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Interactions between Water and Pharmaceutical Polymers Determined by Water-Vapor Sorption Measurement and Differential Scanning Calorimetry

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Interactions between water molecules and various pharmaceutical polymers were studied by water vapor sorption and differential scanning calorimetry (DSC). Water-vapor sorption isotherms at 30°C were determined by gravimetric technique and the monolayer values and moisture content at a relative humidity of 79% were estimated for each sample. The state of the water molecules in moistened polymers was investigated using DSC and one or two exothermal peaks of water crystallization were observed in the DSC cooling curves. The content of non-freezing water, which is restricted by hydrophilic groups in polymer molecules, was determined from the amount of freezing and total water in the polymer. The amount of water sorbed at high relative humidity and non-freezing water in DSC measurement correlated to some extent. In hydrophilic polymers having numerous ether linkages, the amount of non-freezing water was larger than that predicted from the small amount of sorbed water in the vapor phase.

Key words pharmaceutical polymer; water sorption; non-freezing water; freezing water; differential scanning calorimetry

Moisture sorption of pharmaceutical polymers is important in physical and chemical stability of solid preparations. The expansion of a tablet followed by the formation of cracks on its surface is caused by water-vapor sorption in tablets containing a polymer diluent.[1] The mechanical strength of a polymer film or sheet varies with the amount of water sorbed.[2-3] Disintegration and dissolution properties as well as the hardness of granules and tablets are influenced by the water content of a solid preparation containing polymer binders or disintegrants.[4-8]

The function of water sorbed on cellulose and its derivatives has been studied by nuclear magnetic resonance spectroscopy,[9,10] sorption isotherm and heat of sorption measurement,[11-13] thermal analysis,[14] dielectric response,[15] and other techniques. Here, we determined the water-vapor sorption and performed differetial scanning calorimetry (DSC) using various polymers (chiefly cellulose derivatives) to compare these two methods.

Materials and Methods

Materials The polymers used were microcrystalline cellulose, MCC (Asahi Chemical Industry, Avicel PH-101), methylcellulose, MC (Shin Etsu, SM-15, -OCH_3: 29.4%), hydroxyethylcellulose, HEC (Nisso-Iwai, Natrosol, -OC_2H_4OH: 25%), low substituted hydroxypropylcellulose, L-HPC (Shin Etsu, LH-11, -OC_3H_6OH: 11.1%); HPC-L (Nippon Soda, -OC_3H_6OH: 68.3%), hydroxypropylmethylcellulose, HPMC 2208 (Shin Etsu, 90SH-100, -OCH_3: 23.4%, -OC_3H_6OH: 6.5%), HPMC 2208 (Shin Etsu, 90SH-30000, -OCH_3: 23.4%, -OC_3H_6OH: 7.7%), HPMC 2906 (Shin Etsu, 65SH-4000, -OCH_3: 28.5%, -OC_3H_6OH: 5.9%), HPMC 2910 (Shin Etsu, TC-5R, -OCH_3: 28.8%, -OC_3H_6OH: 9.0%), hydroxypropylmethylcellulose phthalate, HPMCP (Shin Etsu, HP-55, -OCH_3: 19.1%, -OC_3H_6OH: 5.8%), hydroxypropylmethylcellulose acetate succinate, HPMCAS (Shin Etsu, AS-MG, -OCH_3: 22.7%, -OC_3H_6OH: 7.3%), cellulose acetate phthalate, CAP (Wako Pure Chemical Industries, -$COCH_3$: 20.3%, -COC_6H_4COOH: 35.4%), carmellose sodium, CMC-Na (Wako Pure Chemical Industries, D. S.: 0.73), carmellose calcium, CMC-Ca (Nichirin Chemical Industries, D. S.: 0.5), polyvinylpyrrolidone, PVP (BSF, PVP-K30, K90, PVP-Cl).

Measurement of Water-Vapor Sorption Polymers dried under the conditions described in the chapter entitled "Loss of Drying" in JP XII or the Japanese Standards of Pharmaceutical Ingredients were placed in desiccators at 30 °C, each containing a different saturated solution of inorganic salt.[16] After sorption equilibrium was reached, the samples were weighed and the moisture content at each relative humidity (R.H.) was computed.

