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Research paper

Quantitative evaluation of polymer concentration profile during swelling of hydrophilic matrix tablets using ^{1}H NMR and MRI methods

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Abstract

Many pharmaceutical tablets are based on hydrophilic polymers, which, after exposure to water, form a gel layer around the tablet that limits the dissolution and diffusion of the drug and provides a mechanism for controlled drug release. Our aim was to determine the thickness of the swollen gel layer of matrix tablets and to develop a method for calculating the polymer concentration profile across the gel layer. MR imaging has been used to investigate the in situ swelling behaviour of cellulose ether matrix tablets and NMR spectroscopy experiments were performed on homogeneous hydrogels with known polymer concentration. The MRI results show that the thickest gel layer was observed for hydroxyethylcellulose tablets, followed by definitely thinner but almost equal gel layer for hydroxypropylcellulose and hydroxypropylmethylcellulose of both molecular weights. The water proton NMR relaxation parameters were combined with the MRI data to obtain a quantitative description of the swelling process on the basis of the concentrations and mobilities of water and polymer as functions of time and distance. The different concentration profiles observed after the same swelling time are the consequence of the different polymer characteristics. The procedure developed here could be used as a general method for calculating polymer concentration profiles on other similar polymeric systems.

Keywords: Matrix tablet; Swelling; Gel layer; Polymer concentration profile; MRI; NMR; Cellulose ether

1. Introduction

Hydrophilic matrix tablets are widely used for controlled delivery of drugs. On contact with water or body fluids the outer surface of these tablets swells by polymer hydration and chain relaxation, forming a hydrogel coat around the dry central core. It is generally accepted that the gel layer constitutes a diffusional barrier that retards water uptake and, hence, drug release. The drug release from such tablets is a very complex process, which is influenced by many different factors [1–3].

During the process of polymer chain hydration in the hydrophilic matrix tablet, three different layers are formed inside the tablet that are important for drug release [2,4]. The central layer, dry at the beginning, contains the reservoir of the drug and the polymer, and is in the glassy state at temperatures below the glass transition temperature T_g. As water penetrates into the dry polymer matrix the polymer is progressively transformed from the glassy to a rubbery state. The interface between the glassy interior and the rubbery polymer layer is called the swelling front, while the interface between the swollen polymer and the bulk water is known as the eroding front. The swelling front moves towards the tablet centre, whereas the eroding front moves outwards as long as swelling prevails. In the region between these two fronts an elastic hydrogel is formed. In the eroding layer the mobility of the chains is increased and, after full hydration of the polymer chains, they begin to disentangle in the surrounding water. When disentangling takes over from the swelling process, both fronts move towards the centre of the tablet and, after the disappearance of the glassy core, the eroding front moves inwards until the polymer is completely dissolved [5–8].

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The polymers swelling process has been studied by a variety of experimental techniques such as weighing the swollen and dry polymer [2,3,7], observing polymer discs between two transparent Plexiglas® discs during the swelling process [6] and observing the swelling process by magnetic resonance imaging (MRI) [9]. Of these, MRI is a powerful tool for following the formation of the gel layer in hydrated tablets, because of its non-invasive nature, molecular specificity, spatial selectivity, and ability to give quantitative information [9–11].

Different approaches have been taken in using MRI to provide a quantitative picture of the swollen gel layer around the dry central core. Hyde and co-workers studied the swelling of biodegradable polymers based on glycolic and lactic acids, and the structural changes following incorporation of a peptide molecule. They compared the MRI signal intensity of hydrated samples with that of a known reference solution [12]. Fyfe and Blazek studied hydroxypropylmethyl cellulose (HPMC) hydrogel formation. To measure the polymer concentration across the gel layer they used a phenomenological equation based on nuclear magnetic resonance (NMR) spectroscopy data from HPMC–water mixtures [11]. Tritt-Goc and Piślewski studied the swelling kinetics of HPMC by MRI at two different pH values [13].

Non-ionic cellulose ether derivatives are the most frequently used polymers in controlling drug release from hydrophilic matrices, so they have been used as model polymers. The hydration rate of these polymers depends on the nature and degree of polymer substitution [14,15].

