International Journal of Pharmaceutics, 18 (1984) 99–116
Elsevier

IJP 00616

Surface area and water vapor sorption of microcrystalline cellulose *

G. Zografi [1], M.J. Kontny [1], A.Y.S. Yang [2,]** and G.S. Brenner [2]

[1] *School of Pharmacy, University of Wisconsin-Madison, Madison, WI 53706 and* [2] *Merck Sharp and Dohme Research Laboratories, West Point, PA 19486 (U.S.A.)*

(Received June 6th, 1983)
(Modified version received August 3rd, 1983)
(Accepted August 8th, 1983)

Summary

A review of the pharmaceutical literature revealed several inconsistencies and uncertainties in values obtained for the specific surface area of microcrystalline cellulose, as well as the proposed mechanisms of water vapor sorption. In the present study, using nitrogen and krypton adsorption following several methods of sample pretreatment, a value of 1.3 m^2/g, with no evidence of extensive microporosity, was determined. The very high values of specific surface area reported for microcrystalline cellulose using water vapor were shown not to reflect a true surface area, but rather, it is felt, to reflect penetration into the amorphous portions of the cellulose structure and interaction with individual anhydroglucose units. Analysis of water vapor sorption isotherms indicated no apparent difference in the mechanism of sorption between various starches and celluloses, including microcrystalline cellulose, after accounting for the degree of cellulose crystallinity. It appears that water sorbed to such polymers most likely exists in at least 3 states: tightly bound to an anhydroglucose unit; less tightly bound; and bulk water.

Introduction

Microcrystalline cellulose (MCC), a modified form of cellulose, has found widespread use in pharmaceutical solid dosage forms because of its unique proper-

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* Taken in part from a M.S. thesis submitted by Mark J. Kontny to the Graduate School, University of Wisconsin-Madison, 1983.

** Present address: Shell Development Co., Biological Sciences Research Center, Modesto, CA 95352.

Correspondence: G. Zografi; School of Pharmacy, University of Wisconsin-Madison, Madison, WI 53706, U.S.A.

ties as an excipient. Significant interest has been shown, therefore, in its powder characteristics, including: particle size; specific surface area; water vapor sorption; and compression (Battista, 1975; Sixsmith, 1976; Marshall and Sixsmith, 1974; Hollenbeck et al., 1978; Nakai et al., 1977a and b). A review of the pharmaceutical literature reveals a number of uncertainties concerning some of these fundamental characteristics. For example, whereas values of 1.0 m^2/g and 1.5 m^2/g, respectively, were reported (Hollenbeck et al., 1978; Nakai et al., 1977a) for one grade of MCC using nitrogen adsorption and the BET equation (Brunauer et al., 1938), another study (Marshall and Sixsmith, 1974) using the same method, reported a value of 11.2 m^2/g. The only apparent difference in these studies was the manner in which the samples were pretreated before being exposed to the nitrogen gas. A value of 1.3 m^2/g obtained by mercury porosimetry and an analysis of porosity using nitrogen adsorption data at higher relative pressures, led to the conclusion (Marshall and Sixsmith, 1974) that 1.3 m^2/g represents the external interparticle specific surface area, while values obtained with nitrogen gas reflect a higher specific surface area due to pores not accessible to the mercury.

Water vapor sorption, with application of the BET equation also has been used in two studies to estimate an apparent specific surface area of MCC (Hollenbeck et al., 1978; Nakai et al., 1977a), and has led to values of 138 m^2/g and 149 m^2/g, respectively. The large apparent discrepancy between water vapor and nitrogen BET surface areas has been explained (Hollenbeck et al., 1978) by drawing analogy to the asbestos system studied by Young and Healey (1954), which exhibits two-fold differences in specific surface area obtained by nitrogen absorption, depending on the presence or absence of residual water. This difference was attributed (Young and Healey, 1954) to frozen water in the hollow tubular fibers of asbestos, which occludes the surface available to the nitrogen adsorbate at liquid nitrogen temperature. Similarly, Hollenbeck et al. (1978) suggested that frozen residual water occludes much of the porous internal structure of MCC when nitrogen is sorbed at liquid nitrogen temperature. The same explanation has been given (Wurster et al., 1982) for the even greater difference in apparent specific surface area of corn starch obtained with nitrogen adsorption and water vapor adsorption; 0.44 m^2/g (Zografi, 1961) and 348 m^2/g (Wurster et al., 1982), respectively.

Several questions arise from these results. What is the most reasonable estimate of the specific surface area of MCC? What effect will various conditions of pretreatment have on the specific surface area obtained by adsorption of a non-polar adsorbate? What are the mechanisms of nitrogen and water vapor adsorption onto MCC and how do these affect the interpretation of BET specific surface areas obtained by such methods? To what extent are intraparticle pores present in MCC and, if present, what role, if any do they play in determining water vapor sorption characteristics?

The present study, therefore, was undertaken with the objectives of: measuring the specific surface area of MCC using nitrogen and krypton as adsorbates under various conditions of sample pretreatment; carrying out a pore analysis to assess the extent, if any, to which intraparticle pores could play a role in adsorptive properties of MCC; critically assessing the meaning of BET surface areas estimated from water vapor sorption data; and carrying out parallel studies and analyses with corn starch, a morphologically better understood system, for the purposes of comparison with MCC.

