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WATER VAPOUR INTERACTION WITH PHARMACEUTICAL CELLULOSE POWDERS

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Summary

Since interaction between water and particulate solid is a major factor in formulation, processing and product performance of pharmaceuticals, the moisture sorption properties of four grades of microfine cellulose (MFC) and three grades of microcrystalline cellulose (MCC) were investigated.

All the powders investigated exhibited type II BDDT sorption isotherms, from which the monolayer capacity and surface area could be evaluated.

The heat of sorption ($-\Delta H_a$) and immersion ($-\Delta H_i$) of water vapour were determined by batch and flow microcalorimetry, which together with the water sorption isotherms gave the integral ($-\Delta H$) and differential heats ($-\overline{\Delta H}$), free

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energies ($-\overline{\Delta F}$) and entropies ($-\overline{\Delta S}$) of sorption. This investigation showed that $-\overline{\Delta H}$ of MFC P050 with a nitrogen surface area of 1.85 mg^{-1} and MCC pH 101 with a nitrogen surface area of 1.22 m^2g^{-1} were -39.5 and -37.08 KJ $mole^{-1}$ of water respectively.

The generally used Braunauer, Emmett and Teller (B.E.T.) relationship in describing full water sorption isotherms was found to be unsatisfactory, but the Guggenheim, Anderson and de Boer (G.A.B.) equation discriminative and meaningful and could be used to give the thermodynamic energetic constants, C_G and K from the various celluloses.

Cellulose powders are widely used in the pharmaceutical industry as excipients, disintegrants, binders for encapsulation, and antiadherents. The interaction of water with pharmaceutical excipients is important in the ultimate release of drugs and storage condition of dosage form.

A review of the literature on pharmaceutical cellulose powders revealed differences in external surface areas when measured by different adsorbents such as nitrogen and water vapour. Hollenbeck et al (1) determined the surface area of microcrystalline cellulose (MCC) Avicel PH 101 by the adsorption method for nitrogen and water vapour. Surface areas calculated from the B.E.T. equation from adsorption isotherms of 1 m^2g^{-1} and 130 m^2g^{-1} were found by nitrogen and water sorption respectively. Nakai et al (2) similarly measured the surface area of MCC PH 101 by nitrogen and water sorption and obtained figures of 1 m^2g^{-1} and 149 m^2g^{-1} respectively. Van den Berg (3), describing in more detail water sorption on dry starch, emphasised the importance of the state of equilibrium. He suggested that this analysis led to a model of sorption which could serve as a basis for further analysis using existing theories and developed hypotheses. Zograffi et al (4) suggested that the B.E.T. equation should be extended and applied, and by using polymer solution theory, water sorption should be treated as a hydration process.

As shown in the work of Van den Berg (3) with starch, the B.E.T. relationship has been extended according to an equation developed by Anderson (5) and Guggenheim (6) and de Boer (7), referred to as the G.A.B. equation (equation 1); Here W is the weight of water absorbed, C_G and K are constants W_m is the weight of water forming monolayer and p/p_o is the relative humidity.

$$W = \frac{C_G . K . W_m p/p_o}{(1-K\ p/p_o)\ (1-K\ p/p_o + C_G K\ p/p_o)} \tag{1}$$

The G.A.B. equation was derived to take into account layers of sorbed vapour having properties intermediate to those in the first layer and those of bulk water. The G.A.B. equation is similar to the B.E.T. equation, except for the addition of third parameter, K, that can be determined by equation (2).

$$K = B\ \exp \frac{H_L - H_m}{RT} \tag{2}$$

where B is 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 can be determined as

$$C_G = D\ \exp \frac{H_1 - H_m}{RT} \tag{3}$$

where D is a constant, H_1 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.

The general character of the G.A.B. analysis has also been realised recently by Dent(8) and Gascoyne and Pothig(9), who applied the G.A.B. equation to consider water vapour sorption on biopolymers.

The objective of this work is to determine the surface energetics of different sources of cellulose powders and to examine the mechanism of interaction and distribution pattern for sorbed water molecules in these materials.

Experimental

Materials: Two different types of high grade pharmaceutical cellulose were examined (a) microfine cellulose, MFC, (Elcema P050, P100, F150 and granulated G250, Degussa), products obtained by a milling process, b) microcrystalline cellulose, MCC, (Avicel PH 105, 102, 101, FMC Corporation) obtained by spray drying.

Methods:

Low temperature nitrogen adsorption: The surface areas of MFC and MCC powders were determined by nitrogen adsorption at 77.5K. The apparatus used as a glass apparatus similar to British Standard specification (10).

Water vapour sorption: The water vapour sorption isotherms and surface area of MFC and MCC powders were determined at 20°C using equipment based on that previously described by Okhamafe and York (11). All samples were dried at 70°C and evacuated overnight to a vacuum of $1X10^{-4}$ torr.

Heats of immersion and sorption: The heats of immersion and sorption of MFC and MCC at 20°C were measured using a LKB microcalorimeter (model 2107). The LKB microcalorimeter was operated in a batch mode to determine the heats of immersion and in a flow made at various humidities in the range 5-75% R.H. to determine the heats of sorption using standard procedures.

