Network Structure of Cellulose Ethers Used in Pharmaceutical Applications during Swelling and at Equilibrium

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Purpose. The purpose of this work was to investigate the swelling behavior of four cellulose ethers that differ in their type and degree of substitution and to elucidate the network structure of the swollen matrices under dynamic and equilibrium conditions.

Methods. Dynamic vapor sorption was performed to assess the ability of polymer chains and water molecules to interact. Dynamic and equilibrium swelling studies were performed to calculate molecular parameters of swollen polymers using the Flory-Rehner theory.

Results. We determined the volume-swelling ratio of the polymer matrices and observed that it was dependent on their hydrophilicity. We determined molecular parameters that characterize the swollen hydrogels of cellulose derivatives, such as the polymer volume fraction in the swollen state, $\upsilon_{2,S}$, the effective molecular weight of the polymer chain between physical entanglements, $\overline{M}_e$, the number of repeating units between two entanglements, u, and the number of entanglements per chain, e. The $\overline{M}_e$ of the cellulose derivatives studied varied significantly depending on the type of cellulose ether and on the swelling time.

Conclusions. The order of mesh size, an important parameter for predicting drug diffusion and release, taking into account all determined parameters, is: hydroxypropyl cellulose < hydroxyethyl cellulose < hydroxypropyl methyl cellulose K100M < hydroxypropyl methyl cellulose K4M.

KEY WORDS: cellulose ethers; swelling; mesh size; network parameters; controlled release.

INTRODUCTION

The chemical and physical characteristics of cellulose derivatives used in pharmaceutical applications have been described in relation to their use in sustained-release formulations (1,2). Upon contact with water, tablets start to swell, forming a gel layer around the dry core. Chain dissolution may take place at the gel surface depending on the type of cellulose ether. Numerous investigators, including our group, have studied these two processes (1,3–6). Significant models have been proposed by Peppas and collaborators (7–9) to describe swelling and erosion of polymeric carriers used in pharmaceutical formulations, as well as the water uptake and drug release behavior.

In general, because the dry core of polymer tablets is glassy, the drug contained in them cannot diffuse unless swelling takes place. On swelling, drug molecules dissolve in water and are released by diffusion. The processes of swelling, erosion, and drug release can occur simultaneously and are interconnected (7–9). Thus, it is rather difficult to develop mathematical models that include all interrelated parameters and that fit accurately the experimental results. Recently, in a series of pioneering contributions, Siepmann *et al.* (10,11) developed numerous accurate models that describe all the processes that take place during the drug release from hydroxypropyl methyl cellulose (HPMC) tablets. Yet, even in these models, there has been no previous analysis to characterize or estimate the molecular structure and size of the continuously swelling matrix during drug release, particularly not for tablets based on cellulose derivatives. To better identify the necessary parameters that will characterize the molecular structure of swollen gels produced by hydration of the cellulose derivatives typically used in pharmaceutical formulations, one needs to examine in more detail the mechanism of swelling of such carriers.

Most hydrophilic cellulose derivatives form hydrogels. To evaluate the feasibility of using a particular hydrogel as a drug-delivery device, it is important to know the structure and properties of the associated polymer network that forms during swelling. As reported earlier (9–11), such networks can form when compressed tablets, e.g., tablets of HPMC, are placed in water or in physiological fluids. Then, individual particles swell and their macromolecular chains start entangling, thus creating diffusional spaces that are controlled by the molecular weight and hydrophilic characteristics of the carrier polymers. Evidently, the average distance between consecutive physical entanglements, tie junctions, or tie points in these physical networks is a most important molecular parameter that will control not only the integrity of the formed swollen network (hydrogel) but also the diffusional characteristics of the drug diffusing through it and being released. This average distance is often called the ′mesh size′ and can be expressed either in units of molecular weight (daltons) or in units of length (typically nm).

From a thermodynamic point of view, the most important parameters that define the behavior of these swollen hydrogels are the polymer volume fraction in the swollen state, $\upsilon_{2,S}$, the average molecular weight of the polymer chains between crosslinked points, $(\overline{M}_c)$, and the associated mesh size, ξ. These parameters can be mutually dependent and are determined either theoretically or experimentally (12,13). Each approach has its own basic theory, with limitations in validity and certain approximations.

The aim of this work was to investigate the swelling of discs of cellulose ethers widely used in pharmaceutical formulations and to quantify the molecular parameters that characterize the diffusional pathway for drug transport. To our knowledge, this is the first time that such an approach has been presented for matrix and gel-forming cellulose derivatives.

