

## Studies on the Interaction of Water with Ethylcellulose: Effect of Polymer Particle Size

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### ABSTRACT

The purpose of this research was to investigate the interaction of water with ethylcellulose samples and assess the effect of particle size on the interaction. The distribution of water within coarse particle ethylcellulose (CPEC; average particle size 310  $\mu\text{m}$ ) and fine particle ethylcellulose (FPEC; average particle size 9.7  $\mu\text{m}$ ) of 7 cps viscosity grade was assessed by differential scanning calorimetry (DSC) and dynamic vapor sorption analysis. The amounts of nonfreezing and freezing water in hydrated samples were determined from melting endotherms obtained by DSC. An increase in water content resulted in an increase in the enthalpy of fusion of water for the two particle size fractions of EC. The amount of nonfreezable water was not affected by the change in particle size at low water contents. Exposure of ethylcellulose to water for 30 minutes is sufficient to achieve equilibration within the hydrated polymer at 47% wt/wt water content. The moisture sorption profiles were analyzed according to the Guggenheim-Anderson-de Boer (GAB) and Young and Nelson equations, which can help to distinguish moisture distribution in different physical forms. The amount of externally adsorbed moisture was greater in the case of FPEC. Internally absorbed moisture was evident only with the CPEC. In light of these results, an explanation is offered for the success of FPEC in wet-granulation methods where CPEC was not successful.

**KEYWORDS:** ethylcellulose, fine particle ethylcellulose, differential scanning calorimetry, dynamic vapor sorption, GAB equations, Young and Nelson equations

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### INTRODUCTION

Polymers are frequently used in drug delivery systems, and these polymers can be expected to experience an aqueous environment in production and in vivo. The interaction of water with such polymers and its distribution within polymeric systems are critical to their applications in wet massing techniques. Water can either plasticize the polymer or, through hydrogen bonding, form stable bridges that result in an antiplasticizing effect. Thus, the interaction of water with the powdered polymeric materials that are used for the development of a dosage form is a major factor in the formulation, processing, and product performance of solid pharmaceutical dosage forms such as tablets and beads.

The states of water in many polymers have been studied, and indeed there is some debate regarding the exact number of water molecules and types of water in a hydrated polymer. The majority of researchers have classified three different types of water in hydrated polymers.<sup>1-10</sup> They are free water, freezing bound water, and nonfreezing bound water. Free water may be categorized as unbound water in polymers. Its transition enthalpy and peak shape in differential scanning calorimetry (DSC) curves are equivalent to those of pure (bulk) water.<sup>2</sup> Nonfreezing bound water is strongly associated with the hydrophilic group(s) of a polymer, and freezing bound water is characterized as having a phase-transition temperature lower than that of bulk water because of a weak interaction with the polymer chain.<sup>6</sup> The freezing or melting of water that is closely associated with a polymer is usually impossible to observe. Such water molecules are called nonfreezing water. The sum of the freezing bound and nonfreezing bound water fractions is the bound water content. The bound water content depends on the chemical and higher-order structure of the polymer.

Various methods have been used in the study of the different types of water in hydrated polymers. These methods include low frequency dielectric spectroscopy,<sup>11</sup> differential scanning calorimetry,<sup>1,2,4,6-8</sup> differential thermal analysis,<sup>12</sup> thermogravimetric analysis,<sup>3,12</sup> immersion calo-

rimetry,<sup>5,13</sup> thermomechanical analysis,<sup>3</sup> and dynamic vapor sorption analysis (DVS).<sup>14-16</sup>

Moisture sorption isotherms, obtained using DVS analysis, are one of the simplest means to study the interaction of water molecules with powdered polymeric materials. The GAB equation, developed by Guggenheim, Anderson, and de Boer, has been successfully applied to sorption of water by celluloses.<sup>14,17,18</sup> It was noted that the mechanism of water sorption onto the powdered polymer could be described in three ways (ie, tightly bound, less tightly bound, and bulk water).<sup>14</sup> Young and Nelson<sup>19</sup> explained that, when diffusional forces exceed the binding forces, the condensed phase of water on the surface of the sorbent could diffuse into the sorbent bulk. They also developed a technique to determine separately the proposed types of water.<sup>19,20</sup> The technique was applied to study sorption of water onto maize starch and some pharmaceutically relevant materials.<sup>21</sup> The amount and distribution of moisture in the different forms, together with the chemical nature or substitution and the particle properties, such as size and porosity, may alter the properties of the polymers (eg, packing and binding in tablet matrices).<sup>15,16</sup>

In the pharmaceutical field, ethylcellulose is a polymer used to prepare sustained-release medications of various types. Although ethylcellulose is considered insoluble, it can take up water.<sup>5</sup> This can be explained on the basis of the hydrogen bonding capability of the polymer with water. There is a polarity difference between the oxygen atom and the ethyl group in the ethoxy group. The presence of hydroxy groups, depending on the degree of substitution, can also contribute to the interaction of the polymer with water. Thus, there is the potential to form weak to strong hydrogen bonds with water molecules. The interaction of water molecules with ethylcellulose polymer and the effect of its particle size on the application of ethylcellulose in wet massing techniques have not been systematically investigated. The focus of the present study was to investigate the interaction of water with ethylcellulose samples and to assess the effect of the particle size on the interaction of water with ethylcellulose using DSC and DVS analysis.