Results and discussion

Figures 1 and 2 represent the water vapour sorption isotherms for MFC and MCC grades respectively. Analysis of the water vapour sorption data as well as nitrogen absorption data for MFC and MCC indicated that the B.E.T. theory (12) can be

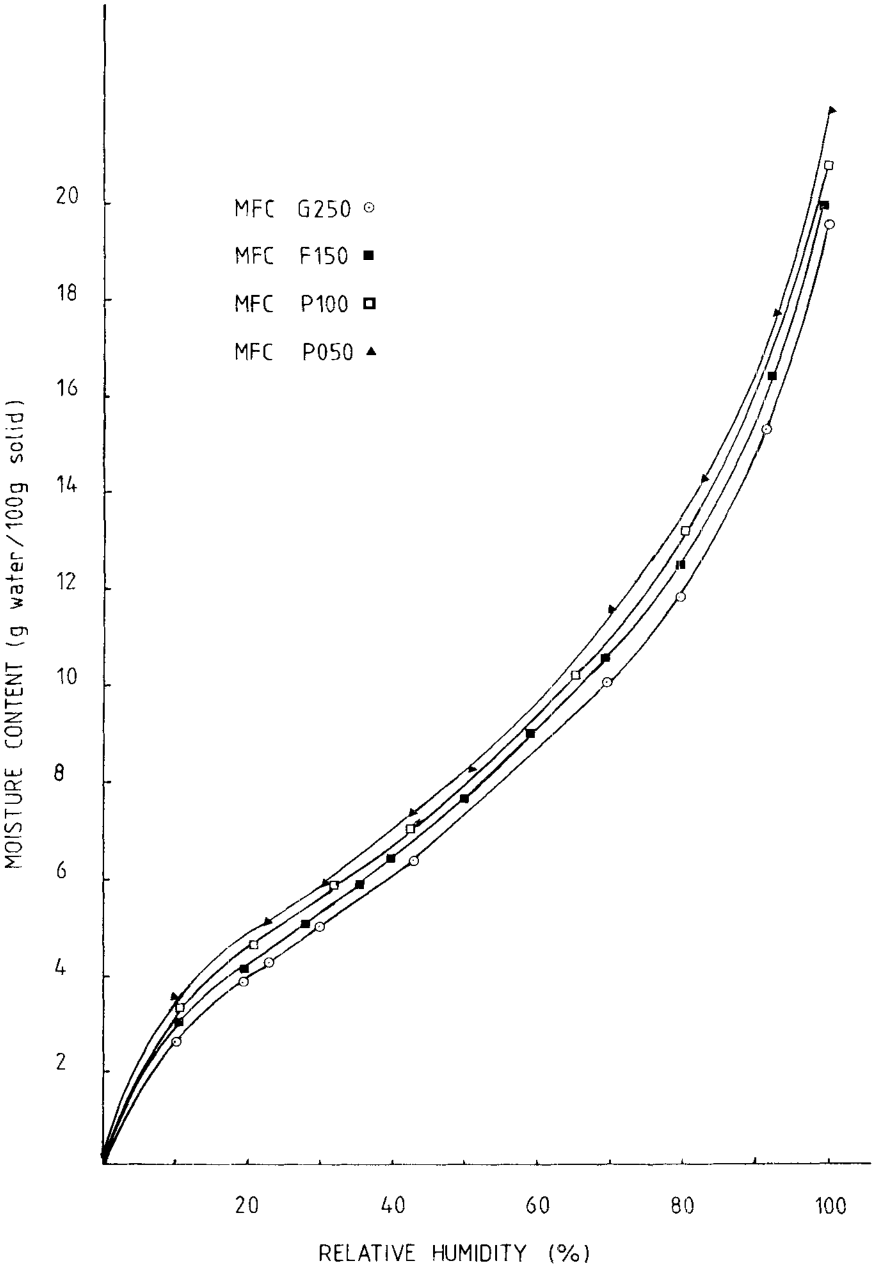

Fig. **1** WATER VAPOUR SORPTION ISOTHERMS AT 20°C FOR MFC POWDERS

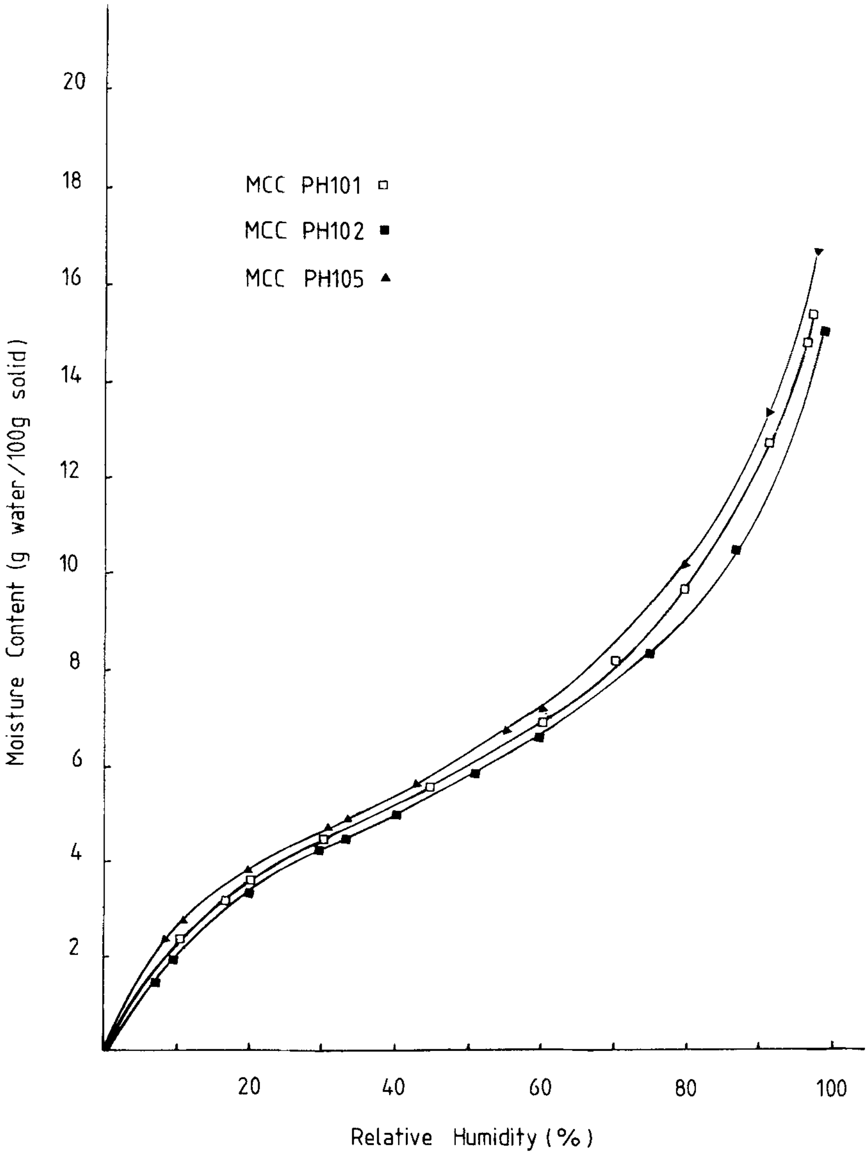

Fig. **2** Water vapour sorption isotherms at 20°C for MCC powders applied in the range of 5-35% R.H. Comparison of surface areas for MFC and MCC obtained from nitrogen adsorption and water sorption (see Table 1) showed an approximate relationship for $S^{H_2O}_{B.E.T.}/S^{N_2}_{B.E.T.}$ of 100 for the materials examined. Young and Healy (13) have observed a similar phenomenon with asbestos powders. Hollenbeck et al (1) suggested that the difference between the size of the nitrogen and water molecules is not sufficient to justify the hundred fold difference observed. However Zograffi et al (4) criticised Hollenbeck et al's explanation that frozen water was blocking the access of nitrogen to MCC pores at the temperature of liquid nitrogen. An alternative explanation is to consider that water interacts with the anhydroglucose molecule in the cellulose polymer chain. In this case the surface area obtained by water sorption should not be regarded as a true internal surface, because the surface area evaluated reflects sorption and the phenomenon of water association with the anhydroglucose