Water Distribution Studies within Cellulose Ethers Using Differential Scanning Calorimetry. 2. Effect of Polymer Substitution Type and Drug Addition

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Abstract □ The distribution of water within gels composed of a range of cellulose ether polymers of similar molecular weights (viscosity grades of 4000–6000 cP) but varying substitution types and levels was assessed by differential scanning calorimetry (DSC). Water loosely bound to the polymer was detected as one or more events appearing at the low-temperature side of the main endotherm for the melting of free water in DSC scans. Polymer substitution types and levels, and added drugs (50 mM propranolol hydrochloride or 50 mM diclofenac sodium) influenced the appearance of these melting events. Hydroxypropylcellulose (HPC) and hydroxypropylmethylcellulose (HPMC F4M) gels showed behavior different to that of the other polymers studied. It is thought that any water binding to HPC gels is tightly attached and is not visible as pre-endothermic events on DSC scans. The amount of water bound per polymer repeating unit (PRU) was influenced by and related to the degree of hydrophilic and hydrophobic substitution on the polymer backbone and by the inclusion of either drug. HPC gels had the highest bound water content after 96 h and this was probably related to the high percentage of hydrophilic hydroxypropoxyl substitutions in this polymer. In contrast, methylcellulose (MC A4M) had the lowest bound water content after 96 h storage, and this was explained by the lack of hydrophilic hydroxypropoxyl substitutions in the polymer.

1. Introduction

The formation of a barrier gel layer in hydrophilic controlled release matrices containing cellulose ethers, and the subsequent water diffusion through this gel layer determine the rate and mechanism of drug release.[1] Different polymer properties have been reported to be responsible for the rate of polymer hydration including polymer viscosity grade,[2−4] polymer particle size,[5−8] polymer concentration,[2] and polymer substitution type.[5]

It was initially proposed by Alderman[5] that cellulose ethers of different substitution levels hydrate at different rates, and this factor may be used to optimize the formulation of sustained release matrices. However, Mitchell et al.,[9] using a combination of differential scanning calorimetry (DSC) and dissolution studies, have shown that the differences in drug release rates from HPMCs with different substitution levels are not due to differences in their hydration rates. Further studies using thermomechanical analysis[9] have shown that gel layer thickness (which will affect the diffusional path length) is similar in HPMCs of different substitution levels. Using NMR imaging, Rajabi-Siahboomi et al.[10] showed that gel layer development in HPMC tablets occurred to the same extent in both axial and radial directions and was similar in HPMCs with different substitution levels.

Differences in drug release patterns between the three HPMC substitution types (Methocels K, E, and F) were found in matrices containing low quantities of the polymers.[11] In addition, Bonferoni et al.[12] reported differences in drug release profiles from HPMC E4M and the other two substitution levels (HPMC K4M and HPMC F4M) at low polymer concentrations. Rajabi-Siahboomi et al.,[1] using NMR imaging, showed that water mobility in the gel layer of hydrated HPMC tablets varied with substitution levels. They found that the lowest value for water mobility was for HPMC K4M. Although no specific reason was given for the differences in water mobility, this differential water mobility may explain the different drug release profiles observed from their matrices.[1] In this article, the water distribution within a range of polymer gels containing cellulose ethers with different substitution types and levels but similar molecular weights are characterized using differential scanning calorimetry (DSC). The influence of drug addition on the distribution of water within these gel systems is also characterized.

2. Experimental Section

2.1 Materials—Methocel cellulose ethers, HPMC K4M, HPMC E4M, HPMC F4M, and methylcellulose (MC) A4M, were obtained from Dow Chemical Co., Midland, MI. Hydroxypropylcellulose (HPC) was obtained from Hercules Limited, Aqualon Division, U.K.

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

2.2 Gel Preparation—HPMC gels of 5−25% w/w (sample size 20 g) were prepared as described previously[13] and stored for 24 or 96 h before use. 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 and George, England) prior to gel preparation. Gel samples greater than 25% w/w were made by preparing gels initially as above, followed by moisture extraction from the gels as described previously.[13]

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 as described previously.[13] 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.

