Calorimetric Studies of Dissolution of Hydroxypropyl Methylcellulose E5 (HPMC E5) in Water

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Abstract ☐ The interaction of water with polymers is important because it directly or indirectly affects various properties such as rheological and transport properties. In this study, the hydration/dissolution of a hydrophilic polymer was investigated by calorimetric techniques. Hydroxypropyl methylcellulose E5 (Methocel, HPMC E5) was used as the model polymer. A water-insoluble, hydrophobic polymer, ethyl cellulose E4 (Ethocel, EC E4), was selected for comparison. The number of moles of non-freezing and freezing water were determined by differential scanning calorimetry. Moles of non-freezing water per polymer repeat unit were 6.2 ± 1.3 and 1.6 ± 0.3 for HPMC E5 and EC E4, respectively. The hydration/dissolution of HPMC E5 was exothermic, with a total heat of dissolution of -24.1 ± 1.1 cal/g (n = 4). The heat of hydration of water-insoluble EC E4 was -2.6 cal/g (n = 2). The specific heat capacity value of HPMC E5 increased due to the addition of water. The heat of solution and an increase in specific heat capacity values were associated mainly with the addition of tightly bound water to the polymer. The dissolution of HPMC E5 in water is believed to have endothermic and exothermic components. In summary, the study provided insight into the dissolution of a representative hydrophilic polymer in water. The heat of solution and the specific heat capacity values were mainly dependent on the addition of tightly bound water.

Water affects the stability as well as the rheological and transport properties of various compounds. As a result, the interaction of compounds with water has been of special importance. The interaction of proteins with water has also been a subject of great interest.2,3 Ling et al.4 observed a reduction in the solubility of sucrose and glycine in water in contact with proteins and polymers. Propagated electrical polarization (association-induction hypothesis) was believed to be the cause of this phenomenon. In the pharmaceutical industry, hydration and swelling properties of polymers have been exploited in several conventional formulations and novel drug delivery systems.5 The processes of hydration/ swelling and dissolution of polymers in water have been known for a long time. The important steps involved during the dissolution of a hydrophilic polymer include absorption/ adsorption of water at the most easily accessible sites on the polymer, breaking of polymer-polymer bonds with a simultaneous creation of water-polymer bonds, separation of polymer chains, swelling, and finally dispersion of polymer chains in the medium. 6,7 Thermodynamically, a negative free energy of dissolution of a polymer results in a spontaneous dissolution. Knowledge of the enthalpic and entropic contributions to the free energy would be necessary to understand the dissolution process. The purpose of this study was to shed more light on the process of polymer dissolution in water with respect to these thermodynamic parameters. With this aim in mind, hydroxypropyl methylcellulose E5 (Methocel, HPMC E5), a widely used water-soluble polymer, was chosen as the model polymer. A water-insoluble polymer, ethyl cellulose E4 (Ethocel, EC E4), was studied for comparison.

Water of hydration in macromolecules has been classified into three types. Jhon and Andrade⁸ defined these three types as follows: (1) Type I—free, freezing water melting at 0 °C; (2) Type II—loosely bound, freezing water with a melting point below that of pure water; and (3) Type III—water tightly bound to hydrophilic groups that does not freeze. With the melting endotherms of water obtained in differential scanning calorimetry (DSC) experiments, the amount of water frozen can be calculated. The difference between total water and the amount of water frozen yields the amount of nonfreezing water in the sample. The total heat of solution involved during the dissolution of dry and partially hydrated polymers in water was determined. Because EC E4 does not dissolve in water, only the heat of hydration value was obtained for this polymer.

Specific heat capacity (C_p) is another important parameter that provides insight to the thermodynamic state of a polymer. Therefore, the effect of water on the specific heat capacity of HPMC E5 was studied. The thermodynamic parameters obtained serve to furnish the microscopic details of the energetics of polymer dissolution that will contribute to a visualization of the process of polymer dissolution in water.

Experimental Section

Drying of Polymers—EC E4 and HPMC E5 samples were obtained from Dow Chemical Company, Midland, MI. HPMC E5/EC E4 powders or HPMC E5 films (cast by the solution method) were dried in an oven at 70 °C under reduced pressure (5 inches of mercury) for 3 days. Special precautions were taken to minimize the exposure of polymers to the atmosphere during handling. It was assumed that the drying procedure used here was adequate to remove all types of water from these polymers.