Materials and Methods

Materials

All studies were carried out on the one grade of MCC [1] used in all previously reported studies to which the results of this study are compared. Once removed from its vacuum-packed container MCC was stored in a capped container over anhydrous calcium sulfate [2] in a partially evacuated dessicator. Samples of corn starch [3] used throughout this study were stored in their original containers prior to use.

The gases used to evaluate specific surface area were nitrogen [4], krypton [4] and premixed samples of krypton and helium [4]. They were all labeled at 99.995% minimum purity. Krypton was used in addition to nitrogen since it is reported to allow more accurate estimation of very low surface areas than does nitrogen (Lowell, 1979).

Moisture determination

Drying experiments were carried out with MCC to determine the relative effectiveness of several methods of pretreatment as well as to determine the final moisture content of samples subjected to different drying procedures.

Sample pretreatment for all drying studies consisted of storing a bulk sample over a saturated solution of potassium carbonate [5] in a dessicator for several weeks at room temperature. This pretreatment was necessary to ensure that all samples were initially of uniform moisture content. Preweighed 5 ml weighing bottles were filled with 500–600 mg of the bulk sample thus treated, weighed to obtain an initial sample weight, and placed in a dry air oven at 100°C with the weighing bottle caps removed. At various times, the bottles were capped, removed from the oven, allowed to cool, weighed and placed back in the oven, again with the caps removed. This procedure was continued until a constant weight was obtained for the respective samples.

Further experiments, which compared the effectiveness of vacuum-drying to oven-drying, were carried out by subjecting MCC to continuous vacuum pumping at 25 or 100°C with continuous monitoring of weight on an electrobalance [6]. Similarly drying experiments were carried out on corn starch at 100°C to determine its overall moisture content. 2–3 g samples were used in these studies.

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[1] Avicel PH 101, FMC Corporation, Philadelphia, PA.

[2] Drierite, indicating, W.A. Hammond Drierite Co., Xenia, OH.

[3] Best Foods, Englewood Cliffs, NJ.

[4] Matheson, Division of Searle Medical Products USA, Inc., East Rutherford, NJ.

[5] Relative humidity over a saturated solution of potassium carbonate is 43% at 24.5°C (Weast, 1973).

[6] Cahn Instruments, Division of Ventron Corp., Cerritos, CA.

Surface area measurement

The Quantasorb Sorption System [7] was employed for all gas adsorption studies. This instrument works on a general principle whereby the adsorbate is mixed with a non-adsorbing carrier gas (helium) in predetermined proportions, and brought in contact with the solid at fixed flow rates below the critical temperature of the adsorbate. Detection of changes in the composition of the mixture due to adsorption or desorption of the adsorbate is made by differences in thermal conductivity. For experiments using nitrogen–helium mixtures, the Quantasorb Flow Control Accessory [7] was used to produce any desired composition of the two gases. Premixed containers of krypton and helium were used to provide the necessary mixtures of krypton and helium. Pressure-Lok gas syringes [8] (0.25, 0.50 or 1.0 ml) were employed for all calibration injections. Standard and side-port needles were used with these syringes. It was found that the side-port needles were better suited for this work as they showed a much lower incidence of coring with repeated use.

Pretreatment of samples

Sample sizes were chosen such that 0.4–0.5 m^2 of total surface area were available. Specific methods for pretreating samples included: (1) purging the sample with pure nitrogen or pure helium at room temperature or at elevated temperatures; and (2) exposing the sample to continuous vacuum pumping at room temperature or at elevated temperatures. Temperature control was achieved by use of a heating mantle connected to a transformer. The mantle encased the sample cell and a thermometer was placed inside the mantle cavity near the sample cell.

Vacuum-drying port

A central uncertainty in the results presented in the literature for the specific surface area of MCC is the possible effect of residual moisture. Consequently, it was imperative to develop a system which would efficiently dry these samples and then allow transfer to the Quantasorb System without any exposure to the atmosphere. The drying port was designed so that it could be connected and removed from a vacuum system which has been described in detail elsewhere (Van Campen et al., 1980). The sample cell, ready to be attached to the Quantasorb System via a Swagelok [9] fitting, was attached to a similar Swagelok fitting connected to the vacuum rack by rubber O-ring connections. The major modification to the sample cell holder involved placing Cajon tee [10] fittings on both legs of the holder. While one side was capped, the opposite leg's tee fitting was connected to a Swagelok Quick-Connect fitting. This fitting, in turn, was connected to a Cajon Glass/Metal Transition tube [10], which in turn was joined to a glass fitting which could be added or removed from the vacuum line. A stopcock was placed between the transition tube and the vacuum line connection.

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[7] Quantachrome Corporation, Syosset, NY.

[8] Series C, Precision Sampling Corp., Anspec, Ann Arbor, MI.

[9] Crawford Fitting, Solon, OH.

[10] Cajon, Macedonia, OH.

