Pharmaceutical Research, Vol. 3, No. 4, 1986

Review

The Interactions of Water with Cellulose- and Starch-Derived Pharmaceutical Excipients

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Water associated with polymeric pharmaceutical excipients derived from cellulose and starch can have a profound effect on the properties of the excipient and on the other ingredients making up a solid dosage form. Important questions which need to be addressed include How much water will be sorbed or desorbed at various relative humidities and temperatures? and What is the thermodynamic state of water associated with the solid as a function of moisture content? A critical review of the literature is presented to demonstrate the most likely answers to these questions. It appears that water exists in at least three thermodynamic states in starch, cellulose, and their derivatives: (1) water directly and tightly bound, with a stoichiometry of one water molecule per anhydroglucose unit; (2) water in a relatively unrestricted form, approaching the properties of bulk or pure liquid water; and (3) water in an intermediate state or states, with properties reflecting a much higher level of structure than bulk water but less than that of tightly bound water. Some implications of such behavior for pharmaceutical systems are discussed.

KEY WORDS: water vapor sorption; starch–water interactions; cellulose–water interactions; polymer–water interactions; water–polymer interactions; water–excipient interactions; excipient–water interactions.

INTRODUCTION

It is well known that water associated with solids used pharmaceutically can greatly influence important physical chemical properties such as chemical stability, powder flow, compaction, and dissolution rate. Although precautions can be taken to eliminate moisture, to reduce contact with the atmosphere, or to control the relative humidity of the atmosphere, such precautions generally add expense to the process of producing drug products, with no guarantee that during the life of a product further problems with moisture can be avoided.

Materials derived from various starches and celluloses are widely used as excipients, usually in a high proportion relative to the total amount of solid making up the dosage form. Since these materials are known to take up and retain significant amounts of moisture, and since they often are present in large amounts, it would appear important to know as much as possible about the mechanisms involved before strategies are developed for their handling, storage, and use. How much water will be sorbed or desorbed at various relative humidities and temperatures? What is the thermodynamic state of water associated with the solid at various levels of moisture content? How does the presence of water in excipients affect their properties and those of other solids in the dosage form?

Any review of the literature dealing with water–solid interaction reveals clearly that there is widespread interest in the subject, covering a number of technologies. Extensive literature, for example, exists for water vapor sorption and wood (1), paper (2), foodstuffs (3), textiles (4), clays (5), proteins (6), synthetic hydrogels (7), and water-soluble salts (8). In the review which follows we have focused our attention on the specific case of cellulose and starch since their use in pharmaceutical dosage forms is so widespread. However, wherever necessary we have made reference to and used information from other areas to support our arguments and to show additional applicability.

GENERAL PROPERTIES OF CELLULOSE AND STARCH

The biological, physical, and chemical characteristics of cellulose and starch derived from natural sources have been extensively reviewed (9). For the purposes of this discussion, therefore, only a few generalizations designed to help us understand the nature of water interactions with these materials are reviewed.

Starch. Starch is found in just about all green plants in the form of a carbohydrate reserve. It is a mixture of polymers consisting of α-D-glucose as the monomeric unit. Two types of starch polymers exist: a mixture of linear polymers, referred to as amylose; and a mixture of branched polymers called amylopectin. These polysaccharides exist in

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the plant as granules that are insoluble in cold water; the size and shape of starch granules vary with plant sources. Corn starch, which is widely used as a pharmaceutical excipient, has nearly spherical granules with an average particle diameter of about 15 μm. The specific surface area, as determined by BET analysis using krypton gas (10), is 0.43 m^2/g. This is in reasonable agreement with the surface area calculated from the particle size, assuming monodisperse spheres.

The crystalline properties of starches have been extensively studied, with the interesting observation that very dry starches exhibit little crystallinity, while the introduction of water to a level of 4–5% initiates the appearance of crystallinity (11). This is thought to be due to the hydration of amylose, which fills in distorted crystal lattices. The major intermolecular forces giving rise to the structure and integrity of the starch system are hydrogen bonds between the hydroxyl groups of different anhydroglucose units and those between these units and water.

