International Journal of Pharmaceutics, 63 (1990) 251–257
Elsevier

IJP 02157

The interaction of various types of microcrystalline cellulose and starch with water

Tina C. Blair [1], Graham Buckton [2], Anthony E. Beezer [3] and Sally F. Bloomfield [1]

[1] *Chelsea Department of Pharmacy, King's College, University of London, Manresa Road, London SW3 6LX (U.K.),*
[2] *Department of Pharmaceutics, The School of Pharmacy, University of London, 29–39 Brunswick Square, London WC1N 1AX (U.K.)*
and [3] *Department of Chemistry, Royal Holloway and Bedford New College, University of London, Egham Hill, Egham, Surrey (U.K.)*

(Received 20 January 1990)
(Modified version received 2 March 1990)
(Accepted 26 March 1990)

Key words: Starch; Microcrystalline cellulose; Microcalorimetry; Vacuum microbalance; Water; Sorption; Thermodynamics

Summary

Sorption isotherms of water onto/into potato, wheat and maize starch and Avicels PH-101, RC-581 and CL-611 have been prepared. In previous publications, a vacuum microbalance and a sorption microcalorimeter have been used to study interactions between water vapour and crystalline solids. In an attempt to extend the application of these techniques, the thermodynamic functions for sorption of water have been calculated for solids where water sorbs in the amorphous regions (i.e. maize and potato starch and Avicel PH-101 and CL-611). Microcalorimetric methods were also used to study the kinetics of the sorption process. As was expected the potato starch sorbed more water than the other two starches, and the Avicel grades sorbed water in proportion to their sodium carboxymethylcellulose content. The numerical values for the thermodynamic functions were lower than those obtained previously from similar studies on crystalline pharmaceutical powders. For starches and celluloses, it is proposed that water binds to anhydroglucose units within the amorphous regions of the solid. It has been suggested that over the sorption process water initially binds as one molecule between two anhydroglucose units, but that these bonds are then broken to form a 1 : 1 stoichiometry. This process of forming and breaking bonds could explain the low values for the net change in thermodynamic functions. The kinetic interpretation demonstrated that the sorption process was split into three discrete regions. The results from vapour sorption microcalorimetry, in combination with a vacuum microbalance, are valuable in probing interactions between water and crystalline or semi-amorphous solids.

Introduction

The interaction between water and pharmaceutical excipients is of vital importance for a number of reasons, including product stability (chemical, physical and microbiological) and the control of drug release.

An extensive literature exists on the interaction between starches and water, and between microcrystalline celluloses (MCC) and water. The aims of this work were to study interactions between three types of starch, three types of MCC and water in order to test the proposed mechanism, and to investigate the value of applying vacuum microbalance and microcalorimetric vapour sorption techniques to this area of study.

Correspondence: G. Buckton, Department of Pharmaceutics, The School of Pharmacy, University of London, 29–39 Brunswick Square, London WC1N 1AX, U.K.

In our previously published work on the use of the vacuum microbalance and the microcalorimeter (Buckton and Beezer, 1988; Buckton et al., 1988) we have investigated the total interaction between water vapour and a crystalline solid surface; that is to say that the reported values have been equilibrium data, based on a standard state where water vapour has reached its maximum level of sorption at the temperature of the experiment. In our published work to date (e.g. Buckton and Beezer, 1988; Buckton et al., 1988) there has been very little consideration of the kinetics of the process(es) that were investigated. Kinetic information indicates how the sorption process proceeds towards equilibrium i.e. mechanism of interaction.

The interaction between MCC and water has been examined by many techniques including sorption isotherms (Morrison and Dzieciuch, 1959; Nakai et al., 1977; Hollenbeck et al., 1978; Zografi et al., 1984; Khan and Pilpel, 1986, 1987), differential scanning calorimetry (Khan and Pilpel, 1986), microcalorimetry (Hollenbeck et al., 1978; Sadeghnejad et al., 1985; Fielden et al., 1988), dielectric spectroscopy (Khan and Pilpel, 1987) and differential thermal analysis and thermogravimetric analysis (Fielden et al., 1988).

The evidence presented to date leads to the conclusion that water binds to celluloses by a three stage process, involving: (1) the water binding tightly to anhydroglucose units and indeed linking adjacent units, i.e. two hydrogen bonds per water molecule; (2) the breaking of some of the initial bonds between water and cellulose and the addition of extra water molecules to bind at the now vacant anhydroglucose sites, i.e. one hydrogen bond per water molecule, but the involvement of more water molecules; (3) the onset of hydrogen bonding between water molecules, i.e. a more loosely bound region of sorbed water (this mechanism is represented diagrammatically by Khan and Pilpel (1987)).

