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THE SWELLING & WATER UPTAKE OF TABLETS III: MOISTURE SORPTION BEHAVIOR OF TABLET DISINTEGRANTS

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ABSTRACT

Water vapor sorption properties and the thermal behavior of four disintegrants including microcrystalline cellulose (Avicel PH102), croscarmellose sodium (Ac-di-sol), corn starch, and sodium starch glycolate (Primojel), were studied. They all exhibited type II-like isotherm. The apparent monolayer sorption for each of disintegrants was found to be significantly greater than the specific surface obtained from nitrogen adsorption. It is proposed that water molecules interact with specific sites on the disintegrant glassy polymer. Water tends to stay as a condensed phase on the polymer, rather than to diffuse into the bulk. Water plasticization caused glass transition temperature (T_g) of all disintegrant polymers to decrease. It facilitated a change from glass to the rubber state. Because the sorption sites were in the glassy state, the change from glass to rubber, which in turn kinetically reduced the available sites, would reflect the sorption capacity of a disintegrant polymer. In addition, the difficulty in freezing a disintegrant's sorbed water was encountered.

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INTRODUCTION

Cellulose, starch, and their derivatives functioning as tablet disintegrants are said to be hygroscopic excipients (1). Present in pharmaceutical tablets, a disintegrant is important to the water uptake and disintegration properties. The water interaction behavior of this excipient is, thus, of interest.

To characterize water associated with the solid, a moisture sorption isotherm, i.e., the mass of moisture taken up per unit mass of dry solid plotted against the relative humidity at constant temperature, is done. Brunauer, Emmett and Teller (2), in 1938, successfully treated the multilayer physical adsorption isotherm. Their method (the B.E.T. treatment) using nitrogen as an adsorbate was acceptable to be a technique to determine the solid surface area (3). The B.E.T. equation, in order to have the better treatment, was modified to be applicable to the wider range of relative pressure (4-5). With some modified assumptions, such as the presence of intermediate adsorbed layers having the heat of adsorption differed from heat of liquefaction of adsorbate or the presence of a finite number of layers of adsorption, an equation was independently developed by Guggenheim, Anderson, and DeBoer (the G.A.B. equation) (6). This equation was successfully applied to water sorption of celluloses by numerous workers (6-8). It was noted that the mechanism of water sorption was different from the physical adsorption proposed by the B.E.T. treatment and the sorbed water could be described as three states, tightly bound, less tightly bound, and bulk water due to capillary condensation (8). It was further hypothesized by Young and Nelson (9) that the condense phase of water on the surface of sorbent could develop a driving force to cause the water to diffuse into sorbent bulk. They also developed a technique to separately determine the proposed states of water, i.e, tightly (monomolecular) bound, normally condensed, and diffused water. The technique, later, was applied to sorption analysis of maize starch and its mixtures with some pharmaceuticals (10). The models discussed above are summarized in Table 1.

The chemical nature of a disintegrant plays an important role in water sorption (8). Cellulose and starch are polymers in nature. In 1930 (11), the three-dimensional network structure consisted of two distinct types amorphous domains, i.e., a bulk mobile-amorphous and interfacial rigid-amorphous portions, and a rigid crystalline component was proposed as a polymeric structural model. One of the methods for characterizing the polymeric structure is to determine glass transition, the state of motion change in which a rigid amorphous turns to be rubbery state.

With the aid of such a modern thermal analysis as differential scanning calorimetry (DSC), the glass transition can be assessed. Water molecules usually act as plasticizers (11) to cause the glass transition temperature, the temperature at which glass-rubber

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Table 1. Different models of moisture sorption treatment.

Model	Function	Note
B.E.T.	$\frac{WmcP/Po}{(1-P/Po)(1+(c-1)P/Po)}$	1
G.A.B.	$\frac{WmckP/Po}{(1-kP/Po)(1+(c-1)kP/Po)}$	1
Young-Nelson	$\frac{(P/Po)}{(P/Po)+(1-P/Po)c}$	2
	$\frac{c(P/Po)}{c-(c-1)P/Po}+\frac{c^2}{c-1}\ln\left[\frac{c-(c-1)P/Po}{c}\right]$ $-(c+1)\ln(1-P/Po)$	3
	$(P/Po)\theta$	4
	$A(\theta+\alpha)+B\phi$	5

Wm is weight corresponding to apparent mpnolayer; P/Po is relative humidity; c is adsorption constant; and k is G.A.B. constant.