Cellulose. Cellulose is a linear, unbranched polymer consisting of anhydroglucose units connected together by 1,4-β-glucosidic linkages. It is the major component of the cell wall of higher plants and is most commonly found in high proportion in seed hairs, bast fibers, leaf fibers, stalks, straws, and wood. The proportion of cellulose varies with different plant tissues; the cotton hair is approximately 98% cellulose, whereas wood contains about 40–50% cellulose on a dry-weight basis. The crystal structure of celluloses has been extensively studied (12). For our purposes the important point to consider is that cellulose consists of long polymeric chains made up of crystalline and amorphous regions. X-ray diffraction studies have revealed that the crystalline regions have lengths of about 600 Å and widths in the range of 50–150 Å (13). With a degree of polymerization as high as 1000–5000 monomer units, it is clear that the individual linear chains are longer than the individual crystalline regions. The percentage of crystallinity for various wood and cotton celluloses is of the order of 70%. In contrast to starch, where water vapor is taken up uniformly throughout the solid, for cellulose water is not taken up in the crystalline regions (9,13).

Microcrystalline cellulose (MCC), which finds widespread use as a pharmaceutical excipient, is a form of cellulose derived from wood pulp. It is essentially cellulose which has been processed to produce particles with a specific surface area in the range of 1–2 m^2/g (10). The degree of crystallinity has been reported to be 63% (14).

SORPTION ISOTHERMS

The equilibrium water sorption isotherms for various celluloses and starches have been reported in numerous studies over the years (10). Such sorption isotherms are generally expressed as the mass of water taken up per unit mass of dry solid versus water vapor pressure, P, relative pressure, P/P_o, or relative humidity, $100(P/P_o)$, where P_o is the vapor pressure of pure liquid water. A typical sorption isotherm for microcrystalline cellulose characterized by the classical sigmoidal shape seen with physical adsorption of gases is shown in Fig. 1. If one measures sorption with increasing pressure up to relative pressures close to unity and then sequentially reduces the pressure, one can estimate both the amount of water taken up and the amount remaining with the solid and, hence, the amount desorbed as the pressure is lowered. Sorption–desorption equilibria with starches and celluloses always give rise to hysteresis, i.e., the amount of water associated with the solid is greater for the desorption isotherm than for the sorption isotherm for a given relative pressure. It is generally accepted that this behavior is due to a change in polymer chain conformation caused by the entry of water into the polymeric structure (15–17).

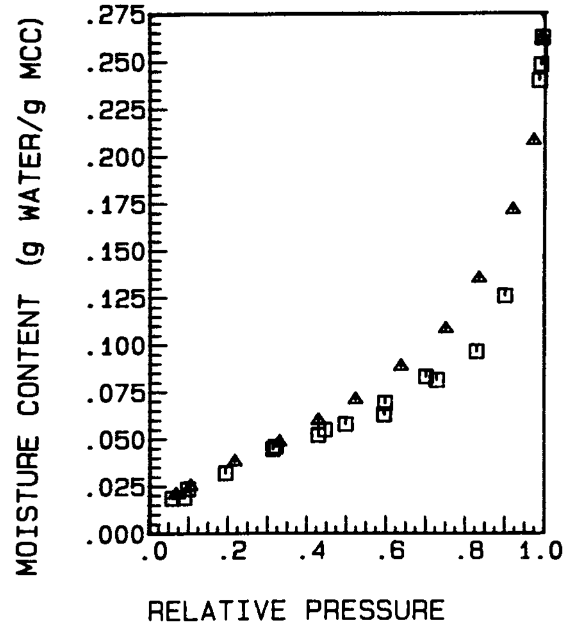

Fig. 1. Water vapor sorption (□) and desorption (△) isotherms for microcrystalline cellulose at 25°C. Taken from Ref. 37.

As generally might be expected for an exothermic process such as vapor sorption, increasing temperature decreases water vapor sorption on celluloses and starches at the same pressure, P. However, since sorption as a function of relative pressure does not vary considerably for corn starch and MCC over the range of 20–50°C (see Fig. 2 for an example), from a practical perspective only one sorption isotherm is necessary to describe the water–solid interaction in this temperature range as a function of the relative pressure. Since many pharmaceutical solid dosage forms are stored at temperatures ranging up to 50°C during stability assessment, such information may be of considerable practical utility.

