Water Distribution Studies within Cellulose Ethers Using Differential Scanning Calorimetry. 1. Effect of Polymer Molecular Weight and Drug Addition

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Abstract □ Differential scanning calorimetry (DSC) was employed to characterize the distribution of water in gels produced from a series of hydroxypropylmethylcelluloses (HPMC, Methocel K-series) of different molecular weights (i.e., different viscosity grades). The presence of loosely bound water was characterized as pre-endothermic events occurring at temperatures below the main melting endotherm of free water. Both the magnitude and occurrence of these pre-endothermic events were affected by polymer molecular weight and gel storage time. In addition, the amount of water bound to the polymer depended on polymer molecular weight and gel storage time. The temperature at which frozen water melted within the gels was dependent on polymer concentration, with a depression of extrapolated endothermic melting peak onset occurring with an increase in polymer concentration. The addition of propranolol hydrochloride or diclofenac sodium, as model drugs, affected both the occurrence of pre-endothermic events and the distribution of water within the gels.

1. Introduction

Hydrophilic cellulose ether polymers commonly used in controlled release matrices form a gel-like structure when hydrated. Different types of water have been reported to exist within such gel systems.[1] The rate at which water diffuses into hydrophilic matrices and forms a barrier gel layer,[2] followed by water diffusion through this gel layer, both modify the rate at which a drug is released from such systems.[3] Detailed study on the gel layer and more specifically on the types of water which exist is fundamental to the optimization of the use of cellulose ethers in sustained release formulations.

Thermal techniques, including differential scanning calorimetry (DSC) and thermogravimetric analysis (TGA), have been employed to study the states of water within some hydrophilic polymer gel systems.[1] The majority of workers have identified three classes of water within hydrophilic polymer gels which may be defined in terms of their thermal analysis as: (a) free water, i.e., unbound water whose transition temperature enthalpy and peak shape in DSC curves are equal to those of pure (bulk) water;[4] (b) nonfreezing water, i.e., bound water which is attached directly to the polymer and does not undergo a detectable phase transition;[5] (c) freezing bound water, which is characterized as having a phase transition temperature lower than that of bulk water due to a weak interaction with the polymer chain.[6]

There have been many studies comparing drug release from hydroxypropylmethylcelluloses (HPMCs) of different molecular weights with some debate existing within the literature regarding the influence of HPMC viscosity grade on drug release.[7−12]

The presence of a drug in a matrix tablet may influence the way water is bound to or taken up by the cellulose ether. The influence of drugs such as propranolol hydrochloride (a water soluble drug) on the interaction of water with polymer has been studied by DSC[13] and in thermal gelation or cloud-point studies.[14] The presence of free water within the barrier gel layer plays an important part in drug movement across this barrier. Increased availability of free water (i.e., not bound to the polymer) may lead to increased drug diffusion across the gel layer. The effect of diclofenac sodium (a sparingly water soluble drug) on polymer hydration within hydrophilic polymer matrices was studied using cryogenic scanning electron microscopy (SEM) and revealed that internal gel structure was modified by drug addition.[15,16] In addition, it has been reported that diclofenac sodium decreases the hydration of HPMC polymers, causing the polymers to precipitate at elevated temperatures.[2]

The distribution of water within HPMC K15M gels has been characterized.[1,17] Nokhodchi et al.[18] characterized the water distribution in powders of different viscosity grades of the HPMC K-series using DSC and concluded that viscosity grade had no significant effect on the amount of water bound to HPMC polymers.

In this paper, the water distribution within gels of a range of HPMC polymers of different molecular weights but with similar substitution types and levels is characterized using DSC. Furthermore, the influence of drug addition on water distribution within the gel systems is also examined.

2. Experimental Section

2.1 Materials—Hydroxypropylmethylcellulose (HPMC) is a cellulose ether with methoxyl and hydroxypropoxyl substituents on the cellulose backbone. Methocel K-series (22% methoxyl and 8.1% hydroxypropoxyl substitutions) with different viscosity grades, i.e., HPMC K100LV, HPMC K4M, HPMC K15M, and HPMC K100M were obtained from Dow Chemical Co., Midland, MI.

