

# Thermal Studies on the Interaction of Water and Microcrystalline Cellulose

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**Abstract**—The interaction between water and microcrystalline cellulose in the absence and presence of lactose has been studied by thermogravimetric analysis, differential thermal analysis and immersion calorimetry. The results indicate that most of the water held within a system used for the preparation of spherical granules by extrusion/spheronization is present as free water which may be readily lost by evaporation. There is approximately 0.856 mol of water per 100 g of microcrystalline cellulose which appears to be absorbed as structured water. Microcrystalline cellulose may therefore be described as a 'molecular sponge'. The enthalpy of fusion of the 'free' water offers a simple method of estimating the effective surface area of the microcrystalline cellulose.

The preparation of spherical granules by the process of extrusion/spheronization has been described by Reynolds (1970). Formulation of such granules is based on the inclusion of microcrystalline cellulose which, when mixed with water, appears to form a consistency which readily extrudes and subsequently spheronizes. Definition of what rheological characteristics are required to ensure that this total system is successful have not been fully evaluated. However, Harrison et al (1984, 1985) have established certain criteria for producing a uniform smooth extrudate. The microcrystalline cellulose is of fundamental importance to the system and its function appears closely related to how water is held within the powder mass, and how mechanical processing influences the mobility of water. If water is held within the microcrystalline cellulose by chemical means, then this should be detectable by thermal analysis and immersion calorimetry. An investigation of the extent of the chemical interaction is described here.

## Materials and Methods

Microcrystalline cellulose was obtained as Avicel PH 101 (FMC Corporation Marcus Hook, Pennsylvania, USA). The lactose was BP quality  $\alpha$ -lactose monohydrate (Unigate Regular Grade). Blends of water with microcrystalline cellulose and microcrystalline cellulose-lactose were prepared in a planetary mixer (Kenwood Chef), and when required, extruded through a 1.5 mm diameter, 6 mm long die of a ram extruder at a cross-head speed of 20 cm min<sup>-1</sup>, as described by Harrison et al (1984).

### Thermogravimetric analysis (TGA)

Samples of a wet powder mass or extrudate (typically 7 mg) were placed in the pan of a Stanton Redcroft TG 750 and heated from room temperature at 2°C min<sup>-1</sup>. Isothermal gravimetric analysis was also undertaken at a range of temperatures using the same instruments. In both cases the

changes in sample weight with temperature and time were recorded.

### Differential thermal analysis (DTA)

Samples (typically 7–15 mg) were heated at 2°C min<sup>-1</sup>, from -20 and 5 to 100°C in a Stanton Redcroft DTA 671 instrument. This was calibrated using Indium ( $\Delta H = 28.4$  MJ g<sup>-1</sup>) and peak areas were estimated by cutting and weighing the graphical output.

### Immersion calorimetry

Enthalpy measurements were carried out at 30°C using an LKB Calorimetry system 8700 (LKB Instruments Ltd, Croydon) using water, and a saturated solution of lactose as immersion liquids for the microcrystalline cellulose and lactose. Both materials were used as supplied with no pretreatment.

## Results and Discussion

### Thermogravimetric analysis

The thermogravimetric curve for the loss of water from a sample of microcrystalline cellulose-water initially containing 41.2% by weight of water, is shown in Fig 1. Two distinct

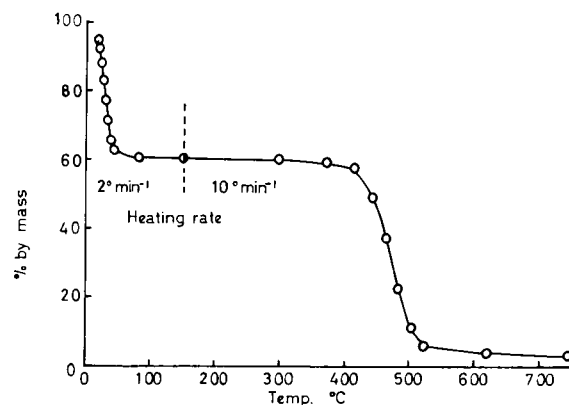


FIG. 1. TGA for microcrystalline cellulose-water granulation in air.