The sigmoidal shape of the isotherms shown in Figs. 1 and 2 suggests also that classical equations, describing physical adsorption of gases, may be used to describe water vapor sorption. The starting point for most analyses is the BET equation:

$$W = \frac{C_B W_M (P/P_o)}{[1 - (P/P_o)][1 - (P/P_o) + C_B(P/P_o)]} \tag{1}$$

where W is the weight of water sorbed per unit weight of dry solid at a relative pressure of P/P_o, W_M is the weight sorbed corresponding to one water molecule per sorption site on the solid, and C_B is a constant related to H_1, the heat of sorption

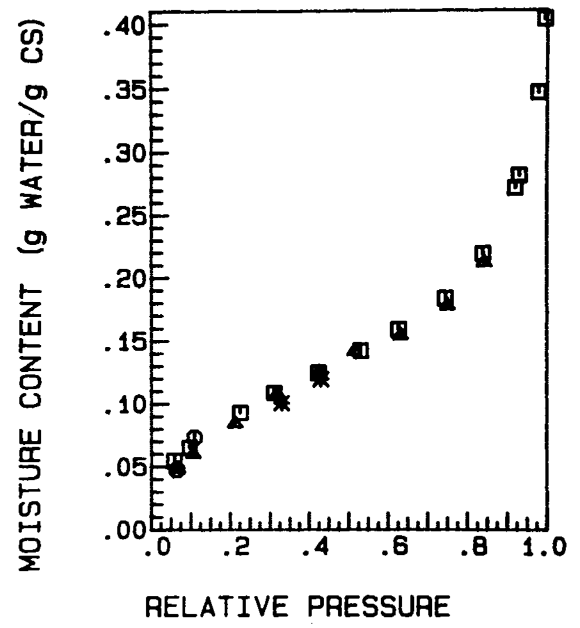

Fig. 2. Water vapor sorption isotherms for corn starch at 20°C (□), 30°C (△), 40°C (∗), and 50°C (○). Taken from Ref. 37.

to the site, and H_L, the heat of liquefaction (condensation) of water, such that

$$C_B = \kappa \exp [(H_1 - H_L)/RT] \qquad (2)$$

where κ is a constant related to the entropy of sorption. This equation was developed on the basis that sorption occurs in two distinct thermodynamic states, a tightly bound portion and multilayers having the properties of bulk free water. Indeed, as seen generally with physical adsorption of gases, water vapor sorption on celluloses and starches does fit the BET equation, but only in the range of relative pressures up to about 0.3 to 0.4.

Assuming that free water exists at the higher relative pressures, it has been shown that at $P/P_o > 0.8$ it is possible to fit the isotherm of cellulose–water (18) and wheat starch–water (19) to a form of the Flory–Huggins equation which describes the properties of polymer solutions (20). Here

$$\ln (P/P_o) = \ln V_1 + V_2 + \mu V^2 \qquad (3)$$

where V_1 is the volume fraction of water, V_2 is the volume fraction of polymer, and μ is a constant related to the Flory–Huggins interaction parameter, χ. The assumption here is that free water mixes with the polymer to form a solution at the higher relative pressures. Thus, for such systems at higher relative pressures we are not dealing with the classical BET model of adsorption where vapor builds up as a multilayer on the external surface of the solid.

There have been numerous attempts to develop equations which would describe the sorption of water vapor over the entire range of relative pressures. Indeed, it was recently reported (21) that over 75 isotherm equations have been developed. Mathematically, it is a simple matter to fit experimental data to a sigmoid curve, if enough parameters are introduced into the equation. What has proven more difficult is the development of relationships which have physical meaning in the description of molecular events.

The state of uncertainty in this area is best typified by briefly examining two equations, developed from two different models, which both fit water sorption data over the entire range of relative pressures. The first is an extension of the BET equation, independently developed by Guggenheim, deBoer, and Anderson, and termed the GAB equation (22). The GAB model introduces a third state of sorbed species intermediate to the tightly bound and free states. The GAB equation is shown in Eq. (4):

$$W = \frac{W_M C_G K(P/P_o)}{[1 - K(P/P_o)][1 - K(P/P_o) + C_G K(P/P_o)]} \qquad (4)$$

where P, P_o, W, and W_M are identical to the parameters found in the BET equation and

$$C_G = \kappa' \exp [(H_1 - H_M)/RT] \qquad (5)$$

and

$$K = \kappa'' \exp [(H_L - H_M)/RT] \qquad (6)$$

where H_M is the heat of sorption for vapor in the intermediate state and H_1 and H_L are as defined previously. The second equation, developed by Hailwood and Horrobin (15) for water sorption on polymers, specifically proposes that water vapor sorption on polymers is governed by the formation of hydrates with the monomeric units of the polymer and by the formation of solid solutions of water in the polymer. Thus, in effect, it combines the simple BET model with the Flory–Huggins concept of a polymer solution. Its simplest form, which assumes only one water of hydration per monomer unit, has been shown to fit water vapor sorption over the entire range of relative pressures:

$$W = \frac{M_p}{M_w} = \frac{Kk(P/P_o)}{1 + Kk(P/P_o)} + \frac{k(P/P_o)}{1 - k(P/P_o)} \qquad (7)$$

where k is the equilibrium constant for the activity of water in the vapor state and that dissolved nonspecifically in the polymer, and K is the equilibrium constant for the specific binding of the hydrate. M_p and M_w are the molecular weights of the polymer and water, respectively. The ratio of these latter two values is directly related to W_M in the BET and GAB equations. In fact it can be shown that Eqs. (4) and (7) are mathematically identical and that the three constants likewise are closely related (22), even though somewhat different starting points were used to develop the models underlying the equations. Figure 3 shows how well sorption isotherm data can be fitted by introducing a third parameter. The difficulty to date, however, with these equations is that independent confirmation of the physical meaning of all the constants has not yet been possible. It has been possible, however, to gain considerable insight into the nature of the primary binding of water vapor in celluloses and starches from the parameter, W_M, in Eqs. (1) and (4). For example, Table I, which gives W_M values for three types of starches, shows that despite significant morphological differences between the various starches, the values of W_M are quite constant. One value of W_M, taken from a fit of desorption data, appears to be slightly higher than that obtained from sorption data. This might be expected if the availability of primary sites had been increased by previous exposure to the

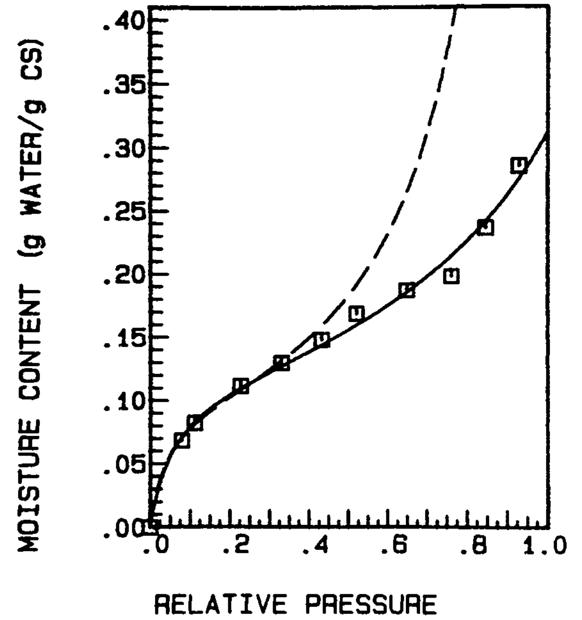

Fig. 3. Fit of BET (- -) and GAB (——) equations to water vapor sorption for corn starch at 20°C. Taken from Ref. 37.

elevated relative humidities with subsequent increased levels of water sorption. As shown by Van den Berg (22), these values of W_M are all close to the value of 0.11 g of water per g of starch, calculated by assuming that one water molecule sorbs per anhydroglucose unit. Since this calculation assumes that all anhydroglucose units are available for primary binding and since this is not likely to be precisely the case, it is not surprising that the value measured from W_M is slightly less.

Zografi *et al.* (10) have extended this analysis to the sorption of water vapor by various celluloses. In this case, a correction was made to account for the fact that only the amorphous regions of cellulose can take up water vapor. Table II lists the degree of crystallinity and the value of W_M, calculated after accounting for the degree of crystallinity. As expected, celluloses with different degrees of crystallinity exhibit different values of W_M and all are considerably less than that seen with the starches. However, when correcting for the degree of crystallinity, all of the values are in reasonable agreement with each other and with W_M obtained for the starches. This conclusion is fortified by the series of results in Table II obtained with microcrystalline cellulose samples having different degrees of crystallinity due to grinding (14). Similar analyses, carried out using literature values for water vapor sorption on other cellulose and starch derivatives used as excipients, give the values of W_M listed in Table III. Indeed, considering the error associated with taking numbers from a published plot, the values of W_M are all quite consistent with each other and with a stoichiometry of one water molecule per anhydroglucose unit. It is interesting to note also that the two samples derived from cellulose, sodium carboxymethylcellulose and sodium croscarmellose, did not require any correction for degree of crystallinity to conform to close to a 1:1 stoichiometry. It appears quite likely, therefore, that the processing of these materials essentially eliminates the crystallinity of cellulose. Another very interesting pharmaceutical example which illustrates the validity and value of this analysis is the excipient compressible sugar. Compressible sugar is a cocrystallized product containing about 97% sucrose and 3% maltodextrins by weight (23). Tabibi and Hollenbeck (24) have measured its water sorption isotherm and have reported a value of W_M equal to about 0.0028 g/g. If one assumes that essentially all of the water interacts with the maltodextrin by the same mechanism suggested for starch and that W_M for maltodextrin is about 0.09 g/g, as shown in Table I for the starches, we can estimate that in a gram of compressible sugar (0.03 g maltodextrins) the amount of water taken up at W_M should be about 0.0027 g/g. This is remarkably close to the value of 0.0028 g/g observed for W_M by Tabibi and Hollenbeck (24) and suggests that, indeed, almost all of the water in compressible sugar is associated with the maltodextrin.