MATERIALS AND METHODS

Materials

Cellulose derivatives used were hydroxyethyl cellulose (HEC, Natrosol 250 - HHX, Aqualon, Hercules; $(\overline{M}_w) \simeq$

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1,200,000, molar substitution ≃ 2.5), hydroxypropyl cellulose (HPC, Klucel 99 - HXF, Aqualon, Hercules; ≃ 1, 150, 000, molar substitution ≃ 3.7), hydroxypropyl methyl cellulose (HPMC, Premium Methocel K4M, Colorcon; ≃ 95, 000, methoxyl groups = 22.9% and hydroxypropoxyl groups = 9.2), and HPMC (Premium Methocel K100M, Colorcon; ≃ 250,000, methoxyl groups = 22.4% and hydroxypropoxyl groups = 10.4).

Methods

Preparation of Disc-Like Specimens

Discs of the various cellulose derivatives were prepared by compressing 500 mg of powder using round flat punches of 12 mm in diameter (tableting machine EKO; Korsch, Germany). Discs (n = 6) of hardness 100 N ± 10 (VanKel VK 200, Cary, NC, USA) were prepared. Before swelling tests, the diameter and height of each tested disc were measured.

Water Sorption Studies

Water sorption experiments of polymeric powders were conducted in a vapor sorption device (DVS, Surface Measurement Systems Ltd, UK). Gas of known relative humidity was passed over a small sample of the polymer carrier to be tested. The sample was hung on a loop attached to a microbalance that monitors the sample mass as a function of time. The temperature was controlled at 26°C, and the sample mass varied from 1 to 1.5 mg. The relative humidity (%) was varied stepwise from 0 to 95% and back over a period of 30 h.

Preparation of Hydrogels

Each cellulose ether hydrogel sample was prepared in three different weight percent concentrations. Accurately weighed HPMC polymer samples were first dispersed in purified water to form a 90% solution, heated at 80 to 90°C, and stirred with a magnetic stirrer. The remainder of the cold water was added, and the hydrogel cooled to room temperature. HPC hydrogels were prepared in the same way except that the water was heated at 45 to 50°C, whereas HEC hydrogels were prepared at 25°C.

True Density Determination

The true density of polymer discs (ρ_t) was measured using a helium pycnometer (AccuPyc1300, Mycromeritics, Norcross, GA, USA) at 24°C ± 1.

Swelling Studies

Swelling studies were performed by placing the polymeric discs in test tubes and measuring their thickness as a function of time during swelling as shown in Fig. 1. Tubes were kept vertical at 37°C.

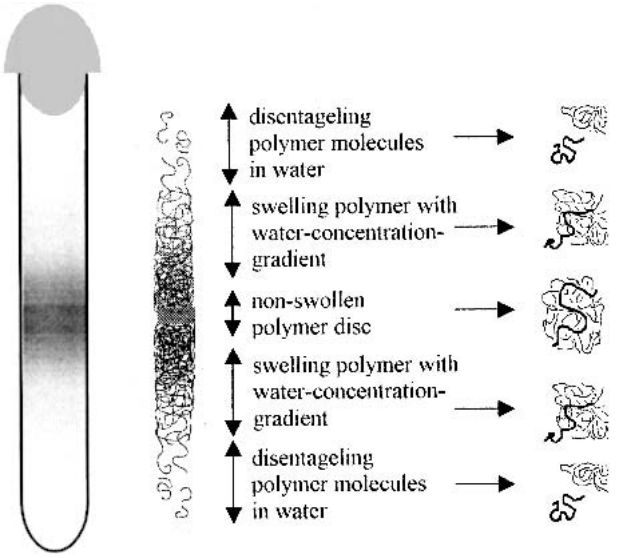

Fig. 1. Experimental set-up of the swelling experiment.

RESULTS AND DISCUSSION

Adsorption Isotherms and Hydrophilicity of Cellulose Ethers

Water sorption measurements were used to study the influence of polymer chemical structure on polymer-water interactions. As shown in Fig. 2, the water adsorption isotherms of HPMC, HPC, and HEC had the same general shape and were characteristic of hydrophilic polymers. HEC was the most hygroscopic polymer, followed by HPMC K4M, HPMC K100M, and HPC. There was no significant hysteresis effect because the polymer mass differences between sorption and desorption were small, i.e., around 2% for HPMC polymers, around 0.7% for HEC polymer, and less than 0.1% for HPC.