We have studied the swelling of cellulose ether tablets, their erosion and the hydrogel structure formed around the dry core of the tablet on contact with water [2,16]. While the water in the hydrogel prevents the polymer network from collapsing and the network prevents the water from flowing away, it also takes part in the release of drugs and serves as the medium for their diffusion within the swollen tablet [17]. The state and dynamics of water within hydrogel samples of different polymer concentration have been studied primarily by water proton NMR. This experiment relies on the fast exchange of water molecules between the bound state on the polymer chains and the free state in the rest of the hydrogel water. It enabled the amount of bound water per polymer repeating unit to be determined. The largest amount of water bound per polymer repeating unit was calculated for HPC, followed by HEC, HPMC K4M and HPMC K100M, which is in good agreement with the degree of hydrophilic substitution of the polymer chains [18].

The aim of this work was to characterize quantitatively the swollen polymer layer in matrix tablets made with different cellulose ethers, using MRI. The physical features of the system, especially the characteristics of the water in hydrogels as determined by NMR, were used to develop a method for calculating the polymer concentration profile across the swollen tablet as a function of swelling time. The procedure presented here should be applicable to calculating polymer concentration profiles of other similar polymeric systems.

2. Experimental

2.1. Materials

The cellulose derivatives used were hydroxyethyl cellulose (HEC, Natrosol 250-HHX, Aqualon, Hercules; $\bar{M}_w \cong 1,200,000$, molar substitution $\cong 2.5$), hydroxypropyl cellulose (HPC, Klucel 99-HXF, Aqualon, Hercules; $\bar{M}_w \cong 1,150,000$, molar substitution $\cong 3.7$), (HPMC, Premium Methocel K4M, Colorcon; $\bar{M}_w \cong 95,000$, methoxyl groups = 22.9% and hydroxypropoxyl groups = 9.2%), and hydroxypropyl methyl cellulose (HPMC, Premium Methocel K100M, Colorcon; $\bar{M}_w \cong 250,000$, methoxyl groups = 22.4% and hydroxypropoxyl groups = 10.4%).

2.2. Methods

2.2.1. Preparation of matrix tablets

Tablets were prepared by direct compression of polymer powders to form tablets of crushing strength 100 N ± 10 (VanKel VK 200, USA; hardness tester; $n = 6$), with $m = 0.50$ g ± 0.01, $2r = 12$ mm, tablet thickness from 4.3 to 5.0 mm. Before MR imaging, the tablets were covered with an impermeable hydrophobic polymer layer in such a way that only one circular surface was left uncovered for water penetration. After coating, the tablets were dried and stored in a desiccator containing silica gel for at least 48 h before testing.

2.2.2. Preparation of hydrogels with known polymer concentration

Hydrogels of each cellulose ether polymer were prepared containing from 1 to 44 wt% polymer. Precisely weighed HPMC was initially dispersed into 90% of the total amount of purified water, heated to 80–90 °C and stirred with a magnetic stirrer. The remainder of the cold water was added and the hydrogel stirred and cooled to room temperature. HPC hydrogels were prepared in the same way, except that the water was heated to 45–50 °C, while HEC hydrogels were made at 25 °C. All hydrogels were stored at 4 °C until fully hydrated. Full hydration of hydrogels was reached approximately after 3 days for low concentrated hydrogels (from 1 to 5 wt%), after 14 days for hydrogels containing maximum 25-wt% of polymer and approximately after 60 days for highly concentrated hydrogels. The homogeneity of hydrogels was checked by MRI.

2.2.3. Experimental parameters for MR-imaging of matrix tablets during swelling

MR-images of matrix tablets during swelling were taken at room temperature using a Bruker Biospec System (Bruker, Rheinstetten, Germany), equipped with

a superconducting magnet (Oxford Instruments Ltd., England) having a static magnetic field strength (B_0) of 2.35 T. The ^{1}H NMR frequency of the spectrometer was ν_H= 100 MHz. A standard spin-echo sequence (ME18) [19] was used with a repetition time (TR) of 200 ms, echo time (TE) of 18 ms and 4 averages to achieve a satisfactory signal-to-noise ratio. The total imaging time was 3 min 58 s. The field of view was approximately 5 cm, with in-plane resolution of 200 μm and the slice thickness of 3 mm. The pixel matrix was 256×256. The swelling experiment was carried out on the tablet in purified water and sequential images of water diffusion into the tablet were taken. The two-dimensional images along the CZ projection were recorded as a function of hydration time. The MR images were taken after hydration times of: 10 min, 20 min, 30 min, 1 h, 1.5 h and, after the 2nd hour of hydration, at hourly intervals up to 9 h. The last image was taken after 24 h of hydration. At least 3 tablets were examined for each type of polymer.

