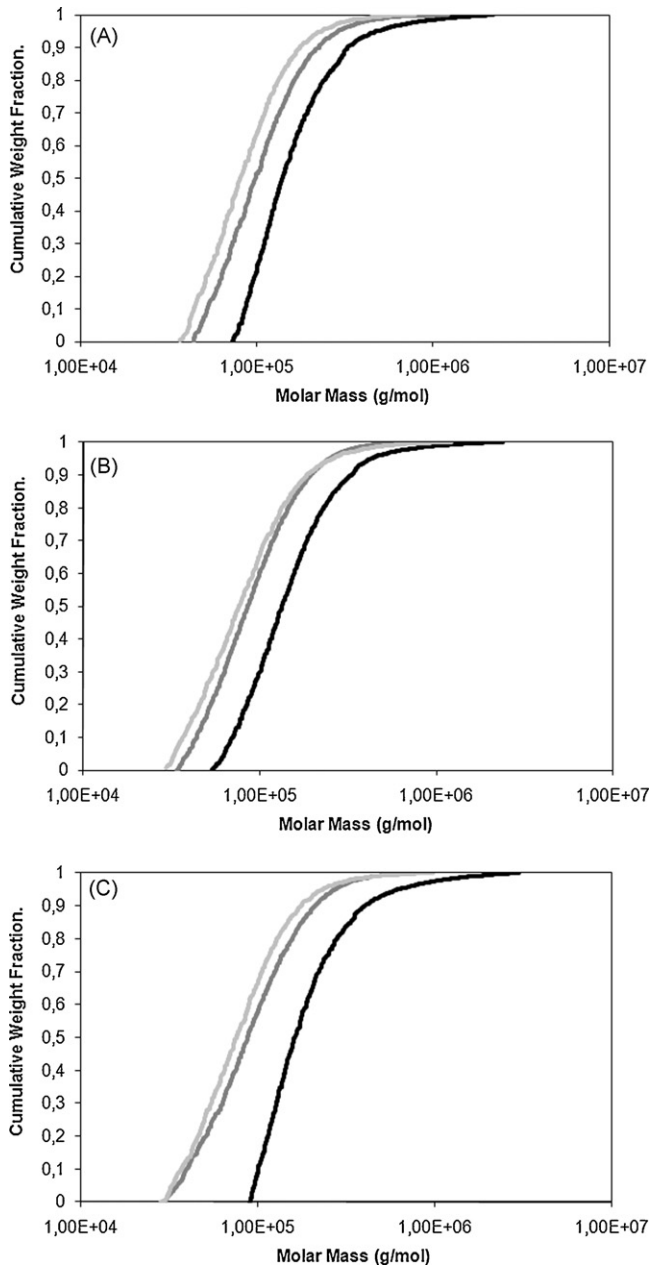

Fig. 2. Molecular weight distributions of the three samples and their fractions. (A) Batch A; (B) batch B; (C) batch C. Black: tablet residue; dark grey: original batch; light grey: bath sample.

though there were only small differences in the average amounts of MeO and HPO between the fractions and the original material, the amount of unsubstituted glucose units from the three tablet residues was a few percent higher than in the original material (Table 1). Since both bath and residue fractions were collected from the original sample, the lower amount of unsubstituted glucose units obtained from the dissolved bath samples was to be expected (Table 1). The higher amount of unsubstituted glucose units liberated from the tablet residue indicates that the substituents were more heterogeneously spread among the glucose units compared to the rest of the sample. Furthermore, a higher amount of unsubstituted glucose units would increase the possibility of having regions that are more or less abundant on substituents along the parent polymer chain. A more specific hydrolysis had to be performed to clarify how the unsubstituted glucose units were distributed along the chain.