Hydroxyethyl substituents of HEC polymer are bound primarily to the hydroxyl group of the basic β-glucopyranose unit and secondarily to the other hydroxyethyl group. There are many possibilities for the interactions between water molecules and unsubstituted hydroxyl and side chain hydroxyethyl groups. HPMC polymers have besides hydrophilic hydroxypropyl substituents also hydrophobic methoxyl groups, and hence exhibited a lower hygroscopicity than HEC. The

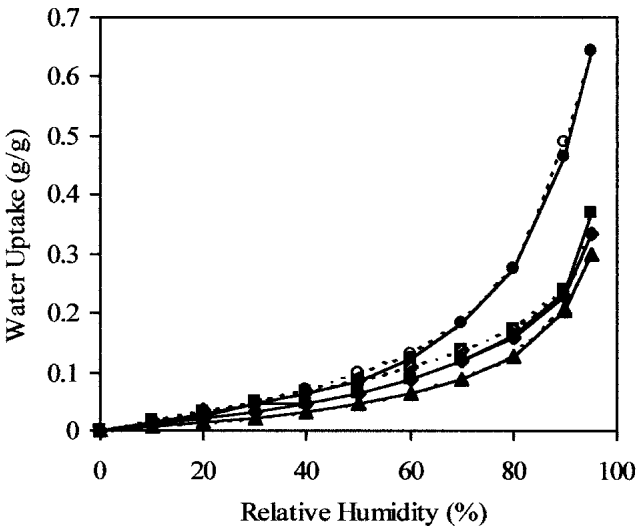

Fig. 2. The change in mass of bulk polymers at equilibrium under different relative humidity using the vapor sorption method: full line, full markers: sorption; dashed line, empty markers: desorption; HEC (●, ○); HPMC K100M (■,□); HPMC K4M(◆,◇); and HPC (▲, Δ).

molar substitution of HPC polymer was 3.7, indicating that most hydroxyl groups are substituted with hydrophilic hydroxypropyl groups, providing many possibilities for interaction between water and the polymer molecules. These interactions are favorable on the surface of HPC. In addition to these interactions, there must be strong interactions between polymer chains, accounting for the low hygroscopicity determined by vapor sorption measurements.

Dynamic and Equilibrium Swelling Studies

The dynamic swelling behavior of hydrogel discs was studied by measuring the thickness of the gel layer formed as swelling occurred in the presence of water at 37°C. Swelling experiments were continued until equilibrium was reached, i.e., until the gel thickness became essentially constant. As noted before by Colombo *et al.* (14), during swelling of the hydrophilic cellulose derivative (HPMC), the macromolecular chains absorb water, leading to an expansion of the network formed and to formation of a quasi-equilibrium structure. This three-dimensional network structure usually is held together by physical chain entanglements, hydrogen bonds, tie junctions, or tie points produced by various types of forces. Upon further absorption of water, these gels may start disentangling, indicating a competitive phenomenon of swelling and dissolution. In our experiments, swelling predominated, as shown by the substantially constant volume of the measured thickness. However, it is important to determine the nature of this three-dimensional network for all cellulose derivatives, even those that might eventually erode.

Figure 3A shows typical plots of the discs thickness as a function of time. The different matrix discs reached equilibrium at different times. The equilibrium state for HEC was reached after 240 h, for HPC and HPMC K100M after 260 h, and for HPMC K4M after 170. The thickness of the HEC gel at equilibrium was almost 4.5 cm. The comparison between different hydrogels is best seen from data normalized to the thickness of the starting discs (Fig. 3B).

The thickness of the samples increased in the following order: HPC, HPMC K4M, HPMC K100M, and HEC up to 190 h of swelling. Beyond that time, differences between HPC and HPMC K4M gel thickness were no longer significant (Fig. 3B). A comparison of swelling data of HPMC polymers showed that equilibrium for HPMC K100M was reached approximately 120 h later than for HPMC K4M. The reason for this phenomenon is that disentanglement of HPMC K100M, and hence erosion, was hindered because of the longer polymer chains. Again, it must be noted that although erosion by disentanglement (7,15) could eventually occur, these studies are relevant for any cellulose material used in tablets.

