



# Investigation of the State and Dynamics of Water in Hydrogels of Cellulose Ethers by $^1\text{H}$ NMR Spectroscopy

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## ABSTRACT

The aim of this work was to study the effect of the type of substituent of the cellulose ethers and the molecular mass on the state and dynamics of water in the respective hydrogels to specify the quantity of adsorbed water on the polymers or, more explicitly, to calculate the average number of water molecules bound to a polymer repeating unit (PRU).  $^1\text{H}$  NMR relaxation experiments were performed on equilibrated systems of cellulose ether polymers (HEC, HPC, HPMC K4M, and HPMC K100M) with water. In particular, the water proton spin-lattice ( $T_1$ ) and spin-spin ( $T_2$ ) relaxation times were measured in these systems at room temperature. The observed proton NMR  $T_1$  and  $T_2$  of water in hydrogels at different cellulose ether concentrations at room temperature were shown to decrease with increasing polymer concentration. The relaxation rate  $1/T_1$  is sensitive to the type of polymer substituent but insensitive to the polymer molecular mass. The rate  $1/T_2$  appears much less influenced by the polymer substitution. The procedure developed for calculating the amount of water bound per PRU, based on the analysis of the  $T_1$  and  $T_2$  data, shows that this amount is the largest for HPC followed by HEC, HPMC K4M, and HPMC K100M. The results correlate well with the degree of hydrophilic substitution of the polymer chains. This NMR analysis deals with a single molecular layer of adsorbed water for the investigated cellulose ether polymers at all concentrations, while the rest of the water in the hydrogel is bulk-like. Therefore, the mesh size of polymer network in the view of a single molecular layer is not effectively changed.

**KEYWORDS:** Cellulose ethers, hydrogel, controlled release, Nuclear Magnetic Resonance, proton NMR relaxation

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## INTRODUCTION

Controlled release of drugs is becoming one of the more dynamic fields of pharmaceutical research. It shows numerous advantages including fewer side effects and better patient compliance. One possible way to control drug release from tablets is to form a polymer matrix that swells after being introduced into an aqueous environment. Cellulose ethers are widely used as important excipients for designing matrix tablets for this purpose. On contact with water, the cellulose ethers, compressed into the tablets, start to swell and the hydrogel layer starts to grow around the dry core of the tablet. The hydrogel presents a diffusional barrier for water molecules penetrating into the polymer matrix and for drug molecules being released.<sup>1-5</sup> Different cellulose ether substitution types control the drug release by different mechanisms, ranging from Fickian diffusion to anomalous transport. Many theories are available that try to ascertain which release mechanism prevails in these swellable systems.<sup>6</sup>

Hydrogels are 3-dimensional complex systems composed of tangled polymer network structures and incorporated water. The polymers are physically or chemically cross-linked, providing the network structure and physical integrity. The high water content allows these materials to exhibit excellent biocompatibility.<sup>3,7</sup> Furthermore, the interaction of water with such polymers and its distribution within the polymeric system are critical for the hydrogel's mechanical strength, and also their ability to control drug release. The rate at which water diffuses into the hydrophilic matrix and forms the barrier gel layer, and the subsequent diffusion of water through this gel layer, are major factors determining the drug release rate from such devices.<sup>8</sup> Drug release is further influenced by the dynamics of the polymer chains and the polymer mesh size,<sup>9</sup> which represent a barrier for drug diffusion from the polymer matrix. Detailed characterization of the gel layer and, more specifically, of the types of water that exist within the gel, are fundamental to the optimization and prediction of drug release from swollen tablets. Three types of water have been classified in hydrophilic polymer gels: non-freezing or bound water, freezing interfacial or intermediate water, and free water.<sup>10,11</sup> Many methods can be used to determine and

**Table 1.** Average Molecular Mass  $\overline{M}_w$ , Molar Substitution, and Substitution Type of Cellulose Ethers, and Calculated Molecular Masses of Polymer-Repeating Units (PRU)

Polymer	HEC	HPC	HPMC K4M	HPMC K100M
Average molecular mass, $\overline{M}_w$	1 200 000	1 150 000	95 000	250 000
Methoxyl substitution %*	0	0	22.9	22.4
Hydroxypropoxyl substitution %*	0	0	9.2	10.4
Molar substitution*	2.5 <sup>†</sup>	3.7	0	0
PRU	272	376	187	189

\*Values from analytical reports.