Determination of porosity

Studies designed to analyze the existence and extent of intraparticle porosity of MCC and corn starch, as suggested previously (Marshall and Sixsmith, 1974; Hollenbeck et al., 1978; Wurster et al., 1982), were carried out using N_2 gas and the Quantasorb System [7]. The procedure used was essentially the same as that used to measure surface area except for the measurement of adsorption in excess of 0.3 relative pressure (i.e. 0.4, 0.5,...0.9, 0.95). All samples were subjected to a pretreatment of high vacuum and elevated temperatures, as described previously. Two methods of pore analysis were applied: (1) the numerical integration method of Pierce (1953), as modified by Orr and Dalla Valle (1959); and (2) the 'modelless' method of Brunauer et al. (1967). Both methods assume that multilayer formation and capillary condensation occur simultaneously at higher relative pressures.

Results

Moisture content

Based on previously reported water sorption isotherms for MCC (Hollenbeck et al., 1978), a sample stored at about 43% relative humidity and room temperature should equilibrate to a moisture content of about 5–6%. Table 1 compares values of water content obtained by drying 500 mg of MCC to constant weight under three conditions. Included also is the time required to reach constant weight. It is concluded that drying under high vacuum at elevated temperatures is necessary to remove most of the residual traces of moisture from microcrystalline cellulose. Similar drying experiments with corn starch indicated an average moisture content of 9.7%. Due to the very low moisture content of MCC and starch following drying studies, Karl Fisher analysis to confirm complete removal of water was deemed to be of limited usefulness because it was not possible to transfer samples for analyses without some contact with the environment and rapid water uptake.

Specific surface area

Values of specific surface area obtained for MCC and corn starch using nitrogen and krypton and a variety of sample pretreatments, with and without vacuum conditions, are given in Table 2. Cross-sectional areas of 16.2×10^{-20} m^2/molecule and 19.5×10^{-20} m^2/molecule were used for nitrogen and krypton, respectively, in

TABLE 1

COMPARISON OF OVEN-DRYING AND VACUUM-DRYING OF MICROCRYSTALLINE CELLULOSE AT VARIOUS TEMPERATURES

Drying conditions	% Weight loss	Time (h)
100°C — no vacuum	5.6	2
25°C — vacuum	4.8	8
100°C — vacuum	6.2	2

TABLE 2

SPECIFIC SURFACE AREA OF MICROCRYSTALLINE CELLULOSE AND CORN STARCH PRETREATED BY VARIOUS METHODS

Gas	Sample pretreatment		Surface Area (m^2/g)
	Temperature (°C)	Vacuum (μm Hg)	
Microcrystalline cellulose			
N_2	100	–	1.31
N_2	50	–	1.31
N_2	100	1	1.30
N_2	50	6.5	1.10
Kr	100	–	1.44
Kr	25	–	1.42
Kr	100	< 1	1.32
Kr	25	6	1.28
Kr	–	–	1.37
Corn starch			
N_2	75	8	0.434
Kr	100	–	0.463
Kr	25	–	0.416

applying the BET equation to the data. It is concluded from these results that the specific surface area, as determined with nitrogen and krypton, is 1.3 m^2/g for MCC and 0.43 m^2/g for corn starch, independent of pretreatment, and hence, independent of water content up to at least 6.2% for MCC and 9.7% for corn starch. This suggests, therefore, that the value of 11.2 m^2/g reported by Marshall and Sixsmith (1974) is not correct.

Pore analysis

Using the standard procedures for pore analysis by N_2 gas adsorption, as described above, appears to indicate that pores exist for MCC with radii in the range of about 10–30 Å, the same range of radii reported by Marshall and Sixsmith (1974) using a similar analysis. Essentially the same results, however, were also obtained with corn starch, a material generally thought to be non-porous (Van den Berg, 1981a). This suggested the possibility that the results with MCC might not be reflective of actual microporosity. To confirm the presence or absence of micropores in corn starch and MCC two additional studies were conducted. First, dried samples of corn starch and MCC were subjected to analyses by mercury porosimetry, up to 60,000 psi using a Quantachrome Autoscan-60-Porosimeter [7]. In both cases no porosity was detected up to pressures which should detect pores at a radius of 18 Å [11].

Second, gas adsorption data obtained from the pore analysis were used to

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[11] The authors wish to thank Dr. Seymour Lowell of the Quantachrome Corporation for carrying out these measurements and assisting in their interpretation.

estimate specific surface area in the usual manner (Lowell, 1979). The values obtained for corn starch and MCC are 0.40 mg^2/g and 0.99 m^2/g, respectively, in reasonable agreement with the values listed in Table 2 obtained at lower relative pressures using the BET equation. When one recognizes that the calculated specific surface area of non-porous spheres having a diameter of 14.5 μm, the average particle diameter of corn starch (El-Khawas et al., 1966), is about 0.4 m^2/g, it is clear that any porosity in corn starch reflected in gas adsorption analysis at best must represent a negligible contribution to the structure of the starch grain. Similarly, although MCC might be expected to have some intraparticle macropores due to its agglomerated structure (Battista, 1975), the low level of total surface area present makes it also unlikely that a microporous structure of any consequence is actually being measured in such analysis. It, therefore, seems reasonable to conclude that MCC does not contain the extent of intrinsic microporous structure which could account for the large apparent specific surface areas measured by water vapor sorption.

