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Research paper

Release of theophylline and carbamazepine from matrix tablets – Consequences of HPMC chemical heterogeneity

Anna Viridén [a,*], Susanna Abrahmsén-Alami [b], Bengt Wittgren [b], Anette Larsson [a]

[a] Dept. of Chemical and Biological Engineering, Chalmers University of Technology, Gothenburg, Sweden
[b] AstraZeneca R&D, Mölndal, Sweden

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ABSTRACT

The release of theophylline and carbamazepine from matrix tablets composed of microcrystalline cellulose, lactose and hydroxypropyl methylcellulose (HPMC) was studied. The aim was to investigate the effect of different substituent heterogeneities of HPMC on the drug release from matrix tablets composed of either 35% or 45% HPMC. The release of the poorly soluble carbamazepine was considerably affected by the HPMC heterogeneity, and the time difference at 80% drug release was more than 12 h between the formulations of different HPMC batches. This was explained by slower polymer erosion of the heterogeneous HPMC and the fact that carbamazepine was mainly released by erosion. In addition, results from magnetic resonance imaging showed that the rate of water transport into the tablets was similar. This explained the comparable results of the release of the sparingly soluble theophylline from the two formulations even though the polymer erosion and the swelling of the tablets were considerably different. Thus, it can be concluded that the drug release was highly affected by the substituent heterogeneity, especially in the case of carbamazepine, which was released mainly by erosion.

1. Introduction

Many studies have investigated the release of drugs and the release mechanism in hydrophilic matrix tablets composed of hydroxypropyl methylcellulose (HPMC) [1–7]. The general picture of the dissolution behaviour of hydrophilic matrix tablets composed of HPMC starts with the diffusion of water into the tablet. The glassy HPMC transforms into a rubbery state as the water plasticizes the HPMC and reduces the glass transition temperature. This rubbery state can be regarded as a highly concentrated polymer solution and is often denoted the gel layer. The solvent continues to penetrate the tablet and the gel layer, and the dimensions of the swollen tablet increase. A polymer concentration gradient is formed in the tablet, starting at a high concentration in the more or less dry core and declining through the gel layer towards the gel layer surface. At the surface of the gel layer, the polymer concentration is assumed to correspond to the critical polymer concentration, c_{crit}. Below this concentration, the polymer chains can no longer withstand the shear forces surrounding the gel and therefore detach from the matrix [8,9]. A matrix tablet is usually multi-component, and there are other excipients than HPMC influencing the dissolution behaviour. Soluble fillers such as lactose and mannitol have been shown to increase the hydration rate when compared to insoluble excipients; hence, the choice of components in a matrix tablet affects the release of the drug [10,11].

There are three fronts in the swollen tablet that are frequently discussed in the literature; the swelling front, located between the glassy HPMC and the gel layer, the erosion front, which separates the gel from the surrounding solution, and the third front, the diffusion front, located somewhere in the gel and separating the undissolved drug from the dissolved drug molecules [12–15]. The position of the diffusion front is dependent on the solubility of the drug molecule, where the front of a more-soluble drug has been shown to lie closer to the swelling front of the tablet when compared to a less-soluble drug [16]. Subsequently, a more-soluble drug will diffuse out of the gel, while a less-soluble drug will be controlled more by the rate of polymer erosion. Hence, the release mechanism and the release rate have for example been shown to depend on the solubility and properties of the drug [16,17], the area from which the drug can diffuse [18,19], the drug concentration gradient formed in the gel [20,21] and the relative front positions [13,19]. Consequently, since the HPMC governs the properties and the thickness of the gel layer, the influence of the HPMC content and the chemical characteristics of the HPMC are extremely important for the overall drug release and release mechanism from matrix tablets [17–19,22–24]. Thus, to form predictable and robust formulations with minor batch-to-batch variations in drug release, it is necessary to find and control the functionality related characteristics (FRC) of HPMC for drug release.

* Corresponding author. Dept. of Chemical and Biological Engineering, Chalmers University of Technology, SE-412 96, Gothenburg, Sweden. Tel.: + 46 317723420; Fax: +46 31 772 3418.
E-mail address: anna.viriden@chalmers.se (A. Viridén).

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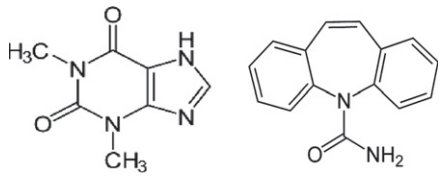

Fig. 1. Illustration of theophylline and carbamazepine.

The molecular weight of HPMC is a known FRC and affects the ability of the gel to be diluted, where a gel of higher molecular weight polymers can be more diluted before being eroded at the erosion front [8,25–27]. The molecular weight is generally not provided by the specifications for pharmaceutical use, instead a viscosity obtained in a 2% solution is given. Thus, even though it is possible with the help of advanced theories to relate the viscosity to a molecular weight, it is quite clear that much deeper insight into the structure–property relationship can be obtained if the molecular parameters are studied directly. The degree of substitution is also an FRC known to affect the hydration of the polymer and the swelling of matrix tablets [1]. The specifications are unfortunately quite broad, and the variation within a certain grade has been shown to affect the release of a drug from matrix tablets [22]. Consequently, to design predictable matrices, extensive polymer characterisation has been found necessary.

Viridén et al. characterised batches of the same grade and found that the distribution of the substituent along the cellulose backbone affected the polymer erosion from matrix tablets [28]. It was found that the heterogeneously substituted batches had an amphiphilic structure that facilitated hydrophobic transient crosslinks. These crosslinks increased with concentration and increased the viscosity of the solutions [29]. Thus, polymer erosion decreased with increased heterogeneity in the matrix tablets. The effect on drug release from binary mixtures of heterogeneously substituted HPMC and model drugs was investigated, and it was shown that the amphiphilic behaviour of the polymer and the lower erosion rate decreased the release of a soluble model drug from the tablets [24]. The question is, however, if the substituent distribution of HPMC is a critical parameter for the drug release from more realistic matrices where the polymer is diluted owing to the presence of other excipients. It is also interesting to study the effects of substituent heterogeneity on a drug with higher solubility as well as on a poorly soluble drug from the same realistic tablet formulations. Thus, to fully investigate the substituent heterogeneity as an FRC for the release from hydrophilic matrix tablets, the release of the soluble theophylline and the poorly soluble carbamazepine (Fig. 1) was studied from tablet formulations with microcrystalline cellulose, lactose and HPMC. The two HPMC batches used in the matrices belonged to the same pharmaceutical grade but had different substituent heterogeneity.