Table I. Amount of Water Vapor Sorbed by Various Starches at the Apparent BET Monolayer Level

Starch	W_M (g/g)	Ref. No.
Corn[a]	0.095[a]	37
Corn	0.083	29
Potato	0.085	22
Wheat	0.080	22

[a] This value is taken from the desorption isotherm. Others are from sorption isotherms.

Table II. Amount of Water Vapor Sorbed by Various Celluloses at the Apparent BET Monolayer Level Corrected for Degree of Crystallinity

Cellulose	% cryst.	W_M corr. (g/g)	Ref. No.
Cotton	70	0.093	13
Cellophane	40	0.098	13
MCC	63	0.095	14
MCC[a]	49	0.076	14
MCC[a]	38	0.107	14
MCC[a]	0	0.086	14

* MCC Ground in a Ball Mill

THERMODYNAMIC STATES OF WATER

The analysis of sorption isotherms, as just described, suggests the existence of at least two states of water, "bound" and "free," with the likely presence of at least one intermediate state. Over the years literally volumes of

Table III. Amount of Water Vapor Sorbed by Various Pharmaceutical Excipients at the Apparent BET Monolayer Level

Excipient	W_M (g/g)	Ref. No.
Starch 1500	0.074	29
Sodium starch glycolate (Explotab)	0.081	53
Sodium starch glycolate (Primogel)	0.092	53
Cross-linked dextrose (CLD-2)	0.098	54
Croscarmellose, sodium	0.094	54
Sodium carboxymethylcellulose	0.103	55

studies have been reported with all types of carbohydrates, proteins, and synthetic hydrogels to understand their hydration properties and, in particular, to elucidate the thermodynamic nature of so-called bound water. Even more general studies have been concerned with the possible structuring of water at interfaces and the effect of various solutes of biological interest on water structure. Since the issue has been addressed in so many fields, much confusion has arisen concerning nomenclature. Terms such as bound, solid-like, irrotational, associated, nonfreezable, hydrated, ordered, etc., all appear in the literature, often meaning the same thing. Below we attempt to present briefly and critically evidence that would support a general model for water sorption on celluloses and starch, which in turn can be used as a basis for understanding how water might behave in other systems and situations of pharmaceutical interest. No attempt is made to cover this literature extensively. Rather, key examples, illustrating major points are emphasized.

Heat of Sorption. Since the sorption of vapor by solids is generally an exothermic process, it should be possible to gain insight into the extent and nature of various interactions by measuring any heat changes calorimetrically. For example, one can measure the heat change associated with the immersion of a solid into water, having previously exposed the solid to various relative pressures of water vapor, and estimate the differential heat of sorption as a function of amount of water sorbed (25). Two useful pieces of information can be gained: (i) a quantitative estimate of the energy of interaction in excess of that expected between water molecules themselves can be derived; and (ii) since it is a differential heat of sorption, any changes in the heat with changing amount sorbed will indicate whether different thermodynamic states of water exist as a function of moisture content, and hence, relative humidity. Such measurements have been made for various celluloses (4,26–28) and starches (16,22,29), and invariably, as shown with one example in Fig. 4, the same pattern is seen. First, the extent of interaction involving water vapor is in excess of that involving the formation of liquid water out to the equivalent of at least three times W_M. This means that water is in a more structured state than bulk water in this range. The fact that something approaching bulk water does exist at higher relative pressures is seen by the fact that sorption at a relative pressure close to unity amounts to as much as seven times W_M in some cases. The values of the enthalpy change are also consistent with hydrogen bonding involving water molecules.