Discussion

Surface area of microcrystalline cellulose obtained by nitrogen vapor adsorption

One of the major questions addressed in this paper centers on the difference in the specific surface area of microcrystalline cellulose obtained by Marshall and Sixsmith (1974) versus the values obtained by Hollenbeck et al. (1978) and Nakai et al. (1977a), using nitrogen adsorption Our results strongly suggest that the specific surface area value of 11.2 m^2/g for microcrystalline cellulose obtained by Marshall and Sixsmith (1974) is incorrect. We have measured the surface area of microcrystalline cellulose using two non-polar gases, nitrogen and krypton, following various sample pretreatments which included vacuum drying (less than 1 μm Hg) at 100°C for 24 h, drying at 100°C under atmospheric pressure for 90 h, vacuum drying (6 μm Hg) at 25°C for 48 h, and no pretreatment whatsoever. No significant differences with the values obtained by Hollenbeck et al. (1978) and Nakai et al. (1977a) were observed. Also significantly important are the range of moisture contents of the various microcrystalline cellulose samples following the various pretreatments, which range from essentially 0% for the initial pretreatment to approximately 6% for the sample subjected to no pretreatment. Thus, up to a least 6% moisture, sorbed water does not appear to influence the specific surface area of MCC. This also holds true for corn starch up to about 10% moisture.

One can only speculate as to what led to Marshall and Sixsmith's (1974) considerably larger values. A closer look at their nitrogen adsorption isotherm [12] for

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[12] Marshall and Sixsmith (1974) present a nitrogen adsorption isotherm for microcrystalline cellulose PH 102, whereas this study, as well as the Hollenbeck et al. (1978) BET plot are for PH 101. Since the nitrogen adsorption surface area presented by Marshall and Sixsmith (1974) is within 12% of that for PH 102, it seems justified to assume that the PH 101 and PH 102 isotherms are identical, at least over the BET range, for purposes of comparison.

MCC reveals that at each respective relative pressure, approximately 10 times more nitrogen is reported to be adsorbed than on the isotherm obtained in this work or that obtained by back-calculating from the Hollenbeck et al. (1978) N_2-BET plot for MCC. It is concluded, therefore, in the absence of any other evidence, that the most likely explanation for the 10-fold larger specific surface area for MCC, obtained by Marshall and Sixsmith (1974), is due to a systematic error in calculating specific surface area from nitrogen adsorption data.

Differences in surface area obtained by nitrogen and water vapor sorption

The second major question addressed in this paper centers on the differences reported for specific surface area of MCC using nitrogen and water vapor sorption.

The significant difference between nitrogen and water vapor-derived values of specific surface area for MCC has been explained (Hollenbeck et al., 1978) by assuming that residual water, not removed by pretreatment, freezes at the liquid nitrogen temperature used during nitrogen adsorption studies. It was assumed that this water effectively blocks access to the porous MCC structure by the nitrogen molecules, thus reducing the total volume of nitrogen adsorbed. In contrast, it was suggested that the adsorption of water vapor is carried out at 25°C where such residual water is not in a frozen state. Evidence for such an explanation is cited from work with asbestos (Young and Healey, 1954) which showed that complete removal of moisture was required to give the same value of specific surface area when nitrogen and water vapor were used; with residual moisture present values obtained with nitrogen were lower.

The results of the present study tend to reject the explanation that frozen water is blocking access of nitrogen to MCC pores at liquid nitrogen temperature for the following reasons: (1) nitrogen and krypton BET surface area values (Table 2) show no significant differences over a wide range of MCC moisture contents, even though one would expect the specific surface area values to increase as water content is decreased, if the frozen water mechanism is correct; (2) nitrogen gas and mercury porosimetry analyses of dry MCC, as discussed in the Results section, give no indication of significant surface area due to intrinsic porosity; (3) using the asbestos system as a basis for the MCC system seems to be a misapplication of Young and Healey's (1954) interpretation. Whereas the asbestos system exhibits an apparent water surface area to nitrogen surface area ratio (S_{H_2O}/S_{N_2}) of 1.8 for untreated asbestos, 1.0 for heat-treated asbestos, and a return to 1.8 for the rehydrated sample, MCC has a S_{H_2O}/S_{N_2} of approximately 100, and does not approach unity as the sample is dried. Similarly, the S_{H_2O}/S_{N_2} obtained for corn starch is independent of moisture content and is even larger, i.e. S_{H_2O}/S_{N_2} is approximately 800; and (4) corn starch, not believed to be porous (Van den Berg, 1981a), exhibits many of the same properties that MCC does, when subjected to similar pore analyses and water vapor sorption studies.

Possible mechanisms of water vapor sorption by microcrystalline cellulose

A review of the literature reveals that a divergency of opinion exists as to the mechanism of water uptake by native celluloses and starches, as well as with MCC.

TABLE 3

AMOUNT OF WATER VAPOR SORBED BY VARIOUS STARCHES AT THE APPARENT[a] BET MONOLAYER LEVEL

Starch	W_m (g H_2O/g starch)	Ref.
Corn	0.083	Wurster et al., 1982
Corn	0.080	Hellman et al., 1952
Potato	0.085	Van den Berg, 1981a
Wheat	0.080	Van den Berg, 1981a

[a] Calculated values for W_m corresponding to one and two water molecules per anhydroglucose unit are 0.111 and 0.222 g, respectively.