Types of Water in Hydrated Polymers—The detection and quantitation of bound and free water in the hydrated polymers was performed by DSC (DSC-4, Perkin Elmer, Norwalk, CT). Polymers in a fine granular form were used for this study. A Cahn automatic electrobalance (model #23, Cahn Industries, Inc., Cerritos, CA) was used for weighing the samples. Partially hydrated samples were prepared by weighing dry polymer in the aluminum sample pans to which water was added. Pans were hermetically sealed and weighed to determine increase in weight and percent hydration. Partially hydrated polymer samples were stored at room temperature overnight to attain an equilibrium between water and the polymer. The DSC was calibrated with indium as the standard. Thermograms were obtained in the temperature range −50 to 10 °C at the scanning rate of 2.5 °C/min. The enthalpy of fusion value for water in the sample was calculated by thermal analysis software from MC2 Thermal Systems (Troy, NY) for use on an IBM/PC interfaced with the DSC. The software also determines the onset temperature or the melting point of water. When the onset temperature was <0 °C, the enthalpy of fusion of the supercooled water was corrected with the following equation10:

$$\Delta H_{\rm f}(T \, \text{K}) = \Delta H_{\rm f}(273 \, \text{K}) - \int C_{\rm p} dT$$
 (1)

In eq 1, ΔH values are the heat of fusion values at the temperatures T or 273 K, $\mathrm{d}T$ is the difference in the melting temperatures of pure

water and water in the polymer, and $C_{\rm p}$ is the heat capacity of water integrated between 273 and T K. If separate endotherms for the melting of free water (Type I) and loosely bound water (Type II) are observed, the ΔH value and the onset temperature for each endotherm can be obtained. From the ΔH values, the total amount of freezable water was calculated. By knowing the total amount of water in the sample and the amount of freezable water, the amount of non-freezing water was calculated. For HPMC E5 and EC E4, the molecular weight of each polymer repeat unit (PRU) was determined from the structure and the moles of non-freezing water per PRU were calculated.

Heat of Hydration/Solution—The heats of hydration/solution values of these polymers were determined with a TRONAC isoperibol (titration) calorimeter (model 450, Orem, UT). The accuracy and reproducibility of the instrument were confirmed with potassium chloride samples. To prepare partially hydrated samples, dry polymer (10-60 mg) was weighed in the sample holders to which water was added. The samples were kept at room temperature for a minimum of 1 h so that the heat evolved during hydration (addition of water to dry polymer during the sample preparation) would dissipate. Sample holders with hydrated polymers were submerged in 50 mL of distilled water in a Dewar flask. The water temperature in the Dewar flask was monitored with a thermistor. The analogue voltage was converted to a digital signal, imported into LOTUS 123, and processed. HPMC E5 is a water-soluble polymer and thus, during these experiments, the polymer dissolved in water in the Dewar flask. The total heat of solution for HPMC E5, which included the heat of hydration, swelling, and dispersion of polymer chains, was determined. The hydration process is further thought to consist of solid-solid bond breaking and solid-water bond making. EC E4 is a hydrophobic, water-insoluble polymer that does not swell significantly in water. Solution calorimetry experiments with this polymer yielded only the heat of hydration values.

 C_p Values of HPMC E5—The C_p values of the dried polymer films prepared in situ (casting films in aluminum sample pans from HPMC E5 solution in water) were determined by DSC in the temperature range 10-90 °C at a scanning rate of 10 °C/min. For each C_p measurement, DSC runs on an empty pan and sapphire (the calibration standard) were performed prior to the sample. The same aluminum pan was used for these three runs (i.e., empty pan, sapphire, and polymer film). The C_p values of sapphire and water were determined to ascertain the accuracy of the instrument. Water was added to dry films in the aluminum pans to prepare partially hydrated samples. Samples with low degrees of hydration were prepared by exposing the dry films to water vapor from a beaker of water held near the sample in the Cahn electrobalance at room temperature. Samples were weighed after the experiments to check for any faulty seals, and the results from samples with faulty seals were discarded.