1 Function describing the weight of moisture sorption.

2 Function describing fraction of surface covered by a monomolecular layer of water molecules (θ).

3 Function describing total amount of normally condensed moisture measured in molecular layers (α).

4 Function describing fraction of surface covered by one or more layers of normally condensed moisture (ϕ).

5 Total moisture sorption.

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Table 2. Salt solutions for maintaining constant relative humidity

% Humidity*	%w/w NaOH	%w/w $CaCl_2$
100	00.00	00.00
90	9.83	14.95
80	16.10	22.25
70	20.80	27.40
60	24.66	31.37
50	28.15	35.64
40	31.58	39.62
30	35.29	44.36
20	40.00	-
15	43.32	-
10	47.97	-
7	**	-

* Relative humidity at 25 degrees C.
**Used as a saturated solution.
Distilled water was employed.

transition occurs, to decrease. This could reflect the water sorption isotherm, and allows one to characterize the water sorption behavior of excipients under study.

The water interaction behaviors of disintegrants and superdisintegrants, commonly used in pharmaceutical tablets, should be studied to gain better understanding of moisture uptake, compared among superdisintegrants and conventional disintegrants, which are very important for a disintegration action study.

EXPERIMENTAL

Four disintegrants including microcrystalline cellulose (Avicel PH102, FMC Crop.), croscarmellose sodium (Ac-di-sol, FMC Crop.), corn starch (A.E. Staley Mfg., Co.), and sodium starch glycolate (Primojel, GeneriChem) were employed. Each of disintegrant powders was subjected to moisture sorption study and thermal analysis to determine the water sorption behavior.

Water Vapor Sorption Study: Pyrex desiccators containing appropriate concentrations of calcium chloride solutions to provide different relative humidity chambers were prepared.

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All of the desiccators were maintained at 25±0.5 degrees C. to obtain the desired relative humidities (Table 2).

The study was divided into two parts, adsorption and desorption. For the adsorption study, four disintegrant powders were pre-dried over anhydrous calcium chloride for 24 hours at room temperature. A 0.5-1.0 gram of a disintegrant was, then, accurately weighed, and placed in a particular relative humidity chamber. Samples were equilibrated in the chambers for 7 days. The moisture content, expressed as weight of water by weight of solid, of each disintegrant with corresponding relative humidity was determined using an automatic Karl Fisher (KF) titrator (Metrohm 701KF titrino, Brinkmann Scientific Crop.). An adsorption isotherm of each disintegrant was constructed.

For the desorption study, the same method was applied except the method of pre-treatment. All accurately weighed sample (0.5-1.0 gram), previously dried over anhydrous calcium chloride at room temperature, were placed in a 100% relative humidity chamber for 7 days prior to equilibration in different relative humidity chambers.

Differential Scanning Calorimetry: To characterize the change in glass transition temperature (T_g) due to water plasticization, the differential scanning calorimetry (DSC7, Perkin Elmer), running from 30 to 250 degrees C. with the heating rate of 10 degrees C./minute, was performed. Thermograms of a 5 mg. disintegrant powder, previously dried in a chamber containing anhydrous calcium chloride, and previously wetted in a 100% relative humidity chamber, at 40 degrees C. for 24 hours, were compared.

Each of four disintegrants was equilibrated in 100%-, 95%- and 90%-relative humidity chambers at 40 degrees C. for 24 hours. The differential scanning calorimetry exotherms (cooling curves) from 25 to -50 degrees C. at cooling rate of 10 degrees C./minute of such pretreated disintegrant powders were obtained to examine the freezable and/or non-freezable sorbed water.

RESULTS AND DISCUSSION

Water Vapor sorption Study

A disintegrant is usually a hydrophilic polymer which is hygroscopic in nature. The equilibrium moisture content of such pharmaceutical solids have been reported in the literature (1). Some of them are summarized in Table 3. It is seen that a superdisintegrant usually takes up moisture to a higher extent compared to a conventional one.

Figures 1-4 illustrate sorption isotherms of each of disintegrants. They all exhibit a type II-like isotherm which could be treated by the B.E.T. equation. Unfortunately, as

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Table 3. Moisture contents of studied excipients with different conditions.

Material	Moisture Content, %w/w			Class[4]
	storage[1]	90% RH[2]	93% RH[3]	
Avicel PH102	3.84	11.2	13.2	II
Ac-di-sol	5.19	31.3	46.2	IV
corn starch	10.3	18.9	21.5	III
Primojel	5.92	37.1	41.4	IV

1) from air-tight containers at 25 degrees C. (Karl Fischer method).
2) stored at 90 % RH, 25 degrees C. for 7 days (Karl Fischer method).
3) data obtained from reference 1.
4) Hygroscopicity classification (1): class I- non-hygroscopic, class II- slightly hygroscopic, class III- moderately hygroscopic, and class IV- very hygroscopic.