2.2.4. Measurements of NMR relaxation times

The water proton NMR spin–lattice (T_1) and spin–spin (T_2) relaxation time were measured at room temperature on hydrogels of known polymer concentration, using the same NMR equipment as for MR-imaging.

The NMR spin–lattice relaxation time (T_1) was determined by the standard inversion recovery sequence (180°–τ–90°–acquisition) [20] by fitting the measured longitudinal magnetization S_z (τ) to the expression:

$$S_z(\tau) = A - B\exp(-\tau/T_1) \quad (1)$$

where A and B are constants. The spin–spin relaxation time (T_2) was determined using the Carr–Purcell –Meiboom–Gill (CPMG) pulse sequence (90°–τ–(180°−2τ)$_n$ [20] with a spacing between the 180° pulses of 30 ms, and fitting the echo amplitude decay to the expression:

$$S_z(\tau) = C\exp(-\tau/T_2) \quad (2)$$

where C is a constant.

3. Results and discussion

3.1. Gel layer thickness during the swelling of matrix tablets

The hydration-induced swelling of cellulose ether tablets was evaluated qualitatively and quantitatively using MRI. T_1-weighted imaging parameters with very short repetition time were chosen to suppress the strong NMR signal of free water on the top of the tablet and to emphasize the difference between gel layers with different polymer concentrations. The differences in signal intensity on the image result from the differences in the physical state of the water in a given sample layer. Thus, under the chosen experimental conditions, concentrated hydrogels with short T_1 give strong signals, while free water and hydrogels with low polymer concentration characterized by longer T_1 contribute weaker signals [19]. Therefore, the MR images of water in swelling tablets go from dark grey (weak signal of the free water above the tablet), through light grey (water within the gel), to white (adsorbed water on the tablet surface, characterized by short water proton T_1) (Fig. 1). The tablet core is dry at the beginning of the experiment, so there is no water NMR signal and the MR image of the tablet looks black. In later stages of the experiment, the core hydrates, but short T_2 and low water concentration keep the MR signal low.

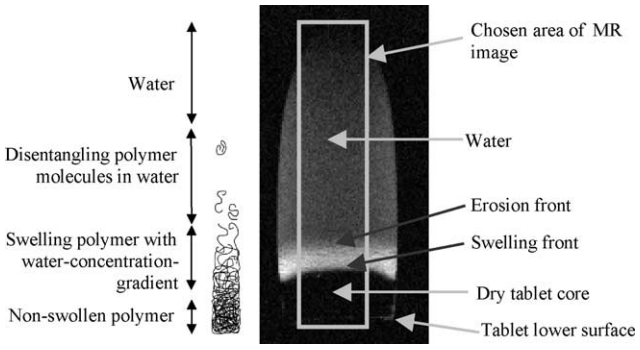

Fig. 1. Schematic representation of the swelling tablet process and the associated MR image area that was chosen for evaluating the polymer concentration profile across the swollen tablet.

Concerning the geometry of tablet hydration, it is important to note that the position of the tablet during swelling has no influence on the process, that radial polymer relaxation is not allowed, and that the swelling process can occur along the axial direction [9–11]. The time protocol of MR imaging was chosen on the basis of the observation that the most water-soluble drugs are released in 24 h. Typical images of the cellulose ether tablets during swelling are presented in Fig. 2.

Inspection of Fig. 2 shows that the depth of the gel layer, indicated by the brightest region of the images, increases with time. The rate of its growth depends mainly on the polymer characteristics. Since the procedure of tablet preparation was the same for all studied polymers this avoided any influence of the manufacturing process on the tablets matrix. Gel layer growth is fastest in HEC tablets, and slowest in HPC tablets. The thickness of the mechanically sensitive gel layers formed on tablet surfaces, as evaluated quantitatively from MR-images, is shown in Fig. 3. It does not differ significantly in the first 30 min of swelling. However, after 30 min, the thickness of the HEC hydrogel layer is significantly greater than that of other polymers and this difference increases during the whole swelling experiment. Differences between HPC and both HPMC polymers were observed after 4 h of polymer swelling, the gel thickness of HPC being smaller than that of HPMC. The largest differences in gel thickness are seen after 24 h of swelling (Fig. 2), when HEC and HPMC K4M tablets no longer retained their original shape, unlike HPC and HPMC K100M tablets. During swelling, ingress of water into the tablet is allowed only from one side