Glass Transition Temperature of HPMC E5—The glass transition temperature of HPMC E5 granules could not be obtained and, therefore, experiments were performed on HPMC E5 films that had higher crystallinity. Preparation of samples was similar to that in the C_n experiments (casting films from HPMC E5 solutions). The temperature range for the experiments was 100-220 °C, with a scanning rate of 5 °C/min. The glass transition temperature values were calculated with the midpoint of the change in the heat capacity during the thermal event. From a small endothermic peak observed during the transition, the heat involved (cal/g) for the glass transition

was determined.

Results

Types of Water in Hydrated Polymers—Table I shows the results for the amount of water (mg) added to HPMC E5 (mg) and the corresponding R values (the number of moles of water added to the HPMC E5 sample per polymer repeat unit, PRU) for several representative samples. This table also lists the onset temperatures for the melting of water in these samples, the percent of freezing or non-freezing water, and the number of moles of water tightly bound per PRU (Type III water). From the ΔH values of water in the samples, the amount of frozen water was calculated. With the total amount of water added to the sample and the amount of water frozen, the amount of non-freezing water was estimated. Figure 1 shows DSC thermograms of hydrated HPMC E5 samples. For a large R value (e.g., R = 254), the melting behavior of water in the sample was similar to that of pure water. As the R value decreased (i.e., percent water in the sample decreased), the onset temperature of the samples decreased. The endotherms also showed fronting. Joshi and Topp¹¹ assumed this fronting of the thermograms to be due to overlapping of endotherms for Type I (free, freezing) and II waters (loosely bound, freezing). A decrease in R value might have resulted in an increase in percent of Type II water. Type II water is loosely bound, having stronger interactions with the polymer chains compared with Type I water. Thus, the decrease observed in the onset temperature suggests an interaction of water with HPMC E5. In the plot of percent freezing water in HPMC E5 samples versus the R values, the percent freezing water in the samples increased and reached a plateau as the R values were increased (plot not shown, data in Table I). Table I also lists moles of water bound per PRU in different samples. For HPMC E5, 6.2 ± 1.3 mol of water were tightly bound to each PRU (n = 10, of which six values are shown in Table I). For the sample with R equal to 4.4 (Figure 1), the endotherm for the melting of water is negligible, and it can be assumed that for samples with R <4.4, the melting endotherm of water would not be observed. This indicates an absence of free water or, in other words, water in those samples would be essentially tightly bound to the polymer.

Figure 2 shows the melting endotherms of water from the hydrated EC E4 samples. Unlike HPMC E5, the endotherms were more symmetrical, and the onset temperatures for all the samples were close to that of pure water. The lack of fronting and the constant onset temperatures for these endotherms indicate a weaker interaction with water that is similar to esters of hyaluronic acid. 11 The weaker interaction of EC E4 with water is reflected in a lower number of moles of water bound per PRU (1.6 \pm 0.3 mol/PRU). The data also suggested the absence of Type II (loosely bound, freezing) water in the EC E4 samples, although the presence of Type II water in the hydrated HPMC E5 samples seems more likely.

Heat of Hydration/Solution—The value for the total heat of solution for dry HPMC E5 was -24.1 ± 1.1 cal/g (n = 4). The value is a sum of heats involved in various processes

Table I-A Representative Tabulation of the Amount of Water per PRUs in the Sample, Melting Point of Water in the Hydrated HPMC E5, and Moles of Water Bound per PRU

Water, mg	HPMC E5, mg	R ^b	Onset Temp., °C	Water Frozen, %	Water Nonfrozen, %	Moles of Water Bound/PRU
1.44	3.10	4.4	-13.6	4.2	95.8	4.3
2.42	2.32	10.0	-10.7	46.3	53.7	5.4
2.25	1.42	15.1	-5.5	69.8	30.2	4.6
3.17	1.49	20.3	-3.7	69.1	30.9	6.3
6.10	0.71	82.1	-0.6	91.9	8.1	6.6
6.05	0.23	254	-0.1	97.4	2.6	6.7

^a Molecular weight, 172.26/PRU. ^b Moles of water added to polymer/PRU.

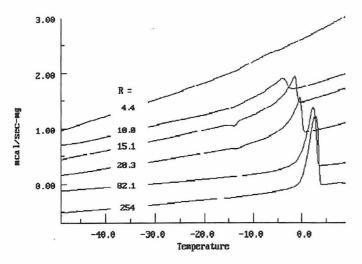


Figure 1—DSC thermograms of partially hydrated HPMC E5 samples (R = number of moles of water added in the sample per PRU).

