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Hydration of Hydroxypropylmethyl Cellulose: Effects of pH and Molecular Mass

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Magnetic resonance imaging was used to study the diffusion of a water solution of hydrochloric acid (HCl) and sodium hydrochloride (NaOH) into hydroxypropylmethyl cellulose matrices. Polymer in the form of a cylinder was hydrated in a water solvent of pH = 2, 7, and 12 at 37°C and monitored at equal intervals with a 300 MHz Bruker AVANCE. The spatially resolved spin–spin relaxations times and spin densities, along with a change in the dimension of the glass core of the polymer were determined for hydroxypropylmethyl cellulose tablets as a function of hydration times. The data showed the effects of the pH solvent and of the molecular mass of the polymer on the swelling process, spin–spin relaxation time, and diffusion of solvent molecules into hydroxypropylmethyl cellulose matrices. The time dependence of the diffusion front, effective T_2, and proton-density ρ analysis clearly indicate a case II diffusion mechanism in the system composed of a water solution of hydrochloric acid (pH = 2) and hydroxypropylmethyl cellulose, whereas in the case of water solutions with pH = 7 and 12 the anomalous and case I diffusion are observed, respectively.

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1. Introduction

Hydroxypropylmethyl cellulose (HPMC) belongs to the family of hydrophilic polymers which in contact with liquid (water or body fluid) swell and make a gel layer around dry core of the polymer matrix [1–13]. The kinetics of the gel layer formation depends on the external parameters like temperature, molecular weight of the polymer, and pH of the solution. HPMC was the subject of many studies, but there still remain the unsolved problems concerning the relations

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between the gel layer formation and the diffusive transport within the gel matrix [1–13]. Gaining exact knowledge about these problems is a very important task, because hydroxypropylmethyl cellulose is the polymer most frequently used in the pharmaceutical industry for production of controlled drug delivery systems. The main issue of such a system is to predict the mechanism of the drug release. One of the important mechanisms that govern the release of the drug is the diffusion of a water solvent or body fluids into a dry hydrophilic polymer. During hydration the gel layer is formed around the dry core of polymer. The gel layer constitutes a barrier for the drug release and decides about the success or failure of the controlled release devices produced on the basis of the HPMC polymer.

The purpose of this study was to investigate the influence of the solvent pH and molecular mass of the polymer on the kinetics of the gel layer formation. As a method we used magnetic resonance imaging (MRI) [14–16]. MRI is very sensitive to mobile protons and can therefore observe liquids within the porous matrix of the polymer. What is more MRI is a non-destructive and non-invasive technique and the experiment can be conducted *in situ*.

2. Experimental

2.1. Sample preparation

The hydroxypropylmethyl celluloses (HPMC 80–120; $\overline{M}_n \approx 12,000$ and HPMC 100M; $\overline{M}_n \approx 120,000$) were purchased from FLUKA as powders and used as supplied. They are characterized by the same group substitutions (methoxyl groups = 21% and hydroxypropyl groups = 5%), average molecular weight of monomer (350), but differ in the number of monomer per polymer chain (35 and 350 for HPMC 80–120 and HPMC 100M, respectively).

For microimaging experiments the samples were prepared in the form of cylindrical tablets with a diameter and length equal to 8 mm and 5 mm, respectively. Tablets were prepared by direct compression of polymer powders under a pressure of 100 MPa. The hydration of HPMC tablets was performed in three types of solvent: acidic (pH = 2), neutral (pH = 7) and alkaline (pH = 12) prepared from hydrochloric acid (HCl) and a sodium hydrochloride (NaOH) water solution. The hydration process started when the HPMC tablet was immersed in the particular solvent. The temperature of the solvents and polymer tablets was maintained constant (37°C). At different hydration times the solvent was removed from the sample tube, the tube was placed in the magnet and then images were taken. Such a procedure was repeated until the beginning of the dissolution of the HPMC tablets was observed.