molecules. In contrast, the nitrogen adsorption technique measures by physical adsorption the internal and external surface. As indicated in Table 1, a linear relationship was found for MFC and MCC grades when the weight of water sorbed at various R.H. was plotted versus nitrogen volume adsorbed at the same relative pressures. The plot also showed the quantity of water sorbed was much greater than nitrogen and thus the affinity of the physical surface for the water moleculer will be greater than for the nitrogen molecules. The concept of frozen water present on the surface of the solid iln the case of MFC and MCC grades is therefore untenable.

In order to analyse the sorption isotherms over a wider range of R.H. the G.A.B. equation was used. Figures 3 and 4 plotting $^1/_W$ versus p/p_o demonstrate the fit of experimental data to the G.A.B. equation. Derived constants W_m,C_G and K together with V_m and C constants from the B.E.T. equation are listed in Table 2. The data show that the results obtained with the B.E.T. and the G.A.B. isotherm equations for values of V_m and C, and W_m and C_G respectively are comparable.

Table 1. Surface areas of cellulose powders by nitrogen adsorption and water vapour sorption

Sample	Surface area by N_2 adsorption S^{N_2} $(m^2 g^{-1})$ B.E.T.	Surface area by Water vapour sorption S^{H_2O} $(m^2 g^{-1})$ B.E.T.
MFC P050	1.85	196
MFC P100	1.58	171
MFC F150	1.39	167
MFC Granulated	0.89	165
MCC PH 105	2.45	173
MCC PH 102	1.12	117
MCC PH 101	1.22	139