Propranolol hydrochloride and diclofenac sodium were obtained from Becpharm, Harlow, Essex, England and Profarmaco, Milan, Italy, respectively.

2.2 Gel Preparation—HPMC gels (5−25% w/w) (sample size 20 g) were prepared by heating the full quantity of distilled water to ~80 °C and adding in two aliquots to the previously weighed HPMC powder in a mortar and pestle. The mixture was triturated vigorously to ensure thorough wetting before adjusting to weight. Gels containing propranolol hydrochloride (50 mM) or diclofenac sodium (50 mM) were prepared by dissolving the drugs in distilled water by mixing with the aid of gentle heat on a hot plate stirrer (Griffin & George, England) prior to gel preparation. Both drugs

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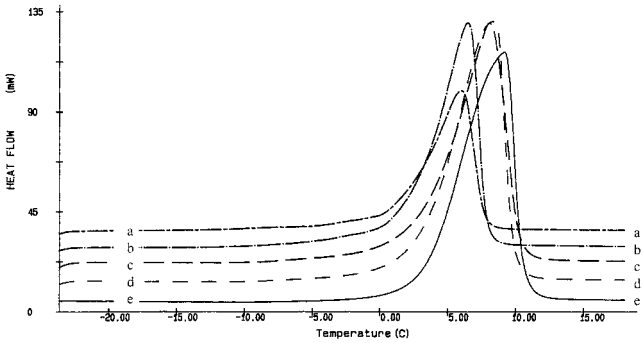

Figure 1—DSC scans of HPMC K15M (5–25% w/w) gels obtained by heating at +10 °C min^{-1} after cooling at –10 °C min^{-1} following storage for 24 h. (a) 5%, (b) 10%, (c) 15%, (d) 20%, (e) 25% (w/w) HPMC K15M.

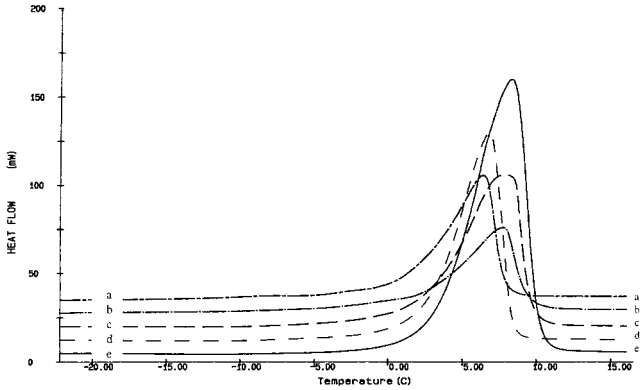

Figure 2—DSC scans of HPMC K15M (5–25% w/w) gels obtained by heating at +10 °C min^{-1} after cooling at –10 °C min^{-1} following storage for 96 h. (a) 5%, (b) 10%, (c) 15%, (d) 20%, (e) 25% (w/w) HPMC K15M.

were fully soluble in warm water at the chosen concentration. Gels were transferred to Pyrex storage vessels which were sealed and stored at 4−6 °C for 24 h before use. Water losses during preparation and storage were taken into account when determining the final polymer concentrations of all gels.

Gel samples >25% w/w were made by preparing gels initially as detailed above in the 10−20% w/w range and storing at 4−6 °C for 24 h. A series of samples (10−16 mg) of the gels were weighed into DSC sample pans (40 μL, Perkin-Elmer) and held at 55 °C in a moisture extraction oven (Townsend & Mercer Ltd., Croydon, England). The samples were removed after defined periods of time to obtain a measurable % weight loss from which the exact polymer:water ratios were calculated.

2.3 Thermal Analysis—A Perkin-Elmer DSC7 (Beaconsfield, UK) with an attached liquid nitrogen based cooling accessory controlled by a Perkin-Elmer TAC-7 was employed. Calibrations with indium (mp onset 156.60 °C) and zinc (mp onset 419.47 °C) were carried out each time the heating rate was changed. Gel samples (5−15 mg) were analyzed in sealed aluminum sample pans (40 μL, Perkin-Elmer, Beaconsfield, UK) by cooling from +20 °C to −35 °C at a cooling rate of −10 °C min^{-1} and then heating from −35 °C to +20 °C at a heating rate of +10 °C min^{-1}.