The thickness of different polymeric discs can be used directly to predict drug release because it is a parameter as relevant to the release process as the swelling front and gel layer parameters used by Colombo *et al.* (8). Of course, in real USP 25, 2001 testing of drug release, swelling, erosion, and release take place in a dissolution apparatus or in a physiological environment where erosion might be somewhat faster. Yet, the overall phenomena observed here are not different. In drug release from polymer matrices under USP conditions, the release is controlled by a combination of swelling, disentanglement and erosion (9,10), and the characteristics of these processes are rate-limiting parameters in drug diffusion (15). Therefore, to use these data for drug release prediction it is necessary to obtain quantitative information about the molecular network structure of the gels.

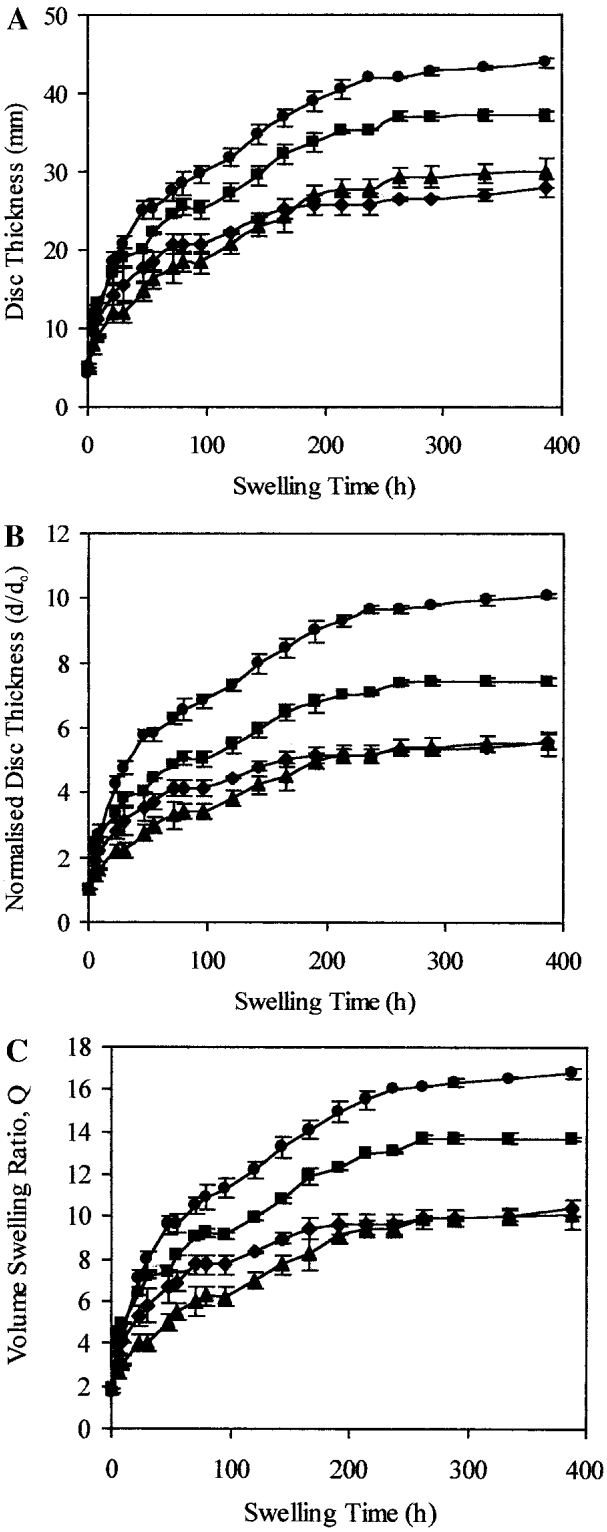

Fig. 3. (A) Thickness of the gel layer formed in a polymer disc as a function of swelling time. (B) Normalized thickness of the gel layer formed in a polymer disc as a function of swelling time. (C) The volume swelling ratio, Q, as a function of swelling time: HEC (●); HPMC K100M (■); HPMC K4M (◆); and HPC (▲).

Volume Swelling Ratio

The dynamic gel thickness data obtained earlier were translated into a volume-swelling ratio, Q, using the following equation:

$$Q = V_s/V_d \quad (1)$$

where V_s is the volume of swollen gel and V_d is the initial volume of the dry disc.

Results of the dynamic swelling behavior of hydrophilic, cellulose-based tablets are presented in Fig. 3C. The volume-swelling ratio correlated well with the hydrophilicity of the polymer determined from vapor sorption measurements. As expected, comparison of the HPMC polymers showed that HPMC K100M, which has a higher molecular weight than HPMC K4M, exhibited a higher Q.