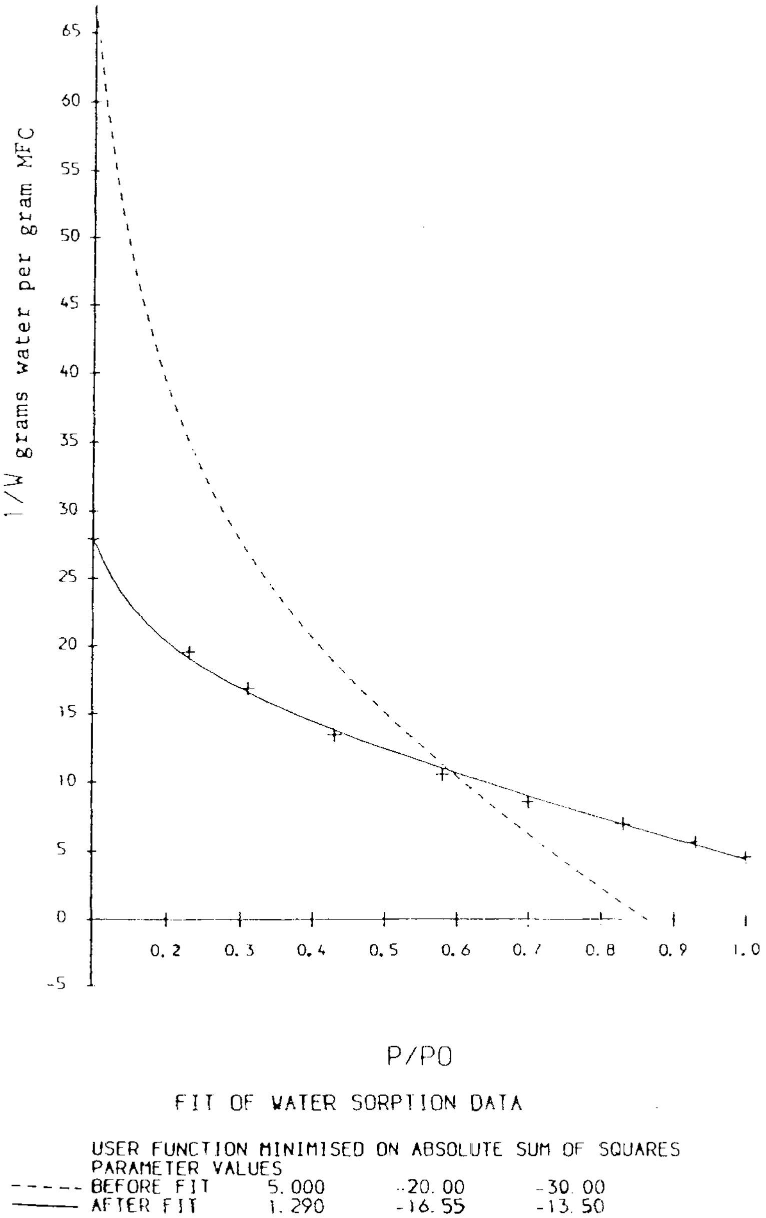

Figure 3 Fit of water sorption data for batch A MFC PO50 to G.A.B. Equation

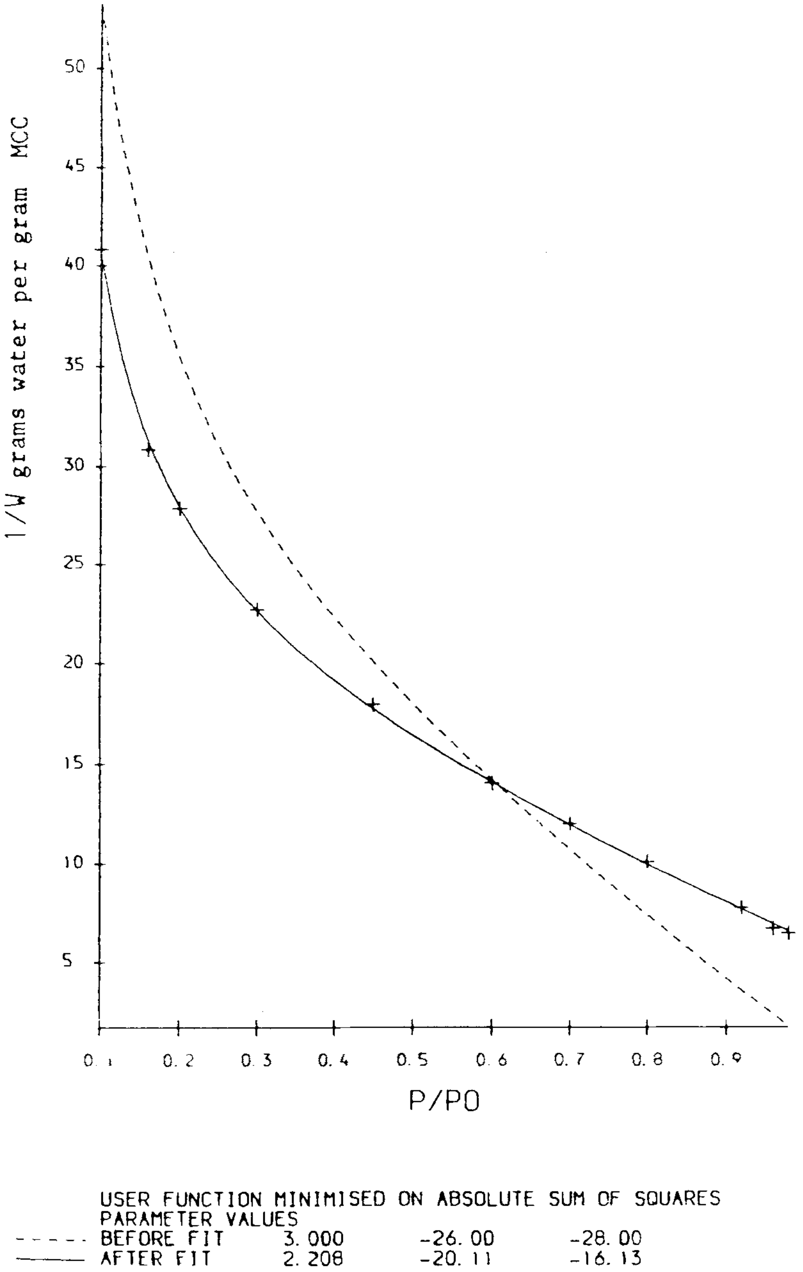

Figure 4 Fit of water sorption data for MCC PH101 to G.A.B. Equation

Table 2. B.E.T. and G.A.B. equation data for all grades at MFC and MCC powders.

	BET equation parameters		GAB equation parameters			
Sample	Vm	C	Wm	C_G	K	Number of data points
MFC P050	0.425	12.27	0.0696	18.66	0.770	9
MFC P100	0.363	10.80	0.0520	17.59	0.772	8
MFC F150	0.319	11.12	0.0484	16.99	0.784	11
MFC Granulated G250	0.205	15.10	0.0500	11.62	0.765	10
MCC PH 105	0.563	35.47	0.0423	18.74	0.761	10
MCC PH 102	0.257	42.63	0.0443	10.98	0.710	10
MCC PH 101	0.280	29.29	0.0420	14.28	0.742	11

These trends may be therefore taken as physically realistic. However, the monolayer values from the G.A.B. equation are considerably higher.

For a test of physical significance the heat of liquefaction, (H_L) and heat of sorption of water in the intermediate layer (H_m) can be determined from equation 2 and 3 respectively and compared with the value obtained calorimetrically (1, 3, 14). Table 3 shows the 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. A reasonable order of magnitude agreement between G.A.B. theoretical and calorimetric experimental values was observed, although not unexpectedly, the $H_m - H_L$ values did exhibit significant differences.