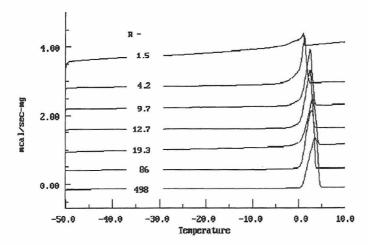


Figure 2—DSC thermograms of partially hydrated EC E4 samples (R = number of moles of water added to the sample per PRU).

during the addition of HPMC E5 to water; for example, hydration, swelling, and dispersion. EC E4 was used for comparison in this study because of its lack of solubility in water. The insolubility of EC E4 in water suggested that the heat evolved during the interaction with water was mainly due to hydration. The polymer did not swell to a significant extent, nor did it dissolve as observed microscopically. The heat of hydration of EC E4 was -2.6 cal/g (n = 2) and, as expected, the value was much smaller compared with the total heat of solution for HPMC E5. Figure 3 shows the heat of solution values for the dry and partially hydrated HPMC E5 samples. During the sample preparation, water was added to dry HPMC and the heat liberated was allowed to dissipate. Thus, partially hydrated HPMC E5 samples would be expected to have lower heats of solution compared with dry HPMC E5. By this experimental technique, it was possible to calculate the amount of heat liberated by the addition of known quantities of water to the sample prior to dissolution experiments (Table II). Addition of 5.07 mol of water per PRU to HPMC E5 resulted in liberation of 17 cal/g of heat. This value corresponds to 71% of the total heat evolved for the dry sample. It can be seen from Figure 3 and Table II that the majority of the heat evolved on dissolution is due to the addition of tightly bound water to the polymer.

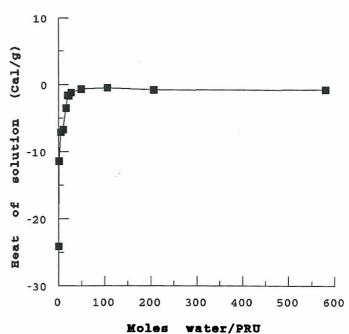


Figure 3—Total heat of solution values (cal/g polymer) of hydroxypropyl methylcellulose samples containing different amounts of water per PRU.

Table II—The Amount of Heat Liberated by the Addition of Different Amounts of Water to Dry HPMC E5 Samples⁴

Moles of Water Added/PRU	Heat Liberated, cal/g	
0	0	
1.2	12.7	
5.1	17.0	
9.8	17.4	
16.4	20.6	
19.6	22.5	
22.7	22.4	
27.4	22.9	
106.3	23.6	

^a The values were obtained from solution calorimetry experiments.

 $C_{\rm p}$ Values of Hydrated HPMC E5 Samples— The $C_{\rm p}$ at constant pressure is defined as follows:

$$C_{\rm p}(T) = \lim (\Delta H/\Delta T), \Delta T \to 0$$
 (2)

In eq 2, ΔH is the change in the specific enthalpy associated with a small temperature change, ΔT . Knowing the enthalpy and temperature changes, it is possible to calculate the C_p of the polymer-water system. Figure 4 shows the C_p values of dry and hydrated HPMC E5 samples at temperatures ranging from 17 to 85 °C. The heat capacity of dry HPMC E5 ranged from 0.32 to 0.39 cal/g °C in this temperature range. The C_p values increased by increasing the amount of water in the sample. Figure 5 shows the effect of the amount of water in the sample on the C_p values at four different temperatures (19.7, 40.7, 61.7, and 82.7 °C). From Figures 4 and 5, it is clear that the addition of the initial 5-10 mol of water per PRU caused the largest change in the $C_{\rm p}$ values. For example, in the sample with 4 mol of water per PRU, the C_p value changed from 0.34 to 0.67 cal/g °C at 40.7 °C. For an ideal binary system, the C_p can be calculated by the following equation:

$$C_{p} = W_{1}C_{p1} + W_{2}C_{p2} \tag{3}$$

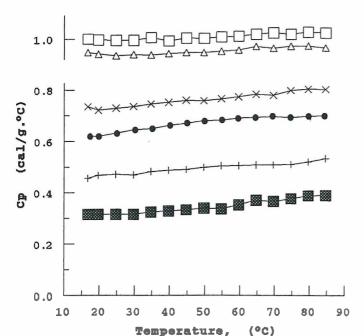


Figure 4—The C_p (cal/g \cdot °C) values of HPMC E5 containing different moles of water per PRU. Key to moles of water added to the sample/PRU (symbol used): (\square) water alone; (\triangle) 79.2; (\times) 10.1; (\blacksquare) 4.0; (+) 1.81; (\blacksquare) 0 (dry HPMC).