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Table 1—The Substitution Levels of Methocels Used in This Study

Methocels	methoxyl (%)	hydroxypropoxyl (%)
HPMC A	30	0
HPMC E	29	8.5
HPMC F	28	5.0
HPMC K	22	8.1

Table 2—Effect of HPC Concentration (% w/w) on the Extrapolated Endothermic Peak Onset, Endothermic Peak, and the Endothermic Melting Enthalpy (Jg^{-1}) ($n = 3$; ±SD) after 24 h Storage

HPC concn (% w/w)	extrapolated endothermic peak onset (°C)	endothermic peak (°C)	endothermic enthalpy (J/g)
	After 24 h Storage		
5	−2.8 ± 0.5	5.4 ± 1.4	303.7 ± 0.9
10	−4.2 ± 0.1	1.4 ± 0.4	274.4 ± 3.9
15	−4.3 ± 0.3	1.8 ± 1.2	251.8 ± 7.4
20	−5.1 ± 0.1	0.6 ± 0.6	218.1 ± 6.7
25	−5.0 ± 0.2	0.0 ± 0.7	208.5 ± 8.4
	After 96 h Storage		
5	−1.5 ± 0.6	5.7 ± 1.9	294.6 ± 13.9
10	−1.8 ± 0.7	5.6 ± 1.8	270.9 ± 2.7
15	−2.1 ± 0.1	4.9 ± 1.0	255.3 ± 14.7
20	−3.1 ± 0.1	3.1 ± 0.7	220.5 ± 9.6
25	−3.7 ± 0.5	2.2 ± 0.9	195.6 ± 8.3

3. Results and Discussion

3.1 Effect of Polymer Substitution Type on the Nature of Water Distribution within Cellulose Ethers—Cellulose ether polymers of varying substitution types and levels possess different degrees of hydrophilic and hydrophobic substituents (Table 1). HPMC E4M and HPMC F4M both have a higher percentage of hydrophobic methoxyl substituents (about 29%) compared to HPMC K4M (22.2%). HPMC E4M has a similar percentage of hydrophilic hydroxypropoxyl substituents to HPMC K4M (about 8%), unlike HPMC F4M which has a lower hydroxypropoxyl percentage content (6%). Methylcellulose (MC A4M) possesses no hydrophilic hydroxypropoxyl substituents whereas hydroxypropylcellulose (HPC) possesses no methoxyl substituents. Therefore, it may be anticipated that water distribution within cellulose ether polymers would be dependent on substitution types and levels.

Table 2 shows the DSC data for HPC gels stored for 24 and 96 h respectively, and they are representative of the data seen for HPMC E4M, HPMC F4M, HPMC K4M, and MC A4M gels. In all cases, as seen in HPMC K-series,[13] increasing the concentration of the polymer from 5 to 25% w/w resulted in a decrease in the temperature of the extrapolated endothermic peak onset. For example, HPMC E4M (−2.1 ± 0.3 to −3.8 ± 0.3 °C; 5 and 25% w/w gels, respectively, 96 h), HPMC F4M (−3.1 ± 0.6 to −5.5 ± 0.3 °C; 5 and 25% w/w gels, respectively, 96 h), HPMC K4M (−2.7 ± 0.2 to −4.2 ± 0.3 °C; 5 and 25% w/w gels, respectively, 96 h), MC A4M (−2.0 ± 0.5 to −4.2 ± 0.4 °C; 5 and 25% w/w gels, respectively, 96 h) and HPC (−1.5 ± 0.6 to −3.7 ± 0.5 °C; 5 and 25% w/w gels, respectively, 96 h) all show a decrease in the temperature of the extrapolated endothermic peak onset. In addition, a decrease in temperature of the endothermic peak and a decrease in the endothermic melting enthalpy with increasing polymer concentration were observed.

There was no specific trend between polymer substitution type and the extent of melting peak depression with increase in polymer concentration.