The integral and differential Gibb's free energy changes associated with the sorption of water vapour on MFC and MCC powders were calculated from the moisture content and values of relative humidities taken at selected intervals from the water sorption isotherms (Figures 1 and 2) using the relationships reported by Hollenbeck et al (1). The integral Gibb's free energy changes were calculated using equation (4).

$$-\Delta F = n_1 RT \ln p/p_o - RT\int n_1 d(\ln p/p_o) \tag{4}$$

where n_1 is number of moles of water sorbed and R is the gas constant, T is temperature, p is the actual vapour pressure and p_o is the vapour pressure of pure liquid. The integral part of the equation can be obtained graphically by plotting n_1 p_o/p against p/p_o and determining the area under the graph to the upper limiting value of p/p_o which is required.

$$-RT\int_o^{p/p_o} n_1 d(\ln p/p_o) = -RT\int_o^{p/p_o} \frac{n_1 p_o}{p} d(p/p_o) \tag{5}$$

Table 3. Comparison of values of enthalpy of sorption obtained from calorimetric experiments and the G.A.B. equation.

Sample	G.A.B. (KCal/mole)		Calorimetric)KCal/mole)	
	$H_m - H_L$	$H_l - H_L$	$H_m - H_L$	$H_l - H_L$
MFC P050	0.153	1.867	4.2	1.3
MFC P100	0.151	1.830		
MFC F150	0.142	1.800		
MFC Granulated G250	0.157	1.593		
MCC PH 105	0.160	1.875		
MCC PH 102	0.200	1.673		
MCC PH 101	0.174	1.731	3.6	1.2

The differential Gibb's free energy changes were determined from equation (6).

$$-\overline{\Delta F} = RT\, l_n\, p/p_o \tag{6}$$

The net integral enthalpies (-ΔH) were calculated for both MFC P050 and MCC PH 101 using equation (7).

$$-\Delta H = \Delta H_s - (-n_1 \lambda) \tag{7}$$

where H_S is the heat of sorption obtained from flow microcalorimetry. Entropy changes associated with the sorption process were determined by equation (8).

$$\Delta S = \frac{\Delta H - \Delta F}{T} \tag{8}$$

Figures 5 and 6 illustrate the relationship between the integral thermodynamic functions and the amount of water vapour sorbed for MFC P050 and MCC PH101 respectively. All curves in Figures 5 and 6 show an increase asymptotically approaching a limiting value which corresponds to the maximum moisture sorbed. However the values of -ΔF, -ΔH and -ΔS in its current form do not differentiate the effect the sorption of each n mole of water vapour has on the change of the thermodynamic state functions. Therefore, the thermodynamic state functions were differentiated with respect to the amount of water vapour sorbed and these values are illustrated in Figures 7 and 8 for MFC P050 and MCC PH 101. The curves for MCC PH 101 are similar to those reported previously by Hollenbeck et al. (1) The curves show that:

1) $-\overline{\Delta H}$ *is constant up to values approaching monolayer with respect to* anhydroglucose molecules suggesting an energetically homogeneous surface available for water vapour molecules and may represent the extent of an