<sup>†</sup>Values on the basis of ideal structure of HEC (Natrosol 250).

distinguish the different states of water. The most useful are nuclear magnetic resonance (NMR) and differential scanning calorimetry (DSC).<sup>12,13</sup> However, there are a number of important considerations regarding the way in which experimental data from DSC and NMR experiments are recorded and interpreted. Results cannot be routinely extrapolated from one temperature regime to another. The equilibrium conditions that prevail anywhere in the system depend sensitively on temperature and water concentration. The terminology of non-freezing, freezing interfacial, and free water can also have different meanings in different temperature regimes.<sup>12</sup>

NMR spectroscopy is a powerful technique for detailed studies of the structure, mobility, and hydration properties of various polymeric systems.<sup>8,14-17</sup> Different types of water can be distinguished in hydrogels. In particular, the fraction of free water in hydrated cellulose ethers is important for predicting rates of drug release from the swollen tablets. Different states of water in hydrogel matrices can be specified by measuring the water proton <sup>1</sup>H NMR spin-lattice ( $T_1$ ) and spin-spin ( $T_2$ ) relaxation times.<sup>18</sup>

The aim of this work was to study the effect of the type of substituent on cellulose ethers and the molecular mass on the water proton  $T_1$  and  $T_2$ , to distinguish different types of water present in the hydrogel, and, through these, to quantify the different layers of the hydrated polymers. To determine the average amount of water bound to a polymer repeating unit (PRU), a calculation procedure was developed based on the measured water proton  $T_1$  and  $T_2$  for hydrogels with different water contents. The measured and calculated parameters led to a better insight into the structure and dynamics of water in these hydrogels.

## MATERIALS AND METHODS

### Materials

The cellulose derivatives used were hydroxyethyl cellulose (HEC; Natrosol 250-HHX, Aqualon, Hercules, Rijswijk, The Netherlands), hydroxypropyl cellulose (HPC; Klucel 99-HXF, Aqualon, Hercules, Rijswijk, The Netherlands), and hydroxypropyl methyl cellulose (HPMC; Premium Methocel K4M [HPMC K4M] and Premium Methocel K100M [HPMC K100M], Colorcon, Dartford Kent, UK). Relevant details of these materials are shown in **Table 1**.

### Preparation of hydrogels

Hydrogels of each cellulose ether polymer were prepared at different weight % concentrations (from 1 to 44 wt/wt%). Precisely weighed HPMC was initially dispersed into 90% of the total amount of purified water, heated to 80 to 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 to 50°C, and HEC hydrogels were made at 25°C. All hydrogels were stored at 4°C until equilibrium was reached.

### NMR studies

NMR measurements were made at room temperature using a Bruker Biospec System (Bruker, Rheinstetten, Germany) equipped with an Oxford Instrument magnet (Oxford Instruments Ltd, Abingdon, England), having a static magnetic field strength of 2.35T. The <sup>1</sup>H NMR frequency of the spectrometer was  $\nu_H = 100$  MHz.

Measurements of the water proton NMR relaxation times  $T_1$  and  $T_2$  were performed on hydrogels at different polymer concentrations. The NMR spin-lattice relaxation time ( $T_1$ ) was determined by the standard inversion recovery sequence ( $180^\circ - \tau - 90^\circ - \text{acquisition}$ ).<sup>19</sup>  $T_1$  was determined by fitting the measured longitudinal magnetization  $S_z(\tau)$  to equation 1:

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

where  $A$  and  $B$  are constants. The spin-spin relaxation time ( $T_2$ ) was determined using the Carr-Purcell-Meiboom-Gill (CPMG) pulse sequence ( $90^\circ - \tau - (180^\circ - 2\tau)_n$ ).<sup>19</sup> The spacing between the  $180^\circ$  pulses was 30 ms.  $T_2$  was determined by fitting the echo amplitude decay to equation 2:

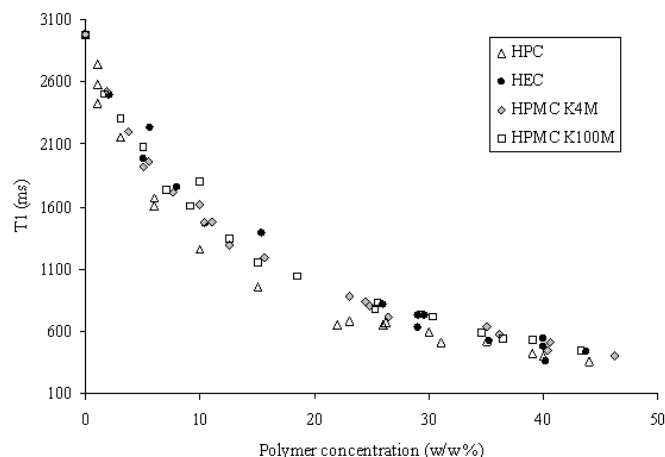
$$S_z(\tau) = C \cdot \exp(-\tau/T_2) \quad (2)$$

where  $C$  is a constant.

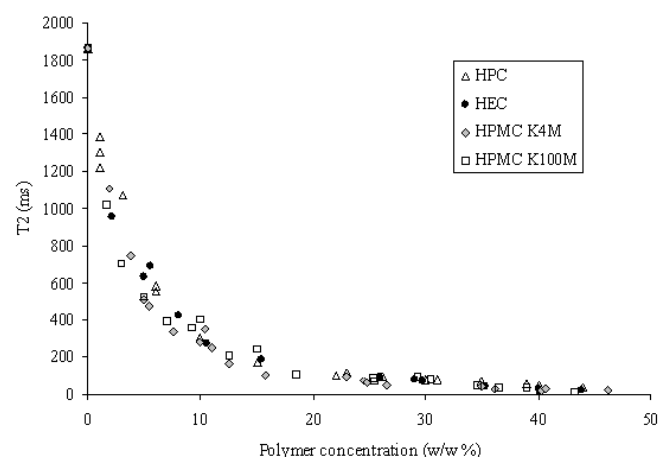
## RESULTS AND DISCUSSION

### *Effect of cellulose ether concentration on water mobility in hydrogels as determined by proton $T_1$ and $T_2$ of water*

The relaxation times  $T_1$  and  $T_2$  of hydrogels, measured at different polymer concentrations, indicated different degrees of mobility of water molecules as a consequence of their different interactions with the polymer lattice (**Figures 1** and **2**). The fastest water proton longitudinal relaxation is achieved when the local magnetic field in the gel polymer lattice fluctuates at the Larmor precessing frequency of protons. If the lattice is composed of only free water molecules, as in bulk water,  $T_1$  would be large, since the frequencies of motion of water molecules are much higher than the Larmor frequency. Thus, it takes longer for the protons to transfer their magnetic energy to the lattice.<sup>19,20</sup> Accordingly, the  $T_1$  of water protons in bulk water is observed to be the largest, in comparison with  $T_1$  values of water protons in hydrogels (see **Figure 1**).



**Figure 1.** Water proton NMR spin-lattice relaxation times ( $T_1$ ) of hydrogels of cellulose ether polymers HPC, HEC, HPMC K4M, and HPMC K100M as a function of polymer concentration. Each point is the average value of several (4 to 10) experimentally determined  $T_1$  values measured on a particular sample.



**Figure 2.** Water proton NMR spin-spin relaxation times ( $T_2$ ) of hydrogels of cellulose ether polymers HPC, HEC, HPMC K4M, and HPMC K100M as a function of polymer concentration. Each point is the average value of several (4 to 10) experimentally determined  $T_2$  values measured on a particular sample.