## MATERIALS AND METHODS

Two samples of ethylcellulose, Ethocel FP Premium with an average particle size of 9.7  $\mu\text{m}$  (fine particle ethylcellulose [FPEC]) and Ethocel Premium with an average particle size of 310  $\mu\text{m}$  (coarse particle ethylcellulose [CPEC]) from Dow Chemical Company (Midland, MI) were selected to study the interaction of water with these polymers. The CPEC and FPEC samples are both 7 cps viscosity grade with an ethoxy content of 48 to 49.5%. Distilled,

deionized water that had passed through a 0.2-micron filter was obtained using an EASYpure UV water system (Barnstead, Dubuque, IA) for use in these studies.

## Differential Scanning Calorimetry

A differential scanning calorimeter (DSC-7, Perkin-Elmer, Boston, MA) controlled by a Perkin-Elmer TAC-7 and equipped with an automatic cooling unit was used to record the DSC thermograms of the samples. The DSC was calibrated using indium and decane as standards. The ethylcellulose samples were dried in an oven at 120°C for 3 days prior to water distribution studies. Weighed quantities of ethylcellulose and water were mixed manually with a steel spatula in 3-mL glass vials for 2 minutes. A water content study and an equilibration study were carried out. For the water content study, the initial water content ranged from 20 to 150% wt/wt of the dry polymer, whereas for the equilibration study the initial water content was 66% wt/wt of the dry polymer. After mixing the polymer and water, the wetted samples were allowed to equilibrate in the tightly capped vial at room temperature for 10, 30, 60, 90, or 1440 minutes for the equilibration study and for 24 h for the water content study. After the holding time, vials were reweighed to check for any moisture loss. Approximately 10 mg of the wetted sample was weighed in a preweighed aluminum DSC pan, and then a lid was secured by crimping. The pans were not hermetically sealed but rather crimped in such a way as to prevent pressure buildup and to allow vaporized moisture to escape easily from the pan during the heating cycle. The samples were placed into the 25°C sample compartment of the DSC under a nitrogen gas flow of 20 mL/min and chilled immediately to -50°C at 10°C/min and held at -50°C for 5 min. Samples were then scanned from -50 to 25°C at 5°C/min to determine the melting endotherm of water and then scanned from 25 to 150°C at 10°C/min to volatilize the water. The sample pans were reweighed after the analysis, and the percentage of actual water content ( $W_c$ ) was calculated as follows:

$$W_c(\%) = \frac{(W_i - W_s)}{W_s} 100\% \quad (1)$$

where  $W_i$  is the initial mass of the sample studied and  $W_s$  is that of the dried sample. The dry sample weight was determined from the weight after heating up to 150°C, where the endotherm indicated that the water had evaporated completely. The extrapolated melting peak onset temperature and the enthalpy of melting of freezing water were determined using Pyris thermal analysis software (Perkin-Elmer, Boston, MA), and the mean of at least three determinations was used to calculate the water uptake by the

samples at each time interval and at each water content. The quantity of nonfreezing bound water was then calculated from the difference between the weight of water in the pan and the amount of freezing water calculated from the observed enthalpy of fusion.<sup>3,16</sup> The molecular weight of each polymer repeating unit (PRU) for CPEC and FPEC was determined from the chemical structure, so that the number of molecules of nonfreezing water bound per PRU could be calculated, as discussed later in the “Results and Discussion” section.

### ***Dynamic Vapor Sorption Analysis***

Moisture sorption and desorption isotherms were generated at 25°C using a Symmetric Vapor Sorption Analyzer (model SGA-100, VTI, Hialeah, FL). The SGA-100 is equipped with an electronic microbalance (CI Electronics, Wiltshire, UK) and a dew point analyzer (Edgetech, Milford, MA) for the accurate measurement of weight and relative humidity (RH), respectively. The instrument was calibrated using sodium chloride and polyvinylpyrrolidone (PVP) K30. The procedure involved 10% steps in RH from 0 to 95% RH following an initial drying at 60°C. Equilibrium was assumed to be established when there was no weight change of more than 1 µg over a period of 5 minutes.

### ***Determination of Crystallinity of the Polymers***

An x-ray diffractometer (model PAD X, Scintag, Cupertino, CA) was used to obtain the x-ray diffraction pattern of the ethylcellulose powder under the following conditions: a monochromatic *CuKα* radiation source was operated at 45 kV and 40 mA, with a scanning rate of 3° (2θ)/min over the range of 5 to 45° (2θ). An x-ray pattern that includes amorphous and crystalline regions was defined. Percentage crystallinity ( $X_{cr}$ ) was calculated as follows:

$$X_{cr} = \frac{I_{cr}}{(I_{cr} + I_a)} 100\% \quad (2)$$

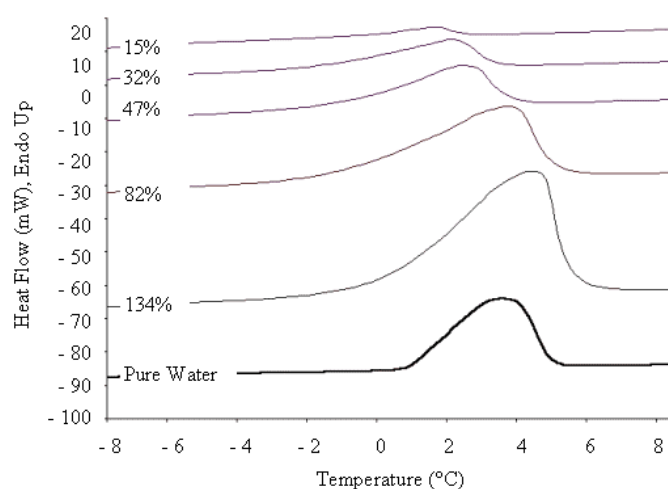
where  $I_{cr}$  and  $I_a$  are the crystalline and amorphous intensities, respectively. The demarcation of  $I_{cr}$  and  $I_a$  was traced with the help of a Crystallinity computer program (Scintag, Cupertino, CA). X-ray diffraction patterns of three samples from each grade of ethylcellulose were measured, and the calculated crystallinity results averaged.