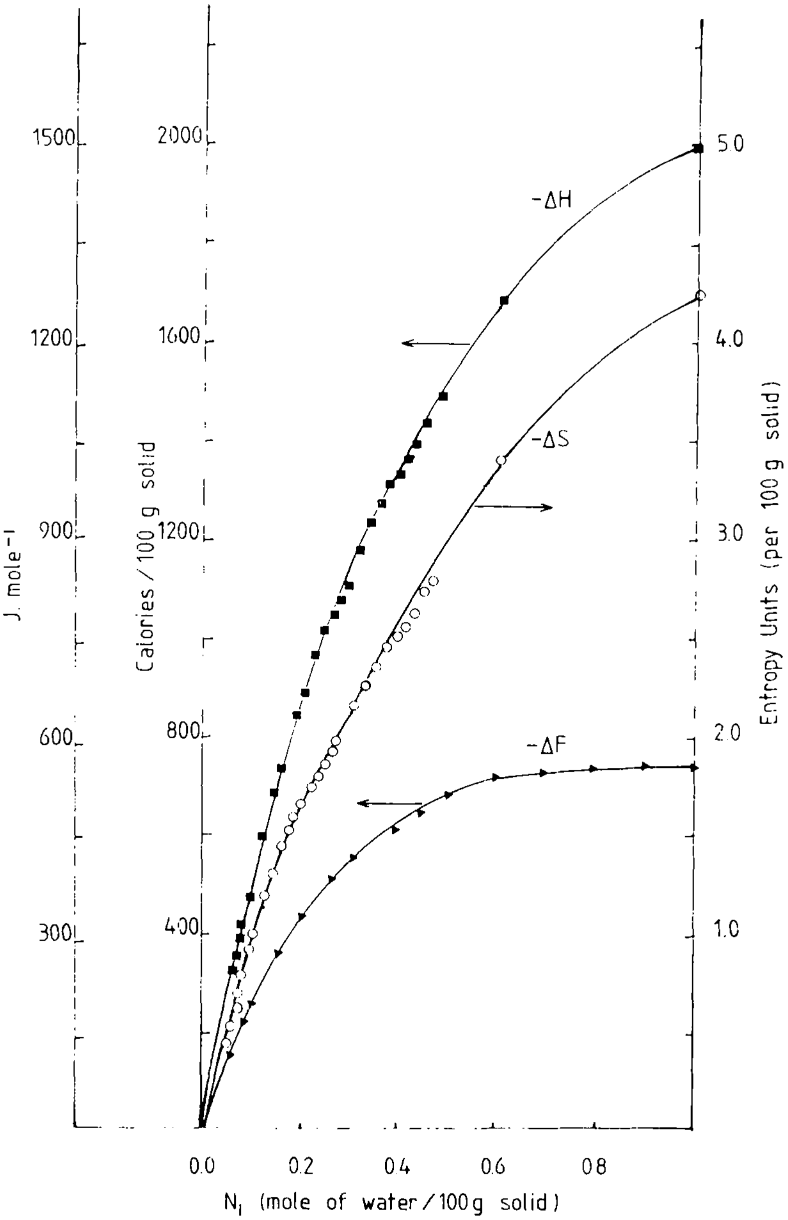

Fig. **5** Integral thermodynamic properties of sorption at 20°C for MFC P050

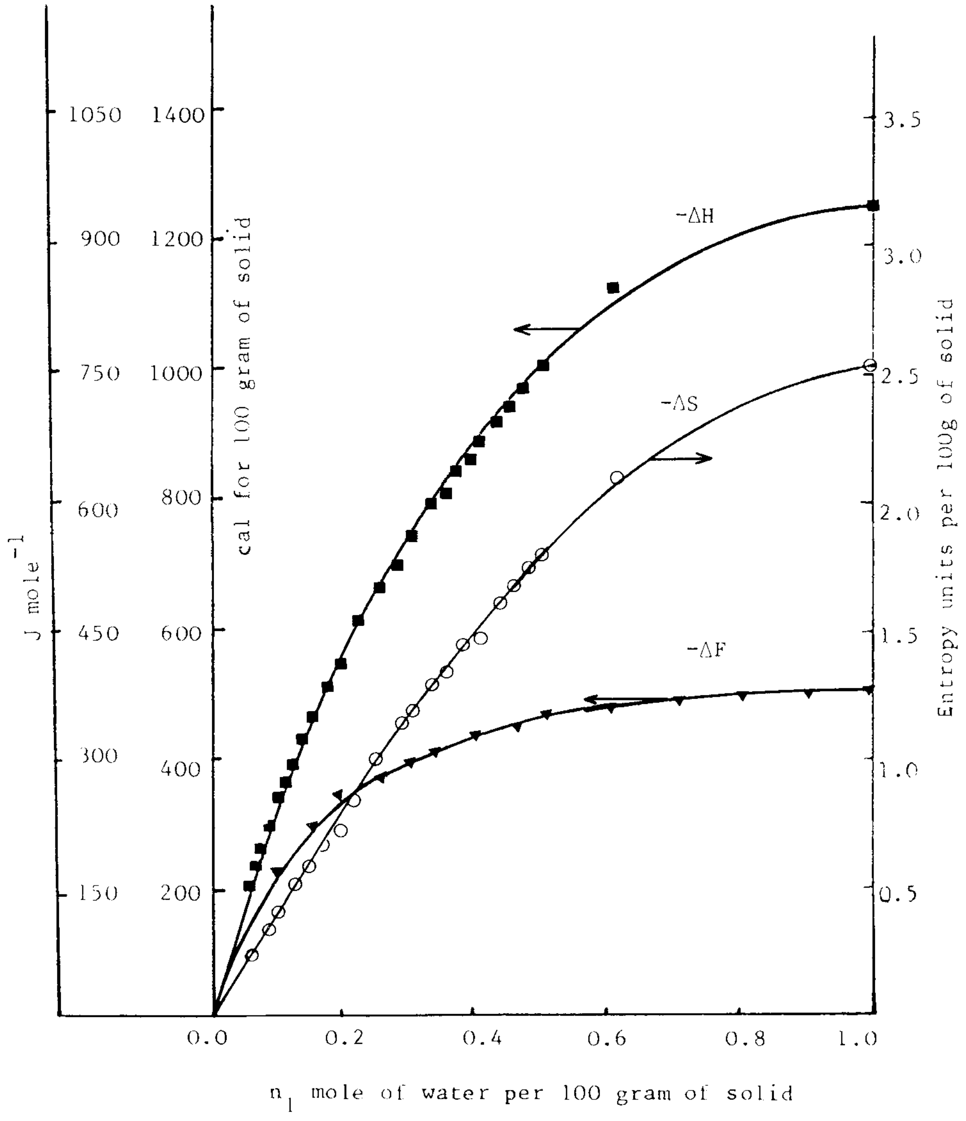

Figure 6 Integral thermodynamic properties of sorption for the MCC PH101

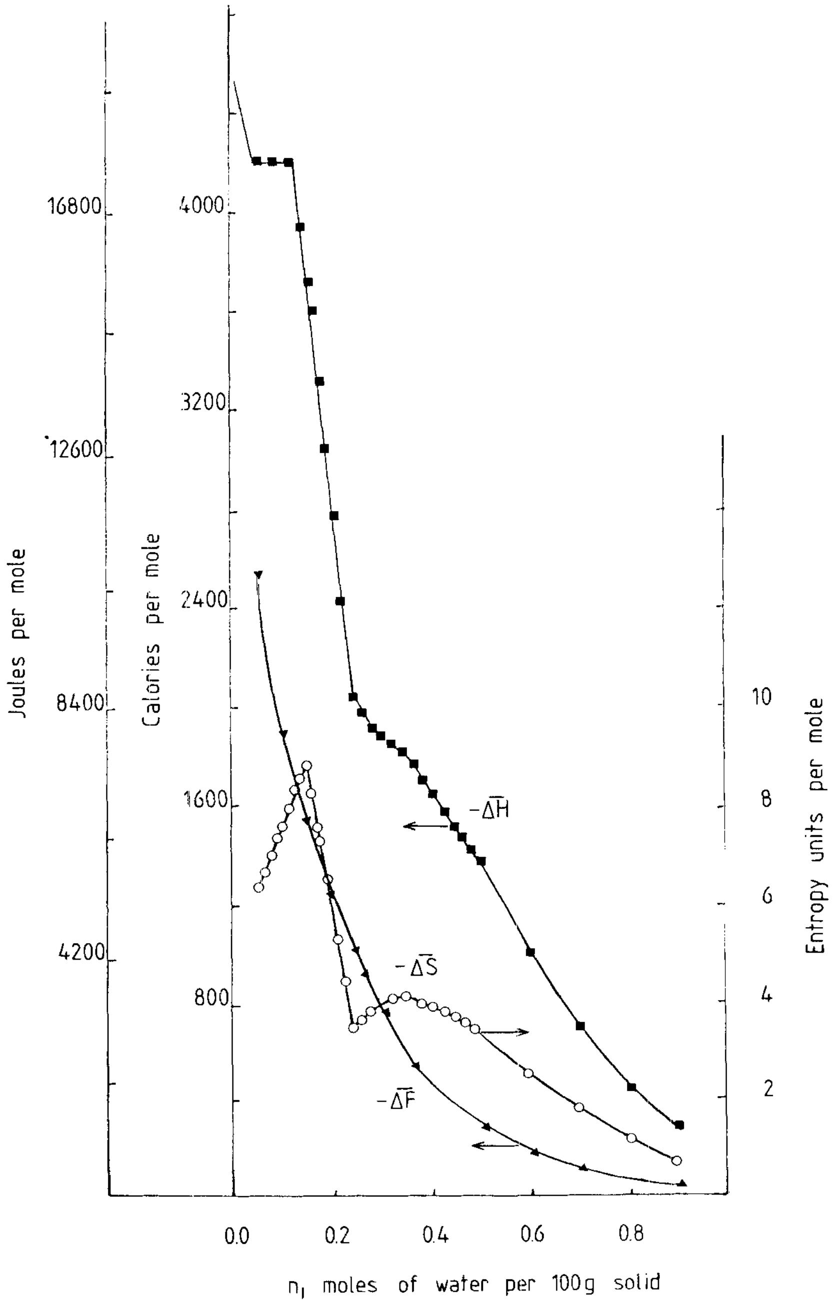

Fig. 7 Differential thermodynamic properties of MFC P050

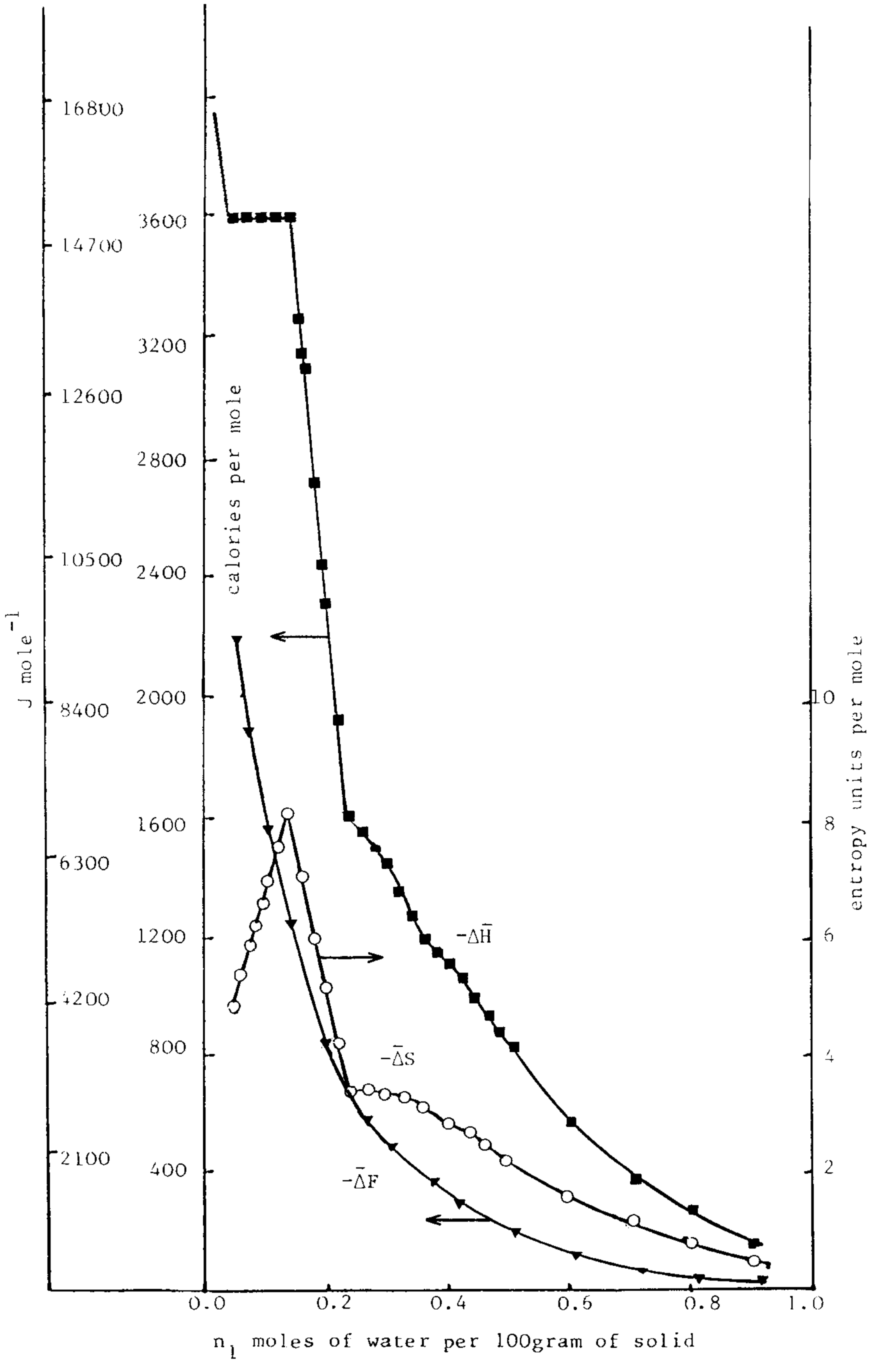

Fig 8 Differential thermodynamic properties of MCC PH101

interaction between a single water vapour molecule with each anhydroglucose molecule:

2) the second region shows a steady fall in $-\overline{\Delta H}$ after a discontinuity between n_1 = 0.18 and 0.22, which suggests weaker bonding of water molecules with less homogeneity of the water - anhydroglucose interaction. This region may be associated with a second sorbed water molecule per anhydroglucose residue:

3) at higher values of n_1 (>0.5), $-\overline{\Delta H}$ falls steadily to low values indicating the uptake of non-specific bulk water.