When a polymer is added to water, the water molecules interact with it by hydrogen bonding and hence the fluctuations of water molecules slow down. As a result, bound water molecules have smaller  $T_1$  and  $T_2$  values. Since unique relaxation times  $T_1$  and  $T_2$  were observed, it follows that the lifetime of a water molecule in a given phase (free or bound) is short compared to the spin relaxation time associated with this phase.<sup>11,18,21</sup> These unique  $T_1$  and  $T_2$  values are given by equation 3:

$$\frac{1}{T_i} = \frac{\eta}{T_{ib}} + \frac{1-\eta}{T_{if}} \quad (3)$$

where  $i = 1, 2$ ,  $T_{ib}$  is the short proton relaxation time of water in the bound state and  $T_{if}$  is the long proton relaxation time of water in the free state. The fraction of bound water molecules,  $\eta$ , is defined as:

$$\eta = \frac{N_b}{N_b + N_f} \quad (4)$$

where  $N_b$  is the number of water molecules bound to the polymer and  $N_f$  the number of free water molecules within the gel.  $\eta$  can also be expressed as

$$\eta = \frac{K \cdot S}{V} \quad (5)$$

where  $S$  is the area of the polymer surface,  $K$  is the thickness of the bound water surface layer, and  $V$  is the total volume of the water.<sup>18,21</sup>

The results show that, on increasing polymer concentration,  $T_1$  becomes smaller due to the increase of the polymer surface and hence to the number of bound water molecules  $N_b$  (**Figure 1**).  $T_2$  is also the largest in bulk water (**Figure 2**). As water molecules in bulk water move very fast, the proton-proton magnetic coupling of the H<sub>2</sub>O molecules is effectively averaged out, the transverse magnetization decays slowly in time, and  $T_2$  is long. With increasing polymer concentration, the dynamics of bound water molecules are slowed down and  $T_2$  becomes shorter.<sup>19,20</sup> However, with increasing polymer concentration, the water proton  $T_2$  decreases faster than  $T_1$ , implying that changes of the hydrogel polymer concentration have a stronger influence on the water proton transverse relaxation rate ( $1/T_2$ ) than on the longitudinal one ( $1/T_1$ ).

### ***Effect of cellulose ether substitution type on water mobility in hydrogels as determined by proton $T_1$ and $T_2$ of water***

The comparison of water proton  $T_1$  relaxation times for different polymers at the same concentration shows that water molecules in HPC hydrogels exhibit the smallest  $T_1$  values (**Figure 1**). Interactions between water molecules and hydroxypropyl groups of the HPC appear to be the strongest of all the polymers studied at this concentration. Alternatively, in terms of equation 3, it could mean that the HPC polymer binds the largest amount of water.

The tendency of the slowest decrease of  $T_1$  with increasing polymer content is noticed for HEC hydrogels (**Figure 1**). The water dynamics in HEC hydrogels are slowed down appreciably less than in HPC hydrogels at the same concentration, implying that the side hy-

droxyethyl groups of HEC polymer do not have as strong an influence on the water molecule movement as those of the hydroxypropyl side groups of HPC polymer.

The magnitude of the spin-lattice relaxation time  $T_1$  of water protons in HPMC hydrogels is higher than in HPC hydrogels of the same concentration (**Figure 1**). A possible reason is that the HPC polymer contains a much higher number of hydroxypropyl substituents than HPMC, which also contains less hydrophilic methoxyl groups. Therefore, there are a relatively smaller number of interactions between the HPMC polymer and water molecules, giving rise to a smaller longitudinal relaxation rate  $1/T_1$ . The water proton  $T_1$  values of the HPMC K100M and HPMC K4M hydrogels at the same polymer concentration show no significant differences, implying that molecular mass has no marked influence on the water proton NMR longitudinal relaxation in these systems.

The spin-lattice relaxation time data lead to the conclusion that it is the polymer substitution type that mostly influences the water proton NMR spin-lattice relaxation rate, due to the differences in the water-polymer side group interactions that vary between different types in strength and in number. This holds also for the water proton NMR spin-spin ( $T_2$ ) relaxation data, though the differences for hydrogels of different cellulose ethers appear less pronounced.

### ***The development of a procedure for calculating the average amount of water bound to a polymer repeating unit***

As mentioned earlier, the determination and characterization of different types of water are strongly dependent on the method used and on the temperature. The experiments presented here were performed at room temperature. In the simplest description of the cellulose ether hydrogels, the water can be considered to exist in free and bound states.<sup>12,14</sup> It is to be expected that the larger the amount of free water, the bigger the pores in the hydrogel, and the easier the diffusion of drugs from the systems. However, the pore size or mesh size in the hydrogels is not dependent only on the amount of free water, but also on the polymer concentration, its molecular weight and substitution, entangling of polymer network in hydrogel, and polymer-polymer and polymer-water interactions.<sup>9</sup> Nevertheless, the amount of free water is one of the essential parameters for the control of drug release.