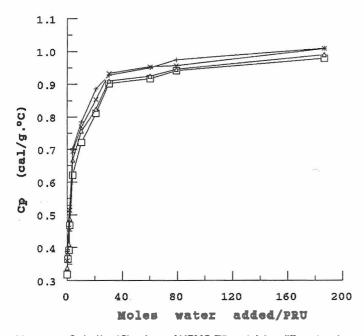


Figure 5— C_p (cal/g · °C) values of HPMC E5 containing different moles of water per PRU unit at 19.7 °C (\square), 40.7 °C (\triangle), 61.7 °C (\times), and 82.7 °C (+).

In eq 3, W_1 and W_2 are the weight fractions of the two components and $C_{\rm p1}$ and $C_{\rm p2}$ are the partial heat capacities of the two components. At 40.7 °C, for different hydrated HPMC samples, the theoretical $C_{\rm p}$ values were calculated with this relation. The trend in the plot of the theoretical $C_{\rm p}$ values versus R (data not shown) was similar to that observed (Figure 5) for the experimental values, with the theoretical $C_{\rm p}$ values, in general, 5–10% lower than the experimental values. As the amount of water in the sample increased, the $C_{\rm p}$ value approached the value for pure water. This means

that the sample became "waterlike" at high water content or, most probably, the sample had dissolved in the water added.

From the C_p values, the amount of tightly bound water in HPMC E5 samples could be calculated. The value of tightly bound water thus obtained was compared with the value from the melting of water data in previous DSC experiments. Yang and Rupley¹² observed a linear decrease in the C_p values of lysozyme with an increase in the weight fraction of lysozyme (0 to 0.73) for the lysozyme-water system. The response was irregular between the weight fractions 0.73 and 1. Plots of C_p values at various temperatures versus weight fraction for the polymer (polymer weight/total hydrated polymer weight) yielded straight lines for low weight fraction values (0 to 0.6 or 0.7), but the graph deviated from linearity for higher weight fraction values in that system. Because of a lack of a large number of data points in the current study, it was not possible to determine the exact weight fractions at which the graphs deviated from linearity; this resulted in only an approximate estimation of the moles of tightly bound water. The number of moles of Type III water per PRU found from C_p values was ~5, and this value was in agreement with the value obtained from previous DSC experiments (6.2 mol/ PRU).

Glass Transition Temperature of HPMC E5—The glass transition temperature of dry polymer films was 154 °C, with an enthalpy of 1.1 cal/g. The glass transition temperature value was consistent with the value reported earlier 13 for HPMC. During the determination of the glass transition temperature of HPMC E5 film, the enthalpy change was so small that it approached the lower limit of detection of the instrument. The glass transition of the sample with 1% water was 152 °C, and no glass transition was observed for samples with >1% water.

Discussion

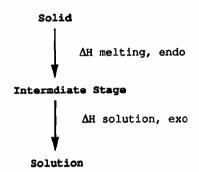
Four types of interactions between solute and solvent, ion-dipole, dipole-dipole, hydrogen bonding, and hydrophobic interactions, have been reported.14 Rowe15 studied the heat of hydration values of nonionic surfactants nonylphenol ethoxylate of increasing molar ratios of ethylene oxide. The heat of hydration value increased with an increase in the molar ratio of ethylene oxide; however, the values decreased above the molar ratio of 10. It was hypothesized that chains with >10 ethylene oxide units were predominantly in the form of expanded helical coils and chains with <10 ethylene oxide units showed fully extended conformation. These results indicate that apart from the interactions mentioned above, the conformation of polymer chains also plays a role in solute-solvent interaction. It was assumed that HPMC E5 polymer chains in dilute solution attain the form of long chains, and the effect of conformation, if any, was negligible.