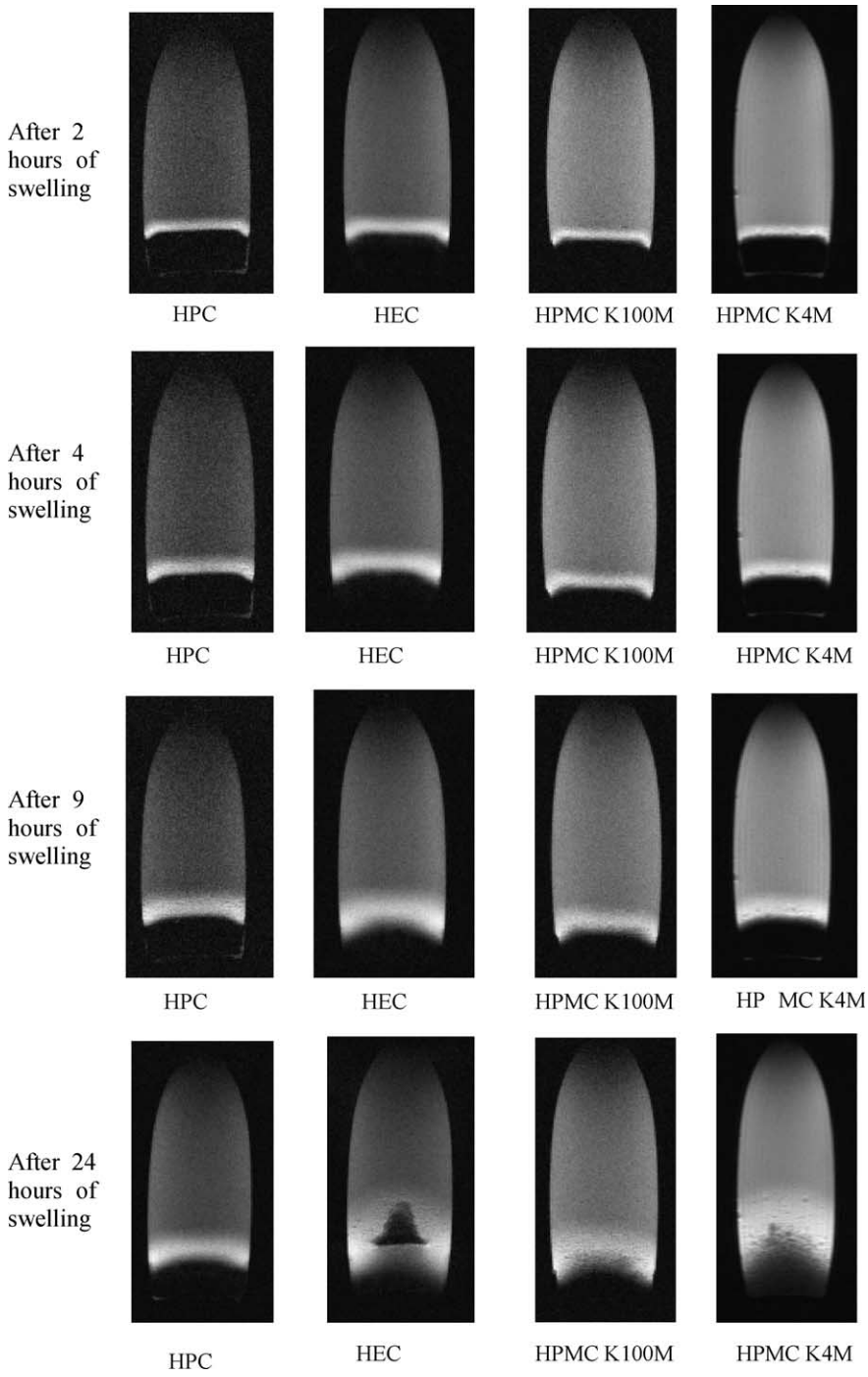

Fig. 2. Typical two-dimensional MR images of swollen cellulose ether tablets after different times of swelling.