The same basic mechanism has also been proposed for the binding of water to starch (Van den Berg, 1981).

Although similar experiments to those which are presented here have been reported, we are not aware of any work in which the interaction between water and cellulosic materials, has been considered by a combination of gravimetric and calorimetric studies of water vapour sorption, at one defined standard state. Other studies involve a combination of results from different processes (e.g. Hollenbeck et al. (1978)), where sorption isotherms (constructed from equilibration over saturated salt solutions) are used in combination with enthalpies of immersion (into liquid water); although the quality of such work is not in question, we believe that there is also value in considering only the solid vapour interaction (see Buckton and Beezer, 1988).

Materials and Methods

Experiments were undertaken on three starches, maize starch BP (special, Roquette (U.K.) Ltd, wheat starch and potato starch (BDH)) and three microcrystalline celluloses, Avicel PH-101, RC-581 and CL-611 (FMC Corp., through Honeywill and Stein Ltd). Avicel PH-101 is microcrystalline cellulose, RC-581 and CL-611 are MCC containing about 11% and 15% sodium carboxymethylcellulose, respectively.

Sorption isotherms

Samples were placed in 10-ml beakers with a depth of coverage of 5 mm and dried to constant weight in a vacuum oven at 80 °C and 10 mmHg. Samples were then transferred to desiccators each at a particular humidity (controlled by saturated salt solutions or solutions of sulphuric acid of differing concentrations) and stored at 25 °C for 8 days. The increase in the weights of the samples was then measured by quickly removing the beakers and weighing them on a digital balance. The equilibrium moisture content was also assessed by measuring the water activity, i.e. the relative humidity formed in the vapour space above the powders, when placed in the sealed cell of a humidity meter (Rotronic Hygroskop) at 25 °C.

Sorption thermodynamics

The thermodynamic functions of water sorption onto two of each of the starch and MCC powders were also assessed (maize and potato starch and Avicels PH-101 and CL-611). The vacuum microbalance and microcalorimetric techniques and methods were exactly as reported before (Buckton and Beezer, 1988) whereby about 10 mg of the sample was spread uniformly in a thin layer, on a high vacuum microbalance and dried to constant weight. Water vapour which was controlled to a constant temperature (298 K) was admitted and allowed to sorb to the surface until equilibrium is reached *.

The vacuum microbalance experiment was then repeated in the cell of a sorption microcalorimeter. By combining the data obtained from using the two techniques it is possible to calculate the thermodynamic functions of sorption relative to a defined standard state (Buckton and Beezer, 1988). In this work, as in our previous publications, the standard state was arbitrarily assigned as the number of moles of water sorbed per gram of powder at the saturated vapour pressure of water at 298 K.

Results

The sorption isotherms of water vapour onto the three starches, and the three celluloses are presented in Figs 1 and 2, respectively. All isotherms are of type II.

The thermodynamic functions of sorption are presented in Table 1. The magnitude of the values obtained for the enthalpy and entropy change are lower than those associated with adsorption onto a crystalline powder (e.g. as reported by Buckton and Beezer (1988)).

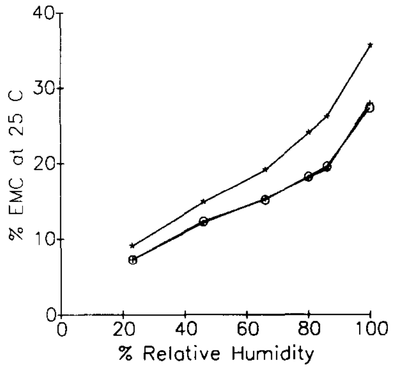

Fig. 1. Sorption isotherm for water onto maize (○), wheat (+) and potato starch (★) at 25.0 °C. Presented as equilibrium moisture content of the powder (EMC) as a function of the relative humidity of the vapour to which it was exposed.

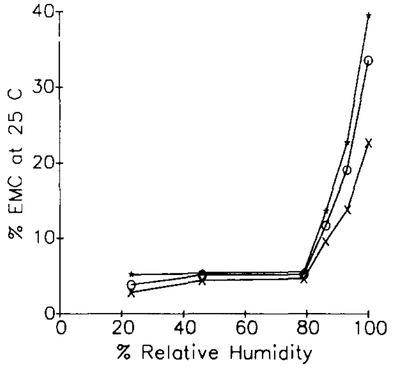

Fig. 2. Sorption isotherm for water onto Avicel PH-101 (×), RC-581 (○) and CL-611 (★). Presented as for Fig. 1.