The existence of events present at the low-temperature side of the main endotherm for the melting of free water

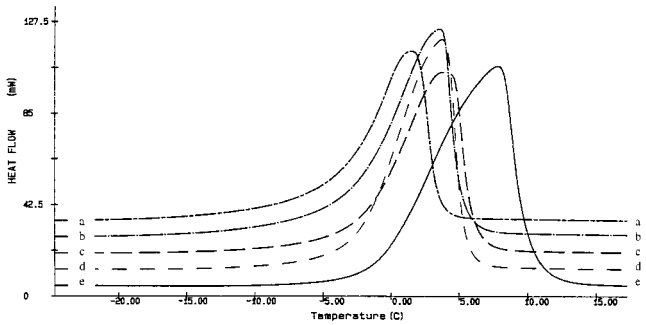

Figure 1—DSC scans of HPC (5–25% w/w) gels obtained by heating at +10 °C min^{-1} after cooling at –10 °C min^{-1} following storage for 96 h: (a) 5%, (b) 10%, (c) 15%, (d) 20%, (e) 25% (w/w) HPC.

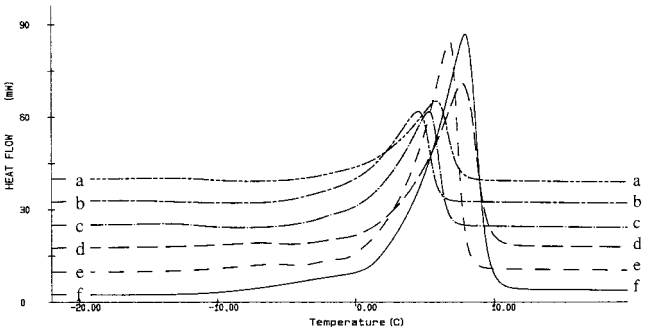

Figure 2—DSC scans of HPMC F4M (19.10–37.80% w/w) gels obtained by heating at +10 °C min^{-1} after cooling at –10 °C min^{-1} following storage for 24 h: (a) 19.10%, (b) 22.49%, (c) 27.14%, (d) 31.71%, (e) 34.07%, (f) 37.80% (w/w) HPMC F4M.

in DSC scans for HPMC K − series gels was discussed previously.[13,14] Such events were related to the presence of different types of water bound to varying degrees to the hydrophilic HPMC polymer and were dependent on polymer molecular weight.[13] Such events were barely visible in HPMC F4M gels, after 24 h storage, but became more pronounced in 20 and 25% w/w gels after 96 h storage. In HPMC E4M, pre-endothermic events were visible in both 20 and 25% w/w gels after 24 and 96 h storage. In the case of methylcellulose, these events were visible in both 20 and 25% w/w gels after 24 h storage, however, they were only visible in 25% w/w gels after 96 h storage. Finally, in all HPC gels, there were no pre-endothermic events visible after either 24 or 96 h (Figure 1). These results indicate that the nature of water distribution within these polymer gels is dependent on substitution types and levels.

Previously, the pre-endothermic events in HPMC K15M gels were found to be exaggerated by an increase in polymer concentration.[14] Therefore, the presence of these events was examined in gels containing higher concentrations of HPC and HPMC F4M.

A series of HPMC F4M 19.10−37.8% w/w and HPC 27.3−48.2% w/w gels were prepared, and their DSC scans were recorded after 24 h storage. Pre-endothermic events were visible in HPMC F4M gels at the higher concentrations studied of >25% w/w (Figure 2). In contrast, in HPC gels, only a small secondary event became visible at concentrations >30% w/w (Figure 3).