(see Methods). Consequently, disintegration of tablets is possible only when the water–polymer interactions exceed the polymer–polymer ones; this happens earlier for shorter and less substituted polymer chains. Thus, the fastest disintegration is observed for HEC tablets because of the high hydrophilicity of the polymer [21]. Of the tablets with HPMC polymers, which are less hydrophilic than HEC, the HPMC K4M tablet with lower polymer molecular mass also disintegrates completely after 24 h, while that with HPMC K100M, having higher polymer mass, still keeps its original shape. The HPC tablets disintegrate slowest, although the HPC polymers bind a lot of water [18,21]. However, it should be noted that the bound water fractions in these polymers were determined under equilibrium conditions. The time required to reach equilibrium differs depending on the strength of the polymer–polymer interactions. If these interactions are strong, as is supposed to be the case of HPC, a longer time is needed for full hydration of polymer chains

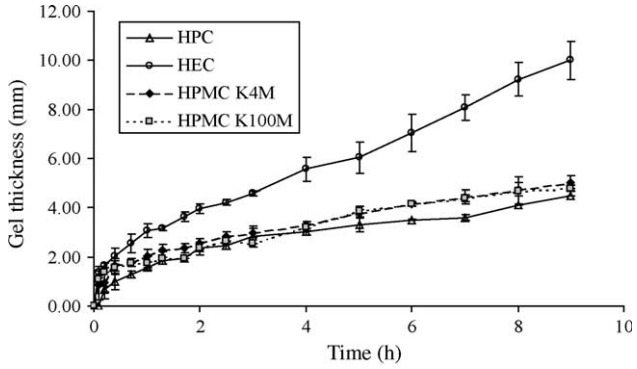

Fig. 3. Thickness of the gel layer formed on the polymer tablet as a function of swelling time, evaluated by MR imaging ($n = 3$–5).

and, consequently, their disentangling. It follows that, even if the gel layer thickness is comparable for the different cellulose ether tablets, the gel layers may still differ in mechanical strength.

3.2. Water proton relaxation times T_1 and T_2 of hydrogels at known polymer concentrations

For a quantitative analysis of MR images of swollen tablets, water proton NMR T_1 and T_2 were measured for the cellulose ether hydrogels at a range of polymer concentrations (Table 1). The room temperature T_1 and T_2 values of water in cellulose ether hydrogels decrease with increasing polymer concentration and, hence, decreasing water content. T_2 decreases faster than T_1, implying a stronger influence of hydrogel polymer concentration on the water proton NMR transverse relaxation rate ($1/T_2$) than on the longitudinal one ($1/T_1$). Further, the longitudinal relaxation rate ($1/T_1$) was generally sensitive to the type of polymer substitution and insensitive to the polymer molecular mass, as indicated by almost equal T_1 values for the HPMC K100M and HPMC K4M hydrogels at the same polymer concentration. On the other hand, different polymer substitutions did not influence the T_2 relaxation. The NMR relaxation data were used for the procedure to calculate polymer concentration profiles across the swollen tablets.

3.3. Polymer concentration profile across the swollen layer of tablet

The polymer concentration across the swollen gel layer is not homogeneous, as shown by the non-uniform colouring of the MRI scan (Figs. 1 and 2). In order to determine the polymer concentration of the gel layer as a function of distance from the tablet core, a series of model samples—homogeneous gels with known polymer concentration—were prepared. T_1 and T_2 values were determined for each of them at the same temperature and resonance frequency conditions. For each polymer concentration the theoretical MRI signal (S) was calculated for the actual imaging parameters. The intensities of the local theoretical MRI signals can be related to those from the MR-imaged tablets during swelling. The derivation is as follows. The signal intensity (S) on an MR-image can be described [11] as

$$S = k\rho\, e^{(-TE/T_2)}(1 - e^{(-TR/T_1)}), \quad (3)$$

where k is a constant independent of polymer, ρ is the water proton density, TE is the echo time, and TR the repetition time. There are three major states of ^1H nuclei in this system. Those that are part of the polymer network have T_1 and T_2 values too short to contribute to the image. The other two are those bound to the surface of the polymer network and free water inside the hydrogel mesh. Unique T_1 and T_2 were obtained on the model hydrogel samples, and were observed to exhibit a strong dependence on gel concentration. These data indicate a fast exchange of water

Table 1
Proton NMR T_1 and T_2 of water in hydrogels of different cellulose ether concentrations at room temperature