stages are visible. The first corresponds to dehydration of the sample between 20–40°C and is almost exactly equivalent to the amount of water added to the system. The sample weight then remains constant until the second mass loss at approximately 425°C (approached at 10°C min<sup>-1</sup>), at which temperature thermal decomposition occurs. Analysis of a sample incorporating a quantity of lactose equivalent to that of microcrystalline cellulose produced slight changes in the curve; typically the median temperature for water loss was 10°C higher. Table 1 represents the temperature at which 50% of the water is lost from the various systems. The water of crystallization of lactose is lost at a much higher temperature than the bulk of the water (150°C).

#### Kinetics of dehydration

In the isothermal study, samples (typically 7 mg) were introduced into the furnace and dehydrated at constant temperature (range from 30 to 65°C). Results were then expressed as the fractional water content of the sample and plotted against reaction time.

The kinetics of solid state reactions are more difficult to interpret than those of homogeneous reactions (Young 1966). In cases where the reaction is controlled by the geometry of the crystal, the kinetics have been extensively reviewed (Jacobs & Tompkins 1955; Sharp et al 1966; Harrison 1969). Under isothermal conditions microcrystalline cellulose-water typically loses 70–80% of the water by a zero order process (Fig. 2). This may imply that the water is bound to the cellulose rather loosely and the reaction may well be controlled simply by the evaporation of free water from the surface of the solid. An analogy may be drawn with the dehydration of calcium oxalate monohydrate in-vacuo (Dollimore et al 1970; O'Brien & Ross 1982).

The zero order rate constants were determined as the slope of linear portion of the weight loss time curve by least squares linear regression analysis. Application of the Arrhenius equation to the linear portion of the zero-order rate constants, at various temperatures, allows the estimation of the activation energies of the process. Least squares linear regression analysis provided the correlation coefficients, slopes and their standard deviation, (given in Table 2). These values are similar for all the samples and are very low for solid state reactions. Such values may be consistent with a surface-controlled reaction (Cordes 1968).

Using samples of extrudate of a constant weight (ca 6 mg) but varying the diameter the possible effect of the surface area of the cylinder generated by extrusion, on the kinetics of

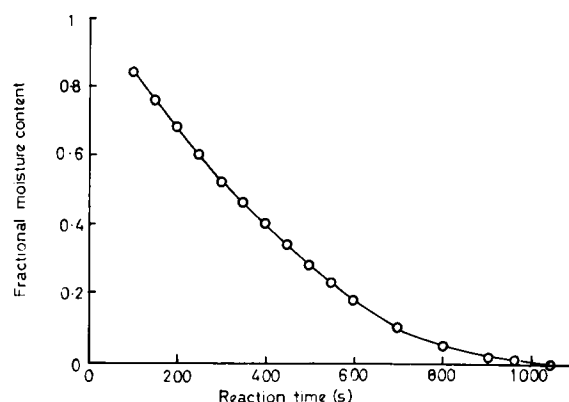


FIG. 2. Isothermogravimetric analysis of microcrystalline cellulose-water granulation. Sample weight 6.5 mg. Temperature 29°C.

dehydration, was investigated. The rate of water loss for 2.0, 1.5 and 1.0 mm diameter extrudate of 47% water with microcrystalline cellulose was 0.3934 ( $\pm 0.46$ ), 0.3943 ( $\pm 0.44$ ) and 0.4529 ( $\pm 0.33$ )  $\times 10^{-3}$  mol s<sup>-1</sup>, respectively (values in brackets providing the standard deviation of the estimates). Such differences are well within the range of variability expected in solid state kinetic studies. The changes in surface area of the extruded cylinder do not appear to influence the loss of water from such systems.

This suggests that it is the surface area of the pore structure of the microcrystalline cellulose which is important; and that extrusion of the sample does not affect the removal of water by thermal processes. The open porous structure of microcrystalline cellulose-water preparations can be clearly seen in the scanning electron micrographs (Fig. 3). The similarity of the surface for extruded and granular samples supports the suggestion that it is the overall pore surface area of the microcrystalline cellulose which is important and not the surface area of the extruded cylinder.

