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Determination of hydration stoichiometries and molar volumes of hydrated complexes in aqueous solutions of cellulosic ether polymers

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ABSTRACT

Methods based on differential scanning calorimetry (DSC) and volumetric measurements were developed and used to determine the hydration stoichiometries and molar volumes of hydrated monomeric complexes of two polymers—methylcellulose (MC) and hydroxypropylmethyl cellulose (HPMC). When fully hydrated, the moles of bound water per mole of monomer were 5.9 and 10.7 for MC-A4M and HPMC-E4M, respectively. The molar volumes of the fully hydrated monomeric complexes were 486.9 and 580.0 mL/mole-monomer for MC-A4M and HPMC-E4M, respectively. The difference in bound water stoichiometries and molar volumes suggest a larger hydration layer consisting of bound water in HPMC than MC, which is consistent with its characteristic water affinity and gelation capabilities.

1. Introduction

Cellulosic ethers, which include methylcellulose (MC) and hydroxypropylmethyl cellulose (HPMC), are widely used in food and pharmaceutical products as fillers, humectants, controlled release agents, and freezing depression agents in freeze-drying and lyophilization processes, among many other applications. MC and HPMC are known hygroscopic polymeric materials that can absorb water in their natural dry state, but they exhibit characteristic hydration behaviors that allow water to be associated differently than bulk water.

Hatakeyama, Nakamura, and Hatakeyama (1998) and McCrystal, Ford, and Rajabi-Siahboomi (1999a, 1999b) studied water interactions in cellulosic ethers using thermal analysis. Those studies identified three states of water association in cellulosic ether polymers: free (unbound) water that resembles bulk water in its enthalpy of melting; non-freezing bound water that undergoes a non-observable transition; and freezing bound water that shows a lower transition temperature than bulk free water. Thermal analysis transition profiles, usually determined by differential scanning calorimetry (DSC), typically exhibit lower than nominal onset temperatures for the endothermic melting transition of frozen unbound water, which corresponds to the colligative effect of the melting point depression of the water–polymer system. The presence of additional endotherms at lower temperatures may indicate the presence of bound water tightly associated with the polymer or water associated with the porosity of the polymer as a result of its high surface tension (Faroongsarng & Peck, 2003).

The different types of water associated with cellulosic ethers can also be quantitatively determined by thermogravimetric analysis (TGA). Profiles of mass changes with respect to temperature can help separate and deconvolute the various stepwise transitions as the various types of water (bound and/or unbound) undergo phase behavioral changes. Many types of carbohydrate polymeric materials, such as starches and derived cellulosic materials, exhibit similar hydration behavior.

Different states of water in polymeric materials can also influence their molar volumes. This is particularly significant in applications involving gels and swollen polymer matrices, where liquid sorption kinetics and other mass transfer processes such as diffusion are controlled. The molar volume of a polymer can describe the extent of plasticization and equilibrium swelling of a polymer in the presence of a solvent, as well as its potential capacity to associate with other molecules (such as drugs or other plasticizers), and the affinity for water and/or polymeric materials (Mutalik & Aminabhavi, 2006; Sperling, 2001; Zhang & Zografi, 2001). In addition, thermo-mechanical properties, such as storage/loss mod-

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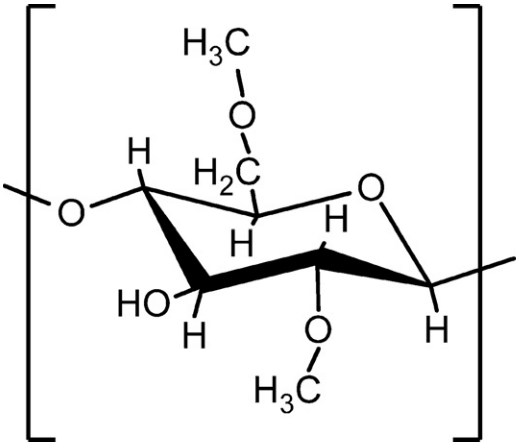

Fig. 1. Monomer structure of methylcellulose (MC-A4M).

uli and the rates of gel deformation, are significantly affected by the composition and physical state of water (Haque & Morris, 1993a, 1993b; Nilson & Porsch, 1995; Sarkar & Walker, 1995).