For cellulose and starch the majority of opinions divide between water vapor sorption into a pre-existent pore structure (Wurster et al., 1982; Morrison and Dzieciuch, 1959; Buloff, 1967; Gupta and Bhatia, 1969) and water vapor penetration into the solid with strong hydration, changes in polymer conformation and swelling (Van den Berg, 1981a; Stamm, 1964; Van den Berg et al., 1975). By far the most comprehensive analysis of this problem has been carried out for starch by Van den Berg (1981a, 1975), who has suggested that water vapor penetrates the starch grain and interacts with anhydroglucose units throughout the entire starch grain. Using the BET equation,

$$W = \frac{C_B W_m \left(\frac{P}{P_0}\right)}{\left(1 - \frac{P}{P_0}\right)\left(1 - \frac{P}{P_0} + C_B \frac{P}{P_0}\right)} \tag{1}$$

where W is the weight of water taken up per g of solid, W_m is the weight of water sorbed at the equivalent of monomolecular coverage at each site, C_B is a constant related to the heat of sorption, P is the pressure of water vapor in the environment, and P_0 is the vapor pressure of liquid water at a particular temperature, he has shown that W_m corresponds to approximately one water molecule per anhydroglucose unit. This calculation was made by taking the molecular weight of one anhydroglucose unit and estimating the number of units in 1 g of starch. Table 3 indicates the weight of water per gram of starch forming a monolayer for various starch samples from other studies calculated using the BET equation, along with the calculated amount of water sorbed per anhydroglucose unit which corresponds to one-to-one and two-to-one stoichiometric relationships. Not only is it interesting to note the relatively good agreement with values necessary for a one-to-one stoichiometric relationship, but perhaps even more importantly, we see a consistency for the different types of starch samples varying in grain size and morphology. If porosity was important we might expect significant differences betwen various starches.

Van den Berg has extended this model to also suggest that an equivalent amount of water vapor is taken up with a weaker degree of binding before being taken up in a more nonspecific manner as bulk water. Evidence for this mechanism comes directly from calorimetric measurement of the heats of sorption (Van den Berg, 1981a). Although the net excess differential heat of sorption decreases up to 2% water content, implying heterogeneous sorption, water is sorbed almost homogeneously between 2% and 10% water content, illustrated by the constant differential heat of sorption over this range. Further water sorbed between 10 and 19% water content again appears to be sorbed homogeneously, although with a considerably lower differential heat of sorption. Water sorbed beyond 19% exhibits a continuous gradual decrease in the excess differential heat of sorption that approaches zero. This implies that this water is becoming more and more like bulk water. Of particular significance are the water contents at which the breaks occur. These occur at 10 and 19% water content, respectively, which roughly approximate the calculated values of water content corresponding to stoichiometries of one-to-one and two-to-one water molecules per anhydroglucose unit as mentioned earlier. Van den Berg (1981a) cited NMR, dielectric constant, unfreezable water and diffusion coefficient studies on various starches as further evidence to support the idea that water vapor binds stoichiometrically up to at least two water molecules per anhydroglucose unit as non-bulk water.

One can extend this approach to native cellulose and MCC by estimating W_m, the amount of water sorbed per gram corresponding to monomolecular coverage per site, from the BET equation (Eqn. 1) using data obtained with various types of cellulose. As can be seen in Table 4, a very small difference between cotton cellulose and MCC is observed, whereas a much greater difference exists between these and cellophane.

Recognizing that water vapor sorption has been reported not to be taken up by the crystalline regions of cellulose (Stamm, 1964; Honeyman, 1959; Howsmon, 1949), it seems more appropriate to estimate the amount of water taken up per gram of *non-crystalline or amorphous cellulose* for the various celluloses. As a first approximation, one can simply divide W_m by the fraction of non-crystalline cellulose and obtain values referred to as W_m^{corr}, which are shown in Table 5. More elaborate calculations correcting for the unavailable fraction of cellulose have been carried out for wood cellulose which consider the dimensions of the crystallites, the fraction of

TABLE 4

AMOUNT OF WATER VAPOR SORBED BY VARIOUS CELLULOSES AT THE APPARENT BET MONOLAYER VALUE

Cellulose	(g water/gW_m cellulose)	Ref.
Cotton	0.028	Stamm, 1964
Cotton	0.032	Morrison and Dzieciuch, 1959
Cellophane	0.059	Sixsmith, 1976
Microcrystalline	0.033	Hollenbeck et al., 1978
Microcrystalline	0.035	Nakai et al., 1977a

TABLE 5

AMOUNT OF WATER SORBED BY VARIOUS CELLULOSES AT THE APPARENT BET MONOLAYER CORRECTED FOR DEGREE OF CRYSTALLINITY

Sample	% Crystallinity	W_m^{corr}	Ref.
Cotton	70	0.093	Stamm, 1964
Cotton	70	0.107	Morrison and Dzieciuch, 1959
Cellophane	40	0.098	Stamm, 1964
Microcrystalline	63	0.089	Hollenbeck et al., 1978
Microcrystalline	63	0.096	Nakai et al., 1977a
Microcrystalline *	49	0.076	Nakai et al., 1977a
Microcrystalline *	38	0.107	Nakai et al., 1977a
Microcrystalline *	0	0.086	Nakai et al., 1977a

* Samples of MCC ball-milled to various percent crystallinities (Nakai et al., 1977a). Crystallinities of cotton cellulose and cellophane are reported by Stamm (1964).