For gel samples >25% w/w, 5−15 mg of each gel was placed in a DSC pan, sealed, and stored for 24 h at ambient temperature to allow equilibration and uniform water distribution in the gels, before DSC analysis.

3. Results and Discussion

3.1 Characterization of HPMC Gels Using DSC Analysis—Figures 1 and 2 show typical DSC scans for HPMC K15M gels after 24 and 96 h storage time. The exothermic enthalpy (from cooling scans) is the energy released when water within the gels freezes. The endothermic enthalpy (from heating scans) is the energy that is required for melting of frozen water within the gels. Increasing the concentration of HPMC K15M resulted in a decrease in both exothermic (cooling) and endothermic (heating) enthalpies (J/g) after gel storage for both 24 or 96 h (Table 1). Assuming that both exothermic and endothermic peaks are attributable mainly to the crystallization and melting of free water, respectively, it is apparent that there is a decrease in the amount of free water present with an increase in HPMC K15M concentration. As the concentration of the polymer increases, the amount of water required to hydrate the polymer increases and thus less free water is available.

Table 1—Effect of HPMC K15M Concentration (% w/w) on the Extrapolated Exothermic and Endothermic Peak Onsets, the Exothermic and Endothermic Crystallization/Melting Enthalpies (Jg^{-1}) ($n = 3$; ± SD)

HPMC K15M (% w/w)	extrapolated exothermic peak onset (°C)	exothermic enthalpy (J/g)	extrapolated endothermic peak onset (°C)	endothermic enthalpy (J/g)
		After 24 h Storage		
5	–13.4 ± 1.4	259.9 ± 13.9	3.4 ± 0.2	334.7 ± 8.0
10	–16.5 ± 3.0	213.4 ± 21.1	2.9 ± 0.2	289.8 ± 11.3
15	–11.7 ± 2.4	248.2 ± 12.1	2.8 ± 0.3	289.7 ± 14.0
20	–16.0 ± 3.4	208.2 ± 31.7	2.4 ± 0.3	263.6 ± 15.8
25	–13.5 ± 3.4	205.0 ± 18.1	1.8 ± 0.5	228.3 ± 15.4
		After 96 h Storage		
5	–14.2 ± 1.9	218.1 ± 78.3	3.6 ± 0.9	343.3 ± 12.5
10	–15.3 ± 4.7	217.0 ± 33.7	2.8 ± 0.3	304.0 ± 13.9
15	–18.1 ± 0.7	216.7 ± 8.4	2.6 ± 0.2	281.6 ± 15.5
20	–11.3 ± 1.1	209.2 ± 26.8	2.0 ± 0.4	246.3 ± 13.7
25	–14.9 ± 3.8	202.2 ± 9.1	1.5 ± 0.1	231.1 ± 6.6

Increasing HPMC K15M concentration from 5 to 25% (w/w) caused a decrease in the extrapolated endothermic melting peak onset. The extrapolated endothermic melting peak onset is defined as the temperature where the extrapolation of the baseline meets the extrapolation of the ascending melting peak.[19] For example, Table 1 and Figures 1 and 2 show a decrease of extrapolated endothermic melting peak onset from 3.4 ± 0.2 to 1.8 ± 0.5 °C for 5 and 25% w/w gels, respectively, after 24 h hydration, and a decrease from 3.6 ± 0.9 to 1.5 ± 0.1 °C for 5 and 25% w/w gels, respectively, after 96 h hydration. This decrease in the extrapolated endothermic melting peak onset may be related to an increase in the quantity of loosely bound water which melts at a lower temperature than free water due to a stronger interaction with the polymer.[20] This phenomena has previously been reported for HPMC K4M gels.[18] Increasing HPMC K15M concentration has no quantifiable effect on the position of the extrapolated exothermic peak onset (Table 1). This may be because crystallization occurs via nucleation which is an uncontrolled phenomena.[21,22] This lack of control during crystallization was also apparent in HPMC K100LV, HPMC K4M, and HPMC K100M gels (data not shown), where increase in polymer concentration had no effect on the position of the extrapolated exothermic peak onset.