3.1.4. Enzymatic hydrolysis

There are various cellulose degrading enzymes used in order to investigate the distribution of the substituents along the chain of cellulose derivatives (Richardson and Gorton, 2003; Schagerlöf, 2006; Schomburg and Salzmann, 1991). Endoglucanases catalyze the hydrolysis of (1 → 4) β-D-glucosidic linkage in cellulose, and the requirement for enzymatic hydrolysis to occur is that the active site of the enzyme can bind a certain number of unmodified glucose units in order to form the essential enzyme–substrate complex (Schomburg and Salzmann, 1991). The presence of substituents on the glucose units, as in the case of HPMC, can cause steric hindrance to the complex and thus restrict hydrolysis (Mischnick et al., 2000). The endoglucanase, *Trichoderma longibrachiatum*, used in this study needs at least two unsubstituted glucose units in order to bind to the cellulose chain, although there are reports indicating that longer parts of unsubstituted regions are preferred by the enzyme (Schagerlöf, 2006). The enzyme's preference for unsubstituted sections makes it possible to study the substituent pattern of the different samples by analysing the amount of glucose units released. The more glucose units that are released, the more heterogeneous are the substituents spread along the chains. The tablet residue from all three batches liberated about 50% more glucose units than the dissolved bath fractions (Table 1). This means that the tablet residue consisted of more frequently occurring unsubstituted parts, and since they were similarly substituted, it can also be concluded that they consisted of regions that were more substituted. The hypothesis was that the heterogeneous substituent pattern gave rise to polymer interactions that affected the release rate from matrix tablets. The even more heterogeneous substituent pattern of the tablet residue further supports that hypothesis, hence the solution properties had to be characterised.

3.2. Solution behaviour

3.2.1. Conformation

As for all other polymers, the conformation of the coil is dependent on the chemistry of the chain and the interactions with the specific solvent at a specific temperature (Cowie, 2001; Richards, 1980). The conformation can be characterised by analysing how the radius varies with the molecular weight. For a flexible polymer, the logarithm of the radius of gyration versus the logarithm of the molecular weight should increase linearly throughout the molecular weight distribution with a slope of $\geq$0.5 (Richards, 1980). This relationship was obtained for the three original batches at the lower molecular weights (Fig. 3). However, at molecular weights above 400 000 g/mol, the slope of the radius versus the molecular weight decreased to a slope of <0.2. This indicated that the conformation of the polymer coils become more compact at the higher molecular weights, raising the question of whether such compact conformations could be representations of some kind of aggregates. The tablet residue from all three batches, which consisted of the higher molecular weight parts, showed the same compact conformations as the original material (Fig. 3). The conformation of the dissolved bath material was similar to that of the original sample, which can be explained by that the material in these fractions corresponds to 80–90% (w/w) of the original batch (Fig. 3).

A larger part of the tablet residue from all three batches consisted of the higher molecular weight parts, which showed a more compact conformation compared to the polymers in the lower molecular weight parts of the distribution. Therefore, from these results it can be concluded that the compact components were enriched in the tablet residue. In addition, since it is likely that these compact components consisted of some kind of aggregates; the results further indicate that the fractionation obtained in the dissolution bath was not solely caused by a molecular weight difference but rather due to a difference in chemical structure. To clarify