DSC DSC was performed to measure the phase transition of water sorbed to polymers, using a type 3100 instrument (Mac Science Co., Ltd.) equipped with a cooling cell. The dried sample was weighed in an aluminum pan and a known amount of water was added with a micro-syringe. The pan was sealed and left at 40 °C for at least 3 d. The water content, W_c, was calculated as follows:

$$W_c = \text{weight of water added/weight of dry sample} \qquad (1)$$

The aluminum pan was boiled in water to prevent it from reacting with water. DSC curves were obtained by cooling the cell with liquid nitrogen from room temperature to 210 K at a rate of 10 K/min.

Results and Discussion

Water-Vapor Sorption Isotherms of Polymers Typical water-vapor sorption isotherms of polymers at 30 °C are shown in Fig. 1. All results are shown as BET type II isotherms, from which BET constants were evaluated:

$$x/[V(1-x)] = 1/(V_m C) + [(C-1)x]/(V_m C) \qquad (2)$$

where x is the R.H., C is a constant related to the heat of sorption, V is the amount sorbed and V_m is the monolayer value. All the BET plots were rectilinear up to $x=0.3$.

The monolayer capacity (V_m) and values at a R.H. of 79% are given in Table 1.

The State of Water Sorbed in the Polymers Figure 2 shows two typical DSC curves of the moisture sorbed to polymers. HPMCP and CAP had two exothermal peaks (Fig. 2(b)) and the other polymers had one, as shown in Fig. 2 (a).

The nature of the water in the polymers was investigated by mean of thermal analysis.[14] Generally, freezing water exhibited a striking exothermal peak at a specific temperature caused by crystallization, and non-freezing water did not crystallize upon cooling at -60 °C. A second peak appeared at a lower temperature than that of peak I.

The amount of freezing water, W_{I} or W_{II} can be calculated from the enthalpy of crystallization peaks I and II, assuming that the crystallization enthalpy of water is

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Table 1. Amounts of Water Sorbed in Vapor Phase and Non-freezing Water Content by DSC

Substance	Amount of water sorbed		Non-freezing water content by DSC			Solubility and solution properties
	V_m[a] (g/g)	V_{79}[b] (g/g)	W_{nf} (g/g)	W_{nf}/V_m	W_{nf}/V_{79}	
MCC	0.033	0.103	0.22	6.6	2.1	[c]
MC	0.034	0.144	0.68	20	4.7	68[d]
EC	0.007	0.034	0.17	24	5.0	[c]
HEC	0.077	0.315	0.58	7.5	1.8	[e]
L-HPC	0.048	0.213	0.49	10.2	2.3	[f]
HPC-L	0.036	0.208	0.68	18.9	3.3	46[d]
HPMC 2208(90SH-100)	0.042	0.155	0.68	16.2	4.3	—
HPMC 2208(90SH-30000)	0.042	0.159	0.72	17.1	4.5	77[d]
HPMC 2906(65SH-4000)	0.031	0.130	0.68	22	5.2	57[d]
HPMC 2910(TC-5R)	0.026	0.127	0.68	26	5.4	55[d]
HPMCP	0.020	0.091	0.20	8.5	2.2	[c]
HPMCAS	0.018	0.076	0.32	17.8	4.2	[c]
CAP	0.030	0.118	0.13	4.3	1.1	[c]
CMC-Na	0.090	0.430	0.87	9.7	2.0	[e]
CMC-Ca	0.074	0.282	0.52	7.0	1.8	[f]
PVP-K30	0.116	0.527	0.67	5.8	1.3	[e]
PVP-K90	0.138	0.425	0.62	4.5	1.5	[e]
PVP-Cl	0.033	0.367	0.60	18.2	1.6	[f]

a) Monolayer capacity. *b*) Amount sorbed at R. H. 79%. *c*) Only slightly soluble or practically insoluble. *d*) Temperature where transmittance at 500 nm of 0.25% polymer solution reached 0.50. *e*) Water soluble; change in turbidity with temperature was rarely observed. *f*) Swelling.

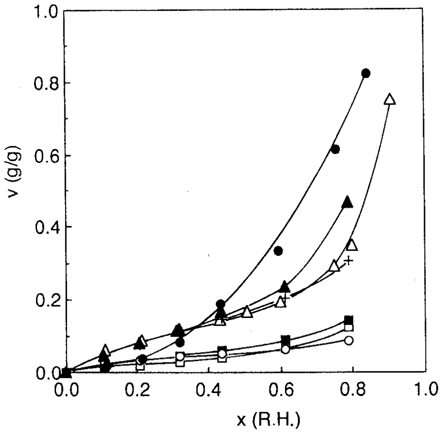

Fig. 1. Water-Vapor Sorption Isotherms at 30 °C

○, MCC; ●, HEC; □, HPC-L; ■, HPMC2208 (90SH-100); △, CMC-Na; ▲, PVP-K90; +, PVP-Cl.