The differential heat of sorption ($-\overline{\Delta H}$) of water on MCC showed similar regions but gave smaller values of $-\overline{\Delta H}$, $-\overline{\Delta F}$ and $-\overline{\Delta S}$ than MFC P050. The different numerical values between these products may reflect the different crystallinity in the two materials at MFC and MCC, with water vapour sorption occurring only in the amorphous regions at cellulose. Morrison and Dzieciuch (14) examining moisture sorption on powders, concluded that the initial decrease of $-\overline{\Delta H}$ was due to a peptization (swelling) of the solid. The energy consumed in the disruption of solid-liquid bond produced a non-constant and lower heat of sorption than expected. This effect, which is carried implicitly through out the determination of $-\Delta H$from immersional data, is not present in the study of MFC and MCC. Therefore, the constant $-\overline{\Delta H}$ period seems to be an indication of zero swelling as well as indication of an energetically homogeneous surface (1).

The differential entropy at very low moisture content (Figure 7 and 8) is positive. The increase in the ordered system is greatest when the first water molecule interacts with the anhydroglucose molecule. After that the rate of ordering diminishes but is still positive. As more moisture is sorbed, however, the differential entropy will continually decrease. The continuous increase in the negative differential entropy value is a result of a decrease in the sorption of water molecule in the surface film. The increase in the negative differential

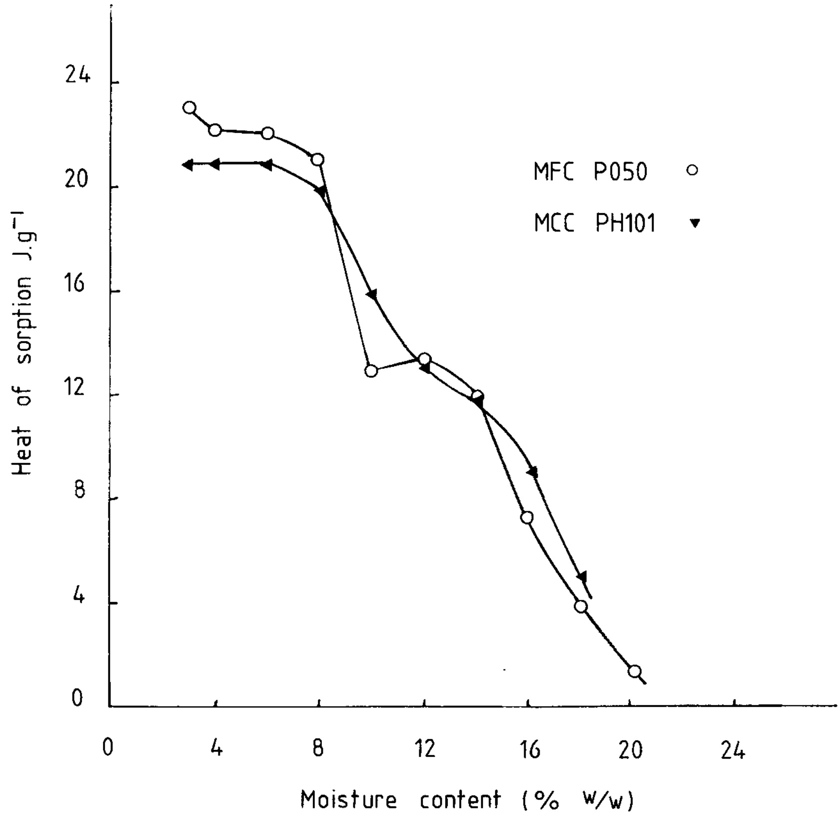

Fig. 9 Differential heat of sorption versus moisture content for MCC PH101 and MFC P050

entropy corresponds to a period of accelerated ordering, due primarily to the approach of monolayer completion.

To examine the water sorption sequence further the differential heat of sorption obtained microcalorimetrially ($\overline{\Delta H_a}$) was correlated with the moisture content of the powders. The graph of $-\overline{\Delta H_a}$ versus moisture content illustrated in Figure 9 indicates three sections and these can be distinguished both for MFC P050 and MCC PH 101. In MCC an initial constant level of $-\overline{\Delta H_a}$ occurs from 3-7% w/w moisture content indicating very strong sorbed water. A second plateau, less defined but still distinguishable, is observed at a lower $-\overline{\Delta H_a}$ between 10-14%

$W/_W$. Above this moisture level, the continuous decrease in - $\overline{\Delta H}_a$ suggests that the sorbed water begins to resemble bulk water. The discontinuities in the curve correspond to stoichimetric ratios of approximately 1:1 and 2:1 of water to anhydroglucose unit assuming a crystallinity figure of 63% (15) and that moisture is taken up by the amorphous regions of cellulose (16). The presence of these plateau regions thus supports the sorption model of a stronger specific interation of a single water vapour molecule per anhydroglucose molecule followed after completion by a weaker interaction by a second water vapour molecule with each anhydroglucose molecule in the amorphous region. For MFC the values of - $\overline{\Delta H}_a$ over the plateau regions are more clearly defined than for MCC. These differences between cellulose powders can be attributed to differences in powder pretreatment, inducing, for example, different degrees of crystallinity or surface energies.

The observations from microcalorimetric study thus clearly support the interpretation and hypotheses put forward from the GAB equation and sorption isotherm analysis. It is interesting to note that the model proposed by Van den Berg (3) for water sorption in starch powders, appears to also hold for cellulose powders.

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