This paper presents a method to determine the hydration stoichiometry (moles of bound water per mole of monomer when fully hydrated) and molar volume of a fully hydrated monomer complex. The hydration stoichiometries were determined using differential scanning calorimetry (DSC), which were then used with experimental volumetric data to calculate the molar volume of fully hydrated monomer complexes. The method was applied to two polymers—MC-A4M and HPMC-E4M.

2. Experimental

2.1. Materials and sample preparation

MC (Methocel® MC-A4M, monomer MW ~ 190 Da, methoxyl DS = 1.8 and methoxyl % = 30%) and HPMC (HPMC-E4M, monomer MW ~ 248 Da, average MW ~ 80,000 Da, methoxyl DS = 1.9 and methoxyl % = 29%, hydroxypropyl MS = 0.23 and hydroxypropyl % = 8.5%) were used to prepare the hydrated polymer gels and solutions in this study. Their chemical structures are shown in Figs. 1 and 2. The listed material properties were obtained from the manufacturer (Dow Chemical Co., 2002). Polymeric materials (on a dry basis) and deionized water were weighed using an analytical balance with a precision of ±0.01 mg (Sartorius, Inc.), and carefully dispersed at room temperature in a graduated cylinder with ±0.1 mL accuracy (VWR Scientific, Inc.). The cylinders were sealed to prevent water evaporation, and allowed to stand in an environmental chamber (Model G8A, Environmental Growth Chambers, Chagrin Falls, OH, USA) at 20 ± 1 °C for at least 18 h.

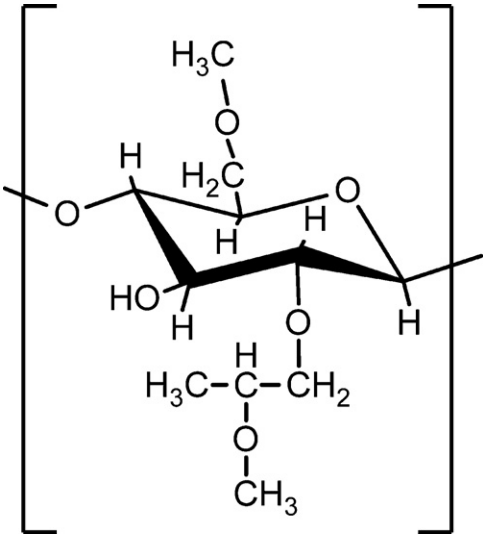

Fig. 2. Monomer structure of hydroxypropyl methylcellulose (HPMC-E4M).

2.2. Volumetric and true density measurements

After adding water to the polymer and equilibration at 20 °C, samples were removed from the environmental chamber and immediately assessed for the total volume of the polymer–water mixture in the graduate cylinders. This was done by visual determinations of volumes in the graduated cylinders with the aid of a high resolution digital camera (Sony, Inc.), which is similar to a previously published method (Baumgartner & Peppas, 2002). All studies were done in duplicate. Total volumes for equilibrated polymer solutions ranged from ~1.7 mL (at the highest polymer concentrations used in data analyses) to over 10 mL (for dilute solutions). Based on accuracies of ±0.1 mL, the corresponding relative errors ranged from ~1% for the most dilute solutions to ~6% for the most concentrated. The observed volumetric measurements, along with the molar composition of water and polymer of the equilibrated mixtures, were used for the water stoichiometry calculations for each respective polymer system.

True densities for dry MC-A4M and HPMC-E4M were determined using an Ultrapycnometer 1000 (Quantachrome, Boynton Beach, FL). Measurements were performed using approximately 2 g ($n = 2$) of dry powder purged for 30 min under helium gas prior to analysis.

2.3. Thermal analysis

Samples of gelation/solution compositions were gravimetrically transferred to hermetic aluminum DSC pans and lids (TA Instruments, Inc.). The lids were carefully punctured to obtain hole radii of ~100 μm to provide the appropriate vapor pressure environment and minimize the effects of expansion and contraction of water upon phase transition. For all samples, thermal analysis was carried out using a Q100 DSC (TA Instruments, Inc.) by a 3-step method—a cooling step from 25 °C to −20 °C at 5 °C/min; an isothermal step at −20 °C for 15 min; and a final heating step from −20 °C to 100 °C at 5 °C/min. The DSC was previously calibrated at 0 °C with ice crystallized from a distilled/deionized purified water standard (Fisher Scientific) and at 156 °C with an indium reference standard (TA Instruments, Inc.). Studies were done in duplicate.