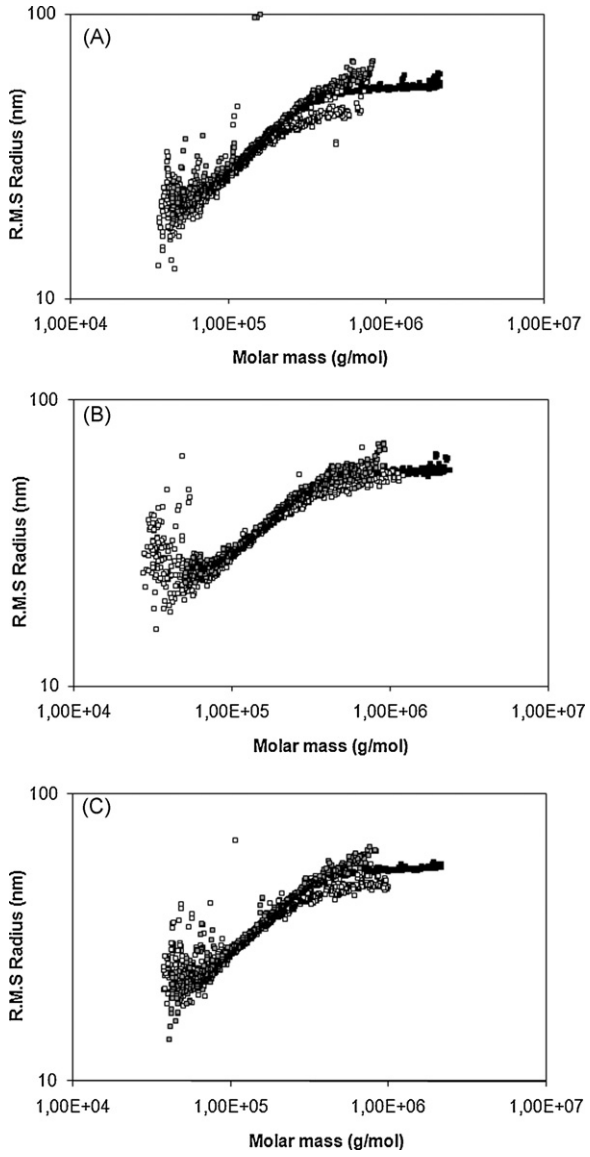

Fig. 3. Conformation plots of the fractions obtained from the three batches. (A) Batch A; (B) batch B; (C) batch C. Black: tablet residue; dark grey: original batch; white: bath sample.

the hypothesis of the present study, the nature of the compact components had to be characterised.

The tablet residue was more heterogeneously substituted, having more unsubstituted glucose units, and thus one explanation would be incomplete substitution during production, resulting in fractions with partly crystalline structures. These have been detected in different cellulose based materials (Andersson et al., 2001; Burchard, 2003; Schulz et al., 1998; Wittgren and Porsch, 2002) as fractions with ultra high molecular weight (Andersson et al., 2001) or/and compact conformation (Burchard, 2003; Schulz et al., 1998; Wittgren and Porsch, 2002). In some contexts aggregates of partly crystalline structures have been referred to as fringed micelles, which have been described as a micelle where the interior consists of insoluble crystalline cellulose with soluble substituted arms towards the solution (Burchard, 2003; Schulz et al., 1998). These structures would be partly soluble and would in the SEC-MALS/RI instrument be seen as components with a more compact conformation.

Another explanation for the compact conformations would be interactions formed between the substituents. These hydrophobic interactions have for example been noticed as gelation upon increased temperature, which is explained by that the solubility of many cellulose derivatives decreases with increasing temperature (Sarkar, 1979). The hydrophobic interactions have especially been observed in samples of methylcellulose (Haque and Morris, 1993; Neely, 1963; Sarkar, 1979), where for example Neely decreased the observed average molecular weight from 200 000 to 120 000 by decreasing the temperature (Neely, 1963). However, this author also showed that by introducing 3% hydroxypropyl groups, the molecular weight did not alter to the same extent, which was explained by that the hydroxypropyl groups prevented the aggregation through steric reasons (Neely, 1963). A previous study by our group showed that a heterogeneous substituent pattern would increase the possibility of HPMC to form more hydrophobic interactions even though the hydroxypropyl groups exceeded 7%, and it was shown that heterogeneously substituted batches formed a gel structure upon temperature increase (Viriden et al., 2009b). If the compact components were domains of gel-like structures created by hydrophobic interactions, their solubility, in contrast to fringed micelles, would have a temperature dependency, displaying higher solubility at lower temperatures. Therefore, one way to examine the solubility of the compact components would be to alter the temperature of the polymer solutions.

Fig. 4 shows chromatograms of the tablet fractions and the original samples, with both the RI and MALS signal. The analyses were performed at two additional temperatures, 37 and 5 °C, respectively. When the temperature was increased to 37 °C, corresponding to the temperature in the dissolution bath, the distribution of the MALS signal of the tablet residue from all three batches was seen to be quite wide with a bimodal shape. Furthermore, the bimodal distribution of the tablet residue shifted towards an earlier elution, which indicated the existence of larger molecules. There was an indication of larger molecules in both the original material and in the dissolved bath material, but not at all to the same extent as in the tablet residue. At a decreased temperature the bimodal appearance of the MALS signal of the tablet residues was almost completely removed. These results are quite astonishing since they indicate that not only is the major part of these aggregates soluble but they are also formed at temperatures considerably lower than the expected precipitation temperature of a 2208 grade, which according to one of the producers should be around 60 °C for a 2% polymer solution. To further elucidate the phase behaviour of these fractions, clouding curves were obtained.