2.2. MRI measurements

MR images of HPMC tablets were taken using a Bruker AVANCE 300 MHz spectrometer equipped with imaging facilities. The static B_0 field of 7.05 T corresponds to a ^{1}H resonance frequency of 300.23 MHz. A Bruker imaging probe

head Micro 2.5 was used with a 25 mm birdcage coil. The spatial distribution of the spin–spin relaxation time T_2 and spin densities $\rho(r)$ were determined from the images using the Carr–Purcell–Meiboom–Gill (CPMG) pulse sequence $(90^\circ - (180^\circ\text{-}2\tau)_n)$ with a spacing between 180° pulses of 10 ms and $n = 64$ [17, 16, 13, 14]. A two-parameter fit of the following exponential equation:

$$A(\tau) = A_0 \exp(-\tau/T_2) \tag{1}$$

to the experimental points of the echo amplitude decay was performed pixel by pixel. In Eq. (1) $A(\tau)$ is the echo amplitude at time τ, and T_2 is the spin–spin relaxation time. The parameter A_0 is equivalent to the spin densities ρ (in our case to the densities of the solvent protons in the particular pixel of the gel layer of HPMC tablets). Therefore, the fitting of Eq. (1) to the experimental data provides a 2D spatial distribution of the spin–spin relaxation time and proton-density or so-called T_2 and ρ maps. These 2D maps give the corresponding 1D profile of the studied parameters in any direction.

The images were acquired with a pixel resolution of approximately 117 μm × 117 μm × 2 mm, where 2 mm was the thickness of the image slice taken from the middle of the sample, along the main axis of the cylindrical sample (axial slice) of HPMC.

3. Results and discussion

Figure 1 shows typical two-dimensional MR images of swollen hydroxypropylmethyl cellulose tablets after different times of swelling. The images are for an acidic solvent, but similar ones were also obtained for neutral and alkaline

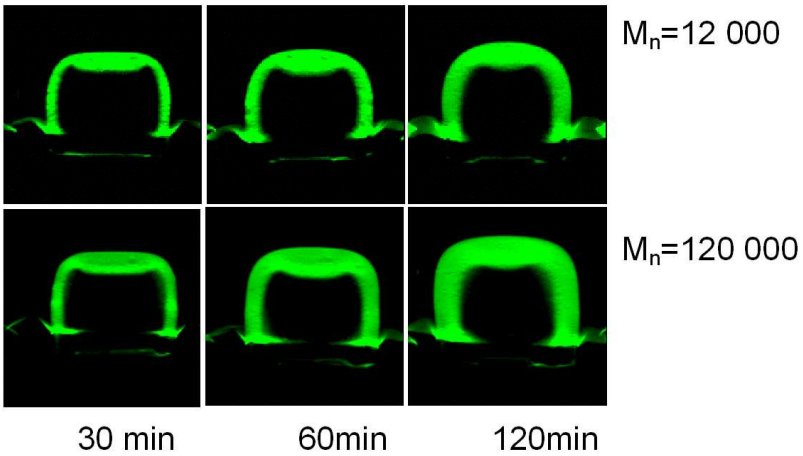

Fig. 1. Typical two-dimensional MR images of swollen hydroxypropylmethyl cellulose tablets after different times of swelling (pH = 2). The in-plane resolution of the images is 117 μm × 117 μm.

solvents. Three features are clearly seen from the images in Fig. 1: the growth of the gel layer with time, the reduction in size of the dry core of the polymer, and the increase in the diameter of the polymer with time. The experimental conditions (the value of the first echo time) were fixed in such a way that only the protons of the solvent gave an NMR signal. The clear border between the dry core of the polymer and the gel layer marked the diffusion front. The distance between the diffusion front and the outer edge of the sample defines the thickness of the gel layer (d) which was determined directly from the images. In Fig. 2 the