A procedure for calculating the average amount of water bound to a PRU was developed based on measurements of the water proton NMR  $T_1$  and  $T_2$  of hydrogels. In bulk (deoxygenated) water there is generally no difference in the magnitude of the proton spin-spin ( $T_2$ ) and spin-lattice ( $T_1$ ) relaxation times. In gels and other porous materials, however, the relaxation rates  $1/T_1$  and  $1/T_2$  are enhanced and usually the spin-spin relaxation

**Table 2.** Parameters for Calculating the Fraction  $\eta$  of Bound Water Molecules in Cellulose Ether Hydrogels (Equations 6 and 7)

Polymer	$T_{1f}$ (ms)	$T_{2f}$ (ms)	$\tau_c$ (s)	$T_{1b}$ (ms)	$T_{2b}$ (ms)
HPC	2983	1865	$3.6 \cdot 10^{-9}$	57.1	10.1
HEC	2983	1865	$5.6 \cdot 10^{-9}$	83.2	7.4
HPMC K4M	2983	1865	$5.6 \cdot 10^{-9}$	83.2	7.4
HPMC K100M	2983	1865	$5.4 \cdot 10^{-9}$	80.6	7.6

rate ( $1/T_2$ ) is larger than the spin-lattice relaxation rate ( $1/T_1$ ). This relaxation rate enhancement depends on the ratio between the pore surface area and the pore volume as well as on the nature of the interaction between the surface of the porous medium and the water molecules. As shown previously,<sup>18,21</sup> the enhanced  $1/T_1$  and  $1/T_2$  values can be used to calculate the fraction of water molecules bound to the polymer surface. The argument goes as follows.

Water molecules bound to the surface of a polymer are exchanging with water molecules in the bulk. This exchange is determined by 2 hierarchical processes: first, a molecule has to diffuse from a free state in the bulk to the surface, and second it has to exchange with a molecule that is bound to the surface.<sup>18</sup> Based on the fact that in this study unique water proton  $T_1$  and  $T_2$  values were found for all hydrogel water contents, it can be concluded that a fast exchange of water molecules between bound and free states takes place. Usually the short proton relaxation times  $T_{1b}$  and  $T_{2b}$  of water in the bound state are not known, but are much shorter than those for the free state ( $T_{1f}$ ,  $T_{2f}$ ), which can be identified with the bulk water value.<sup>18,21,22</sup> In this study,  $T_{1f}$  and  $T_{2f}$  were observed to be  $\approx 3$ s and  $\approx 2$ s respectively (**Table 2**). Assuming that the relaxation of bound water is of intramolecular origin only (ie,  $T_{ib} = (T_{ib})_{INTRA}$ ,  $i = 1, 2$ ), the fraction  $\eta$  of bound water in a hydrogel (equation 3) can be deduced from the following expressions derived by Blinc et al<sup>18,21</sup>:

$$\left(\frac{1}{T_{1b}}\right)_{INTRA} \cdot \eta = \eta \cdot \frac{2}{3} \cdot C \left( \frac{\tau_c}{1 + \omega_L^2 \tau_c^2} + \frac{4\tau_c}{1 + 4\omega_L^2 \tau_c^2} \right) \quad (6)$$

$$= \frac{1}{T_1} - \frac{1}{T_{1f}} = \Delta\left(\frac{1}{T_1}\right)$$

$$\left(\frac{1}{T_{2b}}\right)_{INTRA} \cdot \eta = \eta \cdot C \left( \tau_c + \frac{5\tau_c}{3(1 + \omega_L^2 \tau_c^2)} + \frac{2\tau_c}{3(1 + 4\omega_L^2 \tau_c^2)} \right) \quad (7)$$

$$= \frac{1}{T_2} - \frac{1}{T_{2f}} = \Delta\left(\frac{1}{T_2}\right)$$

Here  $\tau_c$  is a single average correlation time due to hindered rotation of bound water molecules (expected to be in the range  $\tau_c \approx 10^{-8}$  to  $10^{-10}$ s, ie, slower than the rotational time of free water by a factor of  $10^2$  to  $10^4$ ).  $C$  is the proton-proton magnetic dipolar coupling constant for rotational tumbling of the  $H_2O$  molecule;  $C = 2.1 \times 10^{10} s^{-2}$ .<sup>18</sup>