3.2.2. Clouding curve

When a HPMC solution starts to phase separate upon heating, light scattering objects are formed by the polymer-rich phase and the solution becomes turbid. The temperature at which this occurs is generally referred to as the cloud point temperature. A clouding curve can be obtained by measuring how the light transmittance through the polymer solution is reduced with increasing temperature. Such clouding curves were obtained for the three batches and their fractions (Fig. 5). The initial transmittance decrease started at the expected temperature interval of 60–70 °C for all samples, thus giving a similar cloud point temperature at 96% transmittance (Cp96) (Table 1). The aggregates were already detected at room temperature in the SEC/MALS-RI instrument; thus one would have expected a lower CP96 from the tablet residue. The lack of such a result might be explained by the amount and density of the aggregates being too low in a 1% (w/w) solution in order to detect them with the light scattering instrument used for the cloud point measurement.

Although the bath fractions and the residues had similar CP96 values, the appearances of the clouding curves were very diverse, which can be seen in that the dissolved bath material had much steeper clouding curves than the residue, which showed rather

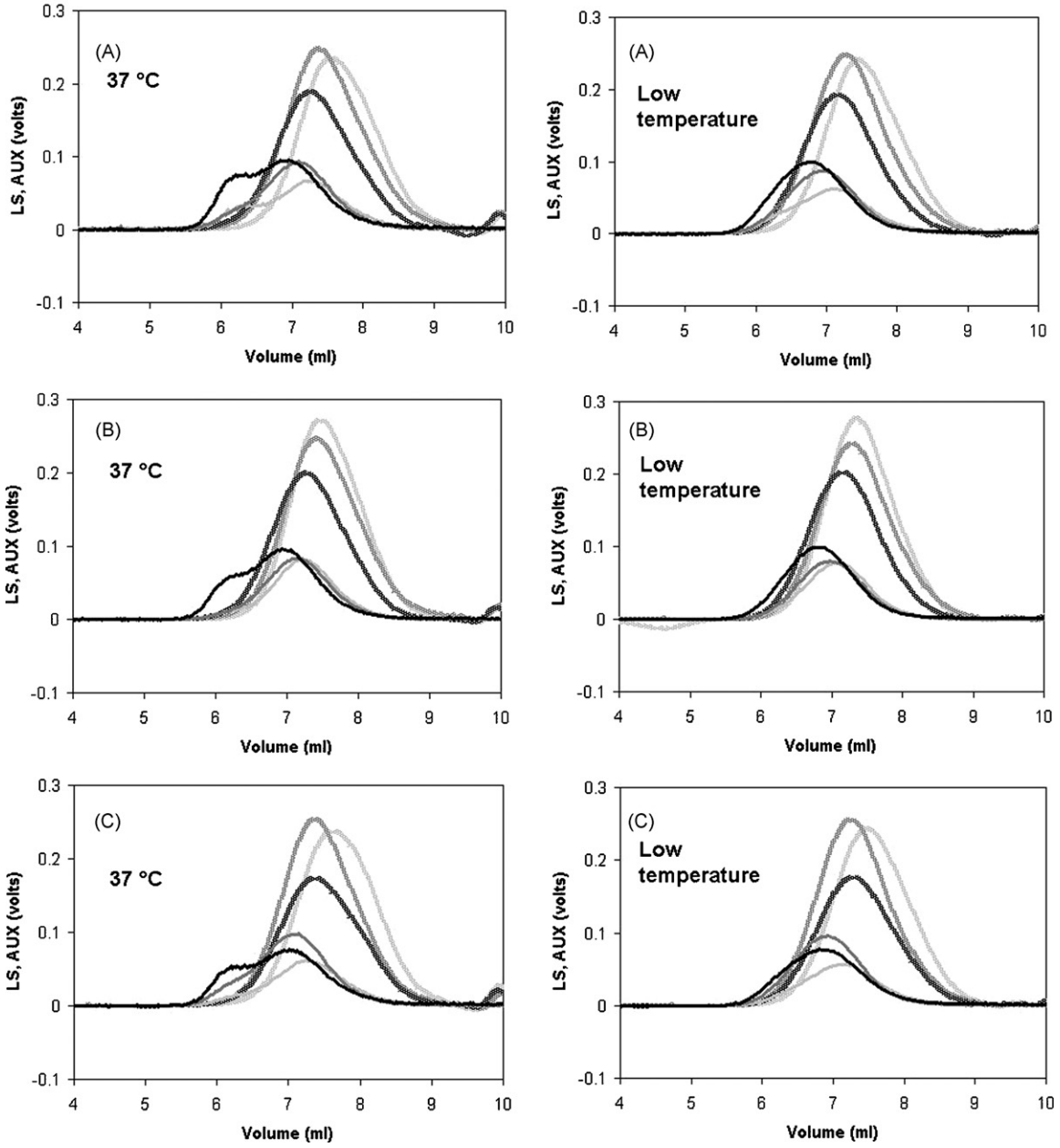

Fig. 4. Chromatograms of the three batches and their fractions. (A) Batch A; (B) batch B; (C) batch C. The solid line represents the MALS signal and the dotted line represents the RI signal. Black: tablet residue; dark grey: original batch; light grey: bath sample.

shallow curves (Fig. 5). The clouding curve of the original batches, which were a blend of the bath fraction and the residue, was positioned in the middle (Fig. 5). Shallow clouding curves have been observed before for heterogeneous samples and fractions of both methylcellulose (Fitzpatrick et al., 2006) and