The response from the microcalorimeter, as observed on a chart recorder, is a plot of the rate of change of heat (power) as a function of time (a pt curve). A typical response for an adsorption process has been presented before (Buckton and Beezer, 1988) and consists of a rapid rise followed by an exponential decline. From the shape of the curve it is possible to determine a rate constant, by calculating the excess power at various times

TABLE 1

Thermodynamic functions for the sorption of water onto the powdered samples

Sample	ΔG (kJ/mol)	$\Delta_{\text{ads}}H$ (J/mol)	$\Delta_{\text{ads}}S$ (J/mol per K)
Maize starch	13.23	−865	−47.3
Wheat starch	13.18	–	–
Potato starch	12.58	−501	−43.9
Avicel PH-101	13.69	−681	−48.2
Avicel RC-581	12.73	–	–
Avicel CL-611	12.33	−352	−42.6

---

* The sorption isotherm described above may be reproduced with greater accuracy if a vacuum microbalance system is designed to allow changes in relative humidity without the need to remove the sample from the controlled humidity before measurement. Such a system is under construction in our laboratories.

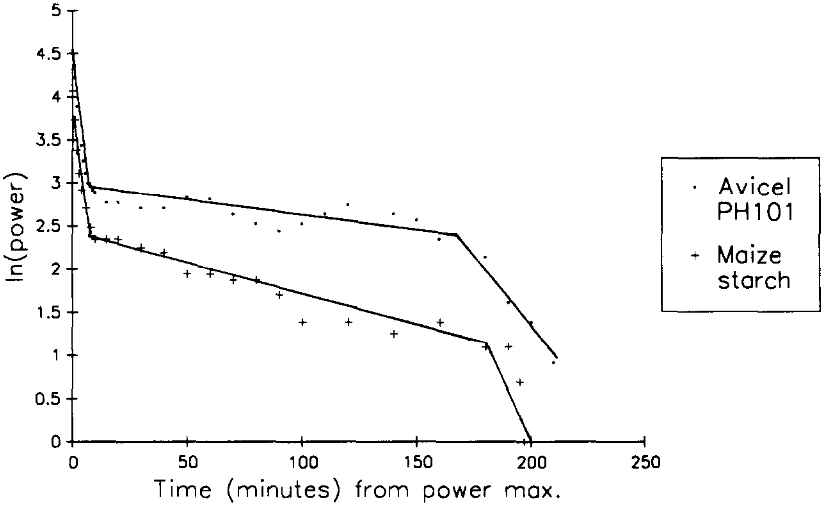

Fig. 3. Ln displacement (power) as a function of time, showing three sequential apparent first-order processes. Stage 1 from 0 to 10 min, stage 2 from 10 to about 160 min and stage 3 from about 160 min until the end.

compared to the output of a calibration heater (instrumental response). The approaches to the calculation of rate constants from calorimetric traces have been dealt with theoretically by Beezer and Tyrrell (1972) and Hunt et al. (1972). The shape of the pt curve obtained in this work is not typical of an adsorption process, since the deflection from baseline persists for a considerable period. The application of theories for the calculation of rate constants in the current experiment is not straightforward; we remain uncertain as to whether the experiment is correctly described as a batch or flow experiment (see Buckton and Beezer (1988) for discussion of this point).

In the paper by Buckton and Beezer (1988), a non-ideal but simple method was used to describe an apparent rate constant. This involved comparing the difference in the displacement from baseline for the test sample and a blank sample (empty cell) at various time intervals. A plot of ln(displacement difference) as a function of time yielded an apparent first-order rate constant. The modified approach (Buckton and Beezer, 1988) was required because of the existence of only a small difference between the test and blank samples making the accepted approach (see Beezer and Tyrrell (1972) and Hunt et al. (1972)) unworkable. In this work, the atypical shape of the responses, together with their extended duration makes measurements of differences in area difficult. Consequently, Fig. 3 is a plot of ln(difference in displacement between blank and test) – shortened to 'displacement' – as a function of time, as used before. The results for only one sample of each type of material are plotted, these are representative of the other samples.