Further support for the above suggestion is provided by considering the pre-exponential factors (Table 2) as derived from Arrhenius plots. Values which are of the order of  $10^{20}$  or more are often held to be associated with processes within the bulk of the solid (Cordes 1968). Lower values in the region of  $10^{14}$  are typical of surface controlled reactions (Dollimore et al 1970). Thus the exceptionally low values for the pre-exponential factor (typically ca 500) observed for the various systems studied here are consistent with a facile loss of the water by a surface-controlled reaction.

Table 1. Median temperatures of water loss for systems of microcrystalline cellulose (M), lactose (L), and water (W).

Preparation	Quantity of water added % w/w	Quantity of water lost % w/w	Median temp for water loss °C
M/W Granulation	41.2	38.3	29.0
M/W Extrudate	41.2	41.0	32.5
M/L/W Granulation	41.2	40.9	32.0
M/L/W Extrudate	41.2	41.6	44.0

Table 2. Activation energies and pre-exponential factors for systems of microcrystalline cellulose (M), lactose (L), and water (W) determined by TGA. Moisture content 41.2% w/w.

Preparation	Correl. coeff.	Activation Energy kJ mol <sup>-1</sup>	s.d.	Pre-exponential factor
M/W Granulation	0.999	31.26	0.717	352
M/W Extrudate	0.930	33.61	2.29	575
M/L/W Extrudate	0.989	34.15	2.60	688

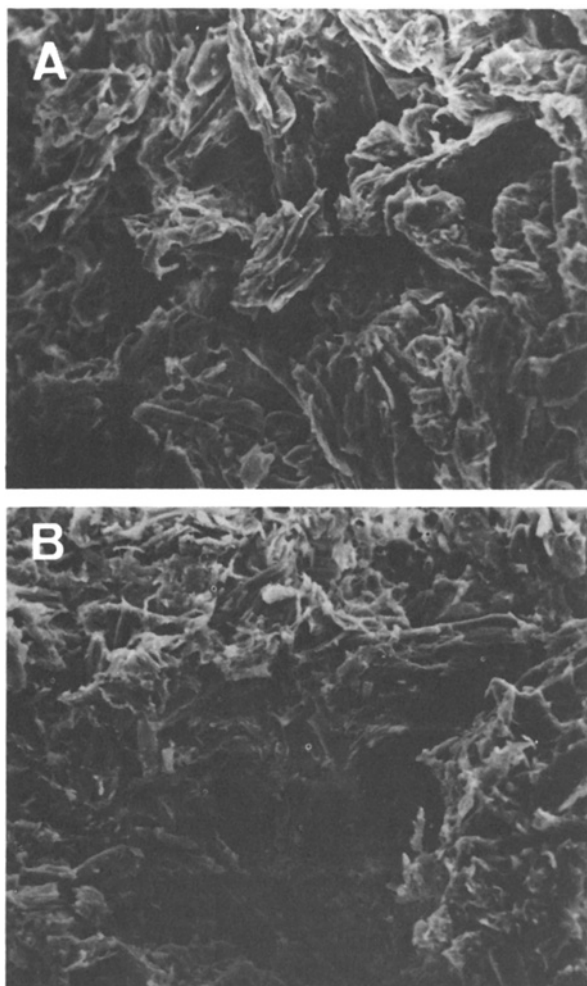


FIG. 3. Scanning electron micrographs of microcrystalline cellulose-water (5:7) mixture. (A) Granulation (B) Extrudate.

#### Differential thermal analysis

Typical DTA curves for dehydration of microcrystalline cellulose and microcrystalline cellulose-lactose extrudates consist of a single broad endotherm peak (Fig. 4). The microcrystalline cellulose-water curve is modified by the inclusion of lactose, the tail end becoming steeper and resulting in a slightly narrower peak. Estimates for the enthalpy of dehydration for microcrystalline cellulose-water and microcrystalline cellulose-lactose-water were  $39.2 (\pm 1.76)$  and  $42.9 (\pm 1.22)$  kJ mol<sup>-1</sup>, respectively, and the corresponding peak temperatures were 56.4 and 57.7°C. The difference between the enthalpies is significant when the results of 10 replicate experiments were assessed by a *t*-test. Addition of lactose to the system, therefore significantly increases the enthalpy of vaporization of the water associated with the sample. The lactose water of crystallization is lost at a significantly higher temperature (150°C) than is achieved during the DTA and did not affect the measurements.