Average Molecular Mass between Physical Entanglements at Equilibrium

The results of gel layer thickness were used to determine the average molecular weight between consecutive entanglements or joints or links by the use of an appropriate theoretical model. In general, the average molecular weight between two consecutive entanglements, ($\overline{M}_e$), can be calculated (12) from the Flory-Rehner equation. This model describes the equilibrium volume-swelling ratio of crosslinked polymers based on the postulate that the elastic retractive forces of the polymer chains and the thermodynamic compatibility of the polymer with the solvent molecules balance each other during swelling. This assumption is valid when the hydrogels are neutral, swelling is isotropic, there are tetra-functional crosslinks at zero volume, four chains are connected at one point, polymer chains are crosslinked in the solid state, and where Gaussian distribution of the polymer chain is assumed (12,13).

The $\overline{M}_e$ was calculated by

$$\frac{1}{\overline{M}_e} = \frac{2}{\overline{M}_n} - \frac{(\upsilon/V_1)\left[\ln(1-\upsilon_{2,s}) + \upsilon_{2,s} + \chi_1\upsilon_{2,s}^2\right]}{\left(\upsilon_{2,s}^{1/3} - \frac{\upsilon_{2,s}}{2}\right)} \quad (2)$$

where $\overline{M}_n$ is the number average molecular weight of the cellulose ether tested, υ is its specific volume, V_1 is the molar volume of water, $\upsilon_{2,S}$ is the polymer fraction in the swollen gel at equilibrium ($\upsilon_{2,S} = 1/Q$), and χ_1 is the Flory or polymer-water interaction parameter (12,13). Values of $\overline{M}_n$ for the cellulose ethers used in these studies are summarized in Table I. Values for HPMC are those provided by the manufacturer, whereas for HEC and HPC they are obtained from $\overline{M}_n$ - $\overline{M}_w/2$. (16). The specific volume of the polymer was the reciprocal value of the true density (Table I), and V_1 was the molar volume of deionized water, 18.1 cm^3/mol.

The polymer-water interaction parameter, χ_1, was introduced independently by Flory and Huggins (12,13). In general, for a polymer to be soluble in water at a particular temperature, χ_1 must be below 0.5. If χ_1 is only slightly greater than 0.5, the polymer will be poorly swollen in water, and the latter is considered as a poor solvent or swelling agent. However, thermodynamically real polymer-water systems do not conform closely to the Flory-Huggins model, and the border value of 0.5 is not strictly valid. Experimental values of χ_1 and their dependence on composition, temperature, and molecular weight provide useful indications of the nature and extent of polymer-water interaction (17). Approximate values of the χ_1 parameter for cellulose ethers in water were used (Table I) on the basis of their chemical structure and interaction with water, determined from sorption measurements.

$\overline{M}_e$ was calculated for each polymer disc under equilibrium swelling conditions (Table I). The resulting order of increasing $\overline{M}_e$ for the cellulose ethers was as follows: HPMC K4M < HPC < HPMC K100M < HEC.

To support the validity of this order, we calculated $\overline{M}_e$ for χ_1 parameters between 0.3 to 0.5 to determine the importance of the thermodynamic compatibility between water and the polymer chains for the calculation of this important molecular parameter. The associated results are presented in Table II. The effect of the Flory interaction parameters on values of $\overline{M}_e$ is somewhat important. However, if we compare the values of $\overline{M}_e$ at the same value of the χ_1 parameter for the polymers investigated, their order always remains as HPMC K4M < HPC < HPMC K100M < HEC. It was concluded that, based on experimental data, this order was valid.

In addition, to confirm the validity of determining $\upsilon_{2,S}$ using a cathetometer, a method based on the buoyancy principle was also used (12). In a typical experiment, a disc was allowed to swell in water, and at different time intervals its

Table I. The Characteristic Data of Cellulose Ethers Needed for Calculation of $\upsilon_{2,s}$ and $\overline{M}_e$ of Hydrogels Formed on Discs in an Equilibrium Swelling Experiment

Polymer disc	Hydroxyethyl cellulose	Hydroxypropyl cellulose	Hydroxypropyl methyl cellulose K4M	Hydroxypropyl methyl cellulose K100M
True density (g/cm^3)	1.3603	1.1985	1.3196	1.3145
$\overline{M}_n$[a]	600,000	570,000	9,000	125,000
υ[b]	0.73519	0.83626	0.75781	0.76075
χ_1[c]	0.35	0.45	0.40	0.40
$\upsilon_{2,s}$[d]	0.05956	0.09897	0.09600	0.07262
$\overline{M}_e$[e]	13,996	10,563	2,868	11,236

[a] Number average molecular weight of polymer.
[b] Specific volume of the polymer (cm^3/g).
[c] Flory interaction parameter or polymer liquid interaction parameter.
[d] Polymer fraction in the swollen gel.
[e] Average molecular weight between two consecutive entanglements.