The water proton  $T_1$  and  $T_2$  values were determined for each type of cellulose ether hydrogel studied over a range of polymer concentrations, together with the corresponding bulk water proton values  $T_{1f}$  and  $T_{2f}$ , in order

to obtain  $\Delta\left(\frac{1}{T_1}\right)$  and  $\Delta\left(\frac{1}{T_2}\right)$  as defined by equations 6 and

7. Dividing the equations 6 and 7,  $\tau_c$  is determined from the  $\Delta\left(\frac{1}{T_1}\right) / \Delta\left(\frac{1}{T_2}\right)$  ratio. Knowing the  $\tau_c$  values,  $T_{1b}$  and

$T_{2b}$  were calculated from equations 6 and 7, respectively (**Table 2**). Finally, from these parameters, the fraction of bound water molecules  $\eta$  was determined for all hydrogel concentrations with the help of equation 6 (**Table 3**). As expected,  $\eta$  increases with increasing polymer concentration. In this respect, there are no major differences between the different cellulose ether polymers. However, a more detailed analysis was made with regard to the number of bound water molecules per PRU. The molecular mass of PRU was calculated on the basis of the polymer substitution characteristics (**Table 1**). Hence, from the known polymer weight percent (wt/wt%), the total mass of water ( $m_{tot}$ ) was calculated per 100 g of hydrogel, and the corresponding mass of bound water ( $m_b$ ) in that sample was obtained from the relation

$$\eta = \frac{m_b}{m_{tot}} = \frac{m_b}{100 - m_{pol}} \quad (8)$$

where  $m_{pol}$  is the mass of a polymer contained in the sample. The number of bound water molecules per polymer in a hydrogel sample is deduced from the known amount of bound water

$m_b$  and molecular mass of water. The number of PRUs in each hydrogel sample is deduced from the specified

**Table 3.** Calculated Fraction of Bound Water Molecules  $\eta$ , in Hydrogels of Different Cellulose Ether Concentrations