## **RESULTS AND DISCUSSION**

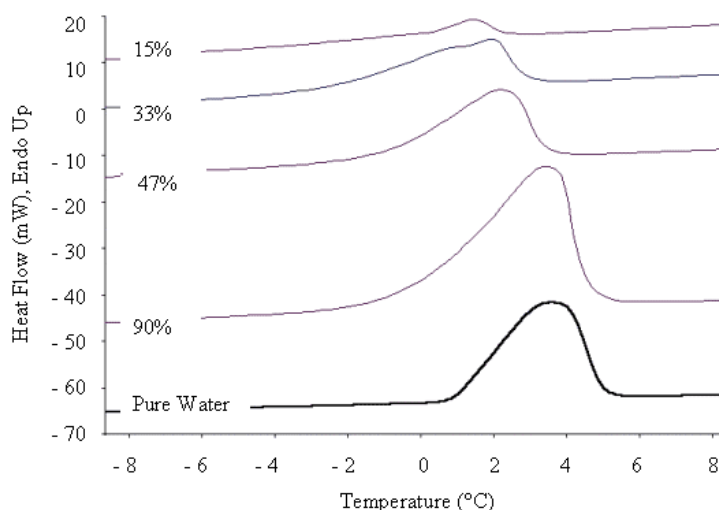
### ***Distribution of Water within Ethylcellulose Samples and the Effect of Particle Size***

Typical DSC scans for CPEC and FPEC at each water content are shown in **Figures 1** and **2**, respectively. In general, the melting endotherms observed for water in the hydrated CPEC or FPEC samples were broad and irregular in comparison with those for pure water; such irregular endotherms can result from the influence of the chemical structure of the polymer on the water molecules. No separate crystallization or melting peak was observed for freezing bound water for either particle size of ethylcellulose. A decrease in the melting peak temperature and the extrapolated onset temperature of the melting endotherm was observed with each water content (**Table 1**), compared with that of pure water. The extrapolated melting peak onset temperature for pure water was 0.913°C, and melting peak temperature was 4.24°C. The experimental enthalpy of fusion of pure water was 316 J/g, which was used as the basis for calculations. In general, the enthalpy of fusion of pure water is between 311 and 334 J/g because of the formation of various polymorphic forms of ice.<sup>22</sup> In the case of CPEC, the extent of melting point depression increased as the water content increased up to 47% wt/wt actual water content, whereas the melting point depression was less at higher water content (**Table 1**), indicating that, at high water content, the melting peak observed is mostly due to freezing free or bulk water. In the case of FPEC, the melting point depression increased as the water content increased only up to 33% wt/wt actual water content, and the melting point depression was less at higher water content (**Table 1**). In general, melting point depression was more in the case of FPEC than of CPEC except at 15% wt/wt actual water content (**Table 1**). The melting peak temperature increased with an increase in water content for both CPEC and FPEC (**Table 1**). As the water content increased, the peaks were less broad and became more regular, and the melting enthalpy calculated from the peak area in the DSC curve increased, indicating that the melting behavior of water in the sample was similar to that of pure water, as observed by Joshi and Wilson.<sup>5</sup>

Water molecules not present at the interface with the polymer will show melting characteristics similar to that of pure water and can be referred to as bulk or free water. Water molecules that are either present at the interface of the hydrophilic/hydrophobic surfaces of polymeric chains or that are between the polymeric strands might be structured, possibly resulting in melting point depression and lowering of the melting enthalpy.<sup>2,23</sup> Melting point depression might also result from weak interactions of some of the water molecules with the polymeric chains. These water molecules are not bound to the primary binding sites of



**Figure 1.** Representative DSC thermograms of pure water and hydrated CPEC at each water content. Equilibration time is 24 hours.



**Figure 2.** Representative DSC thermograms of pure water and hydrated FPEC at each water content. Equilibration time is 24 hours.

**Table 1.** Effect of Water Content on Extrapolated Melting Onset, Melting Peak Temperature, and Bound Water Content for CPEC and FPEC After 24 hour Storage\*

Initial Water Content (W) (% wt/wt)	Actual Water Content (W <sub>c</sub> ) (% wt/wt)	Melting Onset Temp T <sub>m</sub> (°C)	Melting Peak Temp T <sub>p</sub> (°C)	Bound Water Content (C <sub>b</sub> ) (% wt/wt)	Molecules of Bound Water per PRU (M <sub>n</sub> )
CPEC					
23.1 ± 0.577	15.5 ± 1.07	-0.881 ± 0.281	1.57 ± 0.096	13.3 ± 0.441	1.72 ± 0.057
42.6 ± 0.682	31.5 ± 3.39	-1.29 ± 0.172	1.96 ± 0.385	18.0 ± 0.683	2.31 ± 0.087
66.5 ± 0.422	46.9 ± 1.13	-1.57 ± 0.030	2.24 ± 0.096	22.1 ± 0.295	2.85 ± 0.037
102 ± 0.71	82.2 ± 3.65	-0.454 ± 0.246	3.57 ± 0.347	27.5 ± 0.158	3.55 ± 0.02
157 ± 3.37	134 ± 1.97	-0.002 ± 0.281	3.91 ± 0.441	33.2 ± 0.971	4.28 ± 0.125
FPEC					
23.5 ± 1.57	15.3 ± 1.44	-0.331 ± 0.55	1.35 ± 0.441	11.8 ± 1.39	1.52 ± 0.013
42.8 ± 1.54	32.6 ± 1.47	-3.5 ± 1.7	2.02 ± 0.096	16.8 ± 0.042	2.16 ± 0.005
66.4 ± 1.09	46.8 ± 3.93	-1.46 ± 0.433	2.29 ± 0.096	22.1 ± 0.454	2.84 ± 0.058
104 ± 0.119	90.4 ± 5.81	-1.93 ± 0.496	2.63 ± 0.673	30.8 ± 0.421	3.97 ± 0.055