2. Materials and methods

2.1. Materials

Two 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. Microcrystalline cellulose (MCC), Avicel PH-102, was purchased from FMC Corp. (Philadelphia, USA). Lactose Pharmatose, 200 M, was purchased from DMV International (Veghel, The Netherlands). Thephylline and carbamzepine were purchased from Sigma–Aldrich Chemie (GmbH, Switzerland). All powders were used as received.

2.2. Solubility of theophylline and carbamazepine

Solutions with concentrations of about 10 times the solubility of the drug was prepared in phosphate buffer ($I = 0.1$, pH 6.8). The solutions were placed in a shaking water bath at 37 °C for 24 h. The solutions were thereafter filtered and diluted. The absorbance of dissolved theophylline and carbamazepine was measured using a Varian Cary 50 Bio UV–Vis spectrophotometer (Varian, Inc., Palo Alto, CA, USA). The solubility of theophylline and carbamazepine was calculated using a standard calibration curve at the wavelength of 270 nm and 285 nm, respectively.

2.3. Apparent density

The density of each powder was measured using helium pycnometry on an AccoPyc 1330 (Chemical Instrument AB, Sollentuna, Sweden). Prior to analysis, the instrument was calibrated against a standard volume of 12.0169 cm^3. Each determination included 10 purges prior to analyses and 10 analytical runs with a fill pressure of 1.5 bars.

2.4. Particle size

The particle size distribution was determined with laser diffraction using a Mastersizer 2000 equipped with a dry disperser unit, sirocco 2000 (Malvern Instrument Nordic AB, Sweden). The Fraunhofer approximation was used for calculation of the particle size. 10–15 ml of powder, withdrawn from the bulk with a spoon after mixing, was placed in the instrument. The obscuration was in the interval of 0.5–5%. A dispersion pressure of 3 bar was used to disperse the particles sufficiently. The measurements were performed for 65 s each, and the volume particle size distribution and corresponding average values are based on at least three runs.

2.5. Scanning electron microscopy

Particles of theophylline and carbamazepine were examined by scanning electron microscopy. The particles were sputtered coated with gold using an auto sputter coater 108 (Ted Pella Inc., Redding, USA), and images were obtained by a FEI Quanta 200 (FEI, Czech Republic) set at 10 kV and in high vacuum.

2.6. Tabletting

Two different tablet compositions of each HPMC batch were prepared as described in Table 1. The powders were blended with a pestle and mortar for 5 min to obtain a well-mixed composition before tabletting. A single punch tabletting machine (Kilian SP300, Kilian&Co. GmbH, Germany) equipped with 10 mm flat-faced punches was used. The compression force was 10 ± 0.5 kN, and the powder was pre-weighed for each tablet using a Mettler Toledo AX205 Delta Range to get a tablet weight of about 300 ± 5 mg.

2.7. Tensile strength

A tablet hardness tester (Holland C50, UK) was used to measure the force needed to fracture the tablets. The dimensions (the diam-

Table 1
Percentage of each component in the tablet.

	Theophylline or carbamazepine (%)	MCC (%)	HPMC (%)	Lactose (%)
Composition 1	10	15	35	40
Composition 2	10	15	45	30

eter and the thickness) and the weight of the tablets were determined using a micrometer gauge and a Mettler Toledo AX205 Delta Range, respectively. The tensile strength (σ_t) was calculated according to Fell and Newton [30]:

$$\sigma_t = \frac{2F}{\pi Dt} \quad (1)$$

where F is the force needed to fracture the tablet, and D and t are the diameter and thickness of the tablet, respectively. The average values reported are based on five tablets.

2.8. Tablet porosity

Tablet porosity of the tablets was calculated by:

$$Porosity = \frac{V_{tot} - V_{mat}}{V_{tot}} \quad (2)$$

where V_{tot} is the volume of the tablet and is calculated from the tablet dimensions, and V_{mat} is the volume of the powder mixture. The volume of the powder mixture was calculated by:

$$V_{mat} = \frac{w}{\delta_{average}} \quad (3)$$

where w is the weight of the powder mixture and $\delta_{average}$ is the average density of the powder mixture. The reported porosities are the average values of five tablets.

2.9. Polymer and drug release

The release of the drug and the polymer from the dissolving tablets was measured with 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), 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 1.8 ml were removed from the release medium at different predetermined times using a Varian VK8000 fraction collector (North Carolina, USA), and the amounts of drug and polymer released from two tablets were analysed and averaged.

The polymer concentration in the release medium was determined 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 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 absorbance of theophylline and carbamazepine at each sample time was measured using a Varian Cary 50 Bio UV–Vis spectrophotometer (Varian, Inc., Palo Alto, CA, USA). The concentration of theophylline and carbamazepine was calculated using a standard calibration curve at wavelengths of 270 nm and 285 nm, respectively.