Table II. Calculated Values of $\overline{M_e}$ (Eq. 2) for Cellulose Ethers at Different Values of χ_1

χ_1 Parameter	$\overline{M_e}$ Hydroxyethyl cellulose	$\overline{M_e}$ Hydroxypropyl cellulose	$\overline{M_e}$ Hydroxypropyl methyl cellulose K4M	$\overline{M_e}$ Hydroxypropyl methyl cellulose K100M
0.30	10,942	3,882	2,259	6,797
0.35	13,996	4,949	2,528	8,470
0.40	19,415	6,712	2,868	11,236
0.45	31,680	10,563	3,314	16,682
0.50	86,038	24,881	3,926	32,377

mass was measured in air and in a non-solvent (heptane). The value of $\upsilon_{2,S}$ could thus be calculated leading to $\overline{M_e}$. Unfortunately, this technique was somewhat difficult to apply to cellulose ether discs.

Therefore, cellulose ether hydrogels were prepared at different polymer concentrations. A hydrogel sample was first weighed in air, w_a, then in heptane, w_h, and, knowing the density of heptane, ρ_h, the volume of swollen gel, V_s, was calculated from

$$V_s = \frac{w_a - w_h}{\rho_h}. \tag{3}$$

The volume of polymer, V_p, in a swollen hydrogel sample was determined from

$$V_p = \frac{w_a \cdot (c/100)}{\rho_p}, \tag{4}$$

where c is the weight percent of polymer in hydrogel sample, and ρ_p is the density of the dry polymer.

Finally $\upsilon_{2,s}$ was calculated from Eq. (5) and $\overline{M}_e$ using Eq. (2)

$$\upsilon_{2,s} = \frac{V_p}{V_s}. \tag{5}$$

The relationship between $\overline{M_e}$ and polymer concentration (5 to 25 w/w%) in the hydrogels was established by fitting the experimental $\overline{M_e}$ values to an exponential function. The fits and phenomenological equations are presented in Fig. 4. As expected, the higher the concentration of the gel samples, the higher the $\upsilon_{2,S}$ and the lower the $\overline{M_e}$ values.

Additionally, the values of $\overline{M_e}$ for swollen discs in equilibrium (Table I) were placed into the phenomenological equations (Fig. 4) and the corresponding concentrations calculated. The obtained weight percent of polymers in swollen discs at equilibrium were 11.2% for HPMC K4M, 9.3% for HPMC K100M, 11.4% for HPC, and 9.8% for HEC. To check the validity of calculated values, the swollen discs were dried to constant weight at the end of the swelling experiment. Concentrations of polymers in the swollen discs thus determined were: 8.6% for HPMC K4M, 9.5% for HPMC K100M, 12.3% for HPC, and 8.4% for HEC discs. These concentrations were in close agreement with those determined based on the predicted model $\overline{M_e} = f(c)$. The methods for determining $\upsilon_{2,S}$ using a cathetometer or by weighing samples are thus comparable.

Calculation of Other Structural Parameters of the Network

Based on the results in Table I and the order of increasing $\overline{M_e}$ for different cellulose ethers, it may be expected that the mesh size of these hydrogels under equilibrium conditions would follow the same order. The average molecular weight between entanglements, which determines the mesh size, could be used to calculate the number of repeating units between two consecutive entanglements, u, using Eq. (6), where U is the molecular weight of each polymer repeating unit.

$$\frac{\overline{M_e}}{U} = u \tag{6}$$

The approximate molecular weights of the repeating units of each polymer were calculated as shown in Table III. The calculated values of u are direct estimates of the mesh sizes in hydrogels, if we assume that the size (in nm) between two consecutive anhydroglucose units, substituted or not, is the same. At equilibrium, the mesh size of HPMC K100M, estimated from u, was the largest, followed by HEC, HPC, and HPMC K4M. However, the mesh size in the hydrogel is probably somewhat smaller than that predicted from the calculation using u, especially for HPC, where the hydroxypropyl substituent is large and the molar substitution is high.