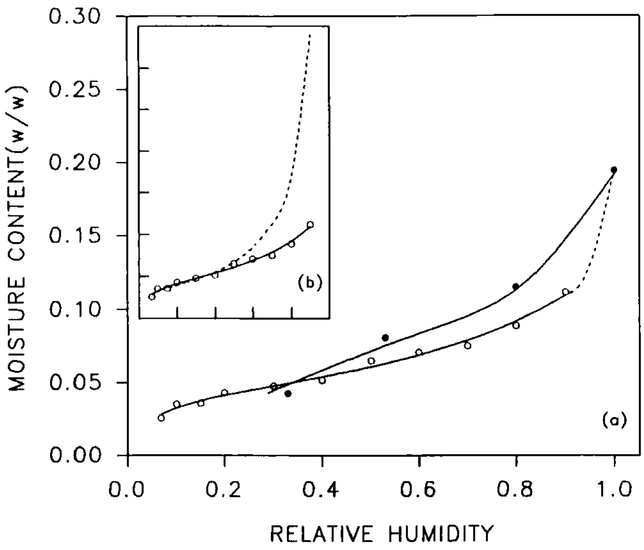

Figure 1. Moisture sorption isotherm of Avicel PH102. (Top-left window), the fitted lines compared between B.E.T. (dotted line) and G.A.B. (solid line) models.

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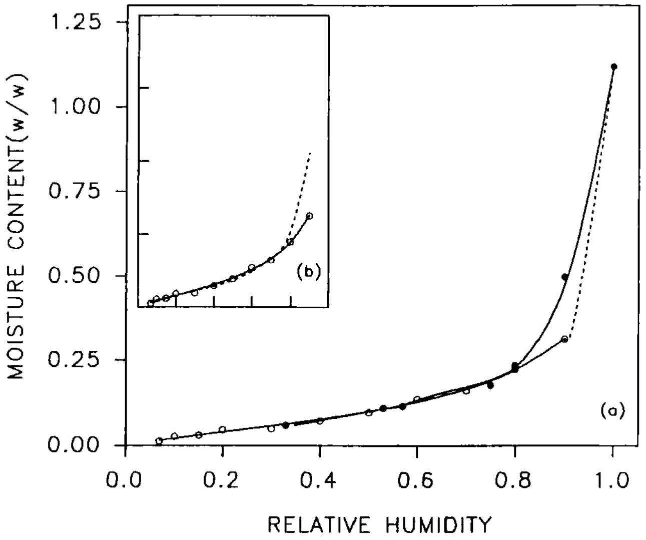

Figure 2. Moisture sorption isotherm of Ac-di-sol. (Top-left window), the fitted lines compared between B.E.T. (dotted line) and G.A.B. (solid line) models.

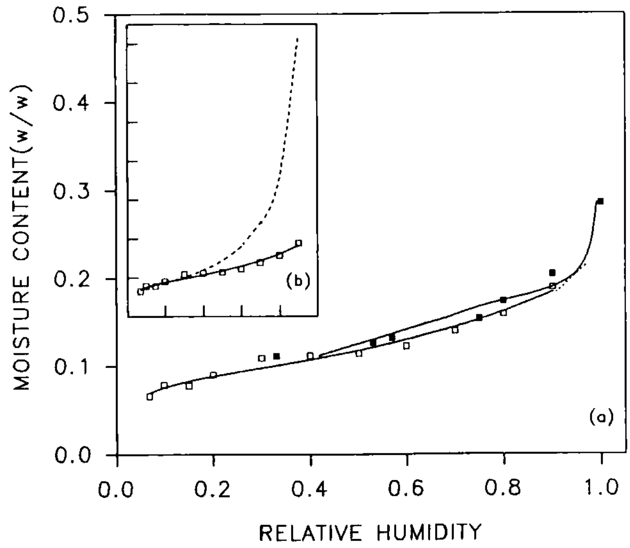

Figure 3. Moisture sorption isotherm of corn starch. (Top-left window), the fitted lines compared between B.E.T. (dotted line) and G.A.B. (solid line) models.

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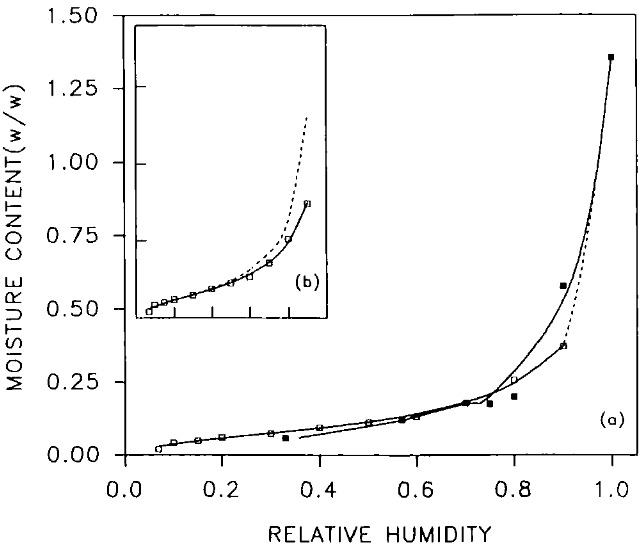