Depression of melting point (extrapolated endothermic peak onset) with increasing concentration of polymer was observed in all HPMC polymers studied here (data not shown). HPMC K100LV (−0.2 ± 0.3 to −2.0 ± 0.1 °C; 5 & 25% w/w gels, respectively, 24 h), HPMC K4M (−2.6 ± 0.1 to −3.4 ± 1.2 °C; 5 & 25% w/w gels respectively, 24 h) and HPMC K100M (−0.2 ± 0.3 to −2.0 ± 0.4 °C; 5 & 25% w/w gels respectively, 24 h), all display this depression in melting point. However, there is no apparent trend between polymer molecular weight and extent of melting point depression with increase in polymer concentration. Similar findings were obtained for HPMC K100LV, HPMC K4M and HPMC K100M gels after 96 h storage.

The presence of endothermic events on low temperature side of the main endotherm for the melting of free water

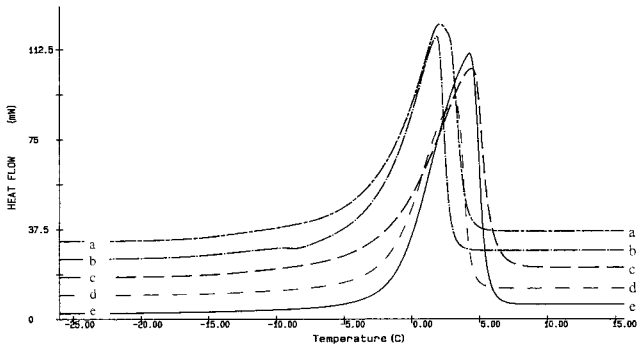

Figure 3—DSC scans of HPMC K100LV (5–25% w/w) gels obtained by heating at +10 °C min^{-1} after cooling at –10 °C min^{-1} following storage for 96 h. (a) 5%, (b) 10%, (c) 15%, (d) 20%, (e) 25% (w/w) HPMC K100LV.

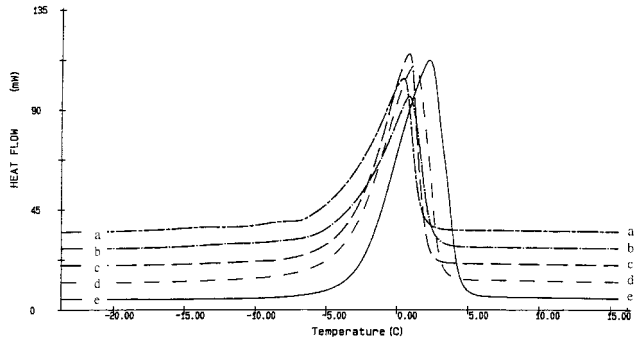

Figure 4—DSC scans of HPMC K4M (5–25% w/w) gels obtained by heating at +10 °C min^{-1} after cooling at –10 °C min^{-1} following storage for 24 h. (a) 5%, (b) 10%, (c) 15%, (d) 20%, (e) 25% (w/w) HPMC K4M.

in DSC scans for HPMC K15M gels was discussed previously.[17] Their occurrence were dependent on polymer concentration, storage time, and scanning rates during DSC analysis. These events were related to the presence of different states of water in the polymer gels. Alternative explanations for similar pre-endothermic events in other systems have been considered in the literature where they were attributed to overlapping ice melting (first-order) and glass transition (second-order) phase transitions.[23] Ratto et al.[24] attributed pre-endothermic events present in water/chitosan systems to cold crystallization. This occurs in systems where only nonfreezing and freezing bound water are present. Upon heating, some of the nonfreezing water becomes mobile, comes into contact with solid freezing bound water, and forms ice. A crystallization exotherm is subsequently visible.

Similar events were also visible prior to the main DSC melting endotherms in gels containing HPMC K100LV, HPMC K4M, or HPMC K100M. Their appearance was dependent on both polymer molecular weight and gel storage time. In HPMC K100LV and HPMC K15M, pre-endothermic events were only visible in 20% w/w and 25% w/w gels after storage for 24 and 96 h (Figures 1−3). In the case of HPMC K15M, pre-endothermic events were more pronounced after 96 h storage.