It was also possible to calculate the number of junctions or entanglements, e, per original chain using Equation (7):

$$\frac{\overline{M_n}}{\overline{M_e}} - 1 = e \tag{7}$$

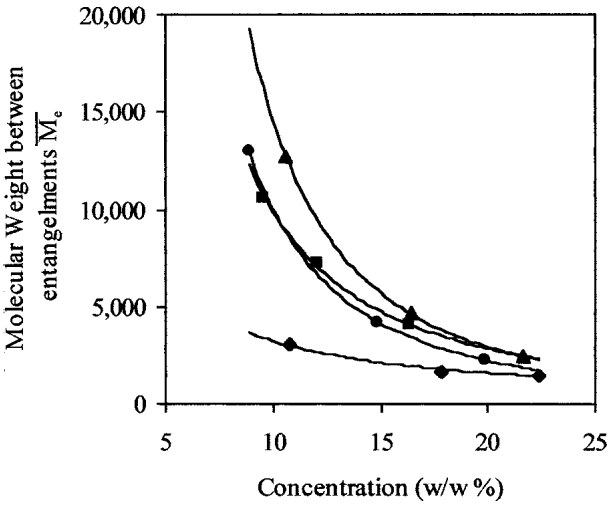

Fig. 4. The relationship between average molecular weight between entanglements, $\overline{M_e}$, and concentration of different cellulose ether in hydrogels: HEC (●); HPMC K100M (■); HPMC K4M (◆); and HPC (▲). The phenomenological equations that describe the fitted curves, are: HEC: $\overline{M_e} = 2 \cdot 10^6 \cdot (concentration)^{-2.179}$; HPMC K100M: $\overline{M_e} = 630{,}000 \cdot (concentration)^{-1.8046}$; HPMC K4M: $\overline{M_e} = 35{,}000 \cdot (concentration)^{-1.042}$; and HPC: $\overline{M_e} = 3 \cdot 10^6 \cdot (concentration)^{-2.3241}$.

Table III. The Molecular Weight of Each Polymer Repeating Unit, *U,* the Number of Repeating Units between Two Entanglements, *u,* and the Number of the Entanglements per Original chain, *e,* at Equilibrium

Polymer	Hydroxyethyl cellulose	Hydroxypropyl cellulose	Hydroxypropyl methyl cellulose K4M	Hydroxypropyl methyl cellulose K100M
U	272	376	187	189
u	51	28	15	60
e	42	53	2	10

where *e* is calculated for the equilibrium state (Table III). The results of this analysis require further explanation. For example, a HEC disc forms a very thick hydrogel layer in the swollen state. The value of $\upsilon_{2,S}$ is the lowest, signifying that the largest amount of water is physically and chemically trapped in the HEC hydrogel structure. As a logical consequence, the mesh size and water content are high compared to those of the other polymers investigated. Because of a high degree of polymerization and high $\overline{M_n}$, the number of entanglements, *e*, is relatively high, which holds the network structure together at equilibrium.

HPC discs form the thinnest hydrogel layers and the $\upsilon_{2,S}$ is relatively high (Table I). This means that the interactions between the HPC chains are very strong and that water molecules occupy a smaller volume than in the case of HEC. Estimation of the mesh size based on $\overline{M_e}$ results would lead to an incorrect conclusion. Indeed, the mesh size of HPC would be expected to be just 1.3 times smaller than that for HEC. However, based on *u* numbers, the mesh size of HPC is 1.8 times smaller than for HEC and the number of entanglements is higher for 11 (Table III). In addition, the molar substitution for HPC is relatively high and the hydroxypropyl substituents occupy a large volume, which means that the mesh size is probably more than 1.8 times smaller than for HEC. The network structure of HPC hydrogel is significantly different from that of the HEC hydrogel despite almost the same average molecular weight of these polymers.

The thickness of the HPMC K100M gel layer is a little smaller than HEC gel layer (Fig. 3A). The value of $\upsilon_{2,S}$ for HPMC K100M is higher than for HEC and lower than for HPC. The mesh size predicted from $\overline{M_e}$ is also intermediate between HEC and HPC but, from the numbers of *u*, HPMC K100M hydrogel has the largest mesh size of all the polymers, and the fewest entanglements. This can also be the consequence of a lower $\overline{M_n}$ than for HEC and HPC. Compared with HPMC K4M, where the number of entanglements per chain is just 2, which could be described as almost a colloid dispersion or very weak gel, HPMC K100M is much more entangled. The mesh size for HPMC K4M predicted from the *u* number is surprising, being the smallest of all those investigated. However, the thickness of the gel layer for HPMC K4M can be compared to the gel layer of HPC. However, HPC is much more entangled than HPMC K4M. In addition, the molar substitution is higher.