Second, the heat of sorption always exhibits discrete breaks with amount sorbed which appear to occur at stoichiometries of one and two water molecules per available anhydroglucose unit. In some cases, as shown in Fig. 4, the heat changes in this range appear constant, indicating homogeneity in binding energies. Other studies with starches and celluloses, however, although showing discontinuities at 1:1 and 2:1 stoichiometries, do not always indicate homogeneous binding. All of these studies support the fact that water out to three times W_M, at least, is not equivalent to bulk water and that at least two states of such structured water may exist. Clearly water sorbed up to W_M represents a very structured amount of water, with intermediate energetic states existing over the next two to three equivalent "layers."

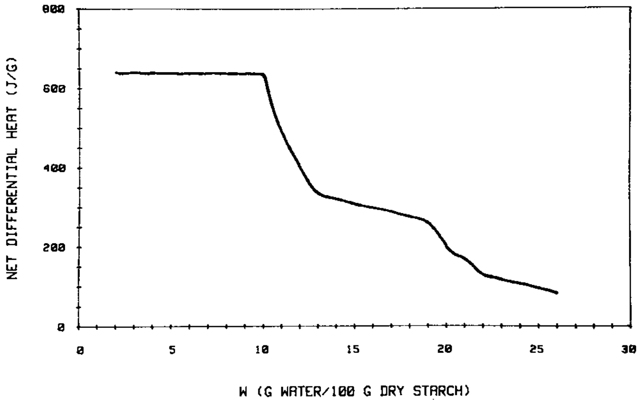

Fig. 4. Net differential heat of sorption for water vapor by native potato starch at 20°C as a function of the amount of water sorbed per mass of dry starch. Taken from Ref. 16.

Thermal Analysis and Nonfreezable Water. When a sample of polymer, such as starch or cellulose, is cooled well below 0°C, bulk or free water should freeze, whereas bound water might be expected to remain in a nonfrozen state. Numerous studies with proteins (see, for example, Ref. 30) down to very low temperatures indicate that unfreezable water exists to the extent of about 0.3–0.4 g/g of dry protein for a wide range of substances. The temperature down to which one can go before freezing occurs should be a reflection of the extent to which the water is in a bound state. When a frozen sample of known water content is heated in a calorimeter, it is possible to ascertain the energy required to melt any frozen water. Thus, by difference one can get a quantitative estimate of the amount of bound water. From any endothermic or exothermic transitions observed during cooling or heating, it is also possible to gain some insight into the number of states of water which might exist. The absence of an endothermic peak at a low water content would be an indication that only very tightly bound water exists.

Studies with various starches seem to consistently indicate unfreezable water at values of about 0.3 g/g, which corresponds to three times W_M (31), the region below which heats of sorption indicate "structured" water. A DTA study by Duckworth with cotton cellulose yielded a level of unfreezable water of 0.131 to 0.147 g/g (32). This amounts to about four to five times W_M. Sisson (33) reported that the rate of drying of microcrystalline cellulose shows distinct transitions at a 3 and 19% moisture content. The value of 3% corresponds closely to W_M, while 19% would amount to about five times W_M. Although such studies clearly provide a basis for differentiating between freezable and nonfreezable water, it is possible that a lack of freezing arises because of metastability in the system, rather than true equilibrium binding energy differences. Franks (34) has suggested that it is quite possible for rapid cooling to cause the formation of metastable supercooled states of water and that some of the residual moisture might resist removal upon drying at higher temperatures because it is trapped in the solid by diffusional barriers and not because it is so tightly bound. This might be the reason bound water as determined by thermal methods often appears at multiples of W_M beyond three times. This is still an unresolved issue, however, which requires additional evaluation experimentally.