Free energy is defined as $\Delta F = \Delta H - T\Delta S$, where S is entropy. For a spontaneous reaction to occur, the free energy associated with the process should decrease or ΔF should be negative. The spontaneous swelling and dissolution of HPMC E5 suggests a negative change in ΔF . If ΔH is positive (endothermic), the product $T\Delta S$ has to be $> \Delta H$ to obtain a negative ΔF value. If ΔS is negative, the product $(-T\Delta S)$ is a positive term and, in this case, ΔH must have a large enough negative value (exothermic) to give a negative ΔF . Mortada et al.14 expected negative enthalpy and entropy terms for the complex formation of oxyphenbutazone with polyvinylpyrrolidone in solution if only hydrogen bonds were the determining interaction. Large positive entropy and enthalpy terms were believed to be the characteristics of hydrophobic bond.16 The presence of an ionizable group suggests possible electrostatic interactions. The spontaneous dissolution of HPMC E5 in water indicates a negative change in ΔF . The

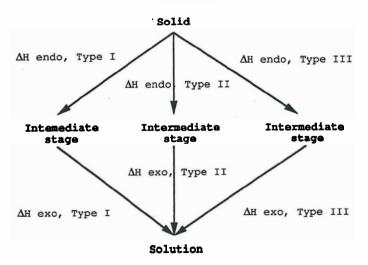
heat of solution was also negative, suggesting a small negative entropic term so that the product $T\Delta S$ is smaller than the enthalpic term or a positive entropic term. According to Rider, 17 polymer dissolution is associated with a positive entropic term which favors dissolution. With this background, one would expect hydrogen bonding to contribute to the heat of solution value for HPMC E5 in water. A commonly employed model for the dissolution of polymers has been described by Craig and Newton¹⁸ (Scheme 1, "Traditional Model"). The dissolution process was divided into two stages: (1) breaking of solid-state bonds, a process similar to the melting of a solid; and (2) incorporation of individual chains into the solution. The breaking of a solid-state bond involves glass transition and actual separation of molecules. This process is generally endothermic. In the present study, the heat involved during glass transition was small (1.0 ± 0.1) cal/g, n = 4). The heat of melting of HPMC has been reported to be 7.7 cal/g.13 The resultant heat of solution for dry HPMC E5 was -24.1 cal/g. Considering the heat of fusion and hydration values for HPMC E5, the net heat of solution would be -32.8 cal/g, assuming a simple addition of heats of hydration and fusion being valid.

With the data presented in this paper about different types of water, it would be possible to visualize the dissolution process beyond the concept presented by Craig and Newton. ¹⁸ A new mathematical model may be proposed to explain

Traditional Model



Proposed Model



Scheme 1—Diagrams of the "Traditional" and the "Proposed" models for the dissolution of polymers (endo = endothermic; exo = exothermic). The ΔH values are the heats involved in various steps during the dissolution process. Types I, II, and III are different types of water absorbed in the dry polymer during dissolution.

processes during the polymer dissolution (Scheme 1, "Proposed Model"). The following assumptions were made: (1) absorption of water (hydration) to Types I, II, and III sites is an exothermic process; (2) there are x, y, and z sites for Types I, II, and III water on a polymer, respectively; and (3) the total heat of hydration is the summation of the heats of hydration for different types of water. It has been proposed in this model that addition of each type of water is associated with an endothermic and an exothermic component. Thus, for the addition of three types of water, three enthalpy terms can be written as follows:

$$\sum_{0}^{X} \Delta H_{I} = \sum_{0}^{X} \Delta H_{I,exo} + \sum_{0}^{X} \Delta H_{I,endo}$$
 (4)

$$\sum_{0}^{\mathbf{Y}} \Delta H_{\mathbf{II}} = \sum_{0}^{\mathbf{Y}} \Delta H_{\mathbf{II}, \text{exo}} + \sum_{0}^{\mathbf{Y}} \Delta H_{\mathbf{II}, \text{endo}}$$
 (5)

$$\sum_{0}^{Z} \Delta H_{\text{III}} + \sum_{0}^{Z} \Delta H_{\text{III,exo}} + \sum_{0}^{Z} \Delta H_{\text{III,endo}}$$
 (6)