\*Values are mean ± SD (n = 3). CPEC indicates coarse particle ethylcellulose; FPEC, fine particle ethylcellulose; and PRU, polymer repeating unit (average molecular weight of the PRU of ethylcellulose = 232).

the ethylcellulose polymer and therefore exhibit first order melting transitions and can be categorized as freezing bound water. In the case of hydrophilic polymers, a separate melting peak for freezing bound water might be observed at temperatures lower than 0°C,<sup>2,3,6</sup> whereas a separate melting peak for freezing bound water might not be observed for relatively hydrophobic polymers, as seen in the present study. This finding indicates that in the case of a relatively hydrophobic polymer, such as ethylcellulose, very weak secondary interactions between the water mole-

cules and the polymer might exist, and therefore freezing bound water will be mostly present as structured water resulting in only slight melting point depression. In the present study, the free-water melting peak and the freezing bound-water melting peak were evidently fused and appeared as one broad melting peak with melting point depression. For each particle size, the melting point depression of the endothermic peak was not considerable, indicating a negligible contribution of freezing bound water, as noted by Joshi and Wilson in their DSC study of hydrated

ethylcellulose E4 polymer.<sup>5</sup> The melting enthalpy of this peak was less than that of pure water added to the sample, indicating that some of the bound water does not freeze; thus, in the present study, the nonfreezing bound water content was determined from the difference between the actual water content and the freezing water content as follows:

$$W_{nf} = W_c - W_f \quad (3)$$

where  $W_{nf}$  is the weight of the nonfreezing bound water;  $W_c$  is the mass associated with the actual water content; and  $W_f$  is the weight of freezing water (sum of the free water and freezing bound water). The percentage of nonfreezing bound water content was calculated by the following equation:

$$C_b = (W_{nf}/W_s)100\% \quad (4)$$

where  $C_b$  is the percentage of nonfreezing bound water and  $W_s$  is the weight of the dry polymer sample.

The number of molecules of nonfreezing bound water attached per PRU was calculated using the following equation:

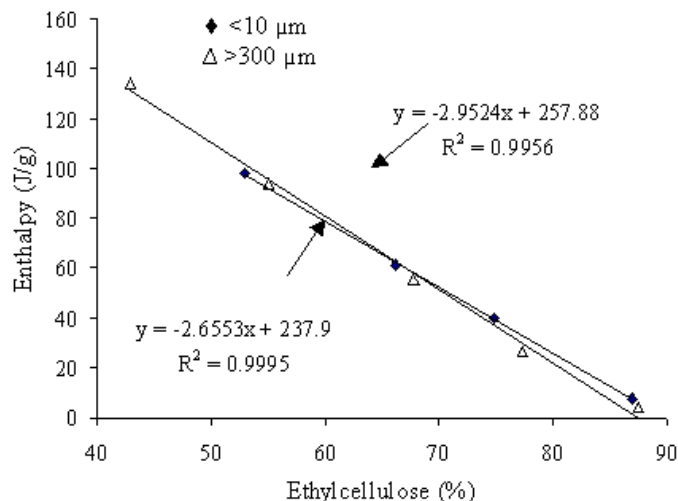
$$M_n = \frac{(M_{EC} \cdot C_b)}{(18 \cdot 100\%)} \quad (5)$$

where  $M_n$  are the molecules of nonfreezing bound water per PRU;  $M_{EC}$  is the average molecular weight of the repeated unit of ethylcellulose; and 18 is the molecular weight of water. The values of  $C_b$  and  $M_n$  at each water content for CPEC and FPEC are presented in **Table 1**.

As the water content increased, the percentage of nonfreezing bound water content ( $C_b$ ) and the number of molecules of nonfreezing bound water per PRU ( $M_n$ ) of CPEC and FPEC increased (**Table 1**). Nonfreezing bound water does not seem to be crystalline, as it shows no melting phenomenon. Tightly bound water can be defined as water molecules that become closely attached to a hydroxyl group of the ethylcellulose polymer. As the water content increases, polymer–polymer hydrogen bonds are disrupted. This results in an increase in primary binding sites. Finally, at high water content, even more primary binding sites can become available, where water molecules can bind. In addition, more water can also bind to water molecules bound to the primary sites, which would still be considered non-freezable.<sup>2,23</sup> These additional sites together account for the increase in the number of nonfreezing bound water molecules per PRU as the water content increased. The  $M_n$  value ranged from 1.7 to 4.3 for CPEC and 1.5 to 4.0 for FPEC over the studied water content range. These values

are somewhat higher than the  $M_n$  value of 1.6 ( $\pm 0.3$ ) that was obtained for ethylcellulose E4 grade by Joshi and Wilson.<sup>5</sup> This could be due to the difference in the sample preparation method. In the present study, interaction between water and polymer was encouraged by mixing, whereas in the study by Joshi and Wilson, water was simply added to the polymer and the DSC pans were crimped.