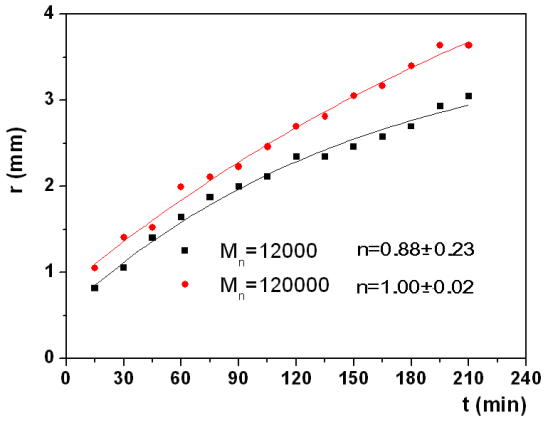

Fig. 2. Thickness of the gel layer formed on the HPMC tablets hydrated in an acidic solvent (pH = 2) evaluated from MRI images taken as a function of hydration time. The solid lines represent the best fit of Eq. (2) to the experimental points.

thickness of the gel layer formed on the polymer tablet as a function of swelling time is presented for a system composed of HPMC and an acidic solvent. The rate of gel growth depends mainly on the polymer characteristics. The fact that the preparation of the tablets was the same for the studied polymers avoided any influence of the manufacturing process on the sample matrix. Of the two tablets of HPMC polymers, the HPMC 100M tablet with higher polymer molecular mass shows faster gel layer growth than the HPMC 80–120 tablet with lower polymer molecular mass. The differences are observed in the whole swelling experiment. The hydrodynamics volume occupied by the hydrated polymer chains is larger in polymers of higher molecular weight. Consequently, greater swollen mass of the matrices was formed. The highest difference in the increase in the initial diameter of the samples, observed after 180 min of hydration, occurs in the alkaline solvent and is equal to about 27% and 48% for HPMC with lower and higher molecular mass, respectively.

The growth of the gel layer as a function of hydration time was analyzed according to equation

$$d(t) = a + bt^n, \tag{2}$$

where d is the gel layer thickness which depends on the hydration time t, n is the exponent characterizing the diffusion mechanism and a, b are the constants. Only in two cases of $n = 0.5$ (pure diffusion called Fickian or case I diffusion) and $n = 1$ (swelling-controlled or case II transport) does the above equation become physically realistic. Other values of n indicate anomalous transport kinetics [18–20] i.e. a combined mechanism of Fickian and case II transport. Equation (2) was used to fit the experimental results shown in Fig. 2 where the solid lines represent the best fit of Eq. (2) to the experimental points. Parameter estimates derived from the fitting of Eq. (2) to the experimental results of the increase in the gel layer thickness as a function of hydration time are shown in Table I, together with the results obtained for neutral and alkaline solvents. In the case of these solvents the gel layer growth shows the same behavior as for acidic solvent i.e. is faster in HPMC tablets with higher molecular mass, and slower in HPMC with lower polymer molecular mass. For the studied solvents the fittings were quite good judging from the R^2 values (0.9999 or 0.9998). The most important fitted parameter is n as its value can be directly compared to the theoretical predictions concerning the mechanism of the diffusion of solvent in a porous matrix. From Table I we can see that n values are equal approximately to 1 and 0.5 for the solvent with pH = 2, 7, and 12. The influence of the solvent's pH is observed on the value of the n parameter, but not the influence of the molecular mass of the polymer.

TABLE I

Parameter estimates derived from the fitting of Eq. (2) to the experimental results of the increase in the gel layer thickness as a function of hydration time.

pH	M_n	a	k	n	R^2
2	12000	1.04 ± 0.36	0.02 ± 0.03	0.88 ± 0.25	0.9998
2	120000	1.23 ± 0.28	0.02 ± 0.01	1.00 ± 0.19	0.9998
7	12000	0.60 ± 0.09	0.15 ± 0.03	0.50 ± 0.03	0.9999
7	120000	0.75 ± 0.04	0.16 ± 0.01	0.51 ± 0.02	0.9999
12	12000	0.64 ± 0.17	0.16 ± 0.06	0.50 ± 0.06	0.9998
12	120000	0.75 ± 0.12	0.17 ± 0.04	0.51 ± 0.04	0.9988

In the literature, the conclusion concerning the mechanism of the diffusion of solvent in a polymer matrix is based more often on the estimates for n and statistical properties of the regression line [9]. Therefore, we can classify the mechanism of the diffusion of solvent into HPMC matrix as Fickian diffusion for neutral and alkaline solvents ($n = 0.5$) and case II for acidic solvent ($n = 1$). However, in the case of anomalous transport kinetics a definite conclusion for the diffusion mechanism cannot be justified based only on the estimates of n.