Figure 4. Moisture sorption isotherm of Primojel. (Top-left window), the fitted lines compared between B.E.T. (dotted line) and G.A.B. (solid line) models.

seen in the top-left portions of the figures, B.E.T. treatment was able to explain the sorption data in only the small values of relative humidity. The G.A.B. equation, on the other hand, was successfully applied to the whole range of the relative humidity studied. The moisture content corresponding to monolayer of sorption (W_m), sorption constants (c, and/or k) according to the equation treatments for the studied disintegrants are summarised in Table 4.

The W_m-values obtained from B.E.T. and G.A.B. treatments for the same disintegrant are not significantly different (Table 4) except those of Ac-di-sol (its paired t-test having the t-value of 2.54 which is significantly different in 95% confidence interval with 15 degrees of freedom). It is noted that the sorption constant (c-value) reported for Ac-di-sol is small (value of 7.56 and 3.21 for B.E.T. and G.A.B. treatments, respectively). This makes the isotherm being categorized in between type II and type III (17) which, in turn, causes the calculated W_m to deviate from actual monolayer. The determined value may not be reliable.

As shown in all of the isotherms (Figure 1-4), there is an amount of sorbed moisture remaining on the disintegrant polymer during desorption. A number of explanations have been proposed. For instances, it may be due to changes in polymer

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Table 4. The fitted parameters according to B.E.T. and G.A.B. equations.

Disintegrant	B.E.T.		G.A.B.		
	Wm (s.e)*	*c* (s.e)	*Wm* (s.e)	*c* (s.e)	*k* (s.e)
Avicel PH102	0.0424 (.00358)	23.61 (10.30)	.0420 (.0023)	34.82 (9.78)	.6917 (.0269)
Ac-di-sol	0.0483 (.01086)	7.56 (4.54)	.0830 (.0083)	3.21 (0.72)	.8438 (.0219)
corn starch	0.0784 (.00356)	50.65 (20.62)	.0842 (.0049)	82.65 (3.88)	.6065 (.0365)
Primojel	0.0681 (.01027)	8.09 (3.42)	.0706 (.0032)	8.85 (1.81)	.9062 (.0097)

* (s.e.) is a standard error of fitted parameter according to non-linear regression.

chain conformation (irreversible swelling), solid-liquid bonding strengths (enthalpy effect), molecular ordering (entropy effect), or a combination caused by the entry of water into polymeric structure (12-13). The plastic deformation of sorbent on the desorption of water vapor caused the development of internal stresses which in turn decreased the vapor pressure on desorption (14). The built-up surface condensed phase of water acted as a driving force to cause water to penetrate into bulk in sorption but not in desorption (9-10) resulting in the different moisture contents of adsorption and desorption at the same relative humidity.

The W_m-values (both B.E.T. and G.A.B. treatments) of these disintegrants were previously reported (6-8, 12-13). They are summarized in Table 5.

The agreement between the results of this study and from the literature is met in cases of Avicel PH102 and corn starch. For Ac-di-sol and Primojel, their fitted c-values are small (Table 4) which may cause W_m calculation to deviate from actual apparent monolayer. This probably explains the differences shown in Table 5.

Since the G.A.B. equation is successfully applied to the results, the sorption behavior of disintegrants may occur by two mechanisms; 1, there would be a finite number of molecular layers at saturation (4), and 2, there would be the intermediate layers having

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Table 5. Amount of moisture sorbed by various disintegrants at the apparent monolayer.

Disintegrant	*Wm* (w/w)		
	This study	Literature values	reference. Number
Avicel PH102	0.042**	0.044**	6
Ac-di-sol	0.083**	0.094*	12
corn starch	0.078*	0.083*	7
Primojel	0.071**	0.092*	12

*from B.E.T. treatment.
**from G.A.B. treatment.

the heat of adsorption differed from heat of liquefaction (5). The former mechanisms may be related to the liquid condensation on the sorbent, whereas the latter one may be the result of the tightly bound water which is more ordered than liquid water.

The condensed, the unimolecular bound, and the internal waters can be separated from the isotherm by employing Young-Nelson hypothesis (9). With the assumption that in early sorption (relative humidity up to approximately 40 %) the liquid condensate on the surface is negligible, the fraction of sorbent surface covered by monomolecular layer of water (Θ) was determined using a statistical non-linear regression. The fractions that covered by normally condensed moisture (ϕ), and total amount of normally condensed moisture (α) were then calculated according to Young-Nelson model (9-10). With the aid of multiple regression, it was found that the coefficient accounting for internal moisture was not statistical significant for all cases (Table 6). The sorbed water tends to condense on a disintegrant surface rather than to diffuse into the bulk. The sorption results can be separately seen as a monolayer sorption, and a condensed water on the surface (Figures 5-8).