3. Results and discussion

3.1. Volumetric measurements and mole fraction determinations

The MC and HPMC displayed distinct solvation and hydration characteristics, with HPMC showing swelling behavior. The equilibrated total volumes V_T (water plus polymer) at 20 °C along with moles of monomer n_M and total moles of water $n_{W,T}$ are reported for MC-A4M and HPMC-E4M in Tables 1 and 2, respectively.

3.2. Thermal analysis and hydration stoichiometry determination

DSC experiments revealed significant effects due to water–polymer interactions, which were characterized by the enthalpy of melting for of the ice-to-water melting transition. It was seen that the heat of melting per amount of water in the sample decreased with increasing polymer weight fractions. Figs. 3 and 4 show representative normalized DSC data (mW

Table 1
Volumetric measurements for MC-A4M/water mixtures.

wt.% MC	V_T (mL)	n_M (mole)	$n_{W,T}$ (mole)
25.3	1.7	0.00181	0.0564
14.3	2.7	0.00179	0.1135
9.6	3.9	0.00169	0.1679
7.3	6.0	0.00207	0.2790
4.4	8.0	0.00171	0.3937
4.0	10.0	0.00199	0.5008

Table 2
Volumetric measurements for HPMC-E4M/water mixtures.

wt.% HPMC	V_T (mL)	n_M (mole)	$n_{W,T}$ (mole)
31.3	1.8	0.00192	0.0581
19.8	2.5	0.00201	0.1120
14.5	3.6	0.00207	0.1678
9.8	5.7	0.00220	0.2789
6.6	7.6	0.00201	0.3905
4.6	9.1	0.00178	0.5026

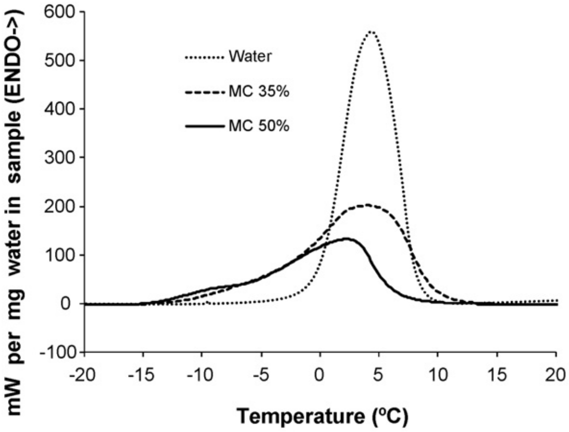

Fig. 3. Examples of DSC data for ice-to-water transitions for water and MC/water mixtures (normalized by weight of water in sample).

per mg of total water in sample) characterizing the ice-to-water transition for pure water, aqueous solutions of MC-A4M (~50% and ~35%, w/w), and aqueous solutions of HPMC-E4M (~50% and ~34%, w/w).

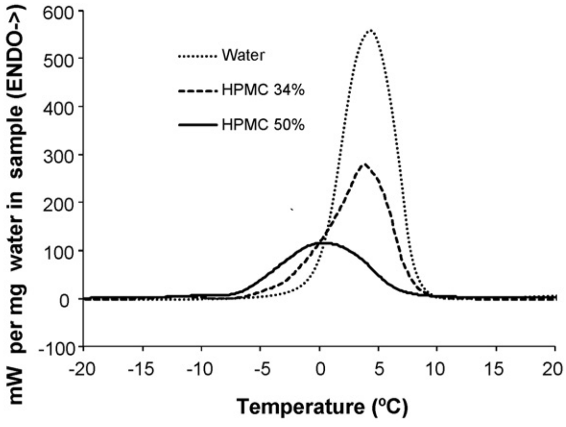

Fig. 4. Examples of DSC data for ice-to-water transitions for water and HPMC/water mixtures (normalized by weight of water in sample).