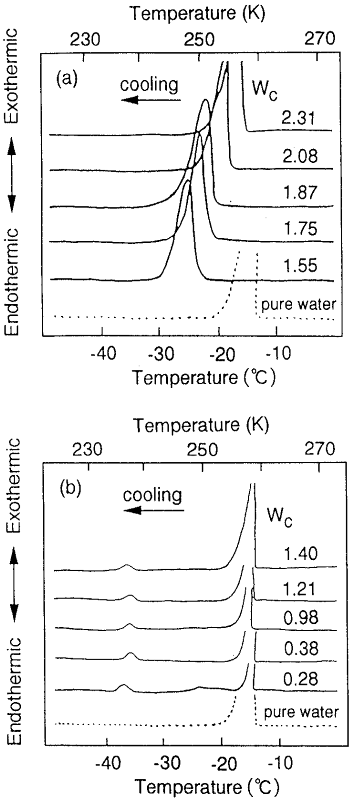

Fig. 2. DSC Cooling Curves of Water Sorbed in Polymers

a, HPMC 2910 (TC-5R); b, HPMCP.

about 334 J/g,

$$W_I = \Delta H_f / 334 \qquad (3)$$

where ΔH_f is the enthalpy of crystallization of freezing water.

The value of W_I or the sum of W_I and W_{II} was usually less than the total amount of water added. The difference between the amount of water added and that calculated from ΔH_f must be water bound to the polymer (non-freezing water, W_{nf}); thus it can be calculated as follows:

$$W_{nf} = W_c - W_f \qquad (4)$$

$$W_f = W_I + W_{II} \qquad (5)$$

where W_c is the water content in the polymer obtained from Eq. 1.

Figure 3 shows the relationship between W_{nf}, W_f and W_c. W_f increased with increasing W_c, but W_{nf} exhibited constant values within the measurement range. The values of non-freezing water W_{nf} are shown in Table 1. The W_{nf}/V_m and W_{nf}/V_{79} ratios are listed in the same table for comparison of adsorption and DSC data.

As a matter of course, amount of water in the BET monolayer V_m is much lower than that at R.H. of 79% V_{79}, which generally corresponds to three molecular

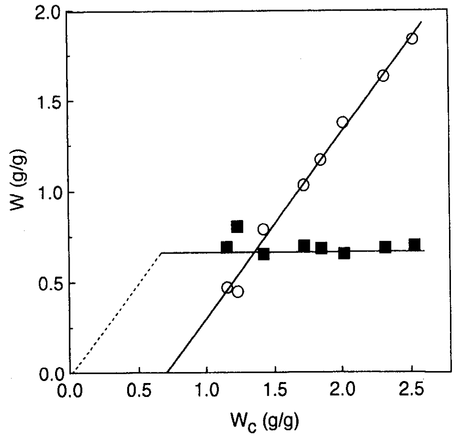

Fig. 3. W_f and W_{nf} with Different Water Content W_c (g H_2O/g dry polymer) for PVP K-30

○, W_f; ■, W_{nf}.

layers. The non-freezing water W_{nf} obtained from DSC measurements contains many more water molecules restricted by polymer.

The W_{nf}/V_{79} ratios turned out to be in the range of about 1 to 2 in polymers with strongly hydrophilic groups such as –OH, –COOH, N–C=O, which are not dependent on the solubility of polymers. Solubility in water and solution properties are shown in the last column in Table 1. On the other hand, the W_{nf}/V_{79} ratios in polymers with numerous ether linkages were 2 or 3 times larger than those in the polymers above mentioned. It is assumed that some water molecules could be associated with oxygen atoms in ether linkages when the total water content W_c is large.

Conclusions

The results obtained in this study led to the following conclusions. 1) The amount of water sorbed at high R.H. was associated with the bound water in DSC measurement, though there were a few exceptions. 2) In polymers having numerous ether linkage molecules, the amount of bound water was more than that expected from the small amount of sorbed water in the vapor phase. In the presence of a great deal of water, it was assumed that water molecules could be associated with oxygen atoms in the ether group which was considered to be less hydrophilic.

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