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

$$\%\text{Released} = \left(\frac{c_n \times (V_0 - V_s(n-1)) + V_s \sum_{n=0}^{n-1} c_n}{x} \right) \times 100 \quad (4)$$

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

2.10. MRI set-up and methodology

MRI studies were performed on compositions with 45% HPMC and theophylline. A detailed description of the hardware and experimental set-up during the MRI studies is provided by Abrahmsen-Alami et al. [31]. In brief, the tablets were glued to the centre of a rotating disc, which was positioned in the MRI release cell and inserted into the MRI probe for imaging. The release cell was connected to a 37 °C tempered beaker, containing the dissolution medium. The solvent was pumped through the release cell by a peristaltic pump via plastic tubes. The dissolution media consisted of 500 ml phosphate buffer at 37 °C (pH 6.8, I = 0.1). The rotation of the disc (100 rpm) was switched off 2 min before the start of imaging sequences, at which time samples from the dissolution media were collected. Images were obtained from both radial and axial scans of the tablets. The scanning direction was altered after each imaging sequence. The duration of each measurement was 21.2 min. The stirring intervals between the images were 20 min between the second and the thirteenth image, after which the length of the stirring sequences was increased to 130 min. The stirring before the first sequence image was 8 and 10 min, while stirring was performed for 17 and 24 min before the second sequence for tablets of batch A and batch B, respectively. Sampling for dissolution studies was taken from image 3 and onwards. A slice thickness of 2 mm was used.

The studies were performed using the Bruker Para Vision 3.0 software and a wb400 Bruker spectrometer with a 2.5 ^{1}H resonator. Diffusion of the dissolution media into the tablet was studied using the original multi-spin pulse sequence (m_msme), supplied by Bruker. Using this method, the signal intensity is weighted according to the proton spin–spin (T_2) and spin–lattice (T_1) relaxation times. Due to the very short T_2-relaxation times of the solid material protons, differences in the image intensity will predominantly depend on the properties of the dissolution media. Under the condition that the repetition time (T_R = 10 s) was 3–5 times longer than the T_1, the intensity of the image signal is given by Eq. (5).

$$I(T_E) = I(0)\exp(-T_E/T_2) + c \quad (5)$$

Here, T_2 and T_E are the "effective" spin–spin relaxation of proton times and the echo times, respectively. $I(0)$ is the total intensity, $I(T_E)$ is the intensity of the signal T_E and c is a constant related to the baseline. The T_1-relaxation time of water in 0.1 M phosphate buffer at pH 6.8 was determined to 3.9 s at 37 °C. With increasing HPMC concentration, the relaxation time decreases, and therefore, a T_R of 10 s was sufficient to obtain a measure of the T_2 in the polymer gel. Images were probed at 20 different echo times (10–200 ms) and used to create images weighted mainly with the T_2 of water protons in the sample.

3. Results

3.1. Chemical composition of the HPMC

Two HPMC batches of the same pharmaceutical substituent (2208) and viscosity (100 cps) grade were used to investigate the effect of substituent heterogeneity on drug release. The batches were chosen since they, despite being of the ordinary assortment of the grade, differed significantly in substituent heterogeneity (Table 2) [24,28]. Batch A had an average MeO and an HPO content

of 23.4% and 10.9%, respectively, while batch B had an average MeO content of 24.6% and HPO content of 7.0%. The substituent heterogeneity along the polymer chains had earlier been characterised by a selective cellulose degrading endoclucanase from *Trichoderma reesei* [24]. This enzyme prefers an unsubstituted region of about 5 glucose units to bind to the HPMC chain and form the essential enzymatic-substrate complex, which is required for the enzyme to hydrolyse the cellulose chain [32]. This means that more glucose is released from HPMC samples that are more heterogeneously substituted, making possible a qualitative comparison between the batches. In addition, β-glucanase, an exo-enzyme that hydrolyses unmodified cellulose into glucose, was added to the hydrolysed samples to degrade larger unsubstituted blocks released by the endoglucanase into glucose. As can be seen in Table 2, batch B released significantly more glucose than batch A. It can therefore be concluded that unsubstituted regions occurred more frequently in batch B, obviously being more heterogeneously substituted than batch A. Furthermore, to reduce the effect of another FRC, the molecular weight, on the drug release the same viscosity grade was chosen. The average molecular weight was of a similar magnitude for the two HPMC batches, with a similar polydispersity index, P.I. (Table 2).

3.2. Characteristics of powders and tablets

The particle size of excipients has been shown to affect the porosity and strength of the tablets and the initial hydration rate of the matrix [19,33,34]. The particle size of the different powders was therefore measured by laser diffraction (Table 3). As seen in Table 3, the mean particle sizes of the two HPMC batches were in the same range, and only a small difference of approximately 10 μm was found between the batches. The mean particle size of the soluble excipient lactose was considerably smaller and found to be 36 μm, while the insoluble swellable MCC had a mean particle size of 108 μm. SEM images were taken to get an estimate of the shape and size of the particles of theophylline and carbamazepine (Fig. 2). As indicated in the images, the particles of theophylline were needle shaped and in general substantially larger in size than the carbamazepine particles, which were seen to be considerably smaller and more spherical in shape.

Tablet porosity and tensile strength are shown in Table 4. Lower tablet porosity was found for tablet formulations with carbamazepine compared to those with theophylline, which might be explained by the smaller particles of carbamazepine allowing a more dense packing of the particles in the tablets. There were also indications that the tablet formulations with carbamazepine showed a higher tensile strength, which might be an effect of the smaller particle size and the lower porosity of these formulations. Furthermore, the tensile strength of all formulations increased with an increased amount of HPMC. Thus, since the amount of lactose decreased as the HPMC increased, the results indicate that HPMC was the better of the two to compact (Table 4).

Table 2
Chemical characteristics of the HPMC batches used.

Sample	%HPO[a,b]	%MeO[a,b]	Glucose released after hydrolysis[c,d]	Mw[b,c]/ 10^4 (g/mol)	Mw/Mn[b,c] (g/mol)
Batch A	10.9	23.4	0.4 (0.0)	14.1 (0.3)	2.8 (0.6)
Batch B	7.0	24.6	1.5 (0.1)	10.4 (0.2)	2.2 (0.3)

[a] RSD of 0.02 according to an in-house validation.
[b] Data obtained by Viriden et al. [28].
[c] The results given are mean values and corresponding standard deviations are given in parentheses ($n = 3$).
[d] Hydrolysis with endoglucanase from *Trichoderma reesei* and β-glucanase from *Aspergillus niger* [24].