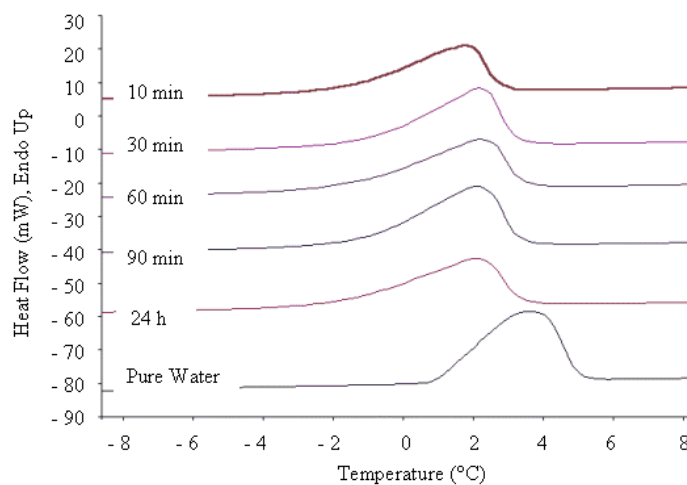
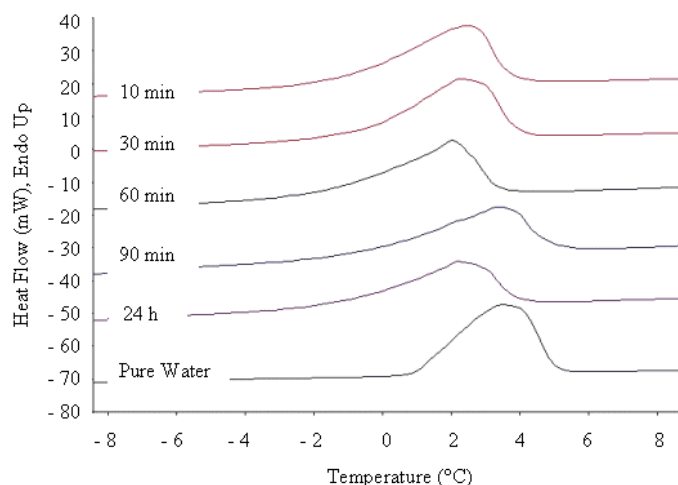
**Figure 3** shows a straight-line relationship between the free water detected as a melting endotherm and the percentage polymer content, as suggested by Ford and Mitchell.<sup>24</sup> Extrapolation to zero enthalpy gave the ratio corresponding to the minimum amount of water required to hydrate the polymer. Any water above that amount would become measurable by DSC and would be classified as freezing water. From the plot, the minimum amount of water required to hydrate the polymer was determined to be  $12.7 \pm 0.142\%$  wt/wt for CPEC and  $10.8 \pm 0.31\%$  wt/wt for FPEC, and the  $M_n$  value would therefore be  $1.87 \pm 0.024$  for CPEC and  $1.55 \pm 0.05$  for FPEC. The similarity between the  $M_n$  values for CPEC and FPEC for the minimum water content and for the low water contents (i.e., 15, 33, and 47%) (**Table 1**) indicates that the particle size of ethylcellulose does not have a profound effect on its ability to bind water molecules per PRU. However, there could be differences in the distribution of freezing water.



**Figure 3.** Enthalpies of fusion (J/g of sample) as a function of the percentage of ethylcellulose content for each particle size sample after 24 hours storage.

### *The Effect of Equilibration Time on the Water Distribution within Ethylcellulose Samples*

**Figures 4** and **5** show the overlay plot of the DSC curves for each equilibration time for CPEC and FPEC, respec-



**Figure 4.** Representative DSC thermograms of pure water and hydrated CPEC equilibrated for various time intervals. Actual water content is 47% wt/wt.

**Figure 5.** Representative DSC thermograms of pure water and hydrated FPEC equilibrated for various time intervals. Actual water content is 47% wt/wt.

**Table 2.** DSC Results of the Effect of Equilibration Time on the Interaction Between CPEC or FPEC and Water\*

Time (min)	Melting Onset Temp $T_m$ (°C)	Melting Peak Temp $T_p$ (°C)	Bound Water Content $C_b$ (% wt/wt)	Molecules of Bound Water per PRU, $M_n$
CPEC				
10	$-1.57 \pm 0.288$	$1.85 \pm 0.167$	$25.4 \pm 0.602$	$3.27 \pm 0.079$
30	$-1.52 \pm 0.391$	$2.41 \pm 0.536$	$20.3 \pm 1.80$	$2.62 \pm 0.228$
60	$-1.77 \pm 0.335$	$1.91 \pm 0.673$	$21.2 \pm 1.74$	$2.73 \pm 0.216$
90	$-1.24 \pm 0.085$	$2.29 \pm 0.948$	$21.1 \pm 1.31$	$2.72 \pm 0.167$
1440	$-1.57 \pm 0.030$	$2.24 \pm 0.096$	$22.1 \pm 0.31$	$2.85 \pm 0.037$
FPEC				
10	$-1.15 \pm 0.031$	$2.68 \pm 0.289$	$24.2 \pm 1.8$	$3.11 \pm 0.231$
30	$-1.87 \pm 0.136$	$2.35 \pm 0.28$	$22.7 \pm 0.301$	$2.93 \pm 0.037$
60	$-1.52 \pm 0.536$	$2.41 \pm 0.536$	$20.5 \pm 0.502$	$2.64 \pm 0.063$
90	$-1.48 \pm 0.321$	$2.02 \pm 0.289$	$21.5 \pm 1.9$	$2.77 \pm 0.251$
1440	$-1.55 \pm 0.312$	$2.24 \pm 0.193$	$22.0 \pm 0.501$	$2.84 \pm 0.058$