Gels of HPMC K4M or HPMC K100M showed pre-endothermic events at 15, 20, or 25% w/w polymer content after storage for both 24 and 96 h (Figure 4 and Figure 5). In both these cases, the appearance of such events was unaffected by storage time. It appears that the occurrence of endothermic events varied between HPMCs of different molecular weights.

3.2 Quantitative Analysis of the Effect of Molecular Weight on Water Distribution within Cellulose Ethers—The number of moles of bound (nonfreezing) water per polymer repeating unit (PRU) was calculated for HPMC

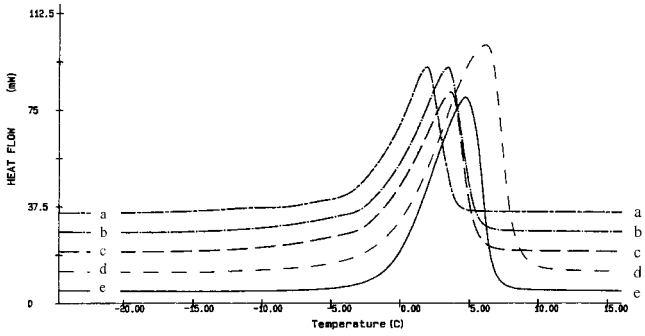

Figure 5—DSC scans of HPMC K100M (5–25% w/w) gels obtained by heating at +10 °C min^{-1} after cooling at –10 °C min^{-1} following storage for 24 h. (a) 5%, (b) 10%, (c) 15%, (d) 20%, (e) 25% (w/w) HPMC K100M.

Table 2—Effect of HPMC Molecular Weight and Equilibration Time on the Bound (nonfreezing) Water (BW) Content per Polymer Repeating Unit (PRU) As Calculated by the Method Proposed by Ford and Mitchell[1]

polymer	viscosity (cP)[a]	PRU value	moles BW per PRU (24 h)	R^2 (24 h)[b]	moles BW per PRU (96 h)	R^2 (96 h)
HPMC K100	93	189	2.4	0.994	4.4	0.973
HPMC K4M	4 196	188	7.1	0.996	4.5	0.973
HPMC K15M	15 825	189	4.5	0.978	6.5	0.934
HPMC K100M	119 768	192	6.0	0.970	6.6	0.963

[a] Values were taken from certificate of analysis provided by the manufacturer of the products. [b] R^2 is the regression coefficient.

K100LV, HPMC K4M, HPMC K15M, and HPMC K100M gels according to the method outlined by Ford and Mitchell[1] and have been reported previously.[17] Enthalpy of fusion of ice (J g^{-1}) was plotted against HPMC concentration (% w/w), and the plots were extrapolated to zero enthalpy through the lines of best fit. The concentration at zero enthalpy was taken as being the minimum ratio of water: HPMC that is required for complete hydration of the polymer. A linear relationship was assumed to exist between enthalpy and polymer concentration. The bound water content was calculated using values for the PRU listed in Table 2 that were calculated for each HPMC viscosity grade based on their % methoxyl and % hydroxypropoxyl substitution on the cellulose ether backbone.

HPMC K4M showed a decrease in bound water content from 24 to 96 h storage, whereas all other polymers showed an increase in their bound water content during this equilibration period (Table 2). The largest change in bound water content occurred in HPMC K100LV (the lowest viscosity grade polymer within the K-series), which shows a 58% increase in the bound water content from 24 to 96 h. Allowing 96 h equilibration, which should be ample time for uniform equilibration in all gel samples, an increase in the bound water content is apparent with an increase in polymer viscosity within the HPMC K-series (Table 2).

3.3 Effect of Drug Addition on Water Distribution in Cellulose Ether Gels—In the absence of a drug, pre-endothermic events were present in 15, 20, and 25% w/w HPMC K4M and HPMC K100M gels and in 20 and 25% w/w HPMC K100LV and HPMC K15M gels after 24 h storage (section 3.2). Incorporation of 50 mM of propranolol hydrochloride did not affect the appearance of such events in HPMC K100LV, HPMC K4M, and HPMC K15M gels. However, in HPMC K100M gels, pre-endothermic events were visible only in 20 and 25% w/w gels after 24 h.