The specific surface can be calculated using the water sorption as the same manner of that of nitrogen adsorption method. Table 7 compares between the B.E.T. surfaces calculated from nitrogen (18) and from water adsorption. The specific surface obtained from water sorption is much greater than that from nitrogen adsorption. It was noted in the literature (8) that surface area of celluloses calculated from water sorption are approximately 100 times greater than that from nitrogen which agrees with the result of the study (Table 7).

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Table 6. Statistical parameters according to Young-Nelson model.

Disintegrant	A*(t***)	B**(t***)	r****
Avicel PH102	.049(6.20)	-.05 (-1.70)	0.9963
Ac-di-sol	.090(2.95)	-.03 (-0.24)	0.9938
corn starch	.110(27.04)	-.16 (-2.15)	0.9914
Primojel	.140(3.59)	-.17 (-1.18)	0.9914

* and ** are parameters based on the model of:

Sorbed water = $A(\Theta+\alpha)+B(\phi)$, where Θ, α, and ϕ are those discussed in the text.

*** t-statistical value tested against zero, the critical t-value (at 95% confidence interval, 7 degrees of freedom) is 2.365 (two-tail). All values of B are, therefore, non-significant.

**** correlation coefficient of the fitted model.

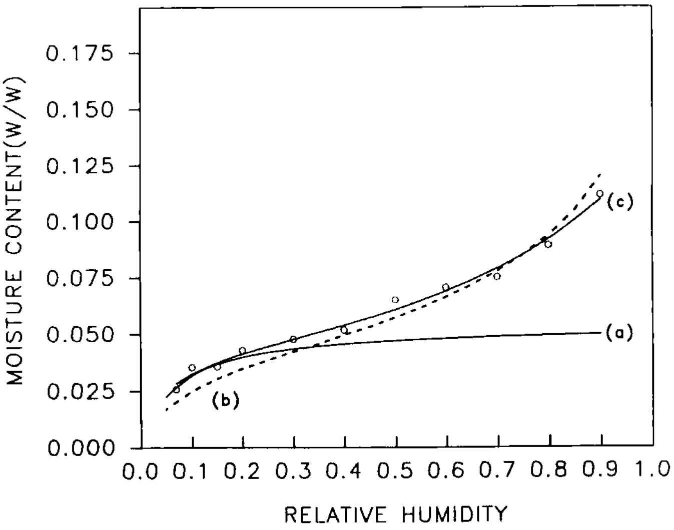

Figure 5. Moisture sorption isothem of Avicel PH102 separately showing the monomolecular moisture (a), normally condensed external moisture (b), and total moisture (c).

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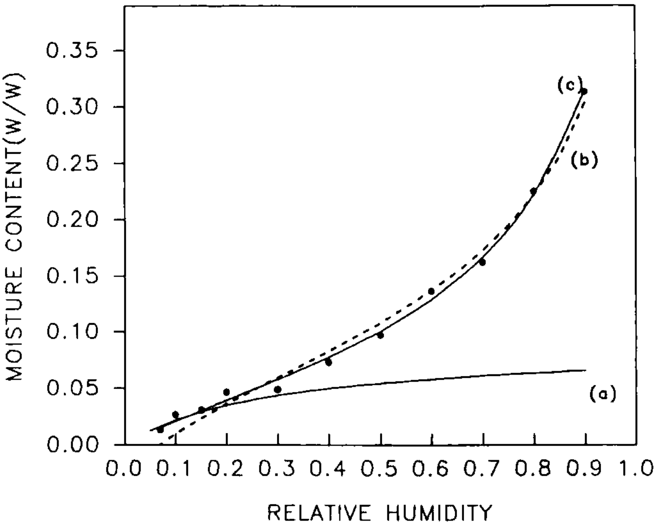

Figure 6. Moisture sorption isothem of Ac-di-sol separately showing the monomolecular moisture (a), normally condensed external moisture (b), and total moisture (c).