\*Values are mean  $\pm$  SD (n = 3). CPEC indicates coarse particle ethylcellulose; FPEC, fine particle ethylcellulose; and PRU, polymer repeating unit (average molecular weight of the PRU of ethylcellulose = 232). Actual water content = 47% wt/wt.

tively. The melting peaks were analyzed for extrapolated onset temperature, peak temperature, and fusion enthalpy. From the enthalpy values, the percentage of nonfreezing bound water content ( $C_b$ ) and the number of molecules of water bound per PRU ( $M_n$ ) were determined, as described in the previous section. The results are presented in **Table 2**. Although the initial water content for the equilibration study was 66% wt/wt of the dry polymer, the actual water content was determined to be 47% wt/wt of the dry polymer, which is

the amount of water in the hydrated polymer. In **Figures 4** and **5**, the bottom curve presents the pure water melting endotherm. In general, broad irregular melting peaks were obtained for the hydrated ethylcellulose samples when compared with the pure water melting peak. The extrapolated onset melting temperature was lower than that of pure water in the case of CPEC and FPEC at each time point (**Table 2**), which is indicative of the structuring of water near the hydrophobic surfaces. In the case of CPEC, no trend was ob-

served in the lowering of onset melting temperature (Table 2). In the case of FPEC, the extrapolated onset melting temperature decreased until 30 minutes and then remained constant for higher equilibration times (Table 2). Approximately 3 molecules of water bind per polymeric repeat unit of CPEC or FPEC at 47% wt/wt water content. Analysis of variance (ANOVA) indicates that the effect of equilibration time was significant ( $P < .05$ ) for both CPEC and FPEC. There is a statistically significant difference in the number of water molecules bound per polymer unit at 10 minutes compared with other equilibration time points. The  $M_n$  values at all other time points (30, 60, and 90 minutes, and 24 hours) are not statistically different from each other. ANOVA also indicated that there is no statistically significant difference between CPEC and FPEC in their ability to bind water molecules per polymeric repeat unit at 47% wt/wt water content ( $P = .709$ ). The interaction between the equilibration time and the particle size was not statistically significant ( $P = .151$ ). From the equilibration study, it is evident that 30 minutes is an adequate time to achieve consistent binding of water to polymeric repeat units at 47% wt/wt water content. Thus, a processing time of less than 30 minutes will probably be sufficient when preparing ethylcellulose granules using water, because the high-speed mixers or planetary mixers used in the manufacturing setting will help to achieve equilibration faster.

### Moisture Sorption Analysis

Moisture sorption isotherms of FPEC and CPEC are shown in Figure 6. Each of the ethylcellulose samples take up very little water from humid air (~5%), and no marked difference is noted in the total amount of water taken up by these samples. The moisture sorption data were analyzed according to the GAB equation:

$$W = \frac{W_m C_G K (P/P_0)}{[1 - K(P/P_0)][1 - K(P/P_0) + C_G K(P/P_0)]} \quad (6)$$

where  $W$  represents the grams of water sorbed per gram of solid;  $W_m$  represents the grams of water in the form of a monolayer;  $C_G$  and  $K$  are parameters related to the heat of sorption of the monolayer and intermediate layer, respectively; and  $P/P_0$  is the water vapor relative pressure. The GAB equation is an extension of the Brunauer, Emmett, and Teller (BET) model, which accounts for the adsorption of an intermediate state of vapor between the tightly bound monolayer water and the condensed molecules adsorbed at higher RH. Molecules in the intermediate state can be considered to interact with the solid, but the interaction is weak compared with the solid interaction with the monolayer. The GAB parameters were determined by nonlinear regression analysis using SPSS 11.5 for Win-

dows (SPSS, Chicago, IL), and the results are presented in Table 3. It can be seen from Figure 6 that the fit of the GAB equation to the experimental data of CPEC and FPEC is excellent. The values of the monomolecular water parameter,  $W_m$ , from the GAB equation indicate that there is only a slight decrease in the  $W_m$  value as the particle size of ethylcellulose decreases. Zografis et al.<sup>14</sup> alluded to the fact that the amorphous regions of a polymer can take up large quantities of water. Thus, the  $W_m$  value obtained from the fit of the data to the GAB equation should be corrected by dividing the  $W_m$  value by the fraction of noncrystalline region and then referred to as  $W_m^{corr}$ . The  $W_m^{corr}$  values obtained for CPEC and FPEC, presented in Table 3, are not markedly different for the two particle size fractions of EC due to their similar amorphous content.