3.3. Release studies

The objective was to study the effect of the substituent heterogeneity of HPMC on drug release from matrix tablets. Thus, investigate whether the amphiphilic behaviour of the heterogeneously substituted HPMC influenced the release of drug substances in realistic matrices, i.e. tablets also containing other excipients than HPMC. The formulations consisted of 10% drug, 15% MCC and 30% or 40% lactose, and thus 35% or 45% HPMC (Table 1). The drugs chosen were theophylline and carbamazepine with a solubility of 11.2 mg/ml and 0.2 mg/ml, respectively, at 37 °C in the phosphate buffer used (Fig. 1). The release rate of the drugs and the HPMC was evaluated from the times (*T*-values) at which 50% (T50) and 80% (T80) were released (Table 5).

3.3.1. Release studies of theophylline

The release profiles of theophylline and HPMC from tablet formulations with 35% and 45% (w/w) HPMC are illustrated in Fig. 3a and b. In general, the release of theophylline from tablets of both batch A and batch B was prolonged with an increased HPMC content in the tablets, and it was also observed that the initial release during the first 30 min was reduced with increased HPMC content. Furthermore, the release of theophylline was faster than the erosion of the HPMC from all formulations, indicating a diffusion-controlled release mechanism of theophylline. However, the release of theophylline from tablets of batch A was quite parallel to the erosion of the polymer, which indicated upon a contribution of erosional dependence. A comparison of the tablet formulations of the two HPMC batches shows that the release of theophylline was delayed to greater extent in tablets of the more heterogeneously substituted batch B when compared to batch A (Fig. 3a–d and Table 5). This can be seen in that the T50 of theophylline from batch B increased in comparison with the T50 from compositions of batch A by 17% and 34% from tablets with HPMC contents of 35% and 45%, respectively. Similar results were seen in a comparison of the T80 values.

The initial polymer erosion from formulations of batch A and B was similar during the first hour. During the remaining part of the release, however, the polymer erosion was significantly slower from formulations of batch B, and the T50 values of batch B were 7.2 and 19 h higher compared to the T50 obtained by batch A at the different HPMC contents (Table 5). Here, not only a higher T50 value was seen of batch B, it was also observed that the T50 of batch B increased more with a greater HPMC content in the tablet. Another observation worth noting was that the erosion

Table 3
Particle characteristics of the different powders.

	HPMC batch A	HPMC batch B	MCC	Lactose	Theophylline	Carbamazepine
Apparent density[a] (g/cm^3)	1.32	1.34	1.57	1.54	1.49	1.46
Particle size[b] $d(0.5)$ (μm)	69.9 (69.7–69.9)	82.8 (82.7–82.9)	107.5 (107.3–107.9)	36.2 (36.2–36.7)	85.8 (84.1–86.3)	Not determined

[a] The results given are mean values ($n = 10$). All standard deviations were less than 0.003.
[b] The results given are mean values ($n = 3$), and the range of the three measurements is given in parentheses.

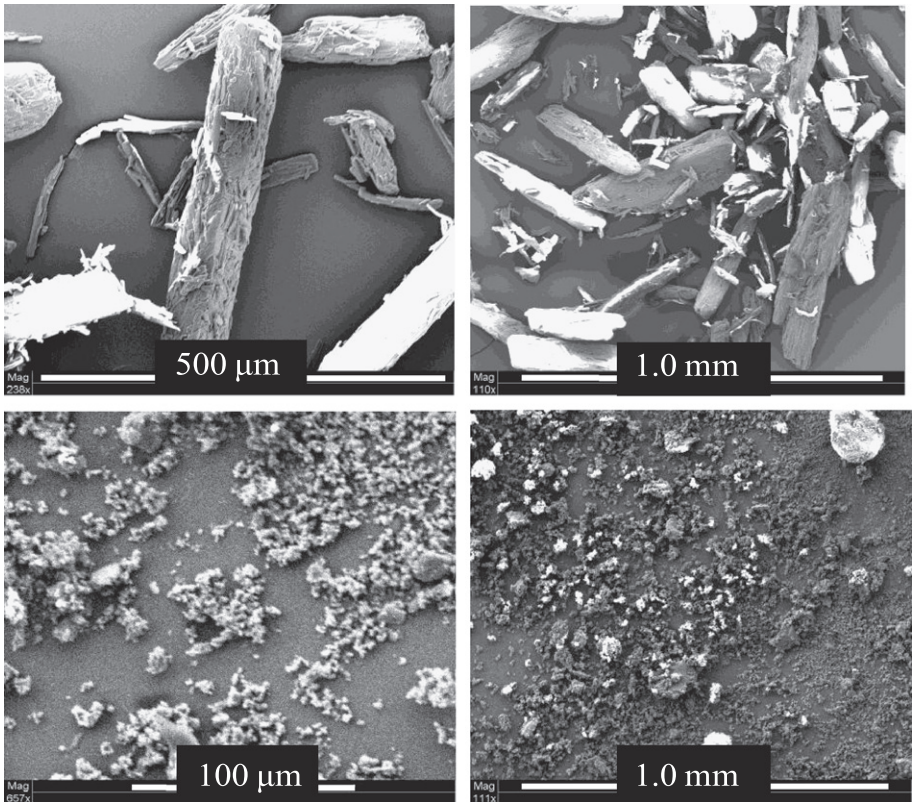

Fig. 2. Images of particles of theophylline (top) and carbamazepine (bottom) taken by scanning electron microscopy (SEM).

Table 4
Tablet porosity and tensile strength of the different compositions.[a]

Tablet composition	Tablet porosity (%) compositions with 35% HPMC	Tablet porosity (%) compositions with 45% HPMC	Tensile strength (MPa) tablets with 35% HPMC	Tensile strength (MPa) tablets with 45% HPMC
Tablets of batch A and theophylline	18.7 (0.5)	18.8 (0.3)	2.2 (0.1)	2.6 (0.1)
Tablets of batch B and theophylline	19.1 (0.5)	19.5 (0.2)	2.0 (0.1)	2.4 (0.2)
Tablets of batch A and carbamazepine	16.6 (0.3)	16.6 (0.1)	2.2 (0.1)	2.9 (0.4)
Tablets of batch B and carbamazepine	16.4 (0.1)	16.7 (0.4)	2.2 (0.1)	2.6 (0.2)

[a] The results given are mean values with corresponding standard deviations in parentheses ($n = 5$).