Figure 6 shows the influence of diclofenac sodium on the appearance of pre-endothermic events in 5−25% w/w HPMC K4M gels which is representative of other polymers studied. After 24 h equilibration, pre-endothermic events

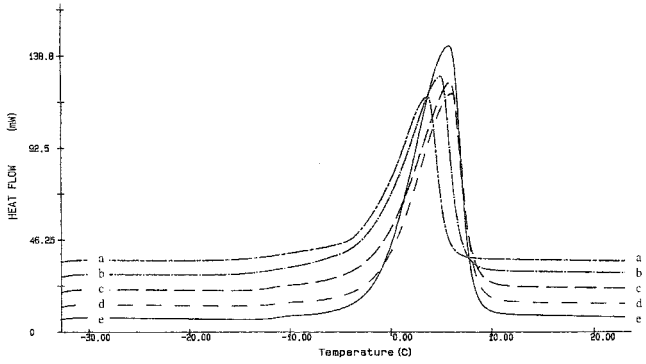

Figure 6—DSC scans of HPMC K4M (5–25% w/w) gels containing 50 mM of diclofenac sodium obtained by heating at +10 °C min^{-1} after cooling at –10 °C min^{-1} following storage for 24 h. (a) 5%, (b) 10%, (c) 15%, (d) 20%, (e) 25% (w/w) HPMC K4M + 50 mM diclofenac sodium.

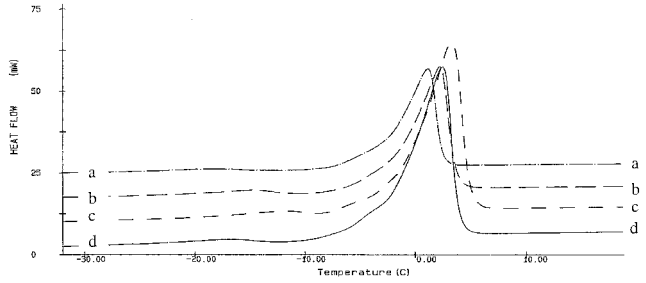

Figure 7—DSC scans of 26.7–32.4% (w/w) HPMC K15M gels in the absence and presence of 50 mM of diclofenac sodium obtained by heating at +10 °C min^{-1} after cooling at –10 °C min^{-1} following storage for 24 h. (a) 26.7% K15M, (b) 30.5% K15M, (c) 29.2% K15M + 50 mM diclofenac sodium, (d) 32.4% (w/w) K15M + 50 mM diclofenac sodium.

were visible in all HPMC K-series studied here, at each concentration (5−25% w/w). It is hypothesized that diclofenac sodium causes the polymer to "salt out", making it less soluble and requiring more water to bind to the polymer to keep it in solution. Therefore, there is more loosely bound water in the system. It is possible that this loosely bound water appears in DSC scans and may explain the appearance of these pre-endothermic events.

Pre-endothermic events in HPMC K15M gels were previously found to be exaggerated in the 25−35% w/w concentration range in comparison to the events observed with 20 and 25% w/w HPMC K15M gels.[17] The influence of each drug on the DSC scans of gels containing 25−40% w/w HPMC K15M was examined.

Following the inclusion of 50 mM of propranolol hydrochloride into HPMC K15M gels, pre-endothermic events were visible at 29.0% w/w but they were not present at the higher concentrations studied (30.7−40.1% w/w). The pre-endothermic events became quite pronounced in the HPMC K15M gels in the 25−35% w/w concentration range when diclofenac sodium (50mM) was added. However, they were not apparent in HPMC K15M gels at concentrations >35% w/w. Figure 7 shows that in 25−33% w/w HPMC K15M gels, secondary events were clearly visible both in the presence and absence of diclofenac sodium.

Increasing HPMC K15M concentration from 5 to 25% w/w caused a decrease in the extrapolated endothermic melting peak onset from 3.4 ± 0.2 to 1.8 ± 0.5 °C after 24 h storage. With the addition of a drug, this depression of melting onset may be expected regardless of polymer molecular weight. For HPMC K15M gels, increasing polymer concentration from 5 to 25% w/w in the presence of 50 mM propranolol hydrochloride caused a depression of the extrapolated endothermic melting peak onset from 3.2 ± 0.7 °C to 0.8 ± 0.2 °C. Similarly, increasing polymer concentration in HPMC K15M gels from 5 to 25% w/w in the presence of 50 mM diclofenac sodium caused a depression of the extrapolated endothermic melting peak onset from 2.9 ± 0.5 °C to 1.3 ± 0.2 °C.