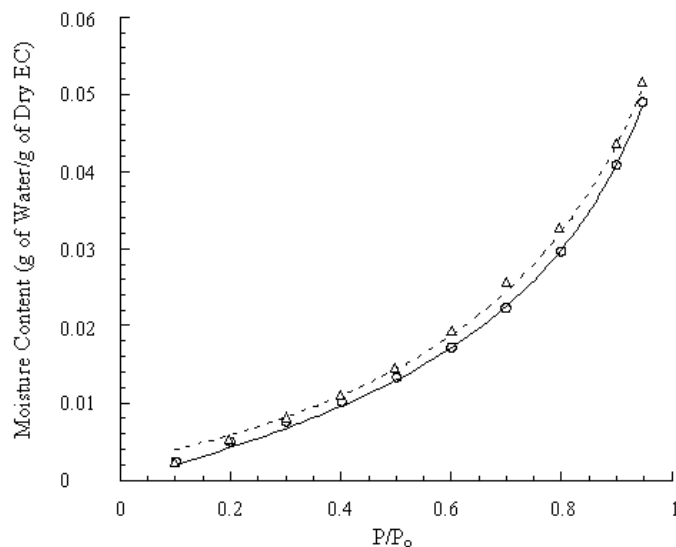


Figure 6. Moisture sorption isotherms for CPEC ( $\Delta$ ) and FPEC ( $\circ$ ) and the fit of the GAB equation; CPEC (---) and FPEC (—).

The values of  $W_m$  obtained from GAB analysis demonstrate that no substantial difference is evident between CPEC and FPEC in the amount of tightly bound monolayer water. Similarly, DSC studies indicate that no substantial difference between CPEC and FPEC is noted in this amount of nonfreezing bound water. Comparison of the computed  $W_m$  values from the DVS analysis and  $M_n$  values from the DSC analysis indicates that the  $M_n$  value is a multiple of  $W_m$ . A number of reasons can be proposed to account for this discrepancy. In the DSC analysis, water was added to the polymer by mixing, similar to a granulation process, which encourages interaction between water molecules and the polymer, whereas in the case of DVS analysis, water is present as condensate from the vapor

**Table 3.** Computed Values of GAB Parameters and Correlation Coefficients Obtained from Analyses of Moisture Sorption Isotherms of Ethylcellulose Samples\*

EC Type	Crystallinity (%)	$C_G$	K	$W_m$ (g/g)	$W_m^{Corr}$ (g/g)	$R^2$	$(H_1-H_L)$ (kcal/mol)
Fine	47.1	2.47	0.814	0.013	0.024	0.999	0.658
Coarse	48.8	1.94	0.78	0.016	0.031	0.999	0.54

\*EC indicates ethylcellulose.  $C_G$  and K are parameters related to the heat of sorption of the monolayer and intermediate layer, respectively;  $W_m$ , grams of water in the form of a monolayer;  $W_m^{Corr}$ ,  $W_m$  corrected for the amorphous content;  $R^2$ , the correlation coefficient;  $H_1$ , the heat of sorption of water in the monolayer; and  $H_L$ , the heat of liquefaction of water.

**Table 4.** Computed Values of Parameters of Young and Nelson Equations and Correlation Coefficients Obtained from Analyses of Moisture Sorption Isotherms of Ethylcellulose Samples\*

EC Type	E	A	B	$R^2$	A $\theta$ (at 95% RH)
Fine	0.330	0.011	0.000	0.996	0.011
Coarse	0.402	0.009	0.012	0.999	0.010

\*EC indicates ethylcellulose;  $R^2$ , the correlation coefficient; A $\theta$ , monolayer adsorbed moisture; and RH, relative humidity.

state. Thus, the interaction of water molecules with the polymer sample might be less in the DVS analysis, thereby resulting in a low value of  $W_m$ . Heat of sorption studies, conducted previously, support the fact that water up to at least 3 times the  $W_m$  value is not considered bulk water and that at least 2 states of such structured water may exist. Water sorbed up to  $W_m$  represents a structured amount of water, with intermediate energetic states existing over the next two or three comparable layers.<sup>23</sup> This water might still be nonfreezable bound water, which accounts for the high  $M_n$  value, as noted by Sisson.<sup>25</sup> It is possible, also, that some water molecules associated with the polymer are in a metastable state relative to pure water or are simply trapped in the polymer matrix, thus only appearing to be in the more structured or bound equilibrium states.<sup>23</sup>

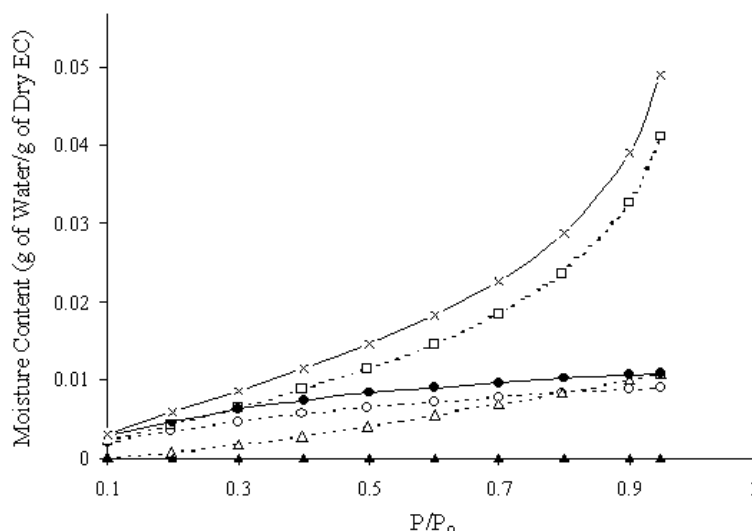
The percentage crystallinity of CPEC was 48.8% and that of FPEC was 47.1%. Thus, the two types of ethylcellulose are similar in their chemical structure, degree of substitution, and amorphous content. As noted above, DSC and DVS studies indicated no marked differences in their ability to tightly bind water. However, recent studies conducted by Agrawal et al.<sup>26</sup> provide the experimental evidence that CPEC is less successful in the manufacture of caffeine-containing tablets by a wet-granulation method as compared with FPEC. In that study, it was observed that aqueous wet granulation in the case of CPEC resulted in formation of few granules, mostly fines. Based on the average particle size and the particle size distribution results following a granulation attempt, it was concluded that the wet-granulation process was far more successful with FPEC than with CPEC. This finding led to the hypothesis that, in the case of CPEC, because of the larger particle