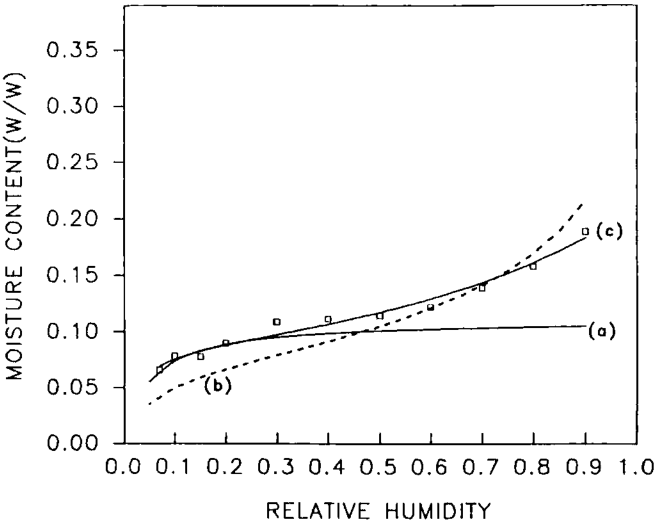

Figure 7. Moisture sorption isothem of corn starch separately showing the monomolecular moisture (a), normally condensed external moisture (b), and total moisture (c).

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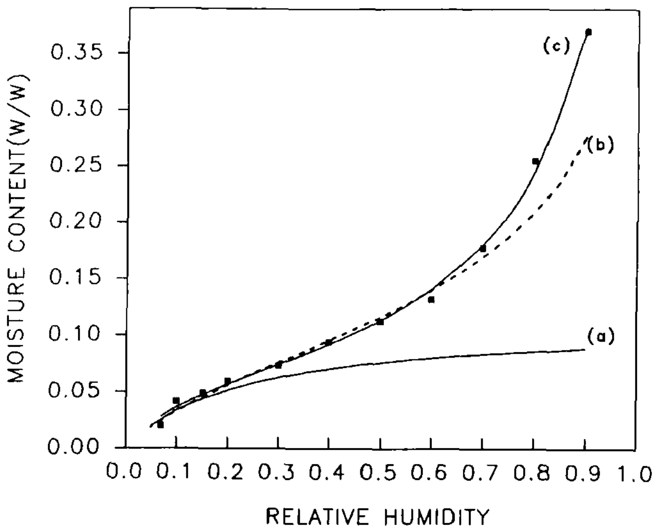

Figure 8. Moisture sorption isothem of Primojel separately showing the monomolecular moisture (a), normally condensed external moisture (b), and total moisture (c).

Table 7. Specific surfaces of disintegrants obtained from nitrogen and water adsorption.

Disintegrant	N_2-BET surface* (m^2/g)	H_20-BET surface* (m^2/g)	S_{H_20}/S_{N_2}**
Avicel PH102	1.18	150.17	127
Ac-di-sol	0.70	171.37	245
Corn starch	0.52	277.87	537
Primojel	0.36	241.28	676

*The areas based on the molecular cross sectional area of nitrogen and water of 16.4 and 10.6 Angstroms^2, respectively.

**The ratio of water-specific surface to nitrogen-specific surface.

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An attempt to explain the significant difference in the specific surfaces of the same disintegrant obtained from different adsorbate was made. Hollenbeck et. al. (13) suggested that the residual moisture on the cellulose surface was frozen at nitrogen adsorption temperature (77 K) and impeded the adsorption of nitrogen molecules on the porous surface. However, this explanation was rejected by Zografi et. al. (8, 12). Their results, which were consistent with the finding in this study, supported the hypothesis that water molecules interact with the specific sites such as anhydroglucose units on surfaces of starches and celluloses.

It was noted that the sorption sites have been located on the amorphous portions of a disintegrant polymer (12). It was reported that microcrystalline cellulose has some crystallinity to as much as ≈60% (15). Evidently, Avicel PH102 exhibits the low SH_2O/SN_2-value (Table 6) compared to other disintegrants which are amorphous. Present in salt forms, the superdisintgrants need water of solvation to interact with the disintegrant polymers. This probably makes the SH_2O/SN_2-value higher.

Differential Scanning Calorimetry

Water in contact with a partially crystalline polymer acts as a plasticizer to ease the change from glassy to rubbery state of the polymer resulting in the glass transition temperature depression (11). One is able to characterize such changes by differential scanning calorimetric (DSC) determination of the glass transition temperatures of disintegrant polymers. The DSC characterization for such a disintegrant is illustrated in Figure 9. The results with two different pre-treated conditions of disintegrants are tabulated in Table 8. The results shown were as expected.

Unfortunately, the water plasticization allows the segmental mobility of a disintegrant polymer to take place at a temperature lower than that of the dry state. This may change the polymer structure, which may be one of the factors affecting the presence of hysteresis in the adsorption-desorption isotherm. Since the decreased glass transition temperatures (Table 8) were significantly greater than the isothermally experimental temperature (25 ±1 degrees C.), the sorption could still be considered to be seen at steady temperature.