According to Alfrey's classification the spatially resolved spin–spin relaxation times and spin densities of solvent molecules within the gel layer of the polymer together with the values of n should be taken into consideration in order to fully classify the mechanisms of the solvent diffusion into the polymer [19]. Table II gives the classification of the diffusion mechanism made on the bases of T_2, ρ, and the time dependence of the gel layer thickness characterized by the n exponent.

TABLE II

Alfrey's classification of diffusion.

Case I or Fickian diffusion	Case II diffusion
Diffusion is subject to Fick's law	Diffusion is not subject to Fick's law
The diffusion of the solution is very slow when compared to the polymer relaxation	The diffusion of the solution is considerably quicker in comparison to the speed of polymer chain relaxation
The concentration of the solution in the gel layer of the polymer increases when going from the dry core of polymer to the external edge of the layer	The concentration of the solution is constant in the gel layer
The spin–spin relaxation time of the solution is constant in the gel layer of the polymer	The spin–spin relaxation time of the solution in the gel layer increases when going from the dry core of polymer to the external edge of the layer
The depth of a proton solvent penetration is proportional to the square root of the diffusion time	The depth of a proton solvent penetration is proportional to the diffusion time

MRI used in our study allows us to obtain the spatially resolved values of T_2 and ρ for the proton solvent within the gel layer of HPMC matrix. The results in the form of a 1D profile taken along the diameter of the tablets are shown in Fig. 3. These profiles (only the left parts are presented) show the distribution of the T_2 and ρ in the gel layer of HPMC swelled in the acidic, neutral, and alkaline solvent for 210 min. An important feature of the profiles is their shape, especially in the inner part of the gel layer. The ρ-profiles show a sharp front between the gel and the dry core of the tablet for acidic solvent and a continuous decrease in the proton concentration from the most outer part of the gel layer toward the dry core of HPMC matrix for the alkaline one.

The T_2-profiles also show a significant difference for acidic and alkaline concentration profiles. The acidic protons have almost the same value of the spin–spin relaxation time within the gel layer whereas a continuous decrease in the value of T_2 is observed for acidic protons. The T_2- and ρ-profiles taken for the neutral solvent diffused into hydroxypropylmethyl cellulose show a behavior that is a mix of that found for the acidic and alkaline solvents.