Table 5
T50 and T80 values from tablet compositions of the two HPMC batches.[a,b]

Sample	T50 (h) 35% HPMC	T80 (h) 35% HPMC	T50 (h) 45% HPMC	T80 (h) 45% HPMC
Released theophylline (formulations of batch A)	1.7 (0.0)	4.0 (0.1)	2.3 (0.0)	5.0 (0.0)
Polymer erosion of batch A (formulations with theophylline)	2.9 (0.0)	6.0 (0.2)	4.4 (0.3)	7.9 (0.0)
Released carbamazepine (formulations of batch A)	3.6 (0.1)	6.4 (0.1)	4.3 (0.1)	7.4 (0.3)
Polymer erosion of batch A (formulations with carbamazepine)	3.4 (0.1)	6.3 (0.0)	4.6 (0.1)	8.3 (0.0)
MRI-released theophylline (formulations of batch A)			4.3	8.1
Released theophylline (formulations of batch B)	2.0 (0.0)	4.9 (0.2)	3.1 (0.0)	7.4 (0.1)
Polymer erosion of batch B (formulations with theophylline)	10.1 (0.0)	21.2 (1.2)	23.4 (1.2)	38.8 (0.7)
Released carbamazepine (formulations of batch B)	7.4 (0.0)	13.3 (0.0)	11.9 (0.7)	20.2 (1.1)
Polymer erosion of batch B (formulations with carbamazepine)	9.4 (0.6)	14.2 (0.4)	14.9 (0.1)	22.0 (0.6)
MRI-released theophylline (formulations of batch B)			5.0	

[a] Times at which 50% (T50) and 80% (T80) of the drug and the polymer were released from the formulations at the paddle speed of 50 rpm (USP bath) and 100 rpm (MRI).
[b] The results tabulated are the 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.

profile of batch B changed shape with the tablets HPMC content. Thus, during the first 5 h was the polymer erosion considerably slower from tablets with 45% HPMC compared to as the erosion rate from the 35% formulations. Consequently, although the average HPMC content was considerably lower than in previous studies [24], there were strong effects of the substituent heterogeneity on the polymer erosion from matrix tablets.

Given that the polymer erosion of batch B was extremely slow, the release of theophylline was surprisingly alike from tablets made of the two HPMC batches (Fig. 3). To investigate whether this

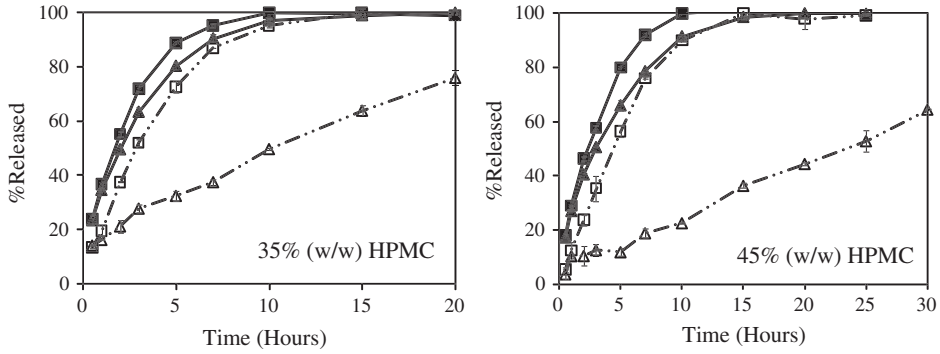

Fig. 3. Release profiles of theophylline and HPMC from tablet formulations composed of batch A and batch B. □ represents the erosion of batch A and ■ the release of theophylline from the formulations of batch A. △ represents the erosion of batch B and ▲ the release of theophylline from the formulations of batch B. The two figures represent tablets with 35% and 45% HPMC, respectively. The symbols denote the calculated average value from two measurements (x_1 and x_2) and the error bars show the deviation from the mean values ($(x_1 - x_2)/2$) above and below the mean value.

depended on similar water transports into the matrices, MRI studies were conducted on formulations with 45% HPMC. During the measurements, the tablet was glued onto a rotating disc. Hence, the experimental set-up was different from the USP, see Section 2.10. The different set-ups hindered the release from one side of the tablet and the release of theophylline was therefore slower compared with the traditionally USP set-up (Table 5). The difference in T50 values of theophylline between the tablet formulations was also small in this set-up, not even an hour, and hence the relative difference was the same as that obtained in the USP bath. The core dimensions of the tablets are illustrated in Fig. 4. The results are only presented for the first hours, since those obtained after 8 h were unreliable because the tablet of batch B swelled and obtained a very cylindrical/sandglass shape before being detached from the disc. However, as seen in the figure, the water front moved at similar rates in the two compositions during the first 8 h. Hence, it is reasonable to suggest that the water transport into the tablets and thus the disappearance of the glassy core were similar in compositions of batch A and batch B in the rotating disc set-up as well as in the USP bath. A small difference in T_g was found between these batches and was explained by the substituent distribution [35]. However, the similar water transports indicate that either the small difference in T_g was insufficient to affect the hydration of the core or that the hydration was different at water contents at which the MRI instrument was not able to detect.