A sorption capacity defined as the product between sorbed water corresponding to a monolayer and sorption constant obtained from the fitted model, is reported. Since the G.A.B. treatment was successfully applied to an isotherm, this sorption capacity of a disintegrant polymer could be assumed as a constant value throughout the studied relative humidities. The sorption capacity (C_m) and the extent of decreased glass transition temperature (ΔT_g) for such a disintegrant are summarized in Table 9. It is noted from the table that the disintegrant with low sorption capacity seems to have a high extent of glass

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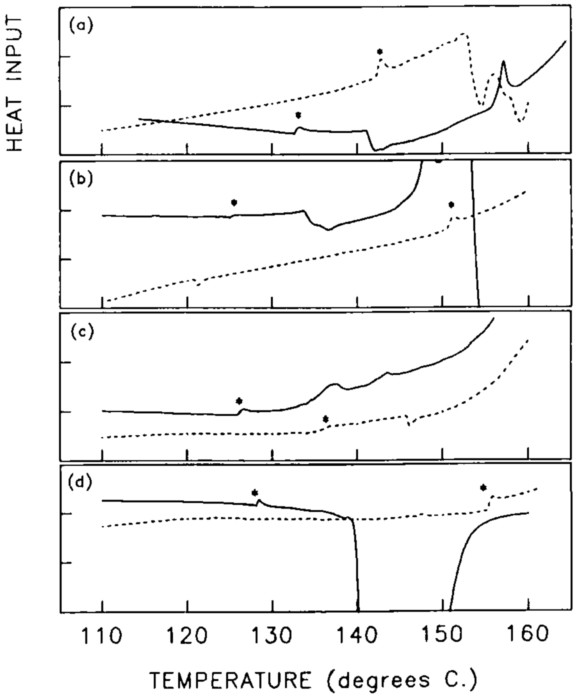

Figure 9. Differential scanning calorimetric endotherms (heating traces) showing glass transition temperature depression of Avicel PH102 from dry (dotted line, pre-treated at 0% RH) to wet (solid line, treated at 100% RH) state. Key: (a), Avicel PH102; (b), Ac-di-sol; (c), corn starch; and (d), Primojel.

Table 8. Glass transition temperature (T_g) of disintegrant in various conditions.

Disintegrant	T_g(dry)* in degrees C.	T_g(wet)** in degrees C.
Avicel PH102	142.5	135.1
Ac-di-sol	150.9	125.3
corn starch	136.2	126.2
Primojel	155.5	127.7

* The disintegrants were dried at 0% relative humidity at 40 degrees C. for 24 hours.
**They were exposed to 100% relative humidity at the same temperature and period of time.

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Table 9. Sorption capacity *vs.* decreased glass transition temperature.

Disintegrant	C_m*, in g/g	ΔT_g, in deg. C.
Avicel PH102	1.4614	7.4
Ac-di-sol	0.2665	25.6
Corn starch	6.9591	10.0
Primojel	0.6247	27.8

*Sorption capacity: $Cm = c \times Wm$, using the parameters from G.A.B. treatment.

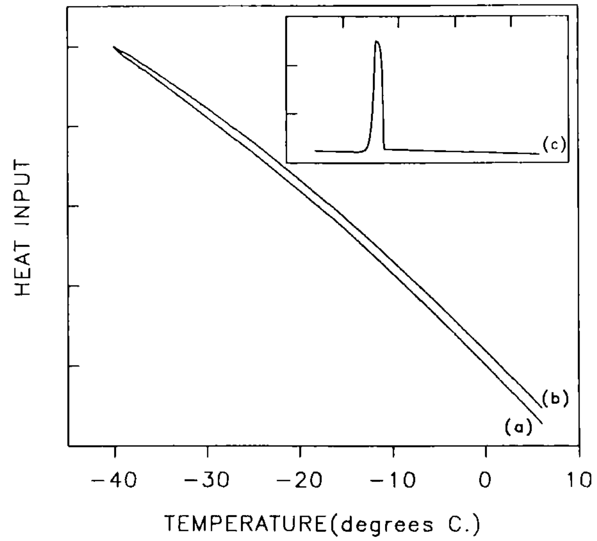

Figure 10. Differential scanning calorimetric exotherms (cooling traces) of Avicel PH102 (a), and corn starch (b). (Window), a cooling trace of water showing the water of crystallization at temperature of about -24 degrees C.