Table 3—The Effect of Addition of 50 mM of Propranolol Hydrochloride or Diclofenac Sodium on the Water Distribution within a Range of Cellulose Ether Gels after 24 h Storage

polymer	viscosity (cP)[a]	polymer (% w/w)	water (% w/w)	R^{2b}	moles bound water per PRU
HPMC K100LV	93	81.2	18.8	0.994	2.4
+ propranolol		80.3	18.3	0.976	2.4
+ diclofenac		70.0	28.5	0.986	4.3
HPMC K4M	4 196	59.6	40.4	0.996	7.1
+ propranolol		79.4	19.2	0.997	2.5
+ diclofenac		65.4	33.1	0.987	5.3
HPMC K15M	15 825	70.2	29.8	0.978	4.5
+ propranolol		76.6	21.9	0.975	3.0
+ diclofenac		71.8	26.8	0.992	3.9
HPMC K100M	119 768	64.1	35.9	0.970	6.0
+ propranolol		81.4	17.2	0.982	2.3
+ diclofenac		65.1	33.4	0.981	5.5

[a] Values were taken from certificate of analysis provided by the manufacturer of the products. [b] R^2 is the regression coefficient.

The number of moles of bound water per PRU (average molecular weight of one polymer repeating unit) were calculated as previously described using the Ford and Mitchell[1] method (section 3.2), and the values chosen for the PRU were as listed in Table 2. In HPMC K4M, HPMC K15M, and HPMC K100M gels, propranolol hydrochloride reduced the amount of water bound to the polymer (Table 3). In effect, less water was required to fully hydrate the polymer, most likely due to the "salting-in" effect of the drug which increases polymer solubility.[25] The ability of propranolol hydrochloride to reduce the amount of water required to fully hydrate HPMC K15M gels has been previously reported.[13]

Addition of propranolol hydrochloride to HPMC K100LV gels did not reduce the amount of bound water. The bound water content initially was very low in these gels. When diclofenac sodium was added to cellulose ether gels, with the exception of HPMC K100LV, the amount of water bound to the polymer was reduced in comparison with that bound in the absence of drug. More water was required to fully hydrate the polymer compared to when propranolol hydrochloride was added. Diclofenac sodium "salts out" cellulose ether polymers making them less soluble. Therefore, more water will be required to hydrate the polymer, and thus the bound water content should increase. For HPMC K100LV, addition of propranolol hydrochloride did not change the bound water content, while addition of diclofenac sodium caused an increase in the amount of water binding to the polymer. Addition of diclofenac sodium would certainly seem to make the polymer less soluble, causing an increase in water required to hydrate the polymer, as reflected in an increase in bound water. In the case of propranolol hydrochloride, the expected reduction in bound water content due to the "salting in" effect of the drug did not occur. It may be that a certain minimum level of water is required to maintain the gel structure and remains tightly bound to the polymer. This amount of tightly bound water cannot be removed even with the addition of a drug like propranolol hydrochloride.

4. Conclusions

The water distribution within cellulose ether polymer gels was found to be dependent on polymer molecular

weight and gel equilibration (or storage) time. The presence of loosely bound water was characterized as pre-endothermic events occurring to the left of the main melting endotherm of free water. The occurrence and magnitude of these pre-endothermic events were affected by polymer molecular weight. The melting of frozen water within the gels, as characterized by the extrapolated endothermic melting peak onset, was dependent on polymer concentration. No apparent trend was found to exist between polymer molecular weight and extent of melting point depression with increase in polymer concentration.

The amount of water tightly bound to the polymer, as calculated by the method proposed by Ford and Mitchell,[1] was dependent on polymer molecular weight. This was further affected by drug addition to the polymer gels. Diclofenac sodium had a marked effect on the appearance of pre-endothermic events in cellulose ether polymer gels; however, a negligible effect was observed with the addition of propranolol hydrochloride.

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