MRI images taken of tablets of batch A and batch B after approximately 3 h and after slightly more than 7 h are shown in Fig. 5. From the images, it is possible to observe the core and the gel layer of the tablets. Surprisingly, although the disappearance of the core

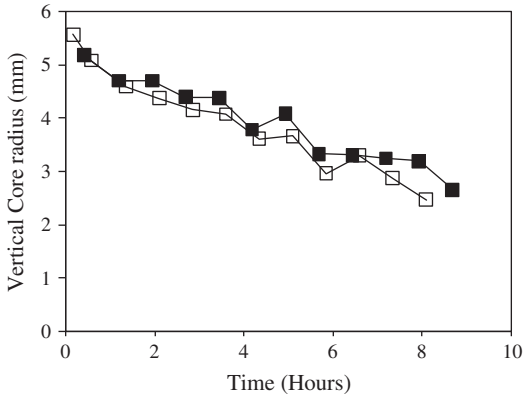

Fig. 4. Disappearance of the tablet core as a function of time. The measurements were obtained by MRI studies on tablets composed of 45% HPMC. ■ represent tablets of batch A and □ tablets of batch B.

was similar, there was a completely different swelling behaviour. The gel of batch B was larger than that of batch A after only 3 h and the differences were even larger after 7 h. Thus, since the disappearance of the core was similar, the greater swelling of batch B indicates that the water transport was not very affected by the thickness of the gel layer. It should also be noted that the shapes of the gel layers were dissimilar, where the gel of batch A was more eroded at the edges while the gel of batch B was more swelled at the edges. This might be explained by the fact that water can hydrate the tablets from two sides at the edges between the height and the planar surface of the tablet; hence, the effect of the polymer concentration on erosion is more apparent there [31,36]. It can be concluded from the measurements that the water transport into the tablet was about the same and that the erosion of batch A was faster than that of batch B (Fig. 5). This implies that the gel of batch B was more diluted than the gel of batch A before the polymers were eroded from the surface of the tablet. Consequently, at the edges where hydration was faster, the tablet of batch A was more eroded, while the gel layer of the tablet of batch B was more swelled.

3.3.2. Release studies of carbamazepine

To investigate the effect of the substituent heterogeneity on the release of a poorly soluble drug, release studies were performed on tablets containing carbamazepine with a solubility of 0.2 mg/ml. The release of carbamazepine was also studied from matrices having an HPMC content of 35% and 45% (Fig. 6 and Table 5). As for theophylline, the release of carbamazepine from all tablet formulations decreased with increased HPMC content. However, the effect was much greater for carbamazepine compared to theophylline. This can be explained by carbamazepine following the erosion of the polymer and that it was released mainly by an erosion controlled mechanism. However, the release of carbamazepine was slightly ahead of the polymer erosion of batch B, which indicates a small diffusional contribution to the release mechanism.

A comparison of the release rates of carbamazepine from tablets of the two HPMC batches showed a considerably slower release from batch B formulations. At 35% HPMC, the T50 values of carbamazepine were 3.6 and 6.4 h and the T80 values were 7.4 and 13.3 h for formulations of batch A and batch B, respectively. At an increased HPMC content (45%) in the matrices, the T50 values of carbamazepine increased to 4.3 and 11.9 h and the T80 values to 7.4 and 20.2 h for tablets of batch A and B. Consequently, it can be seen that not only was the drug release from compositions of batch B more than 2.5 times slower, but the effect of the HPMC content on the release of carbamazepine was much more pronounced from compositions of batch B. This can be seen from

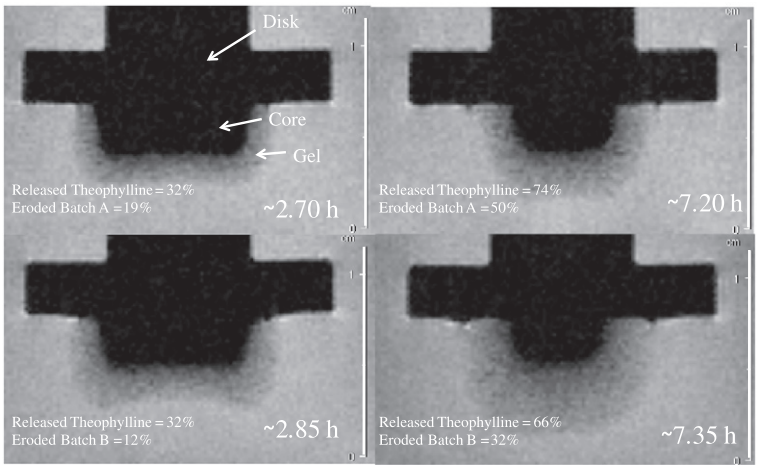

Fig. 5. MRI images taken at the time of almost 3 h and slightly more than 7 h. The tablets were composed of 45% HPMC and theophylline. The top images represent tablets of batch A and the bottom images tablets of batch B.

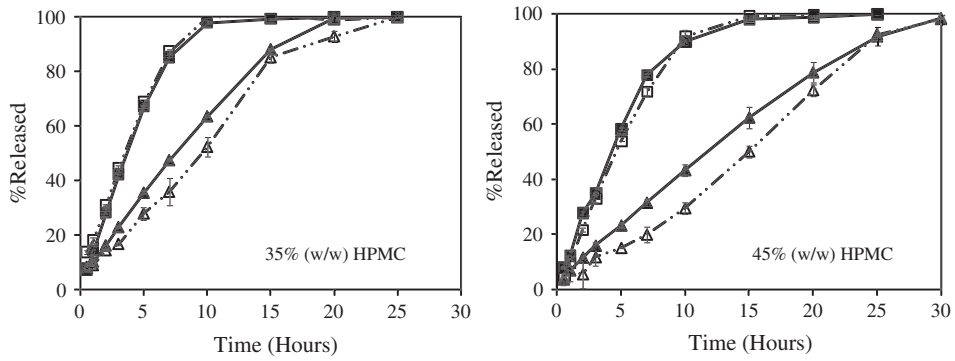

Fig. 6. Release profiles of carbamazepine and HPMC from tablet formulations composed of batch A and batch B. □ represents the erosion of batch A and ■ the release of carbamazepine from the formulations of batch A. △ represents the erosion of batch B and ▲ the release of carbamazepine from the formulations of batch B. The two figures represent tablets with 35% and 45% HPMC, respectively. The symbols denote the calculated average value from two measurements (x_1 and x_2), and the error bars show the deviation from the mean values ($(x_1 - x_2)/2$) above and below the mean value.

the increase in the T80 value of carbamazepine with increased HPMC content, where the increase was 19% from tablets of batch A and as much as 68% from tablets of batch B. The polymer erosion of batch A and B was consequently also considerably different, where tablets of batch A were dissolved more than 15 h prior to tablets of batch B at both HPMC contents (Fig. 6a and b).