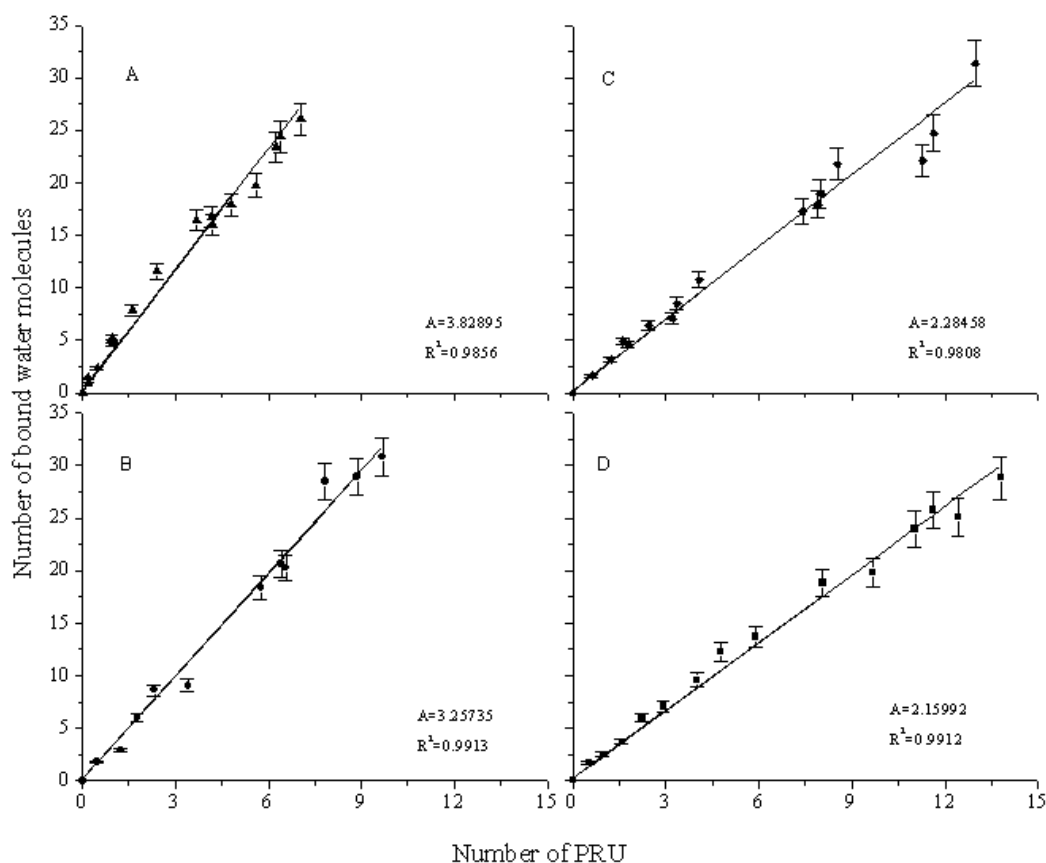
HPC		HEC		HPMC K4M		HPMC K100M	
(wt/wt %)	$\eta$	(wt/wt %)	$\eta$	(wt/wt %)	$\eta$	(wt/wt %)	$\eta$
0	0	0	0	0	0	0	0
1.1	0.002 95	2.1	0.005 52	1.9	0.005 01	1.6	0.005 15
3.1	0.007 25	5.6	0.009 29	3.8	0.009 90	3.0	0.007 81
6.0	0.014 94	8.0	0.019 36	5.0	0.015 43	5.0	0.011 71
10.0	0.026 09	10.5	0.028 87	7.6	0.020 74	7.0	0.019 30
15.0	0.040 63	15.4	0.032 11	10.0	0.023 54	9.2	0.023 25
23.0	0.063 70	26.0	0.074 35	10.4	0.028 34	12.6	0.032 79
26.0	0.067 74	29.0	0.086 89	12.6	0.036 72	15.0	0.043 16
26.2	0.064 92	29.7	0.086 11	23.0	0.067 00	18.5	0.050 23
30.0	0.076 47	35.3	0.131 54	24.5	0.071 06	25.3	0.075 35
35.0	0.090 83	40.0	0.144 06	24.8	0.075 36	30.4	0.085 19
39.0	0.114 53	43.8	0.163 87	26.5	0.088 50	34.6	0.109 52
40.0	0.121 44			35.0	0.101 54	36.5	0.121 34
44.0	0.138 96			36.1	0.115 59	39.0	0.122 99
				40.3	0.157 05	43.3	0.152 00

molecular mass of PRU and the known mass of polymer in the hydrogel sample ( $m_{poi}$ ).

The numbers of bound water molecules as a function of the number of PRUs for hydrogels containing different concentrations of each cellulose ether are presented in **Figure 3**. The slopes A of the linear dependences represent the number of bound water molecules per PRU of the polymers HPC (**Figure 3A**), HEC (**Figure 3B**), HPMC K4M (**Figure 3C**), and HPMC K100M (**Figure 3D**). The highest amount of water is bound on an HPC monomer unit: the average value is 3.8 water molecules per PRU. This is followed by HEC with an average value of 3.3. On the HPMC K4M monomer unit there are bound 2.3 water molecules on average and on the HPMC K100M monomer unit, 2.2 water molecules. The last 2 values are for the same polymer species differing only in molecular weight (95 000 for HPMC K4M and 250 000 for HPMC K100M), indicating the lack of influence of molecular mass on the number of bound water molecules per PRU. The number of bound water molecules per PRU, however, depends predominantly on the type of cellulose ether and on its degree of molar substitution. The HPC polymer is the most highly substituted one (**Table 1**). The hydroxypropyl groups are hydrophilic

and most likely to form hydrogen bonds to the water molecules. On the monomer unit of HEC there are 3.3 bound water molecules, in spite of the fact that the degree of substitution is around 2.5 (**Table 1**). This can be explained by the fact that water molecules are bound not only on hydroxyethyl side groups but also on free hydroxyl groups of the basic glucopyranose unit. Hydroxyethyl groups hence present only a minor steric barrier for the access of water molecules to the free hydroxyl groups.