The microcrystalline cellulose-water system is further characterized by a freezing phenomenon. When the sample was cooled to -25°C an exothermic peak at -10°C was observed. On subsequently heating this sample (2°C min<sup>-1</sup>),

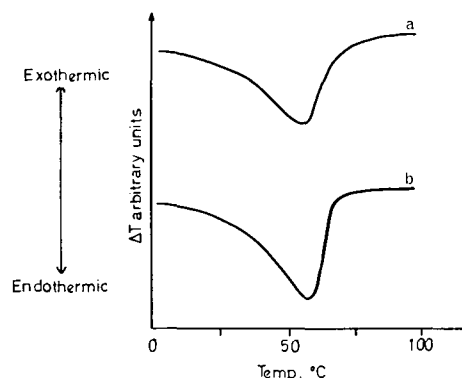


FIG. 4. Typical DTA curves (at 2°C min<sup>-1</sup>) for (a) microcrystalline cellulose-water and (b) microcrystalline cellulose-lactose-water mixtures.

an endotherm peak corresponding to the melting of water within the sample was then observed, almost immediately before the water starts to vaporize from the sample. Fig. 5 and Table 3 summarize the DTA results.

The presence of lactose in the system markedly lowers the temperature of freezing, implying that some of the lactose is dissolved in the 'free' water. It was, therefore, important to control experiments in which the latent heat of vaporization was being estimated, carefully so that the freezing did not influence the measured peak areas. The dissolution of soluble components of a wet granulation has previously been reported by Sherrington (1968), who investigated the granulation properties of fertilizer mixtures composed of one or more soluble ingredients. The term solution phase was applied to the liquid phase, which was recognized as a solution of the fertilizer salts in water.

The enthalpy of fusion of the 'free' water in the microcrystalline cellulose-water system also seems to provide a novel method by which the internal surface area of the microcrystalline cellulose may be estimated. The assumption was made that only the water absorbed in the pores freezes (in contrast to the water adsorbed on the surface). The surface area of the microcrystalline cellulose can then be estimated from the discrepancy in the heat of fusion (the value for pure water was taken to be 6.008 kJ mol<sup>-1</sup> by Kaye & Laby 1986). Details of the calculation are given below:

$(\Delta H_{\text{fusion water}} - \Delta H_{\text{fusion microcrystalline cellulose-water extrudate}}) = (6.008 - 4.682)$  kJ mol<sup>-1</sup> ie. a discrepancy of 22.07%.

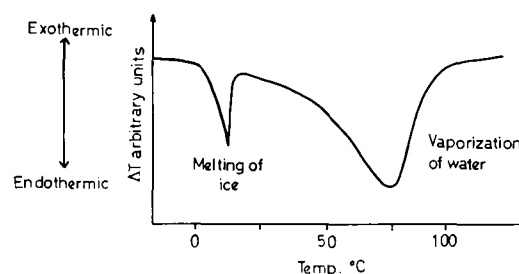


FIG. 5. DTA curve (at 2°C min<sup>-1</sup>) for microcrystalline cellulose-water illustrating the 'freezing' phenomenon.

Table 3. Onset of freezing temperature, freezing temperature, and heats of vaporization and fusion for systems of microcrystalline cellulose (M), lactose (L) and water (W). Moisture content 41.2 % w/w.