4. Discussions

It has been shown in former studies that the HPMC substituent heterogeneity influenced both the drug release and the polymer erosion from matrix tablets and that this was linked to the amphiphilic behaviour of the heterogeneously substituted HPMC batches [24,28,29]. However, these studies were carried out on matrices with $\geqslant$90% HPMC where the polymer properties have a great impact on the matrix. The aim of the present study was thus to investigate whether the effect of the substituent heterogeneity was also crucial for the drug release from tablet formulations with a more realistic HPMC composition that contained other excipients and hence less HPMC. Thus, drug release from tablet formulations of two HPMC batches with different substituent heterogeneity was compared.

Initially, as the tablet comes in contact with water, it is important that the HPMC rapidly forms a coherent gel to prevent the matrix from disintegrating. The ability to form a coherent gel has for example been shown to depend on the particle size, tablet porosity, rate of hydration and the HPMC content [11,18,19,33,37]. The particle size of the two HPMC batches was fairly similar as well as the tablet porosity in the two HPMC formulations. However, depending on the distance between the polymer particles in the tablet, a certain time is needed before a coherent gel is formed and thus initially a less entangled and more fragile gel could be obtained [33,37]. As seen in the present study, the polymer erosion during the first 30 min increased with a lower amount of HPMC; hence, it is reasonable to suggest that the larger distance between the polymer particles was more critical before a coherent gel was established. Moreover, the faster erosion during the initial stage of the release process obtained for the 35% tablet formulations might have been influenced by the higher content of lactose in the same formulations. Lactose would increase the osmotic pressure and hence also the water transport into the tablets [11]. To avoid burst affects with a faster water transport, it is thus more critical that the HPMC quickly forms a coherent gel. Although, no burst was seen in the present study, the lower amount of polymer and the higher amount of lactose initially resulted in a more fragile gel where faster polymer erosion was obtained from the 35% formulations during the first 30 min compared to the 45% formulations. Given that the initial polymer erosion was about the same from formulations of both batch A and batch B, the substituent het-

erogeneity does not seem to be critical at these HPMC content for either the initial water transport, which was shown by the MRI, or the primary HPMC hydration.

Once a coherent gel is established, a polymer concentration gradient is formed in the tablet as the solvent dilutes the gel. The polymer concentration at the erosion front is assumed to correspond to the critical polymer concentration, c_{crit}, related to the viscosity needed to withstand the shear forces surrounding the gel [8,9]. Different HPMC contents in the tablets would then alter the polymer concentration gradient and the tablet dissolution time, since more HPMC needs to be dissolved and eroded from the surface. Consequently, as seen in the present study, the *T*-values of the polymers from all compositions decreased with a decreased HPMC content. However, although the HPMC content was limited, the erosion rates were much lower and the *T*-values were consequently higher from compositions of batch B. This can be explained by the amphiphilic structure of batch B that facilitates hydrophobic transient crosslinks [29]. These crosslinks increased the viscosity of the solution, and hence the matrices could be diluted to a greater extent before the critical viscosity at the erosion front was reached. This explanation seems to agree with the results in the present study although the amount of polymer in the tablets was reduced compared to the pure polymer tablets that were investigated in the former study. The MRI images thus showed that the gel of batch B could be much more diluted, and hence an increased swelling was obtained simultaneously as less amount of polymer was eroded from the surface.

Another way to examine the polymer erosion from the matrixes is by studying the amount of polymer that is eroded with time (Fig. 7). A completely different behaviour was seen from the two batches. The polymer erosion from all formulations of batch A showed the same rate (mg/h). This implies that as long as a coherent gel was formed, the rate of erosion was unaffected by the polymer concentration in the remaining gel, and hence, the rate limiting step was the removal of the outer gel layer. The same erosion behaviour was seen in another study, where HPMC (2208, 100 cps) was eroded from tablets at similar rates regardless of the amount of polymer in the tablets [11]. In contrast, the erosion rate of batch B was different from the different compositions depending on both the drug and the HPMC content. The slopes of the same drug compositions were parallel; however, the 35% compositions were ahead of the 45% compositions (Fig. 7). This can most likely be explained by that the concentration dependency on the viscosity of batch B was higher and hence, at higher HPMC contents in the gel, more water is needed initially to dilute the gel until the viscosity limit is reached at the erosion front [29]. As was seen, the polymer erosion of batch B was initially slower from tablets with 45% HPMC, which explains the displacement of the erosion profiles of the 35% formulations in comparison with the erosion profiles of the 45% formulations in Fig. 7. It can thus be concluded that this concentration dependency observed already at 35% and 45% HPMC formulations makes it difficult to predict the effect of HPMC content on the erosion rate from tablets composed of heterogeneously substituted HPMC. In addition, a gel composed of transient hydrophobic interactions reduces the ability to model the effect of excipients and drug substances on the erosion rate of the polymer.