hydroxypropyl methylcellulose (Schagerlöf, 2006; Viriden et al., 2009b, 2009c). In our former study, it was concluded that the shallow clouding curve of HPMC was not solely a result of a gradual phase separation of chains with different solubility but was rather due to the formation of different structures in the polymer-rich phase that scattered the light differently. These structures grew in size with temperature and increased the viscosity. Thus, it was concluded that the more heterogeneously substituted batches formed a gel-like network before complete phase separation. Furthermore, the concentration dependency of the aggregate formation was very different for the heterogeneously substituted batches, and it was shown that the CP96 decreased more than 15 °C when the polymer concentration was increased from 1% to 10% (w/w). In the gel layer of the matrix tablet, the polymer concentration is increased towards the core, and thus it is possible that these hydrophobic interactions will be formed somewhere along this gradient already at lower temperatures. To elucidate the impact of the hydrophobic interactions on the viscosity, flow curves were obtained on the different fractions.

3.2.3. Rheology

Flow curves were obtained at both room temperature (23 °C) and at 37 °C in 5% (w/w) solutions of the tablet residue and the dissolved bath sample of batch A, which obtained the slowest release (Fig. 6). At room temperature, the viscosity of the tablet residue was found to be 23 and 12 times as high as the dissolved bath fraction at the shear rates of 1 and 100 s^{-1}, respectively. Thus it can be concluded that the viscosity of the tablet residue was throughout the shear rate interval both higher and more shear thinning. Even

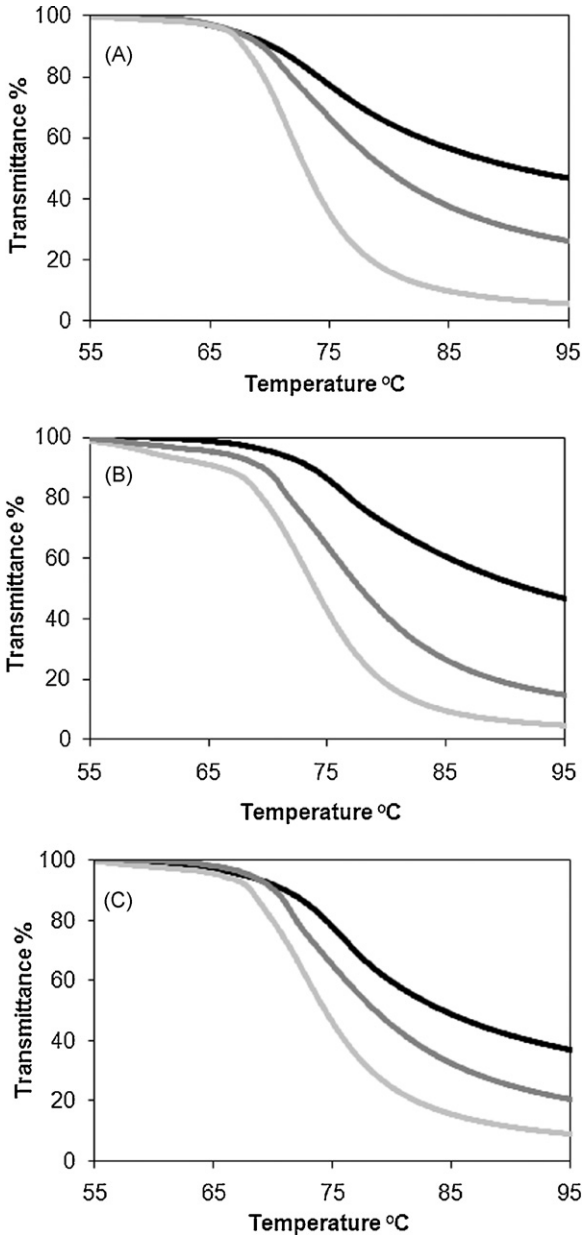

Fig. 5. Cloud point curves of the three batches and their fractions (A–C). Black: tablet residue; dark grey: original batch; light grey: bath sample.