size, the ability to internalize water might exist, which would result in the difference in the distribution of freezing water. Thus, experimental results were tested against the theoretical relationships derived by Young and Nelson<sup>19,20</sup> who hypothesized three mechanisms by which water could be held. According to their hypothesis, if a dry material is exposed to moisture, water molecules first adsorb onto the surface to form a monolayer, which is subject to both surface binding and diffusional forces, the latter tending to cause the moisture to move into the material. The diffusional forces exceed the binding forces as more water molecules adhere to the surface, encouraging further diffusion of water into the material. Although some aspects of the Young and Nelson equations have been criticized,<sup>27</sup> in general it is a useful compromise between theory and practice. These equations quantitatively describe moisture distribution in the sample and have not been replaced by a better alternative. For that reason these equations have been extensively used in the literature.<sup>15,16,19-21,28,29</sup>

The moisture sorption isotherms of CPEC and FPEC were analyzed for 3 locations of moisture, namely, monolayer adsorbed moisture (A $\theta$ ), externally adsorbed moisture (A[ $\theta + \beta$ ]), and internally absorbed moisture (B $\psi$ ). The analysis was carried out by using a combination of iterations and a multiple regression technique, as described in detail by Young and Nelson.<sup>19</sup> The multiple regression analysis was accomplished using SPSS 11.5 for Windows. The computed values of the parameters E, A, and B in the Young and Nelson equations and the correlation coefficients are presented in **Table 4**.

The moisture distribution patterns of the two samples of ethylcellulose, presented in **Figure 7**, show that, as the RH





**Figure 7.** Moisture distribution pattern for CPEC (---) and FPEC (—) according to the Young and Nelson equations. Symbols (-o-), (-□-), and (-Δ-) represent monolayer, externally adsorbed, and internally absorbed moisture for CPEC, respectively. Symbols (-●-), (-x-), and (-▲-) represent monolayer, externally adsorbed, and internally absorbed moisture for FPEC, respectively.

**Table 5.** The Effect of Particle Size of Ethylcellulose on the Moisture Distribution for the 50% and 95% Relative Humidities\*

RH (%)	CPEC			FPEC				
	Moisture Content (g/g)	Aθ	A(θ + β)	Bψ	Moisture Content (g/g)	Aθ	A(θ + β)	Bψ
50	0.015	0.007 (46.7%)	0.011 (73.3%)	0.004 (26.7%)	0.015	0.008 (53.3%)	0.015 (100%)	0.00 (0.00%)
95	0.052	0.010 (19.2%)	0.041 (78.8%)	0.011 (21.2%)	0.049	0.011 (22.5%)	0.049 (100%)	0.00 (0.00%)

\*Aθ indicates monolayer adsorbed moisture; A(θ + β), contribution of monolayer and multilayer adsorption; Bψ, internally absorbed moisture; and RH, relative humidity. Figures in parentheses represent the amount of moisture associated with each particular location as a percentage of the total moisture content at that particular relative humidity.

increased, the externally adsorbed water increased to the same extent for each particle size sample of ethylcellulose. The pattern of monolayer adsorption of water was similar for CPEC and FPEC. It can be seen from **Tables 3** and **4** that the values of the monolayer water parameter from the GAB equation,  $W_m$ , and the amount of monolayer water,  $A\theta$ , at 95% RH, obtained from the Young and Nelson equations are comparable for CPEC and FPEC. The internal absorption of water was observed only in the case of CPEC (**Figure 7**). The effects of particle size on the three locations of moisture, monolayer adsorption ( $A\theta$ ), external adsorption ( $A[\theta + \beta]$ ), and internal absorption ( $B\psi$ ), at RH

of 50 and 95%, are given in **Table 5**. An increase in particle size resulted in an increase in the internal absorption of water and the resultant reduction in the amount of water externally adsorbed.

The externally adsorbed water in the ethylcellulose can assist in formation of liquid bridges between the particles. Any soluble component present in the formulation could dissolve in these liquid bridges and thus assist in formation of solid bridges between the particles on drying, which will sustain the granule integrity. In the case of CPEC, because of internal absorption of water, the amount of water avail-

able to form liquid bridges between the particles will be less, solid bridges will not be formed, and therefore the granulation will be less successful.

## CONCLUSION

From the DSC and DVS analysis results, a number of conclusions or comments concerning the interaction of water with ethylcellulose can be made that bear directly on their use in pharmaceutical systems. The DSC study showed the presence of both freezing and nonfreezing water in the hydrated samples. It was observed that up to 10% to 12% wt/wt moisture content there was no free water in ethylcellulose-water systems, and all the moisture could be considered tightly bound water. The study also showed that the particle size had no substantial effect on the amount of nonfreezing bound water per PRU at low water content.

The DVS study revealed differences in the externally adsorbed and the internally absorbed water between CPEC and FPEC. Because of the larger particle size, the capacity for internalization of water was observed only in the case of CPEC. In general, the percentage of externally adsorbed water was greater in the case of FPEC.

Based on these studies on the interaction between water and the 2 particle size fractions of ethylcellulose, it can be concluded that a difference in the moisture distribution pattern between CPEC and FPEC could be identified. This difference can explain why FPEC was more successful than CPEC in the production of granules by a wet-granulation method using water as the granulating fluid.

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