There was no effect of the drug substances on the erosion of batch A. However, the erosion rate of batch B from compositions with carbamazepine was considerably faster compared to the erosion rate from formulations with theophylline for which the T80-value decreased with as much as 16 h, as seen in Table 5. This might again be explained by the transient hydrophobic interactions formed in the gel of batch B, which give rise to a pronounced swelling and a shallow polymer concentration gradient in the gel layer. Consequently, a drug molecule that would disturb the transient hydrophobic interactions would alter the viscosity and give large effects on the erosion rate from the matrix, as was seen in formulations of batch B and carbamazepine. It has been reported that carbamazepine and HPMC form hydrogen bonds between the HPMC hydroxyl groups and the hydrogen or the carboxamide group of carbamazepine [38]. Thus, a possible explanation could be that the amphiphilic structure of batch B facilitated the formation of these hydrogen bonds. This would have reduced the ability to form the transient hydrophobic interactions, and hence faster polymer erosion would have been seen as a result. Another possible scenario could be that the hydrophobic part of carbamazepine interacts with the longer hydrophobic parts in batch B and hence affects the formation of the transient crosslinks. In either case, a faster polymer erosion was seen from compositions with carbamazepine compared to formulations with theophylline, and it can be concluded that both the chemical structure of the drug and the HPMC affect the erosion rate and in turn the drug release rate from matrix tablets.

As seen from above, without characterising the FRCs of the HPMC, it is difficult to design predictable drug formulations using HPMC matrices. However, the differences in drug release from matrices of HPMC with different substituent heterogeneity might be smaller in formulations with soluble drug substances such as theophylline. The explanation for this can be that theophylline seemed to be rather unaffected by the polymer erosion and matrix swelling. Theophylline was instead affected more by the rate of

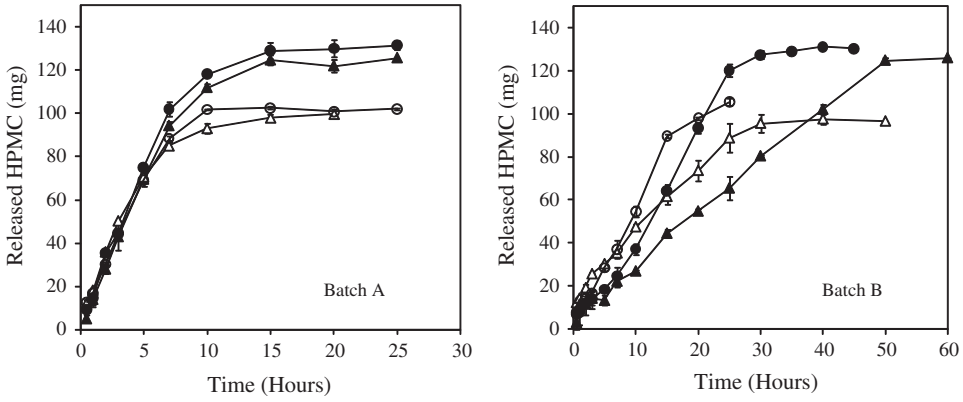

Fig. 7. Amount HPMC eroded in the dissolution bath versus time. The symbols represent the eroded HPMC from the different tablet formulations: △ 35% HPMC and theophylline, ▲ 45% HPMC and theophylline, ○ 35% HPMC and carbamazepine, ● 45% HPMC and carbamazepine. The two figures represent the two HPMC batches. The symbols denote the calculated average value from two measurements (x_1 and x_2), and the error bars show the deviation from the mean values ($(x_1 - x_2)/2$) above and below the mean value.

matrix hydration. Thus, as was seen in the MRI experiments, most of the core disappeared within 8 h in both tablet formulations, thus giving a similar matrix hydration. Furthermore, more than 80% of theophylline had been released from both batches within 8 h, which suggests that the diffusion front of theophylline was close to the swelling front. The similar swelling fronts and diffusion fronts in both tablets could therefore explain the surprisingly similar release rates of theophylline. Consequently, since the hydration of the two batches with the different substituent heterogeneities was similar, only small differences in the release rates of the soluble drug were found as the drug was rather unaffected by the polymer erosion and swelling.

In designing formulations with a poorly soluble drug, the above results would lead us to expect great effects of the substituent heterogeneity on the drug release. This can be explained by a poorly soluble drug not dissolving in the gel to the same extent as for example theophylline. The diffusion front of the drug would therefore lie closer to the erosion front of the matrix, and the contribution of diffusion to the release mechanism of carbamazepine was found to be limited from all compositions. Thus, as the erosion front movement showed to be very important, the HPMC properties had a significant impact on the release of carbamazepine. Consequently, since compositions with the heterogeneously substituted HPMC were eroded at considerably lower rates than the more homogeneous HPMC, the release was reduced and there were more than 12 h between the T80 values of carbamazepine from the two compositions. The present study also shows that a prediction of drug release cannot be made on the basis of the erosion behaviour of pure HPMC systems, which can be explained by the large concentration dependency on the erosion rate of the heterogeneously substituted HPMC. The result of the present study further imply that depending on the substituent distribution, different interactions between the drug and the HPMC can be created that alter the erosion of the polymer and in turn the release of the drug. It can be concluded that to design predictable formulations of HPMC matrices, it is important to characterise the chemical composition of the HPMC and the drug–HPMC interactions.

5. Conclusions

Significant effects of HPMC substituent heterogeneity on drug release were seen. The effects were explained by the much slower polymer erosion and the greater swelling of tablets composed of the heterogeneously substituted HPMC. In addition, the effect of substituent heterogeneity of HPMC on drug release was larger for the poorly soluble carbamazepine, which was released at about the same rate as the polymer was eroded from the tablets. When the HPMC content in the formulations was increased, it was clearly shown that the polymer erosion and hence also the drug release from the heterogeneously substituted HPMC was delayed to a greater extent, and it was also shown that the release was more unpredictable. Moreover, the erosion rate of the heterogeneously substituted HPMC decreased considerably when carbamazepine was present in the formulations. One should thus be aware that the drug substance and the HPMC could interact differently depending on their respective chemical structures, which can affect the release of the drug. Measuring the substituent heterogeneity and the possible interactions between the HPMC and the drug, it will be possible to improve the design and prediction of HPMC matrices with regard to drug release. It can therefore be concluded that to be able to form robust formulations with predictable behaviour and with minor variations in drug release, it is necessary to carefully control the distribution of the substituents along the HPMC chain. The substituent heterogeneity has thus been found to be a true functionality related characteristic of HPMC for the drug release from matrix tablets.

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