HPC			HEC			HPMC K4M			HPMC K100M		
wt/wt%	T_1 (ms)	T_2 (ms)	wt/wt%	T_1 (ms)	T_2 (ms)	wt/wt%	T_1 (ms)	T_2 (ms)	wt/wt%	T_1 (ms)	T_2 (ms)
0	2983	1865	0	2983	1865	0	2983	1865	0	2983	1865
1.1	2429	1390	2.1	2490	957	1.9	2529	1110	1.6	2505	1023
1.1	2741	1221	5	1981	633	3.8	2200	745	3	2314	704
1.1	2585	1305.5	5.6	2238	689	5	1921	510	5	2081	528
3.1	2163	1070	8	1761	424	5.5	1958	474	7	1740	396
6	1606	584	10.5	1466	271	7.6	1711	340	9.2	1603	362
6	1675	554	15.4	1387	190	10	1618	283	12.6	1347	206
10	1262	303	26	814	93.9	11	1471	251	18.5	1043	110
15	955	171	29	627	80	12.6	1288	169	25.3	787	85
22	657	101	29	725	81	15.7	1190	103	25.5	823	69
23	689	114	29.7	730	73.8	24.5	841	72	29.3	736	90
30	597	82	35.3	522	41	24.8	806	63	30.4	718	77
35	519	71	40	545	31	26.5	715	50	34.6	590	48
39	427	57	40	484	29	36.1	580	29	36.5	543	34
40	406	53	40.2	362	17	40.6	511	28	39	537	33
44	361	36	43.8	434	22	46.2	400	23	43.3	450	17

molecules between their bound and free states. The observed unique T_1 and T_2 values can be described as [18,22]:

$$\frac{1}{T_i} = \frac{x}{T_{i,\mathrm{b}}} + \frac{1-x}{T_{i,\mathrm{f}}} \tag{4}$$

where $i = 1,2$, $T_{i,\mathrm{b}}$ is the short proton relaxation time of water in the bound state and $T_{i,\mathrm{f}}$ the long proton relaxation time of water in the free state, and x is the fraction of bound water molecules, which is proportional to the polymer concentration of the hydrogel [18]. Hence, the signal intensity given by Eq. (3) is determined by the unique T_1 and T_2 values given by Eq. (4). Substituting Eq. (4) into Eq. (3) we get:

$$S = k\rho\, \mathrm{e}^{-\mathrm{TE}\left[\frac{x}{T_{2\mathrm{b}}}+\frac{1-x}{T_{2\mathrm{f}}}\right]}\left(1 - \mathrm{e}^{-\mathrm{TR}\left[\frac{x}{T_{1\mathrm{b}}}+\frac{1-x}{T_{1\mathrm{f}}}\right]}\right) \tag{5}$$

$T_{2\mathrm{b}}$ in Eq. (5) is the proton transverse relaxation time characteristic of exchangeable hydrogens on the hydroxyl groups of the polymer chain, or of water molecules hydrogen-bonded to the polymer hydroxyl groups. A typical $1/T_{2\mathrm{b}}$ versus x relationship, obtained by analyzing the experimental T_2 data in terms of Eq. (4) for various values of x, and with the measured bulk water $T_{2\mathrm{f}}$ of 1865 ms, is shown in Fig. 4. The data points indicate that $1/T_{2\mathrm{b}}$ is proportional to x, the polymer concentration.

$$\frac{1}{T_{2\mathrm{b}}} = Kx, \tag{6}$$

where K is a constant characteristic for each polymer species (Table 2). By inserting Eq. (6) into Eq. (5) the image brightness (S) can be expressed as:

$$S = k\rho\, \mathrm{e}^{-\mathrm{TE}\left[Kx^2+\frac{1-x}{T_{2\mathrm{f}}}\right]}\left(1 - \mathrm{e}^{-\mathrm{TR}\left[\frac{x}{T_{1\mathrm{b}}}+\frac{1-x}{T_{1\mathrm{f}}}\right]}\right) \tag{7}$$

By fitting the normalized image brightness (S) of the samples with known polymer concentration ($1-\rho$) to Eq. (7) (Fig. 5), we obtain two new parameters, k and $T_{1\mathrm{b}}$, which are characteristic for each kind of polymer (Table 2). From the dependence of S on polymer concentration (Fig. 5) the highest theoretical signal intensity (S) can be deduced. This indicates the polymer concentration, which corresponds to the highest signal intensity S, which in turn means the brightest area on the MR image of the tablet.

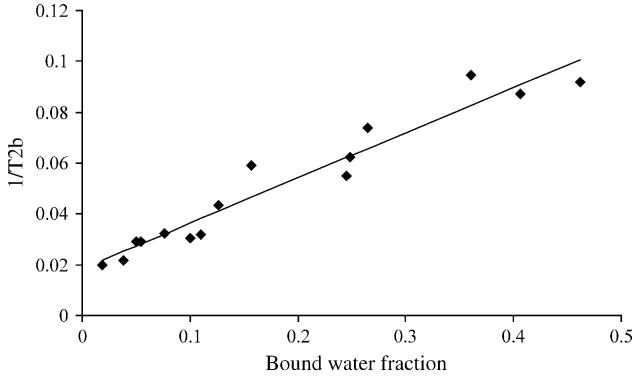

Fig. 4. The calculated $1/T_{2b}$ values for HPMC K4M polymer (as an example) as a function of the fraction of bound water molecules x, which is proportional to the polymer concentration in hydrogels. The points represent calculated values, while the line indicates the linear relationship between $1/T_{2b}$ and the fraction of bound water.