Hydroxypropylcellulose gels clearly behaved differently in comparison to the HPMC and MC gels. HPC contains a high percentage of hydrophilic hydroypropoxyl groups and therefore it may be expected to have a larger amount of bound water which is not visible as pre-endothermic events on DSC scans. It is possible that after 96 h storage, the water is tightly attached to the polymer and does not freeze upon cooling. This would explain the nonappearance of pre-endothermic events which have been attributed to loosly

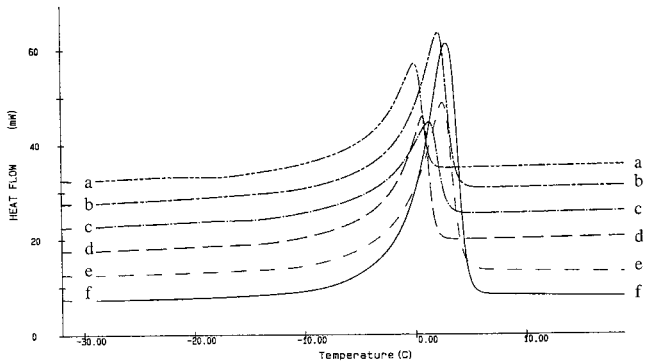

Figure 3—DSC scans of HPC (27.3–35.5% w/w) gels obtained by heating at +10 °C min^{-1} after cooling at –10 °C min^{-1} following storage for 24 h: (a) 27.3%, (b) 29.2%, (c) 30.1%, (d) 31.3%, (e) 32.9%, (f) 35.5% (w/w) HPC.

Table 3—Effect of Polymer Substitution Type 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[15]

polymer	viscosity (cP)[a]	PRU value	moles BW per PRU (24 h)	R^2 [b] (24 h)	moles BW per PRU (96 h)	R^2 [b] (96 h)
HPMC K4M	4196	188	7.1	0.996	4.5	0.973
HPMC F4M	5218	187	3.2	0.968	5.4	0.993
HPMC E4M	3970	190	6.2	0.974	5.6	0.966
MC A4M	3811	177	5.3	0.999	3.8	0.988
HPC	5950	171	5.5	0.983	6.1	0.990

[a] Values were taken from certificate of analysis provided by the manufacturer of the products. [b] Regression coefficient.

bound water. If this theory is indeed correct, the amount of nonfreezing bound water in HPC gels would be quite high.

3.2 Quantitative Analysis of the Effect of Substitution Type on Water Distribution within Cellulose Ethers—The number of moles of bound (nonfreezing) water per polymer repeating unit (PRU) was calculated for HPMC K4M, HPMC E4M, HPMC F4M, MC A4M, and HPC according to the method outlined by Ford and Mitchell.[15] The PRU value for each polymer was calculated as previously decribed,[13] and they are in Table 3 along with the values for bound water after both 24 and 96 h storage.

HPMC K4M, HPMC E4M, and MC A4M all showed a decrease in their bound water content from 24 to 96 h storage, whereas HPMC F4M and HPC showed an increase in their bound water content during this equilibration period. Considering the bound water content after 96 h to be the equilibrium of the water distribution within these gels, MC A4M has the lowest bound water content compared to other substitution types. This may be due to the fact that MC A4M contains a high hydrophobic methoxyl (29.9%) with no hydrophilic hydroxypropoxyl substitution. A high methoxyl substituent content will not favor large amounts of water binding to the polymer. Previous studies have shown that methoxyl substituent levels are the major factor in causing an apparent decrease in cellulose ether solubility and causing precipitation of the polymer in cloud-point studies.[9]

After 96 h equilibration time, HPC had a high bound water content. HPC contains only hydroxypropoxyl substituents, and a large value for bound water content after equilibration would be expected. This was thought to be the reason for the nonappearance of pre-endothermic events in the DSC scans of HPC gels (Figure 3), indicating that only tightly bound water was present which were not detectable by DSC.