the available hydroxyl groups on the planar surface, as well as on the corners of the crystallites, in addition to the percent crystallinity (Stamm, 1941). However, considering the assumptions necessary in such a method, and the uncertainty of the exact percent crystallinity, little or no improvement is made over the method used in this study. Accounting for the fraction of the sample which is available for water vapor sorption in this way gives values which are quite consistent between the types of celluloses, and which also agree quite well with the results presented for starch (Table 3), where complete accessibility to water vapor is assumed (Van den Berg, 1981a). As seen also in Table 5, this explains very well the phenomena observed by Nakai et al. (1977a), whereby grinding of microcrystalline cellulose for various time periods increased its apparent specific surface area as measured by water vapor sorption, but produced no change as measured by nitrogen adsorption. Thus, no significant change in the average MCC surface area occurred by grinding the sample; only a reduction in the degree of crystallinity, which allowed more water vapor uptake. It is concluded,therefore, *that water vapor is taken up by cellulose, including MCC, by the same basic mechanism as starch and that in all likelihood, this occurs as suggested by Van den Berg (1981a).*

Direct experimental evidence which seems to support this model of sorption on celluloses is not as obvious as in the starch case, but differential heat of sorption plots for MCC (Hollenbeck et al., 1978) and cotton cellulose (Morrison and Dzieciuch, 1959) do show breaks near the amounts sorbed corresponding to one and two water molecules per gram of 'available' cellulose. NMR evidence for three types of water in cotton cellulose, bound, associated and free, is also available (Froix and Nelson, 1975).

Further analysis of sorption isotherms

Attempts to model water vapor sorption on polymers have generally followed two directions: (1) extensions of the BET equation; and (2) application of polymer solution theory, treating sorption as a hydration process involving well-defined stoichiometric relationships rather than adsorption on available surface. The latter approach has led (Van den Berg, 1981; Skaar, 1972; Van den Berg and Bruin, 1981b) to the use of the Flory-Huggins equation (1953), the Hailwood-Horrobin equation (1946), the Dual Sorption equations of Stennett, et al. (1980) and other similar analyses (Lüscher-Mattli and Rüegg, 1982) to describe sorption, with good fit over a wide range of relative pressures. Although the process of water vapor sorption by starch and cellulose seems most likely to occur by a mechanism related to polymer hydration and solution and that these equations can be made to fit such sorption isotherms, this approach has not proven too useful in elucidating actual molecular mechanisms. A major reason for this is that such analyses generally involve the simultaneous fit of 3 and 4 parameter equations using a computer. In many cases, with so many unknown constants of unknown physical meaning such a process is often reduced to a curve fitting exercise of limited physical significance.

With this potential pitfall in mind, it was still of some interest to the present authors to extend the analysis further so that possible mechanisms and stoichiometries of water sorption on native starches and celluloses could be further compared to that on MCC. In the approach chosen, suggested in the work of Van den Berg (1981a) with starch, the BET equation is extended according to an equation developed by Guggenheim (1966), Anderson (1946) and de Boer (1968). This equation, referred to as the GAB equation, was derived to take into account a layer or layers of sorbed vapor having properties intermediate to those in the first layer and those of bulk water. The GAB equation:

$$W = \frac{C_G \cdot K \cdot W_m\left(\frac{P}{P_o}\right)}{\left(1 - K\frac{P}{P_o}\right)\left(1 - K\frac{P}{P_o} + C_G K\frac{P}{P_o}\right)} \qquad (2)$$

is quite similar to the BET equation, except for the addition of a third parameter, K, which equals:

$$K = B \exp\left[\frac{H_L - H_m}{RT}\right] \qquad (3)$$

where B is a constant, H_L is the heat of liquefaction, and H_m is the heat of sorption of water sorbed in the intermediate layer. The constant, C_G, is defined as:

$$C_G = D \exp\left[\frac{H_l - H_m}{RT}\right] \qquad (4)$$

where D is a constant, H_l is the heat of sorption of water in the first sorbed layer and H_m is the heat of sorption of water sorbed in the intermediate layer.

Thus, appropriate estimation of C_G and K, could provide some additional insight into the mechanism of water sorption, namely the sequential formation of a

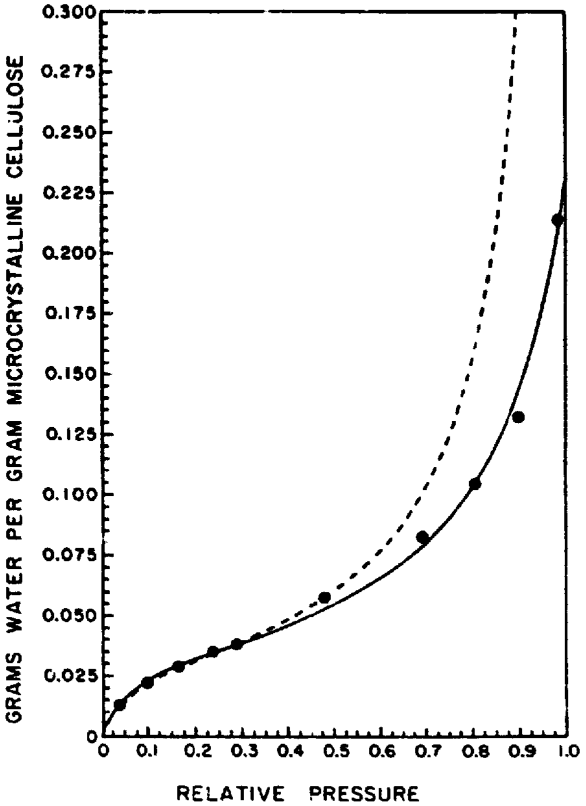

Fig. 1. Water vapor sorption by microcrystalline cellulose: ●, data from Hollenbeck et al. (1978); ------, fit to the BET equation; ———, fit to the GAB equation.