Table 2
The characteristic parameters (Eq. (7)) that describe the dependence of theoretical signal intensity (S) on polymer concentration in hydrogels

Polymer	k	K	T_{1b} (ms)
HPC	1.00	0.22	252
HEC	0.93	0.29	302
HPMC K4M	1.00	0.27	390
HPMC K100M	0.98	0.26	342

After the theoretical MR signals for hydrogels were obtained, the real MR images of the tablets during swelling were taken under detailed consideration. The area that includes a tablet with the gel layer on its surface was chosen for each image (Fig. 1). Using the parameters from Table 2 as well as those under which images were taken, we calculated the polymer concentration from the image brightness of the swollen tablet for consecutive hydration times, using Eq. (7).

Concentration profiles of the gel layers on the surface of different cellulose ether tablets at different swelling times are presented in Fig. 6. The gel layer for each cellulose ether tablet becomes thicker during the swelling process and its concentration profile changes continuously. After the first hour of swelling there are no appreciable differences between the polymers. The polymer concentrations increase very steeply towards the tablet centre. Thin gel layers are formed there and the gel is seen to grow outwards. After 4 h of swelling the gel layers are more pronounced, but the growth rates still do not differ significantly.

After 9 h of swelling, the steepest slope of the concentration profile and the thinnest gel layer are observed for HPC tablets (Fig. 6A). In contrast, the gel layer of HEC tablets is

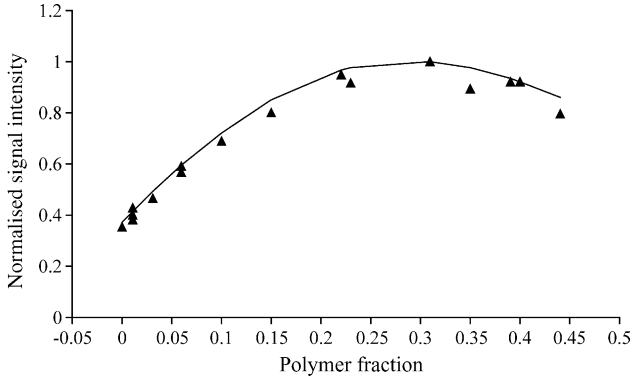

Fig. 5. The calculated theoretical signal intensity (S) of water protons in HPC hydrogels (represented by points) as a function of polymer fraction in hydrogels. The line represents the fitted function on the basis of Eq. (7).