Nuclear Magnetic Resonance. One of the most direct methods available for studying the issue of bound and unbound water in solids is pulsed nuclear magnetic resonance (NMR). With water it is possible to use H^1, H^2, and O^{17} as probes; proton and deuteron magnetic resonance have almost exclusively been used to date for a wide range of polymers in the solid state. Pulsed NMR, in general, involves supplying short bursts of radiofrequency (rf) power at a distinct frequency to a sample in a fixed magnetic field and observing the resultant net intensity of the magnetic field upon turning off the rf power while the nuclei are returning to their original equilibrium state with respect to their surroundings. This rate, assumed to be first order, is characterized by T_1, the spin-lattice relaxation time. A second relaxation time, T_2 (spin-spin relaxation time), is attributed to processes that cause nuclei to come to equilibrium with each other. It follows that the estimation of relaxation times allows an assessment of the number of water molecules associated with a certain state of immobility due to interaction with the solid under study. The details of pulsed NMR from a theoretical and experimental perspective are beyond the scope of this review, so more general references (35,36) should be consulted by the interested reader.

Numerous studies of starches and celluloses using pulsed NMR have been reported over the years. In general, relaxation measurements, using proton magnetic resonance, indicate that water in starch and cellulose in excess of 1 g/g moves in a relatively unrestricted manner similarly to, but not exactly the same as, bulk water. Studies of relaxation time for starches exposed to the whole range of relative pressures generally confirm that the unrestricted water appears about three to four times W_M (37–41). For cellulose, values of 0.12–0.15 g/g have been reported (37,42–45).

From studies using proton NMR at various field strengths it has not been possible to isolate clearly the differences between any highly bound water and a more intermediately structured water. This has been particularly troublesome with the celluloses since W_M is of the order of only 0.03 g/g. This problem, however, appears to have been overcome by Tait *et al.* (40,41), who used deuteron, H^2, magnetic resonance to study water–carbohydrate interactions. Deuterons are preferred to protons since DMR spectra are less sensitive to proton or water molecule exchange and are not influenced by any restricted diffusion of water molecules. Samples of a solid containing 77% starch were equilibrated with various amounts of D_2O over the temperature range of −40 to 25°C. Sorption isotherms indicated that W_M was about 0.07 ± 0.01 g/g, in good agreement with W_M for pure starch when allowing that only 77% of the product was starch. From these studies (40,41) it was shown clearly that two types of sorbed water exist in addition to bulk water. The first, termed "solid-like" or "irrotationally bound," was shown at 20°C and higher to exhibit a maximum concentration very close to W_M, with only one water molecule associated per anhydroglucose unit. At lower temperatures the number of solid-like molecules increased, but no additional binding directly to the starch OH groups was observed. X-ray evidence was cited (46) to suggest that the site of hydration was the primary hydroxyl group on the number 6 carbon and that the 2- and 3-OH groups were unavailable because they were bound to other anhydroglucose units. The second type of water, which is more mobile, was believed to arise from water–water interactions with rotational frequencies reduced relative to liquid water by as much as 10^4 to 10^5. This water, termed bound water, did not form until W_M was reached and was not affected by passing below the freezing point of water. Since no bulk water was detected within three times W_M, it was concluded that the bound water was water at least two molecular dimensions from the solid-like water but still under the influence of the solid. Further evidence was presented to suggest a single sorption-site energy for the interaction of solid-like water and starch. All of these results provided excellent confirmation of the earlier interpretations based on sorption isotherms and heats of sorption.

Diffusion Studies. Insight into the effects that the state of water might have in practical situations can be seen by examining studies which directly measure diffusion in hydrated polymer systems. Fish (47) measured diffusion coefficients of water in starch gels at 25° and 1°C. In both cases diffusion was not affected until the sample was dried down to 0.31 g/g sorbed water. With additional reduction in the water content, a gradual decrease in the diffusion coefficient occurred, until at about 0.08 to 0.1 g/g, about W_M, the diffusion coefficient was almost zero. Duckworth (48), using radiolabeled glucose in various starch-containing foodstuffs, showed no net movement of the label at moisture contents below W_M. Thus some diffusion of glucose was possible through the bound water but not through the solid-like water.

GENERAL MODEL FOR WATER SORPTION ON STARCHES AND CELLULOSES

From work presented above and the large body of work done with the hydration of polymers and proteins reported over the years, the most reasonable model for water vapor sorption on celluloses and starches appears to be as follows. At low relative pressures, water is bound directly to available anhydroglucose units throughout the starch grain and in the amorphous regions of cellulose with a stoichiometry of one water molecule per anhydroglucose unit. At intermediate relative pressures, up to about 0.6 or so, polymer–polymer hydrogen bonds are caused to break. This makes an increase in primary binding sites available and allows water to begin to bind to other water molecules already bound to anhydroglucose units. Finally, at higher relative pressures, even more primary binding sites can become available, while water can now also bind to other water molecules, including those not bound to primary sites. In this model, therefore, at least two distinct thermodynamic states of water can exist: (i) water directly bound to one hydroxyl group per anhydroglucose unit and (ii) water bound to other water molecules as in something like bulk water. There is clear evidence also for an intermediate state or states involving water not bound to the primary site but still influenced by the chemical structure of the anhydroglucose unit. This intermediate water appears to exist out to about three times the value of W_M for starches and celluloses. It is possible, also, that some water molecules associated with starches and celluloses are in a metastable state relative to pure water or are simply trapped in the polymer matrix, thus only appearing to be in more structured or bound equilibrium states.