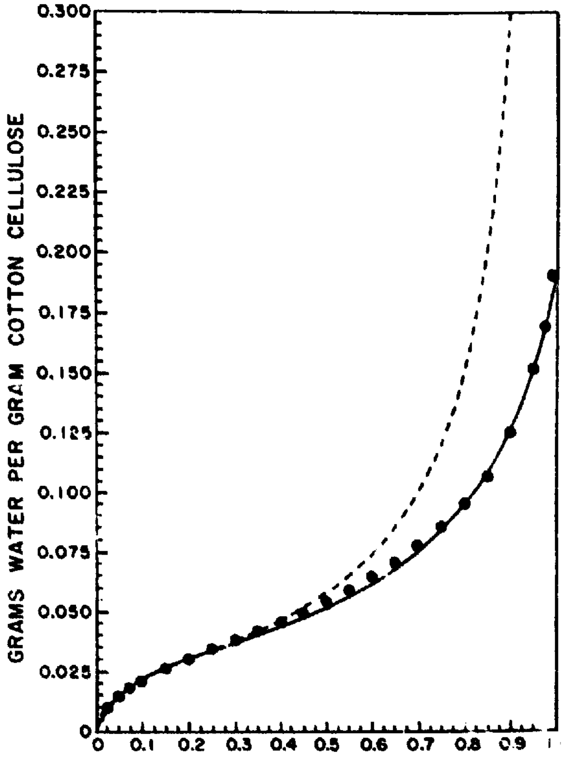

Fig. 2. Water vapor sorption by cotton cellulose: ●, data from Mc ieciuch, 1959; ------, fit to the BET equation; ———, fit to the GAB equation.

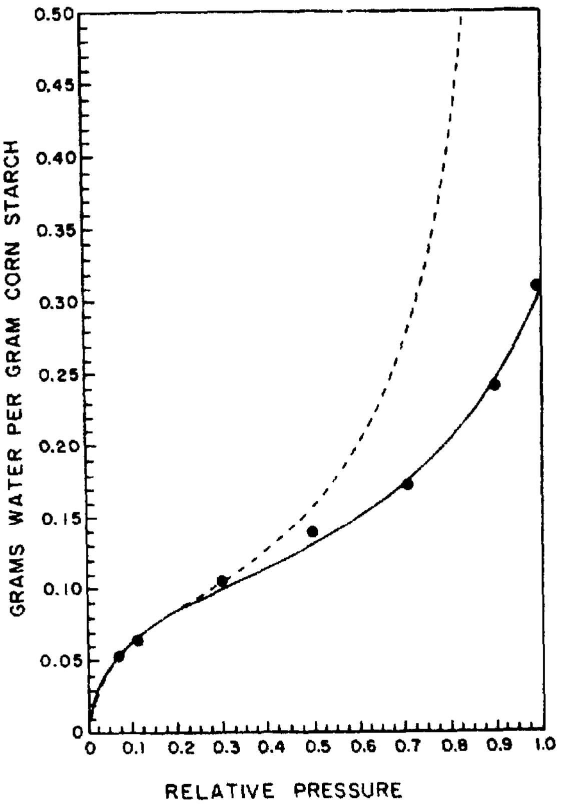

Fig. 3. Water vapor sorption by corn starch: ●, data from Wurster et al., 1982; ------, fit to the BET equation; ———, fit to the GAB equation.

monolayer, intermediate layer(s) and finally bulk water. Figs. 1–3 indicate the extent to which data involving sorption by cotton cellulose, corn starch and MCC fit the BET and GAB equations. Table 6 contains the 3 constants obtained from the GAB equation for these solids plus two more starches. These constants were obtained

TABLE 6

FIT OF WATER SORPTION DATA FOR VARIOUS CELLULOSES AND STARCHES TO THE GAB EQUATION

Sample	Number of data points	W_m	C_G	K	Average deviation	Ref.
Microcrystalline cellulose	10	0.030	14	0.88	2.7×10^{-3}	Maloney et al., 1966
	8	0.033	20	0.86	1.9×10^{-3}	Hollenbeck et al., 1978
Cotton cellulose	22	0.033	18	0.83	1.5×10^{-3}	Morrison and Dzieciuch, 1959
Corn starch	8	0.089	22	0.70	3.1×10^{-3}	Hellman and Melvin, 1952
	7	0.091	24	0.71	4.4×10^{-3}	Wurster et al., 1982
Potato starch	15	0.086	32	0.81	4.4×10^{-3}	Van den Berg et al., 1975
Wheat starch	11	0.098	27	0.68	1.5×10^{-3}	Van den Berg et al., 1974