Discussion

The sorption isotherms tend towards a type II physical sorption model (Figs 1 and 2). For the starch samples, at any given RH, potato starch sorbs a greater quantity of water than either wheat or maize starch, which have essentially identical isotherms. It has been established that tuber starches, such as potato starch, have more free cellulose hydroxyl groups available to bond with water than do cereal starches (Sair and Fetzer, 1944), this may account for the differences in sorption.

The Avicel samples all sorb very little water at low humidities, over which region there is little difference between the powders. At humidities greater than 80% RH, the sorption is increased significantly, and much enhanced for the samples containing sodium carboxymethylcellulose. Sodium carboxymethylcellulose is composed of amorphous cellulose, the crystalline portion being eliminated during the manufacturing process: this gives a greater capacity for water sorption and explains the increased levels of uptake. The quantity of water sorbed to the MCC samples at normal ambient humidities is reported to be approx. 5% (FMC information sheet), this is in keeping with the results reported here.

The values for the thermodynamic functions of sorption (Table 1) would suggest that the values of ΔG are essentially identical. However, the level of accuracy and reproducibility was extremely high, such that even though there was no significant difference between the maize and wheat starches, the difference between these two starches and potato starch was significant. Statistical analysis of the MCC results revealed that a significant difference existed between PH-101 and the other two MCC samples, but not between RC-581 and CL-611.

It can be observed that the maize and wheat starches (which sorb identical quantities of water; Fig. 1), have higher values for ΔG than potato starch, which sorbs the largest amount of water. For the MCC samples, the values of ΔG rank inversely to the relative affinity for water (Fig. 2). It is reassuring that all the sorption results fit in with expected rankings, but surprising that this does not have a more profound effect on the ultimate value of ΔG.

For the adsorption of water onto crystalline drug samples it has been our experience that the enthalpy term will be in the order of magnitude of -5 to -30 kJ/mol (Buckton and Beezer, 1988; Buckton et al., 1988); the values obtained for the enthalpy of sorption reported here (Table 1) are significantly lower than this range. These $\Delta_{\mathrm{ads}}H$ values (approx. 600 J mol^{-1}) are overall changes, that is they reflect the sum of all enthalpy changes that occur throughout the entire sorption process. If the model of water sorption that has been suggested for starches and celluloses (see Introduction) is correct, then a three-stage process is to be expected (i.e. one water molecule binding between two anhydroglucose units, followed by one water molecule binding to each anhydroglucose unit and finally the sorption of loosely bound water). As will be discussed below, the results presented in this work provide further evidence to support a three-stage process (see Fig. 3). It is, therefore, to be expected that the total enthalpy change will be a sum composite value that includes the enthalpy change associated with the formation and breaking of many hydrogen bonds (the enthalpy of formation of each individual bond being in the order of -5 to -30 kJ/mol) and as such it is not surprising that the values of $\Delta_{\mathrm{ads}}H$ are lower than for the less complex adsorption of water onto a crystalline solid. In keeping with the model that has been proposed in previous studies (e.g Buckton and Beezer, 1988), the most hydrophilic samples (potato starch and Avicel CL-611) have a smaller negative value for $\Delta_{\mathrm{ads}}H$ than the less well wetted samples. This apparent inconsistency has been explained in terms of a dominant entropic factor (Buckton and Beezer, 1988).

The values for the entropy change due to the water sorption also are composite values for the three defined stages. The magnitude of the entropy change cannot be used to describe the degree of ordering at any one stage of the process, but only the sum of the three stages. Experiments to provide the necessary information on each separate stage are described below.

Fig. 3 demonstrates that the kinetics do not approximate to first order, as would be expected for any simple sorption process. The kinetic profile clearly fits into three distinct regions; there is an initial rapid sorption process, followed by a very slow stage and then a final more rapid region moving towards equilibrium. If these results are fitted to the model that was outlined in the Introduction, the initial response coincides with the binding of one molecule of water between two anhydroglucose moieties (about 10% water content), the protracted slow process equates to the breaking of water/anhydroglucose bonds and the formation of a one water molecule to one anhydroglucose binding site stoichiometry (which occurs at about 19% water content), with the final rapid process being the sorption of loosely bound water. It is obvious that the sorption process will not follow this mechanism exactly, because these three stages will not be entirely discrete, there will be some overlap between the three processes. The kinetic data do, however, support the argument that water sorption to such systems is a three-stage process.