Table 3
DSC measurements for MC-A4M/water mixtures.

wt.% MC	$\Delta H_{melt}/n_{W,T}$	$n_M/n_{W,T}$
49.6	2540.8	0.09337
35.0	4015.8	0.05094
25.0	4704.0	0.03162
15.0	5358.8	0.01675
8.0	5517.2	0.00825
1.0	5606.3	0.00096
0.5	5724.1	0.00048

There, it can be seen that at similar polymer concentrations, the values of the heat of melting per mole of total water in the system were different for MC and HPMC. Values for the heat of melting per mole of total water in the system, along with the molar ratio of monomer to total water, are reported for MC-A4M and HPMC-E4M in Tables 3 and 4, respectively. Figs. 3 and 4 also show that the range of −20 to +20 °C was sufficient to characterize the melting behavior of ice formed from the free water in the systems used for this study. (It should be noted that this range should not be expected to be appropriate for all systems. For each system, an appropriate temperature range must be chosen that will allow the heat of melting of ice from free water to be determined, but not include temperatures low enough to include freezing of bound water.)

It is well known that most cellulosic polymers strongly associate with water molecules (McCrystal et al., 1999a, 1999b) to form what will be referred to here as hydrated monomer complexes. The hydration stoichiometry, which is defined as the number of moles of bound water per mole of monomer when fully hydrated, depends on the monomer. It is possible to obtain the hydration stoichiometry based on the following assumptions. (1) At higher water-to-polymer ratios, the monomers are essentially fully hydrated and there is additional free water that is available for freezing. (2) The free water behaves like pure water, with a constant heat of melting Δh_{melt} for the ice-to-water transition. (3) Only free water can freeze in the range of temperatures used in this study. Based on these assumptions, the amount of bound water is identified as the difference between the total water and the free water.

From the above assumptions, at higher water-to-polymer ratios, the moles of ice (corresponding to the moles of free water) in a sample may be determined from the heat of melting of the sample, denoted as ΔH_{melt}. In turn, the hydration stoichiometry may be found by a plot of ΔH_{melt} vs. the moles of monomer content (at constant total water content). For systems containing fully hydrated monomer complexes and free water, the average number of water molecules associated with each monomer a remains constant with respect to the total amount of water, and the moles of free water n_W are given by

$$n_W = n_{W,T} - an_C \tag{1}$$

where $n_{W,T}$ denotes the total moles of water and n_C denotes the moles of hydrated monomer complex. Thus, the observed heat of melting of ice in a sample can be expressed as

$$\Delta H_{melt} = \Delta h_{melt} n_W = \Delta h_{melt}(n_{W,T} - an_C) \tag{2}$$

Since the amount of water varies from sample to sample, it is preferable to analyze the heat of melting per mole of total water. Also,

Table 4
DSC measurements for HPMC-E4M/water mixtures.

wt.% HPMC	$\Delta H_{melt}/n_{W,T}$	$n_M/n_{W,T}$
34.1	3414.7	0.03761
24.1	4578.0	0.02301
14.4	4838.5	0.01217
9.9	5233.5	0.00802
3.8	5732.8	0.00284
1.0	5732.0	0.00070
0.2	5851.9	0.00015

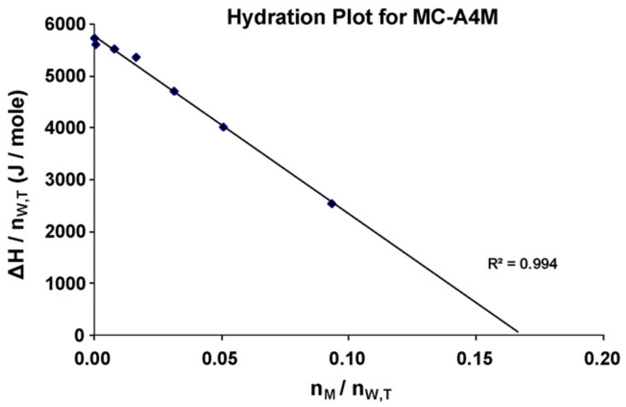

Fig. 5. Extrapolated plot of Eq. (4) for MC-A4M/water mixtures.

when fully hydrated, the moles of hydrated monomer complex n_C is the same as the moles of monomer n_M, where

$$n_M = \frac{\text{grams of polymer}}{\text{gram MW of monomer}} \tag{3}$$

These considerations lead to

$$\frac{\Delta H_{melt}}{n_{W,T}} = \Delta h_{melt}\left(1 - a\frac{n_M}{n_{W,T}}\right) \tag{4}$$