Therefore, to predict drug release from these cellulose ethers, more realistic data obtained from dynamic swelling are required.

Changes of Molecular Parameters during Swelling

From the alteration of $\overline{M_e}$ with time shown in Fig. 5A, it can be seen that the rate of approach to the equilibrium $\overline{M_e}$ value is the highest for HEC, followed by HPMC K100M, HPC and HPMC K4M. As mentioned previously, $\overline{M_e}$ is proportional to the mesh size indicating that the release of incorporated drug in those matrices would be expected to be of the same order. However, the order of HPMC K100M and HPMC K4M would be reversed because release from HPMC K4M would be faster because of the fact that the number of entanglements is lower than in HPMC K100M hydrogel (see

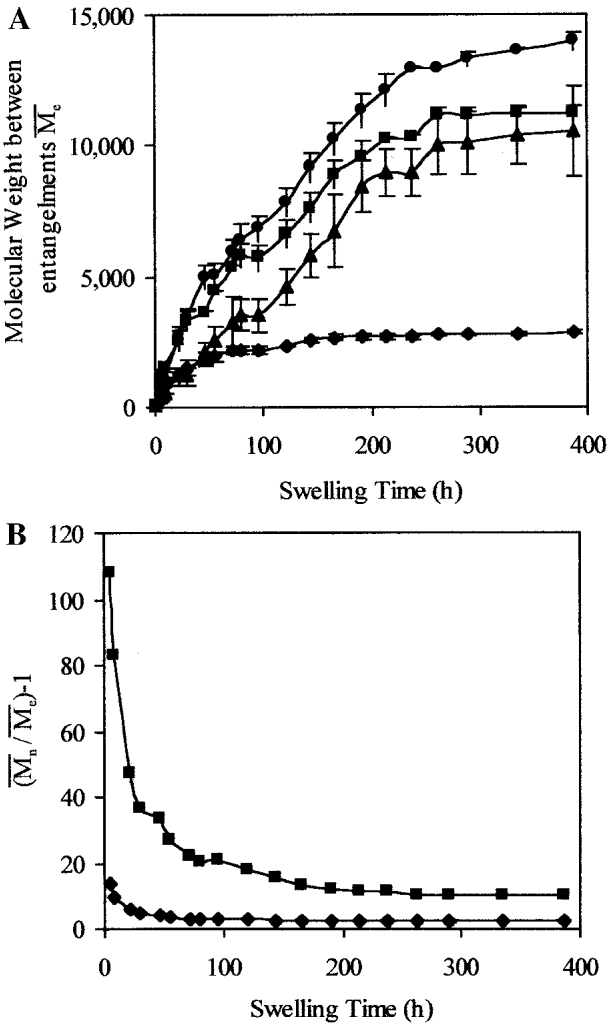

Fig. 5. Changes of molecular parameters during swelling. (A) The calculated average molecular weight between entanglements, $\overline{M_e}$, as a function of swelling time: HEC (●); HPMC K100M (■); HPMC K4M (◆); and HPC (▲). (B) The number of entanglements, *e,* per chain as a function of swelling time for HPMC discs of different polymer molecular weights: HPMC K100M (■) and HPMC K4M (◆).

also Fig. 5B). Consequently, the process of erosion of HPMC K4M tablets would be faster, as observed also by other authors (4).

CONCLUSIONS

From the present study it can be concluded that the results of dynamic vapor sorption measurements for cellulose ethers correlated well with the volume-swelling ratio. The $\overline{M}_e$, was calculated from the following parameters: the polymer fraction in the swollen gel at equilibrium, $\upsilon_{2,S}$, the number average molecular weight of the polymer, $\overline{M}_n$, its specific volume, υ, the molar volume of the solvent, V_1, and the χ_1 parameter. The order of $\overline{M}_e$ values for the four cellulose ethers is HPMC K4M < HPC < HPMC K100M < HEC. The number of repeating units between two entanglements, u, and the number of entanglements per chain, e, which describe the mesh size, were also obtained. Comparison of the mesh sizes at equilibrium for the different cellulose ethers showed that HPMC K100M were the biggest, followed by HEC, HPC, and HPMC K4M.

To predict the behavior of drug release, however, the number of entanglements per chain, e, also has to be taken into account, and this parameter has been shown to be lowest for HPMC K4M, followed by HPMC K100M, HEC, and HPC, which is the most entangled of those investigated.

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