PHARMACEUTICAL SIGNIFICANCE

From the general picture presented in this brief review there are a number of conclusions or comments concerning water in starches and celluloses that can be made which bear directly on their use in pharmaceutical systems. First, it appears that the basic mechanisms of water sorbing to starch and cellulose, and probably all related polysaccharides, are the same. The lack of availability of the crystalline regions of unmodified celluloses, however, must be recognized. Although its exact physical chemical significance is not yet clear, an extension of the BET equation, the so-called GAB equation, can be used to describe the entire isotherm, giving the important parameter, W_M, and some measure of sorption energies.

Since we generally plot sorption isotherms in terms of relative pressure, and since relative pressures are essentially equivalent to the thermodynamic activity of water, it is possible to use one isotherm determined at one temperature to estimate the isotherm at any other temperature. It has been shown that both corn starch and microcrystalline cellulose in the range of 20 to 50°C exhibit this property. Hence, for example, sorption isotherms at room termperature can be used to analyze solid-state stability results carried out up to 50°C when starch and MCC are used as major excipients.

It is well established that water associated with such excipients can cause major changes in chemical stability of admixed drugs (49). Two possibilities exist for the manner in which water may be transferred from excipient to drug, either via the vapor state or by capillarity in the liquid state. Knowledge of the complete sorption isotherm for all ingredients will allow one to know the extent to which water can equilibrate among the various components via the vapor state. Theoretically, whether the solids are mixed or not should not influence water vapor transfer. On the other hand, if the degree of mixing and extent of contact do appear important, we may be dealing with movement of water molecules via the liquid state.

Since the specific surface area of starch and cellulose determined by N_2 or Kr gas adsorption is only a small fraction of the available binding sites, as reflected in W_M, we can conclude that most of the water "solid-like," "bound," or "free" is located in the internal structure of these solids. Consequently, when, for example, microcrystalline cellulose containing 5% water is mixed with a drug, not much of that water initially will be in direct contact with the drug, regardless of the degree of mixing. Therefore, the kinetics of water movement in the vapor or liquid states within the solid may be a major factor. The ability to move will obviously depend strongly on the thermodynamic state of the water molecule. Can such transfer be prevented or retarded sufficiently to prevent stability problems? It is difficult to make generalizations, but certainly on the basis of diffusion experiments by Fish (47) and Duckworth (48) cited earlier, having only solid-like water and even bound or "intermediate" water present may be enough to avoid serious problems. Studies designed to address these questions more directly are presently being conducted in this laboratory.

To this point we have focused our discussion on the effect sorbed water from an excipient might have on other ingredients in the formulation. It is also possible that moisture levels and the thermodynamic state of water can influence the functionality of the exicipient. Clearly, free water on the external surface of powders can influence particle flow (50). Water within the particle, as with cellulose and starch, might be expected to influence strongly the compaction properties by affecting the degree of viscoelasticity. For example, whether or not water present is solid-like or free should influence the degree of interpolymer chain interaction. Indeed, with microcrystalline cellulose (51) and compressible sugar (52), the reduction of water levels below W_M appears to reduce their ability to act as direct compaction materials, presumably because water bound to a lesser degree is needed to provide plasticity to the system.

Finally, it is important to recognize that the principles discussed in terms of starch and cellulose are also applicable to other polymer systems of pharmaceutical interest, such as proteins (gelatin, keratin) and various synthetic hydrogels. The stoichiometries may be different, but in all cases we are talking about very similar molecular events. Consequently, the various experimental tools and methods of data analysis described herein should be useful in a much wider range of application.

ACKNOWLEDGMENTS

The authors wish to thank W. H. Rorer, Inc., for its general support of research in this area. Mark Kontny gratefully acknowledges the support he received as a United States Pharmacopeia Fellow during 1983–1985.

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