From Eq. (4), a plot of $\Delta H_{melt}/n_{W,T}$ vs. $n_M/n_{W,T}$ made using data obtained from samples of lower polymer content (corresponding to fully hydrated monomers plus free water) should be linear. Extrapolating the plot, it intercepts the horizontal axis (corresponding to $\Delta H_{melt}/n_{W,T} = 0$) at $n_M^0/n_{W,T}$, where n_M^0 corresponds to the theoretical moles of monomer at which there is no free water. From the horizontal intercept of Eq. (4), the hydration stoichiometry is given by

$$a = \frac{n_{W,T}}{n_M^0} \tag{5}$$

Figs. 5 and 6 show the extrapolated plots of Eq. (4) that were used to determine the factor a. From the horizontal intercepts, it was calculated that $a = 5.9$ and 10.7 for MC-A4M and HPMC-E4M, respectively. The higher number of non-freezing water molecules observed in HPMC is likely attributable to the additional propylene group substitution on the cellulosic backbone. This may also support the observed gelation and swelling properties of HPMC as compared to MC.

In plots of Eq. (4), the vertical axis intercept corresponds melting of ice with no polymer present (e.g., pure ice/water). The intercepts from Figs. 5 and 6 are 5772 and 5806 J/mole, respectively, which are close to the nominal value of 6000 J/mole and consistent with assumption (2) above.

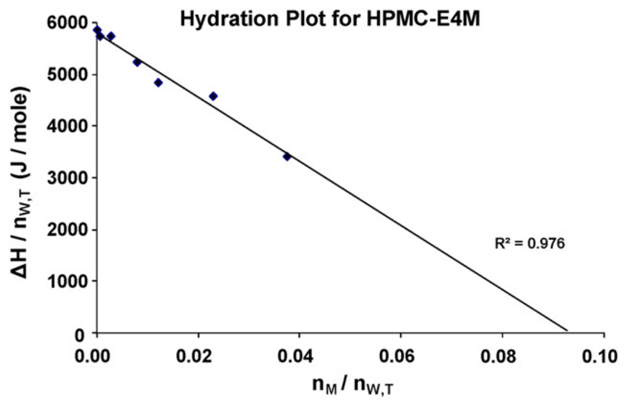

Fig. 6. Extrapolated plot of Eq. (4) for HPMC-E4M/water mixtures.

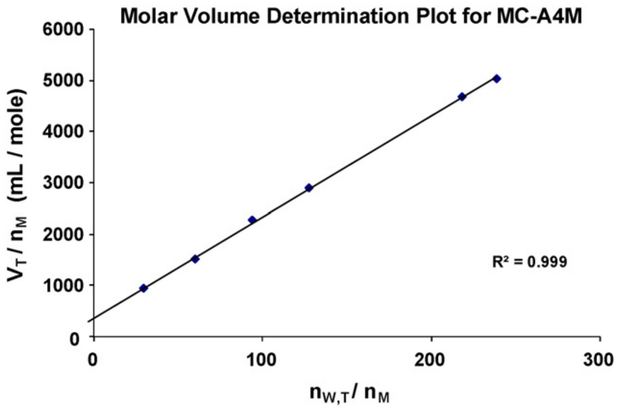

Fig. 7. Plot of Eq. (9) for MC-A4M/water mixtures.

3.3. *Molar volume determination for MC-A4M and HPMC-E4M hydrated monomer complexes*

A fully hydrated water–polymer system consists of n_W moles of free water and n_C moles of hydrated monomer complex. The Euler form for the total volume V_T (water plus hydrated monomer) is given by (Klotz & Rosenberg, 2000)

$$V_T = \left(\frac{\partial V_T}{\partial n_W}\right)\bigg|_{n_C} n_W + \left(\frac{\partial V_T}{\partial n_C}\right)\bigg|_{n_W} n_C \tag{6}$$