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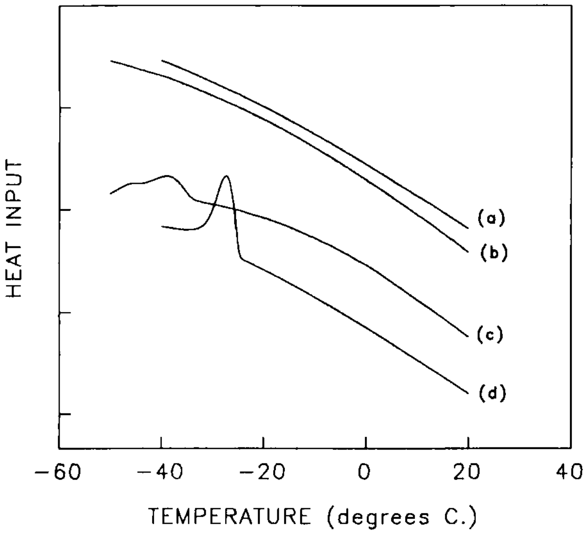

Figure 11. Differential scanning calorimetric endotherms of Ac-di-sol treated at different relative humidities. Key: (a), 84%; (b), 90%; (c), 95%; and (d), 100% RH's.

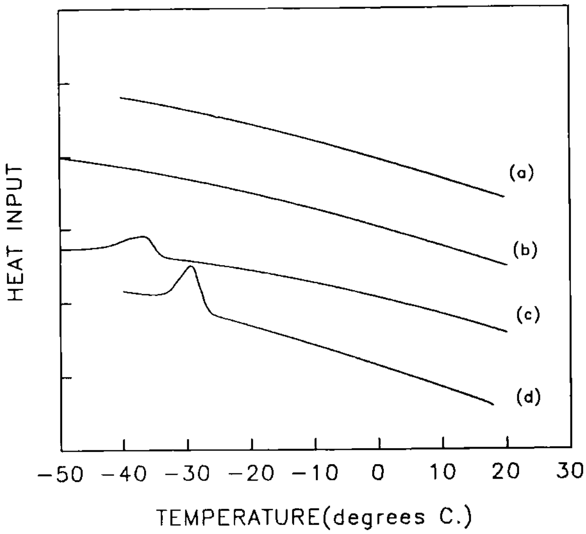

Figure 12. Differential scanning calorimetric endotherms of Primojel treated at different relative humidities. Key: (a), 84%; (b), 90%; (c), 95%; and (d), 100% RH's.

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Table 10. Sorbed water freezing temperatures on superdisintegrant.

	Freezing point(degrees C.)	
Disintegrant	95% RH*	100% RH*
Ac-di-sol	-38.5	-36.8
Primojel	-27.1	-20.3

*The samples were pre-treated in different relative humidity chambers at 40 degrees C. for 24 hours.

transition temperature depression. This may be reflected by the kinetic decrease of sorption sites available on glassy polymers during water plasticization.

Non-freezable Bound Water

Zografi and Kontny (12) noted that sorbed water could not be frozen. Franks (16), however, argued that ice did not show up during the thermal treatment because of crystallization difficulty. An attempt to separate the sorbed water phase was done. No evidence of ice was found in cases of Avicel PH102 and corn starch exposed to 100% relative humidity (Figure 10). In contrast, water phases in the cases of the superdisintegrants could be seen. Figures 11-12 illustrate the exotherms (cooling curves) of Ac-di-sol and Primojel pre-treated with different relative humidities. The trace of ice started to show up in the samples equilibrated at 95% relative humidity. The freezing temperatures of sorbed water for various pre-treated superdisintegrants are listed in Table 10. As shown in Figures 11-12 and Table 10, sorbed water in a sample with high relative humidity equilibration tends to crystallize to a great extent as well as at high temperature compared to that with low relative humidity equilibration. However, the experimental time period may not be long enough to allow the water to crystallize (16). Ice could not be seen at the temperature of zero degrees C., even in the case of water alone (freezing point of -24.0 degrees C., as seen in window (c) of Figure 10) because of the difficulty in crystallization as noted by Franks. The peaks of ice in the case of the superdisintegrants may be the water that solvates the sodium ions of superdisintegrant polymers.

CONCLUSIONS

Moisture sorption properties of four disintegrants, i.e., Avicel PH102, Ac-di-sol, corn starch, and Primojel were studied. Their sorption isotherms were Type-II which

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could be treated by the G.A.B. equation. The B.E.T. equation, on the other hand, could be applicable only within a very low range of relative humidity. It was evident that there would be a finite layer of moisture sorption, and/or the intermediate layers of sorption having the heat of sorption differed from that of liquefaction. The isotherms also showed the hystereses due to the change of polymer structure during sorption. The sorbed moisture tended to be on the disintegrant surfaces as a normally condensed phase, rather than diffusing into the bulk.

The differential scanning calorimetry (DSC) analysis showed that water interaction caused glass transition temperature of a disintegrant to decrease. It was hypothesized that water interacted with the specific sites, e.g. anhydro-glucose units, located on the glassy portion of polymer chains. Water plastcization facilitates glass-rubber transition which, in turn, kinetically reduces the available sites of interaction. This may be reflected in the sorption constant obtained from the isotherm. Sorbed water could not be easily frozen due to the crystallization difficulty.

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