It is reported that HPMC K4M, having a similar hydroxypropoxyl constituent to HPMC E4M, but with smaller

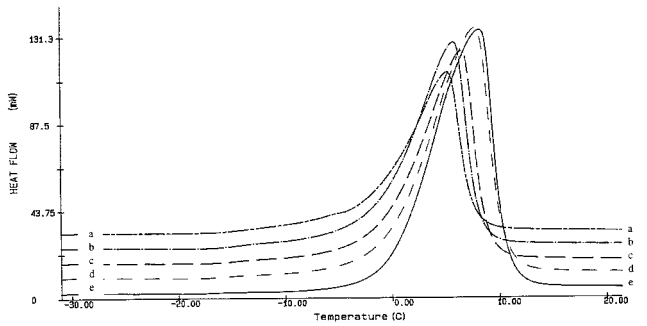

Figure 4—DSC scans of HPMC F4M (5–25% w/w) gels containing 50 mM of propranolol hydrochloride obtained by heating at +10 °C min^{-1} after cooling at –10 °C min^{-1} following storage for 24 h: (a) 5%, (b) 10%, (c) 15%, (d) 20%, (e) 25% (w/w) HPMC F4M + 50 mM propranolol hydrochloride.

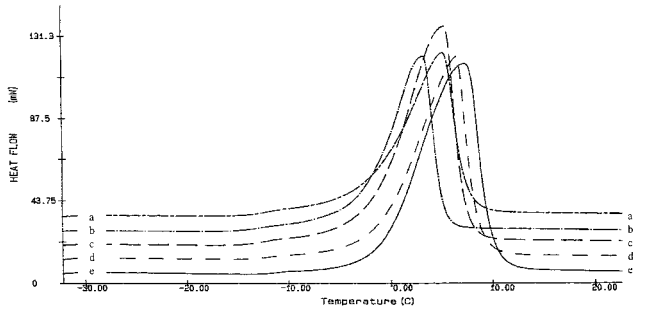

Figure 5—DSC scans of MC A4M (5–25% w/w) gels containing 50 mM of diclofenac sodium obtained by heating at +10 °C min^{-1} after cooling at –10 °C min^{-1} following storage for 24 h: (a) 5%, (b) 10%, (c) 15%, (d) 20%, (e) 25% (w/w) MC A4M + 50 mM diclofenac sodium.

methoxyl substituent levels than HPMC E4M, HPMC F4M, or MC A4M, is more water soluble[5] and undergoes precipitation at higher temperatures than polymers of other substitution types.[9] This may explain the high value for bound water content (7 mol BW per PRU) for HPMC K4M after 24 h storage. However, this high bound water content is not reflected after 96 h storage.

3.3 Effect of Drug Addition on Water Distribution in Cellulose Ether Polymer Gels—In the absence of drug, pre-endothermic events were very slight or not visible in 5−25% w/w HPMC F4M and HPC gels after 24 h equilibration (section 3.2). Figure 4 shows that incorporation of propranolol hydrochloride (50 mM) resulted in the appearance of such events in HPMC F4M gels at concentrations of 15, 20, and 25% w/w. However, no pre-endothermic events were visible in 5−25% w/w HPC gels after incorporation of propranolol hydrochloride (50 mM).

Propranolol hydrochloride addition had no effect on pre-endothermic events in HPMC K4M, HPMC E4M and MC A4M gels after 24 h equilibration with such events being visible in 20 and 25% w/w gels both in the absence or presence of the drug.

Figure 5 illustrates how incorporation of diclofenac sodium into gels resulted in the appearance of pre-endothermic events in 5−25% w/w MC A4M gels. Pre-endothermic events were visible in 5−25% w/w HPMC K4M, HPMC E4M and HPMC F4M gels at all concentrations studied. In HPC gels, however, no pre-endothermic events were visible after addition of diclofenac sodium at any gel concentrations between 5 and 25% w/w.

DSC analysis of 27.3−48.2% w/w HPC gels (with no drug addition) revealed that, even at high concentrations, only a small secondary event was visible at concentrations greater than 30% w/w (section 3.1). In addition, in HPC gels greater than 25% w/w, containing 50 mM of propranolol hydrochloride, pre-endothermic events were barely visible and were similar to the events observed in HPC gels