This equation can be used to define the molar volumes of the free water υ_W and hydrated monomer complex υ_C by the equation

$$V_T = \upsilon_W n_W + \upsilon_C n_C \tag{7}$$

Combining Eqs. (1) and (7) leads to

$$V_T = \upsilon_W n_{W,T} + \upsilon_C n_C - a\upsilon_W n_C \tag{8}$$

Noting again that $n_C = n_M$ for fully hydrated systems and rearranging gives

$$\frac{V_T}{n_M} = \left(\frac{n_{W,T}}{n_P}\right)\upsilon_W + (\upsilon_C - a\upsilon_W) \tag{9}$$

For systems with free water, Eq. (9) predicts that a plot of V_T/n_M vs. $n_{W,T}/n_M$ is linear, with slope υ_W. The molar volume of the hydrated monomer complex can be found from the intercept with the vertical axis as

$$\upsilon_C = a\upsilon_W + \text{intercept} \tag{10}$$

Experimental volumetric data for MC and HPMC are given in Tables 1 and 2, respectively, and the corresponding plots of Eq. (9) are shown in Figs. 7 and 8. The slopes of the MC-A4M and HPMC-E4M plots were 19.7 and 17.9 mL/mole, respectively, which are consistent with the nominal value of 18.0 mL/mole. Table 5 shows the measured true densities for the dry polymers and calculated molar volumes of the hydrated monomer complexes. For the MC-A4M and HPMC-E4M, the hydrated complex molar volumes were

Table 5
Monomer molar volumes and true densities for dry and fully hydrated MC-A4M and HPMC-E4M.

	$\upsilon_{M\text{-}dry}$ (mL/mole)	υ_C (mL/mole)	ρ_{dry} (g/mL)[a]	ρ_C (g/mL)
MC-A4M	143.2	486.9	1.341	0.394
HPMC-E4M	187.0	580.0	1.326	0.428

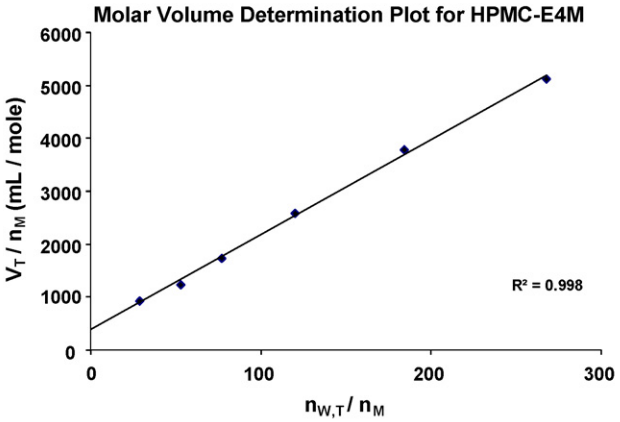

Fig. 8. Plot of Eq. (9) for HMPC-E4M/water mixtures.

486.9 cm^3/mole and 580.0 cm^3/mole, respectively. These results highlight differences in their hydration layers, and are consistent with the fact that HPMC swells significantly more than MC in water (Baumgartner & Peppas, 2002; Colombo, Bettini, & Peppas, 2000).

3.4. Discussion

In this work, aqueous solutions of MC and HPMC were used as systems to develop methods to determine two quantities of interest—the hydration stoichiometry a (the moles of water per mole of monomer for a fully hydrated polymer) and the molar volume of a fully hydrated monomer complex v_C.

Here, the data used in the thermal and volumetric analyses were obtained from mixtures that were sufficiently dilute with respect to the polymer to assume that the monomers were fully hydrated on average. This dictated the range of concentrations that were used in plots of Eq. (4), shown in Figs. 3 and 4, and Eq. (9), shown in Figs. 5 and 6. Two criteria were used to determine the upper values of the polymer concentrations to be used. First, polymer concentrations that were high enough to cause plots of Eq. (4) to deviate from being linear were excluded. Second, the ratio of moles of total water to moles of monomer in a solution ($n_{W,T}/n_M$) was roughly two or more times higher than the hydration stoichiometry a determined from the included points. The second criterion was imposed because it is possible that the deviation from linearity can be visually subtle, but result in differences in the calculated value of a of 10% or more. For instance, as shown in Fig. 5 for MC, the maximum value of $n_M/n_{W,T}$ plotted was ~0.093, corresponding to a minimum value of $n_{W,T}/n_M \sim 11$ (roughly twice the calculated stoichiometry of $a \sim 5.9$). Similarly, as shown in Fig. 6 for HPMC, the maximum value of $n_M/n_{W,T}$ plotted was ~approximately 0.037, corresponding to a minimum value of $n_{W,T}/n_M \sim 26$ (slightly more than twice the calculated stoichiometry of $a \sim 10.7$).