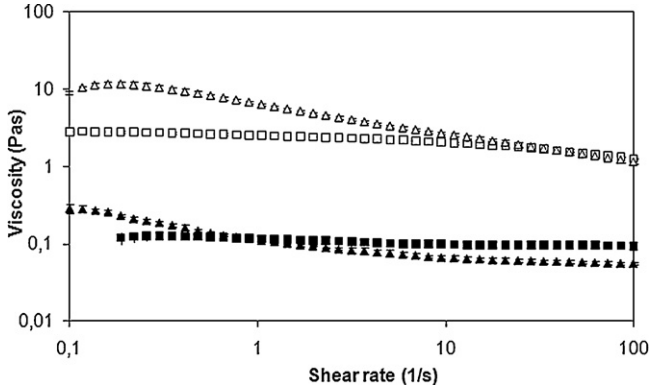

Fig. 6. Flow curves obtained from the fractions from batch A. (□) tablet residue at room temperature; (Δ) tablet residue at 37 °C; (■) dissolved bath material at room temperature; (▲) dissolved bath material at 37 °C. The symbols denote the calculated average value from three measurements and the error bars show the standard deviation.

though polymer solutions of higher molecular weight would obtain a higher viscosity, the 23 times higher viscosity of the tablet residue cannot solely be explained by the difference in molecular weight between the two fractions. This can be explained by the tube model, where the viscosity of a polymer solution is related to the degree of polymerisation according to De Gennes (1972):

$$\eta - N^m \quad (3)$$

where η is the viscosity and N is the degree of polymerisation. The exponent, m, is dependent on the concentration and is increased for solutions above the so-called overlap concentration, which is the semi-diluted region where the overall concentration becomes equal to the concentration inside the polymer coil. The exact value of exponent m in the semi-diluted region is still a theme for research but is positioned in the region 3–3.5 (De Gennes, 1979). The 5% (w/w) solutions in the present study were presumably above the semi-diluted region and thus the viscosity of the residue solution should have been 9–14 times as high compared to the dissolved bath fraction. Therefore, the even higher viscosity of the residue solution indicates that there were polymer structures in solution that increased the viscosity above that expected at low shear rates but were disrupted at higher shear rates. At 37 °C the viscosity of the tablet residue increased even more and became much more shear thinning. At the shear rate of 1 s^{-1} the viscosity of the tablet residue had increased more than 150% compared to the viscosity obtained at room temperature. The viscosity of the dissolved bath fraction did not change to the same extent and, at a shear rate of 1 s^{-1}, the viscosity was the same at both temperatures.

It is generally accepted that HPMC solutions have the property of forming a reversible gel with temperature and that this gelation is due to hydrophobic interactions (Sarkar, 1979). These interactions have been shown to be very sensitive to shear rates (Silva et al., 2008), which is in accordance with the results obtained in the present study. However, even though the gelation temperature is known to be affected by the amount of the different substituents (Haque et al., 1993), the present study has shown that gelation can occur already at room temperature for heterogeneously substituted batches. Moreover, the 150% viscosity increase at 37 °C further indicates that these structures become more frequent at temperatures correlated to the dissolution bath. The hypothesis was that these structures affected the dissolution rate of matrix tablets by decreasing c_{crit} and thus to elucidate this hypothesis pure polymer tablets were made of the fractions of batch A.