The obvious extension to the work, which may provide further evidence for the proposed mechanism, is to redesign the calorimeter cell to achieve the sorption conditions which allow the sample to be titrated with small quantities of water vapour. It would then be possible to obtain the thermodynamic functions for adsorption after 10% water sorption, and then to allow a rise to 19% water content (2 : 1 and 1 : 1 stoichiometries of anhydroglucose units to water, respectively), before bringing the surface to final equilibrium. Such a titration of the surface would allow enthalpies for the proposed individual binding mechanisms to be calculated, and for the kinetics to be examined in more detail and thus more clearly defined. It would be expected that for the first stage of the sorption process in which water binds to the anhydroglucose with a 2 : 1 stoichiometry, for example, that an enthalpy change would be observed that reflected the formation of many bonds with an enthalpy of formation of -5 to -30 kJ/mol, similarly a large change in entropy may be expected at this stage. As the quantity of water exposed to the sample increased the corresponding thermodynamic changes could be calculated. The final sum of the changes obtained by such a titration should be equal to the values reported in Table 1 of this work (analogous to Hess's Law).

Conclusions

The studies on the starch and MCC powders demonstrate two points:

Firstly, the results are consistent with the proposed mechanism for the complex series of events that occur when the powders are exposed to water.

Secondly, the experiments demonstrate that the combination of the vacuum microbalance and the microcalorimeter has a potential for application to the studies of sorption to a wide variety of sample types. These studies yield information which provides detail not only on equilibrium thermodynamics, reflecting the total changes that occur, but also on the mechanism by which the process occurred (via kinetic interpretations). The values for the enthalpy change reported here are consistent with the formation and breaking of many hydrogen bonds.

Acknowledgements

The SERC are acknowledged for provision of a studentship to T.C.B. We would like to thank Glaxo Group Research for their support of this work.

References

Beezer, A.E. and Tyrrell, H.J.V., Applications of flow microcalorimetry to biological problems. I. Theoretical aspects. *Sci. Tools*, 19 (1972) 13–16.

Buckton, G. and Beezer, A.E., A microcalorimetric study of powder surface energetics. *Int. J. Pharm.*, 41 (1988) 139–145.

Buckton, G., Choularton, A., Beezer, A.E. and Chatham, S.M., The effect of comminution technique on the surface energy of a powder. *Int. J. Pharm.*, 47 (1988) 121–128.

Fielden, K.E., Newton, J.M., O'Brien, P. and Rowe, R.C., Thermal studies on the interaction between water and microcrystalline cellulose. *J. Pharm. Pharmacol.*, 40 (1988) 674–678.

Hollenbeck, R.G., Peck, G.E., and Kildsig, D.O., Application of immersional calorimetry to the investigation of solid liquid interactions: microcrystalline cellulose-water system. *J. Pharm. Sci.*, 67 (1978) 1599–1606.

Hunt, J.B., Ross, P.D. and Ginsberg, A., A calorimetric study of the interaction of Mn^{2+} with glutamine synthetase from *Escherichia coli. Biochemistry*, 11 (1972) 3716–3722.

Khan, F. and Pilpel, N., The effect of particle size and moisture on the tensile strength of microcrystalline cellulose powder. *Powder Technol.*, 48 (1986) 145–150.

Khan, F. and Pilpel, N., An investigation of moisture sorption in microcrystalline cellulose using sorption isotherm data and dielectric response. *Powder Technol.*, 50 (1987) 237–241.

Morrison, J.L. and Dzieciuch, M.A., The thermodynamic properties of the system cellulose-water vapour. *Can. J. Chem.*, 37 (1959) 1379–1390.

Nakai, Y., Fukuoka, E., Nakajima, S. and Yamamoto, K., Crystallinity and physical properties of microcrystalline cellulose. *Chem Bull Pharm.*, 25 (1977) 96–101.

Sadeghnejad, G., York, P. and Stanley-Wood, N.G., Microcalorimetric studies of sorption in microcrystalline and microfine cellulose powders. *J. Pharm. Pharmacol.*, 37 (1985) 110P.

Sair, L. and Fetzer, W.R., Water sorption by starches. *In* *Eng. Chem.*, 36 (1944) 205–208.

Van den Berg, C., Vapour sorption equilibria and other wate starch interactions; a physicochemical approach. Ph.D. the sis, 1981, Agricultural University, Wageningen, The Nethe lands, pp. 26–31, 33, 55–57, 65, 85–91, 94–99. Cited in Zografi et al., 1984.

Zografi, G., Kontny, M.J., Yang, A.Y.S. and Brenner, G.S., Surface area and water sorption of microcrystalline cellulose. *Int. J. Pharm.*, 18 (1984) 99–106.