Preparation	Onset temp. of freezing	Peak temp. of freezing	Heat of reaction kJ mol <sup>-1</sup>	
			Vaporization	Fusion
M/W Extrudate	-7.2 °C	4.62 °C	39.15	4.68
M/L/W Extrudate	-21.8 °C	1.47 °C	42.88	6.90

Thus, 22.07% of the water in microcrystalline cellulose-water (10:7) extrudate remains unfrozen, and represents 0.856 mol water per 100 g of microcrystalline cellulose. This is in close agreement to the level of unfreezable water in cotton cellulose, between 0.728 and 0.817 mol water per 100 g, values obtained by Duckworth (1971), in a DTA study. Assuming this water remains unfrozen due to adsorption, then, taking the area of a water molecule to be 12.5 Å<sup>2</sup>, the surface area of microcrystalline cellulose is given by:

$$(0.856 \times 12.5 \times 6.022 \times 10^{23} \times 10^{-20}) / 100 \text{ m}^2 \text{ g}^{-1} = 634 \text{ m}^2 \text{ g}^{-1} \text{ microcrystalline cellulose.}$$

This value differs from the result of Hollenbeck et al (1978), who used vapour adsorption and immersional wetting techniques to arrive at a value of 130–270 m<sup>2</sup> g<sup>-1</sup> for the total surface area of microcrystalline cellulose. The discrepancy in the values may be explained as follows. The relationship between the differential enthalpy of adsorption  $H_a$ , and the quantity of water adsorbed by microcrystalline cellulose is described in Hollenbeck's work, Fig. 6. The constant  $H_a$  period observed in the range 0–0.15 mol adsorbate per 100 g of solid, represents monolayer adsorption, and is an indication of an energetically homogeneous surface. The dashed line corresponds to the monolayer capacity as estimated from BET treatment of the sorption data. Slightly before completion of the monolayer,  $H_a$  begins to decrease rapidly. The end of the constant period indicates the point where lateral adsorbate interactions begin to influence the heat of adsorption. The sharply decreasing values of  $H_a$  seem to indicate the transition from a situation where most water molecules interact by forming two bonds with cellulose to a completed monolayer involving one solid-liquid bond per water molecule. In other words, a partial transition from solid-liquid to liquid-liquid bonding is responsible for the observed decrease in  $H_a$  with increasing moisture content.

Hollenbeck et al (1978) determined a value of 0.183 mol water per 100 g microcrystalline cellulose as being the monolayer capacity. The value arrived at from the DTA is 0.835 mol per 100 g solid. This is close to the value of 0.9 mol water per 100 g solid obtained from Fig. 6, the point at which no more water interacts with the microcrystalline cellulose. Therefore water exists in its unstructured, bulk form. From Fig. 6 it can be seen that this method of estimating the surface area takes into account adsorption of more than one layer of water molecules, which explains the higher value obtained. Nevertheless, this method would seem to extend the use of the DTA measurements to provide a rough estimation of the

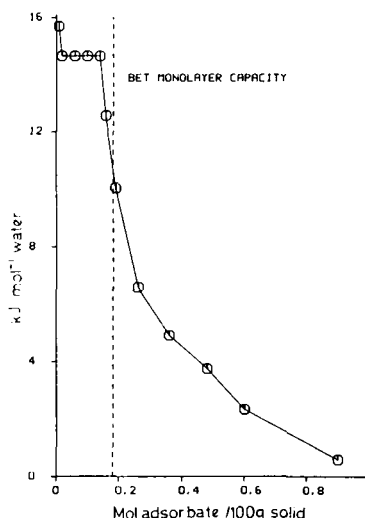


FIG. 6. Differential enthalpy of adsorption for microcrystalline cellulose-water. After Hollenbeck et al (1978)

surface area of the solid. The situation is more complicated in the microcrystalline cellulose-lactose-water preparations in which lactose will also precipitate from solution on freezing, therefore the data derived from this system cannot be put to similar use.