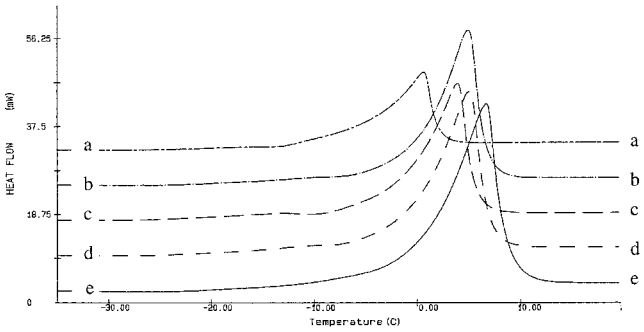

Figure 6—DSC scans of HPC (23.1–32.8% w/w) gels containing 50 mM of diclofenac sodium obtained by heating at +10 °C min^{-1} after cooling at −10 °C min^{-1} following storage for 24 h: (a) 23.1%, (b) 24.9%, (c) 25.3%, (d) 30.0%, (e) 32.8% (w/w) HPC + 50 mM diclofenac sodium.

Table 4—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 Equilibration

polymer	viscosity grade (cP)	polymer (% w/w)	water (% w/w)	regression coefficient (R^2)	moles bound water per PRU
HPMC K4M	4196	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 F4M	5218	76.4	23.6	0.968	3.2
+ propranolol		76.3	22.2	0.986	3.0
+ diclofenac		83.3	15.3	0.992	1.9
HPMC E4M	3970	63.1	36.9	0.974	6.2
+ propranolol		71.3	27.2	0.951	4.0
+ diclofenac		67.9	30.6	0.958	4.8
MC A4M	3811	65.1	34.9	0.999	5.3
+ propranolol		77.4	21.2	0.995	2.7
+ diclofenac		71.8	26.8	0.998	3.7
HPC	5950	61.6	38.4	0.983	5.5
+ propranolol		67.4	31.1	0.981	4.4
+ diclofenac		63.4	35.2	0.984	5.3

in the absence of drug over a similar concentration range. In contrast, Figure 6 shows that pre-endothermic events are clearly visible in HPC gels containing diclofenac sodium in the 25−35% w/w concentration range. These pre-endothermic events may indicate the presence of loosely bound water which has resulted from the "salting-out" effect of diclofenac sodium.

The number of moles of bound water per PRU were calculated as previously described using the Ford and Mitchell[15] method, and the values chosen for the PRU are as listed in Table 3. In all cases, propranolol hydrochloride reduced the amount of water bound to the polymer (Table 4), i.e., less water was required to fully hydrate the polymer, most likely due to its "salting in" effect. No particular trend was apparent in the extent to which the amount of bound water was reduced by propranolol hydrochloride among the polymers studied. In contrast, diclofenac sodium has a "salting out" effect on cellulose ether polymers. With the exception of HPMC F4M, more water was required to fully hydrate the polymer compared to when propranolol hydrochloride was added.

Differences in the bound water content of polymer gels of different substitution types were previously explained by the degree of substitution of hydrophilic and hydrophobic substituents on the polymer backbone (section 3.2). The bound water content of HPMC F4M in the absence or presence of drug did not follow the pattern shown by other polymer gels studied here. HPMC F4M would be expected to have a fairly low bound water content on the basis that it has a high methoxyl substitution level (28.9%) combined with a low hydroxypropoxyl substitution level (6.1%). This is found to be the case; however, while propranolol hydrochloride exhibits its "salting in" effect, diclofenac sodium does not show its "salting out" properties as in other polymers. A different mechanism may be operating in this case which requires further exploration.

4. Conclusions

Polymer substitution type is an important factor in the distribution of water within cellulose ether polymer gel systems. Polymers of different substitution types possess different degrees of hydrophilic and hydrophobic substitution, and it is thought that these substituents influence the way water attaches itself to the polymer. Pre-endothermic events occurring to the left of the main melting endotherm for the melting of free water in DSC scans, thought to be due to the melting of water loosely bound to the polymer, were dependent on polymer substitution type. HPC gels behaved differently in comparison to the HPMC and MC polymers studied.

The amount of water tightly bound to the polymer, as calculated by the Ford and Mitchell[15] method, was dependent on polymer substitution type. Drug addition influenced both the amount of water bound to the polymer and the appearance of pre-endothermic melting events.

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