TABLE 7

COMPARISON OF VALUES FOR ENTHALPY OF SORPTION OBTAINED FROM CALORIMETRIC EXPERIMENTS AND THE GAB EQUATION

Sample	Calorimetric (kcal/mol)		GAB (kcal/mol)	
	$(H_1 - H_L)$	$(H_m - H_L)$	$(H_1 - H_L)$	$(H_m - H_L)$
Potato starch	2.8 [a]	1.3 [a]	1.9	0.2
Microcrystalline cellulose	3.5 [b]	1.2 [b]	1.9	0.1

[a] Van den Berg, 1981a.
[b] Hollenbeck et al., 1978.

using an iterative technique which utilizes the non-linear regression routine, NREG.[13] As seen in Figs. 1–3, fit to the GAB equation is excellent over a wide range of relative pressures, and as expected, only in good agreement with the BET equation at lower relative pressures. The good fit to the GAB equation in all cases suggests strongly that the picture presented earlier from Van den Berg's (1981a) analysis of starch water vapor sorption can be extended to include the native celluloses and MCC, i.e. very tightly bound water, an intermediately bound water and bulk water. The only exact test of physical significance for such a conclusion would be to calculate H_L and H_m from Eqns. 3 and 4, respectively and to compare them with values obtained calorimetrically (Hollenbeck et al., 1978; Van den Berg, 1981; Morrison and Dziecіuch, 1959). In order to do this, however, one must assume that the values of the constants B and D in Eqns. 3 and 4 are known or are unity. Since the constants strongly reflect an entropic contribution to sorption, and since the entropy of the second layer is expected to be greater than the first, one would not expect B and D to be equal, much less equal to unity. As seen in Table 7, where we compare values of $H_1 - H_L$ and $H_m - H_L$, assuming B and D to be unity, with calorimetric values presumed to represent sorption in the first and second layers, reasonable agreement between predicted and experimental values is observed by order of magnitude, although not unexpectedly, the absolute values do exhibit significant differences.

We, therefore, conclude that, although improved fit of data to the GAB equation does not prove the existence of an intermediate type of bound water in these systems, taken together with calorimetric evidence cited earlier for water sorption on starch and some limited evidence with celluloses, it appears very likely that a model involving: (1) tightly bound water, consisting of one water molecule per anhydroglucose unit; (2) a second less tightly bound water molecule per anhydroglucose unit; and (3) additional layers of bulk water, fits the picture of water vapor sorption on MCC. *In contrast to starch, water is only sorbed in the non-crystalline regions.* In order to establish the validity of any model, however, sorption isotherm data for MCC will have to be combined with more direct studies using techniques such as calorimetry and NMR in future studies.

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[13] Academic Computing Center, University of Wisconsin, Madison, WI.

Pharmaceutical significance

The use of MCC as a tablet excipient is widespread in the pharmaceutical field. It is of interest, therefore, to know to what extent, if any, the presence of sorbed water can affect the properties of MCC and the performance of dosage forms containing this excipient. This study suggests that water present up to about 3–4% is in a tightly bound state. By analogy to what is known about water sorption on starch, this water is most likely not as available as liquid water to act as a solvent for other substances mixed with the excipient. We may further speculate that water sorbed up to a level of 6–8%, likewise, may not be fully available as 'free' water. Based on the sorption isotherm for MCC obtained at 25°C (Hollenbeck et al., 1978), we may conclude that water vapor sorbed up to a relative humidity of 70% falls into the 'non-free' category. Assuming that 5–6% water is present when routinely handling the material under ambient conditions (40–50% relative humidity), such material certainly falls into this classification. Likewise, the 10–15% moisture normally found in corn starch falls into this range of tightly bound water. Thus, in most normal handling of these materials, a significant proportion of the water present is strongly bound and is most likely a relatively integral part of the structure of the amorphous portions (cellulose) or the amorphous and crystalline portions (starch) of the solid.

This has serious implications for helping to understand the role of such water in affecting the chemical stability of drugs mixed into these materials. Likewise, it could have serious implications in determining the unique compressional properties of MCC. Future work, therefore, on the thermodynamic state of water in such materials, should be very useful in providing insights into their role in determining various pharmaceutical properties.

Conclusions

The results of experiments and analyses carried out in this study lead to the following conclusions.

(1) The specific surface area of MCC, as determined by nitrogen and krypton adsorption, is 1.3 m^2/g, independent of sample pretreatment.

(2) Differences in the apparent surface area of celluloses and starches using non-polar gas adsorption and water vapor sorption are not due to preexistent pores, but, rather to the penetration of water into the material and its specific interaction with individual anhydroglucose units. Therefore, it is better not to use the term 'specific surface area' when water vapor sorption is involved.

(3) Water vapor sorption by MCC occurs by the same basic mechanism as with other types of celluloses and starches, and this appears to be best described by the sorption of one tightly bound water molecule at an anhydroglucose unit, followed by a second less tightly bound water molecule, with further water sorbed in a more non-specific manner.

Acknowledgements

The authors express their appreciation to Mr. R. Szymanski of Merck Sharp and Dohme Research Labs for his assistance in the early stages of this study. Appreciation is also expressed to Mr. George Raynor, FMC Corporation for providing valuable information concerning cellulose and microcrystalline cellulose. Part of this work was carried out while G.Z. was a visiting scientist at the Merck Sharp and Dohme Research Labs. M.J.K. also acknowledges the financial support provided by Merck Sharp and Dohme Research Labs during this study.

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