In comparing the results obtained for the enthalpy of dehydration with the work of Hollenbeck et al (1978), it was noted that water initially binds exothermally ( $-54.6 \text{ J g}^{-1}$  of microcrystalline cellulose) to the surface of the microcrystalline cellulose. Therefore, theoretically, the enthalpy of vaporization of water from microcrystalline cellulose-water should be slightly greater than that of free water itself, by  $54.6 \text{ J g}^{-1}$  of microcrystalline cellulose. This should lead to elevation of the apparent enthalpy required to vaporize the water of  $1.42 \text{ kJ mol}^{-1}$ . However, the DTA value which was obtained for the enthalpy, was  $39.2 \text{ kJ mol}^{-1}$ . This is close to, but lower, than that of water at the median temperature of the reaction ( $+42.4 \text{ kJ mol}^{-1}$  at  $60^\circ\text{C}$ , Kaye & Laby 1986). However, the DTA did not provide either an absolute or isothermal measurement. The value for the enthalpy of vaporization of water from microcrystalline cellulose-water of  $39.2 \text{ kJ mol}^{-1}$  ( $871 \text{ J g}^{-1}$  of wet solid), less the enthalpy of vaporization of water at  $60^\circ\text{C}$ , is  $3.2 \text{ kJ mol}^{-1}$ . This may be due to experimental error or the disruption of the hydrogen-bonded network of the water contained in the pores of the microcrystalline cellulose.

The larger enthalpy of  $42.9 \text{ kJ mol}^{-1}$  ( $951 \text{ J g}^{-1}$  of wet solid) measured for the microcrystalline cellulose-lactose-water system cannot be explained in terms of the heat of dissolution and wetting of lactose, which are both endothermic processes. The heat of immersion of lactose in a saturated solution of lactose was found to be  $+18.1 \text{ J g}^{-1}$ ; a value of  $+59.5 \text{ J g}^{-1}$  was obtained for the heat of solution of lactose in water. These two enthalpies would hence make the loss of water from these samples occur with a lower overall enthalpy. Hence, this result implies a strong exothermic interaction between saturated solutions of lactose and microcrystalline cellulose. This was confirmed by the large exothermic value,  $-57.5 \text{ J g}^{-1}$ , that was obtained for the heat

of immersion of microcrystalline cellulose into saturated lactose solution. The corresponding heat of immersion of microcrystalline cellulose into water was found to be lower,  $-18.2 \text{ J g}^{-1}$ .

A discrepancy was also obtained between the activation energy values determined for microcrystalline cellulose-water in the TG analysis, and the enthalpy of vaporization from the DTA. Theoretically the activation energy for an endothermic reaction such as this must be greater than or equal to the heat of the reaction. However, the value of the activation energy,  $33.6 \text{ kJ mol}^{-1}$  of water, was  $5.44 \text{ kJ mol}^{-1}$  less than the value for the enthalpy of the reaction. There are three possible explanations: (i) The activation energy measured may be valid only for the initial stages of the reaction. The last 20% or so of the water, possibly bound at the surface, may be lost in a higher activation energy process. (ii) The hydrogen bonded network of water molecules contained in the pores of the microcrystalline cellulose may be disrupted. This effect could be caused by close packing of the cellulose fibres. Some evidence for this is seen in the electron micrographs of the extrudate (Fig. 3). (iii) Evaporative cooling during the rapid dehydration of the sample may lead to an erroneously low value for the activation energy. This has been found to occur in related systems (Le May Jr 1970).

#### Conclusions

Thermal analysis provides fundamental information about the properties of microcrystalline cellulose-water preparations. This work has shown that the bulk of the water held within the system is present as free water which may be readily lost by evaporation, with a small quantity,  $0.856 \text{ mol}$  per  $100 \text{ g}$  of microcrystalline cellulose, being present as adsorbed structured water. Microcrystalline cellulose may therefore be described as a 'molecular sponge', in the sense that the material is capable of physically retaining a high percentage of water within itself, but allowing removal by evaporation to take place with great ease. This is substantiated by the freezing phenomenon observed in the DTA, showing that liquid water is free to solidify to ice on cooling. This property may be of importance in controlling the movement or the distribution of the liquid in wet powder masses that are to be processed by extrusion-spheronization.

Thermal analysis may also be of use in quality control and related applications, for example in the determination of

optimal drying times and temperatures to be used during production. TGA provides a simple and reliable method for the determination of the water content of preparations. DTA provides a method by which an effect of the incorporation of the drug model may be investigated. This technique may eventually be useful in assessing the suitability of a granular material for extrusion. The enthalpy of fusion of the 'free' water may provide a simple method for the estimation of surface areas of similar substances.

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