The basic monomer unit of the HPMC polymers also contains hydrophobic methoxyl substituents having very low probability of binding water. Hence, it is expected that water molecules are bound to the hydroxypropyl groups of HPMC and to the free hydroxyl groups of the basic polymer chain. There are approximately 0.3 moles of hydroxypropyl substituent per mole PRU of HPMC and 2 unsubstituted or free hydroxyl groups per PRU of HPMC. The results of number of bound water molecules per PRU of polymers studied correlate well with the hydrophilic substitution or precisely with the amount of adsorbed water on cellulose ether investigated as determined from adsorption isotherms using the dynamic vapor sorption (DVS) technique.<sup>23</sup>



**Figure 3.** Average number of bound water molecules as a function of the number of PRU for cellulose ether hydrogels at different polymer concentrations: A shows HPC; B, HEC; C, HPMC K4M; and D, HPMC K100M. The slopes (A) of least squares lines indicate an average number of water molecules per PRU. The error bars represent the SE for each measured sample ( $n = 4-10$ ).

These measurements were done at room temperature, where water dynamics are different from those at low temperatures. Therefore, this room temperature study could not discriminate between non-freezing and freezing water as found by independent NMR studies of other hydrogel systems at low temperatures.<sup>21,24</sup> Instead, in this case, unique water proton NMR relaxation times were observed as a result of fast exchange of water molecules between the adsorbed state on the polymer surface and the free state in the surrounding bulk solution within the hydrogel. This NMR analysis deals with a single molecular layer of adsorbed water for all 4 studied cellulose ether polymers, with the rest of the hydrogel water being considered as free water. While the water in the hydrogel prevents the polymer network from collapsing and the network prevents the water from flowing away,<sup>25</sup> it also takes part in the release of drugs and serves as a medium for their diffusion within the swollen tablet. Nevertheless, the mesh size or pore size of the polymer network is the major factor restricting the release of drug molecules.

## CONCLUSION

The state and dynamics of water in hydrogels of 4 polymer cellulose ethers (HPC, HEC, HPMC K4M, and HPMC K100M) were studied using water proton NMR. In particular, the proton NMR spin-lattice ( $T_1$ ) and spin-spin ( $T_2$ ) relaxation times of water in hydrogels of different concentrations were determined at room temperature. The measured ratio  $T_1/T_2$  allowed the determination of the fraction  $\eta$  of bound water on the polymer as a function of the latter's concentration in the hydrogel (**Table 3**). In view of the observed unique water proton NMR relaxation times  $T_1$  and  $T_2$ , the lifetime of a water molecule in each of the 2 states (free or bound) is short compared to the spin relaxation time associated with this state. Hence, due to fast exchange of water molecules between the 2 states, the parameter  $\eta$  can be interpreted also as a fraction of time that an average water molecule in the gel spends bonded to the polymer network and the rest  $1 - \eta$  in the bulk (free state). The exchange of bound and free water is fast on the measured  $T_1$  and  $T_2$  time scales at room temperature. The rate  $1/T_1$  has been ob-

served to be sensitive to the type of polymer substitution and insensitive to the polymer molecular mass (**Figure 1**). On the other hand, the rate  $1/T_2$  appears much less influenced by the polymer substitution.

A procedure for calculating average numbers of water molecules bound per PRU was developed based on the  $T_1$  and  $T_2$  data for various model hydrogels. The numbers obtained are 3.8 for HPC, 3.3 for HEC, 2.3 for HPMC K4M, and 2.2 for HPMC K100M. The numbers for the last 2 polymers differ only slightly, indicating the lack of influence of molecular mass within a given polymer type. These results correlate well with the degree of substitution of polymer chains by hydrophilic substituents. Knowing the dynamics and state of water molecules in hydrogels of cellulose ethers enables a better understanding of the swelling process of cellulose ether-based matrices and of the release of drugs from these systems.

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