The characterizations of a and v_C are general, representing the average behavior of the entire polymer, and do not depend on specific knowledge of the polymer chemistry beyond average molecular monomer weights. Thus, the method is consistent with how the chemistry is reported. (For instance, parameters such as the degree of substitution DS are reported by the manufacturer as fractions over the entire polymer.) On the other hand, if the specific nature of the monomers (e.g., DS) are varied in a quantifiable manner, the method does provide experimental means to detect changes in average values of a and v_C. This would presumably be of interest to compare e with other methods such as in silico predictions, etc.

It is worth noting the hydration stoichiometry a most directly reflects the amount of water that is free to form ice, rather than directly measuring the amount of water that is actually bound to the monomers. However, as evidenced by the linearity of plots of Eqs. (4) and (9), the calculated value of a is consistent over a significant range of polymer concentrations, so it is plausible to interpret a as a stoichiometry representing the water molecules that are associated with the monomer and not with free water.

It is also worth noting that, although the heat of melting for ice was assumed to equal its nominal value (~6 kJ/mole) and be constant over the temperature range in the studies (as low as −20 °C), it will in fact vary with the temperature. However, the relative variations would be expected to be small over that temperature range, so assuming the nominal heat of melting represents an acceptable approximation for this work. (Additionally, since solutions are being studied, it would be necessary to determine the heat of melting vs. temperature profile for each polymer solution, which is beyond the scope and intent of this study.)

In this study, the choice of polymers was made (in part) because the observed molar volumes of the hydrated complex can be compared with that of the dry state to obtain swelling ratios, which in turn can be compared with values obtained by other methods. The swelling expansion factors relative to the dry state (swelling ratios) found in this work were 3.4 for MC-A4M and 3.1 for HPMC-E4M. These values can be compared with those of several studies on expansion in gel states. (Although we are comparing gel and solution studies, the comparisons are still of interest because polymers in the gel state are significantly, if not fully, hydrated.) For instance, Ford et al. (1995) used thermal mechanical analysis to perform polymer expansion and gel layer studies on compacted discs of both MC-A4M and HPMC-E4M. They found swelling expansions factors of approximately 3.0 and 2.0 for MC and HPMC, respectively. These results are consistent with published values for similar polymers. For instance, a swelling expansion factor of approximately 3.5 has been reported for HPMC-K4M, which is slightly different from E4M grade in its -methoxy content (19–24% for K4M and 28–30% for E4M, respectively). Similar findings were also reported by Baumgartner and Peppas (2002), who found an approximate factor of 4.5 (based on normalized gel thickness) for the K4M grade. Given the polydisperse nature of cellulosic ethers, these values are consistent with the swelling expansion factors found in this study.

It is possible that the ratio between the molar volume of the hydrated complex species and its dry state can be used to empirically predict the extent of swelling for a given polymer/solvent system at a particular set of equilibrium conditions, as in the case of the cellulose ethers studied. A further refinement to the thermodynamic treatment of such a relationship would be of interest, but is beyond the scope of this paper. However, a method is currently being developed that is an extension to the one presented here, which can be used for higher polymer concentrations (removing the assumption that the monomers are fully hydrated) and applied to gels. These results will be presented in a future report.

4. Conclusions

Methylcellulose (MC-A4M) and hydroxypropylmethyl cellulose (HPMC-E4M) hydration stoichiometries a and the molar volumes of the fully hydrated monomer complexes v_C were determined using DSC and volumetric fraction measurements. The data and analyses resulted in calculated values of $a \sim 5.9$ and $v_C \sim 487$ cm^3/mole for MC-A4M and $a \sim 10.7$ and 580 ~ cm^3/mole for HPMC-E4M. The results of this work are potentially important because hydration stoichiometries and volumes can have significant effects on the physical and chemical properties of the backbone structure, which may elicit implications in the presence of other molecules such as drug candidates, cryoprotectants, proteins and other biological compounds.

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