3.2.4. Polymer release of the fractions

The release profiles of both the bath fraction and the residue are shown in Fig. 7. The bath fraction that corresponds to 80% of the original batch also showed similar dissolution behaviour and released approximately 90% over a period of 100 h. The residue that was enriched on the even more heterogeneously substituted components showed an even slower release, and only 40% was released within the same amount of time. Although the former study revealed the effect of the substituent pattern of HPMC on polymer release, the batches used had a different average degree of substitution covering the specification limits for a 2208 grade (Viriden et al., 2009a). In this study, however, the bath fraction and the residue had a similar average degree of substitution and the main chemical difference was the heterogeneity of the substituents. Therefore, both the fractionation obtained in the gel-layer of the tablet and the slower release of the tablet residue can be ascribed to the effect of the substituent pattern of HPMC.

4. Concluding remarks

A comprehensive characterisation of the bath and residue fractions demonstrated that the tablet residue that was left in the

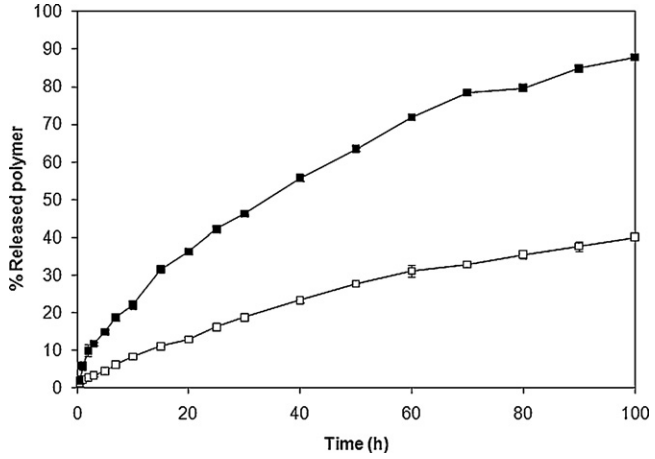

Fig. 7. Polymer release of fractions of batch A, obtained in a modified USP II apparatus at the paddle speed of 50 rpm. (■) Dissolved bath fraction; (□) tablet residue. The symbols denote the calculated average value from two measurements and the error bars show the deviation from the mean value.

dissolution bath after 100 h was enriched in components that displayed a higher M_w compared to the dissolved bath material. It was also found that, although the tablet residue and the dissolved bath material had a similar average degree of substitution, the acid and enzymatic hydrolysis showed that the tablet residue was more heterogeneous with respect to the substituent distribution along the chain. Analysis of the conformation of the fractions at room temperature showed that the residue consisted mainly of components that had a rather compact conformation. The amount of compact components increased when the temperature was increased to 37 °C. However, decreasing the temperature to 5 °C almost completely dissolved them and thus it could be concluded from the solubility that the components were mainly formed as a result of hydrophobic interactions. The hypothesis was that the compact components were domains of gel-like particles that at higher concentrations formed a more coherent network and thus would increase the viscosity. An analysis of the clouding curves of the fractions revealed that the residue had very shallow clouding curves, which was an indication that gel-like components were formed before complete phase separation already at very dilute solutions. The flow curves supported the previous results, and it was found that the viscosity of the residue was higher than expected from the molecular weight and moreover increased by 150% at a temperature of 37 °C.

On the basis of the results presented we suggest that a heterogeneous substitution pattern along the chain facilitates an amphiphilic behaviour of the polymer, where more long-lived hydrophobic interactions between the chains can take place far below expected concentrations and precipitation temperatures for HPMC. However, the polymers will not precipitate out of solution because of the frequently occurring unsubstituted domains that will stay soluble, and thus swellable aggregates are formed. As the polymer concentration is increased, these aggregates will form a more coherent gel, which increases the viscosity above that expected. Consequently, the gel layer of the matrix tablet composed of the residue could at the investigated shear rates be more diluted and hence obtaining a lower c_{crit} without being eroded from the surface. This was seen in the matrix tablets, where the gel layer eventually was enriched on components having the highest impact on the viscosity. Thus from these results it can be concluded that the release mechanism of heterogeneously substituted batches cannot directly be compared to the release mechanism found for more homogeneously substituted batches, where the main interactions are entanglements. Furthermore, since the polymers' complex structure generates a wide variety of solution properties, small differences in heterogeneity could affect the polymer dissolution, and thus also the drug dissolution, to a major extent. In addition, one should be aware that additives as well as the drug substance itself might affect the hydration of the polymer; hence unpredictable release rates might occur. It is therefore evident that the substituent distribution of HPMC needs to be added to the functional related characteristics listed by the European Pharmacopoeia.

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