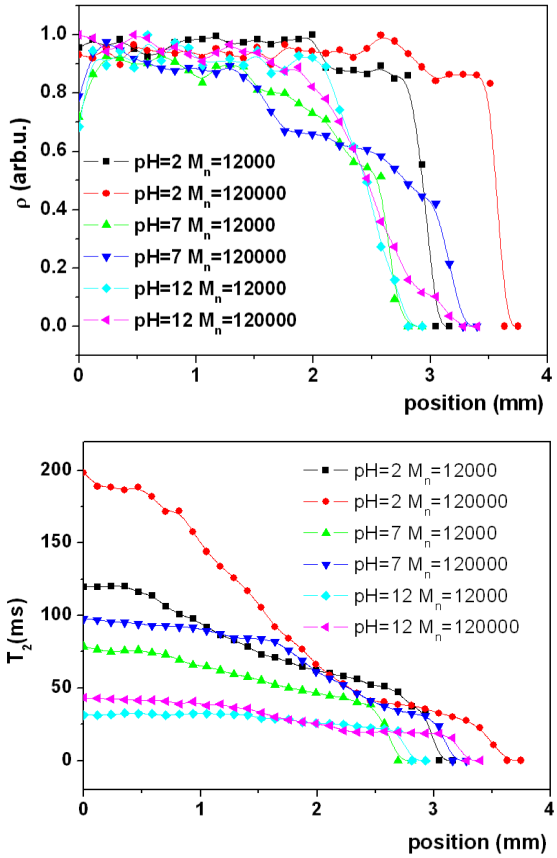

Fig. 3. The spin–density (ρ) and spin–spin (T_2) profiles of acidic, neutral, and alkaline solvent protons within the gel layer of hydroxypropylmethyl cellulose taken after 210 min of hydration time. The profiles (only the left parts are presented) were obtained along the diameter of the tablets from images like those shown in Fig. 1.

Taking into consideration the combined results of the spatially resolved spin–spin relaxation times and spin densities of solvent molecules within the gel layer of the HPMC polymer together with the values of n we conclude the diffusion mechanisms for the acidic and alkaline solvents within the HPMC polymer to be Fickian and case II, respectively. However, in the case of a neutral solvent diffusing in the HPMC, judging only from the value of n ($n = 0.53$), the diffusion mechanism was classified as Fickian. As can be seen from Fig. 3 and Table I, such a conclusion is not correct. The diffusion mechanism in the case of the neutral solvent should be classified as an anomalous diffusion. Therefore, our results show that indeed MRI is the only method which allows the distinguishing of the abnormal diffusion.

The spatially resolved relaxation data presented in Fig. 3 not only serves the classification of the diffusion mechanisms, but also gives information about the mobility of the solvent molecules within the polymer gel and their interactions

with the macromolecules. There is a significant difference in the values of the spin–spin relaxation times of solvent protons within the gel layer of the same HPMC polymer, depending on the solvent pH value. The values of T_2 are equal to 45 ms, 120 ms, and 200 ms for acidic, neutral, and alkaline protons, respectively, for HPMC with higher molecular mass and after 210 min of hydration. For the HPMC with lower molecular mass the T_2 values for acidic, neutral, and alkaline solvent are correspondingly equal to 30 ms, 52 ms, and 95 ms. Thus, for each of the studied solvents the highest value of T_2 is always observed for hydroxypropylmethyl cellulose with $\overline{M}_n \approx 120,000$, rather than for the one with $\overline{M}_n \approx 12,000$.

Analysis of the echo amplitude decay dependence on the echo time (Eq. (1)) gives a single relaxation time for acidic, neutral, and alkaline proton solvents in the gel of HPMC. Such results indicate that the protons in the studied systems are involved in the fast exchange process. Therefore, the T_2 measurements of acidic solvent protons presented in Fig. 3 have been interpreted, like in other polysaccharides gels [21–25], in terms of a fast exchange which takes place between the free and bound state of water. However, in order to explain the reduction in the relaxation time observed for neutral and especially for acidic solvents, we have to assume that in addition to the fast exchange of water molecules, other mechanisms of the relaxation take place. This is a chemical exchange between water protons and hydrogen of hydroxyl groups of side chains of the monomeric units of polymer, but also between water protons and the hydroxyl group of alkaline solvent [26–29]. The chemical exchange relaxation process is the major contribution to the relaxation in the alkaline solvent and as a result a significant reduction of the T_2 values is observed when compared to T_2 in the acidic solvent.

4. Conclusions

The results presented in the paper clearly show that the MRI method can give valuable information about the polymer–solvent system. The amount of gelatinous layer formed varied with the molecular weight of HPMC. With a higher molecular mass of the polymer, a thicker layer of swollen mass was obtained. Thanks to the MRI method we were able to distinguish the anomalous diffusion of the neutral solvent into an HPMC matrix.

We think that the studies of the diffusion of the solvent molecules in HPMC and of the influence of the gel layer formation on the pH of the solvent and molecular mass of the polymer are very important in order to optimize and develop controlled release formulation of such systems.

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