In eqs 4–6, $\Delta H_{\rm I}$, $\Delta H_{\rm II}$, and $\Delta H_{\rm III}$ are the heats involved in the addition of Types I, II, and III water, respectively. The total heat of solution of a polymer is the summation of heats for the addition of three types of water:

$$\Delta H_{\text{total}} = \sum_{0}^{X} \Delta H_{\text{I}} + \sum_{0}^{Y} \Delta H_{\text{II}} + \sum_{0}^{Z} \Delta H_{\text{III}}$$
 (7)

For HPMC E5, it was not possible to differentiate the amounts of Types I and II waters. For EC E4, Type II water was absent. Thus, the above equation could be simplified in terms of freezing (Type I) and non-freezing (Type III) water:

$$\Delta H_{\text{total}} = \sum_{0}^{X} \Delta H_{\text{freezing}} + \sum_{0}^{Z} \Delta H_{\text{nonfreezing}}$$
 (8)

The drawback of this equation at this point is that with this experimental procedure, one can determine only the exothermic component during the addition of freezing and nonfreezing water to HPMC E5. Future work should involve identification of various endothermic and exothermic processes during the addition of different types of water and determination of entropic and free energy change during the addition of each type of water.

Solid dosage forms often contain small percentages of water. This water is important for the maintenance of integrity of the product and at the same time may affect drug stability. Knowing different types of water in HPMC or in other excipients would make it possible to determine their effect on product integrity and drug stability.

Conclusions

The results of DSC experiments indicated the presence of nonfreezing (Type III) and freezing water (Type I and/or II) in HPMC E5 or EC E4 polymers. The evolution of heat during hydration and dissolution of HPMC E5 and the changes in polymer heat capacities were significant during the addition

of tightly bound water. The dissolution process showed endothermic and exothermic components that would support the proposed model on types of water/dissolution. In summary, the study provided a better insight into dissolution of hydrophilic and dispersion of hydrophobic polymers in water.

References and Notes

- 1. Water-A Comprehensive Treatise; Frank, F., Ed.; Plenum: New York, 1972.
- Nemethy, G.; Scheraga, H. S. J. Chem. Phys. 1962, 36, 3382-3400.
- 3. Muffett, D. J.; Snyder, H. E. J. Agric. Food Chem. 1980, 28, 1303-1305.
- Ling, G. N.; Ochsenfeld, M. M.; Walton, C.; Bersinger, T. J. Physiol. Chem. Phys. 1980, 12, 3-10.
 Kim, S. W.; Cardinal, J. R.; Wisniewski, S.; Zentner, G. M. Water in Polymers, ACS Symposium Series 127; American Chemical Society: Weshington, DC, 1980, pp. 347, 359. Society: Washington, DC, 1980; pp 347-359.
- 6. Bettelheim, F. A.; Block, A.; Kaufman, L. J. Biopolymer 1970, 9, 1531-1538.
- 7. Wan, L. S. C.; Heng, P. W. S.; Wong, L. F. Int. J. Pharm. 1991, 73, 111-116.

- 8. Jhon, M. S.; Andrade, J. D. J. Biomed. Mater. Res. 1973, 7, 509-522.
- Kuntz, I. D., Jr.; Kauzmann, W. In Advances in Protein Chemistry; Anfinsen, C. B.; Edsall, J. T.; Richards, F. M., Eds.; Academic: New York, 1974; pp 239–345.
 Zhang, W. Z.; Satoh, M.; Komiyama, J. J. Membr. Sci. 1989, 42, 303–314.
- Joshi, H. N.; Topp, E. M. Int. J. Pharm. 1992, 80, 213–225.
- 12. Yang, P. H.; Rupley, J. A. Biochemistry 1979, 18, 2654-2661.
- 13. Pharmaceutical Thermal Analysis: Techniques and Applications; Ford, J. L.; Timmins, P., Eds.; Ellis Horwood Ltd., West Sussex, England, 1989; Chapter 9, p 224.
- 14. Mortada, L. M.; Bostanian, L. A.; Salib, N. N. Pharmazie 1990, H.5, 350-353.
- 15. Rowe, R. C. Int. J. Pharm. 1992, 79, 251-255.
- 16. Poland, D. C.; Scheraga, H. A. J. Phys. Chem. 1965, 69, 2431.
- 17. Rider, P. Polym. Mater. Sci. Eng. 1984, 51, 528-531.
- Craig, D. Q. M.; Newton, J. M. Int. J. Pharm. 1991, 74, 43–48.

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