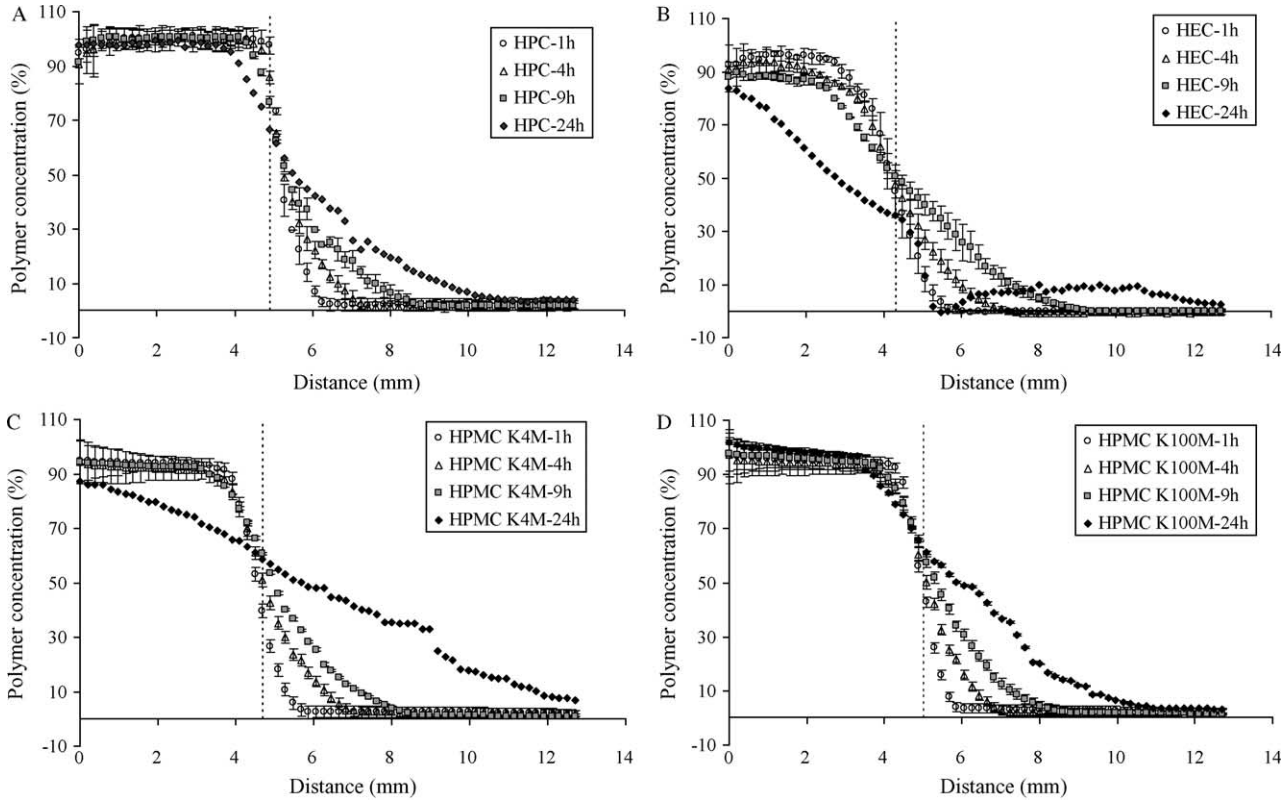

Fig. 6. Concentration profiles of polymers ((A) HPC, (B) HEC, (C) HPMC K4M, (D) HPMC K100M) after different times of swelling. The dashed line indicates the initial position of the water–tablet interface.

the thickest (Fig. 6B) and the polymer chain concentration through the gel layer increases relatively slowly. This means that the HEC chains relax rapidly and that water molecules enter the tablet matrix relatively quickly. For the two types of HPMC tablets there are no significant differences either in the gel layer thickness or in the rate of increase of polymer concentration through the gel layer (Fig. 6C and D). The swelling behaviour of the HPMC polymers is intermediate between those of the HPC and HEC polymers. On the basis of these results, the fastest drug release would be expected from the HEC tablets, followed by the two HPMC tablets, and the slowest release from the HPC tablets.

After 24 h of swelling, the gel formed in the HEC tablet was inhomogeneous (Fig. 2) and was present through the whole tube in which the swelling experiment took place. The steepest concentration profile through the gel layer was found in HPC, followed by HPMC K100M and HPMC K4M. The slowest erosion, observed in the HPC tablet, is due to the strength of the interactions between the HPC polymer chains, and to its lower hydrophilicity, as determined by DVS [21]. The most pronounced differences between the HPMC polymers are seen after 24 h, where it is obvious that the largest HPMC K100M chains need more time to disentangle and dissolve into the surrounding medium.

Fig. 6 demonstrates that the gel layers move towards the tablet interior with the same speed as the swelling front, thus enabling the swelling-controlled release of drug molecules. When, at a certain position in the gel there is sufficient unbound water, it dissolves the drug and enables its diffusion out of the tablet matrix. Our previous studies suggested that, in cellulose ether polymers, there is sufficient unbound water for drug release at a wide range of polymer concentration [18]. Drug release is determined, not merely by the amount of free water available, but also by the mesh size of the polymer network, which is smaller at higher polymer concentration [16].

4. Conclusion

We have developed a method by which MRI and NMR relaxation data obtained on the swelling tablet can be combined for non-destructive determination of the concentration profile in gel layers as a function of time. The thickest hydrogel layer was observed for the HEC polymer tablet, followed by definitely thinner but almost equal gel layer thicknesses for the HPC, HPMC K4M and HPMC K100M tablets. Water proton NMR relaxation measurements were combined with MRI data to determine the polymer concentration profile across the swollen tablet. It was found, in particular, that the differences in concentration profiles after the same swelling time are

the consequence of the different polymer characteristics (different substitution type, molecular mass, hydrophilicity, polymer–water and polymer–polymer interactions). The thickness of the gel layer not only increases with swelling time, but its polymer concentration profile is continuously changing.

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