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STATES OF WATER ASSOCIATED WITH SOLIDS

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ABSTRACT

This paper critically reviews the underlying factors which influence the physical chemical states of water when it is associated with solids, as well as the effects that this water can have on the properties of the solid. Situations considered include: adsorption to solid surfaces, absorption into amorphous solids, capillary condensation into micropores, deliquescence, and the formation of crystal hydrates.

INTRODUCTION

Relative to the dry state, solids containing residual moisture from processing or because of exposure to various relative humidities exhibit significant changes in many of their physical chemical properties. Such properties include: chemical stability, crystal structure, powder flow, compaction, lubricity, dissolution rate, and polymer film permeability. Interest in the states of water in solids as a topic of discussion arises because a variety of physical chemical properties of water in contact with solids appear to be different from those of pure water[1]. This has given rise to the perception that water in the presence of solids exists in at least two thermodynamic states, "bound" and "solvent-like." Water which exists in the "solvent-like" state, thought to be capable of "dissolving" some of the solid, is generally perceived to be the major source of problems caused by exposure to moisture. Maintaining water at levels where only the "bound" form exists is believed to prevent such "dissolution" from occurring[2]. Recently, it has become apparent, that this perception of the underlying thermodynamic behavior of water in solids is somewhat oversimplified, incomplete, and indeed in some cases, not correct in interpreting observations in many systems of practical importance[3].

This review will attempt to bring together the latest thinking on this issue and to interpret it in the context of the many pharmaceutical problems and situations in which moisture plays a role. It is designed to address two major questions:

1. What is the physical chemical state of water associated with solids under a given set of conditions?

2. How does the presence of water affect the physical chemical properties of the solid?

In addressing these questions it will be important to keep in mind that water associates with solids in a number of different ways, each with its own unique set of underlying mechanisms. Some of the phenomena relevant to systems of pharmaceutical interest are: adsorption to a surface as a monolayer and as multilayers, capillary condensation into micropores, crystal hydrate formation, deliquescence, and absorption into the bulk phase of amorphous solids.

DISCUSSION

Hydrogen Bonding in Water

It is well established that the state of water molecules under a given set of conditions, and hence their many physical chemical properties, depend on their hydrogen-bonding ability[4]. For water molecules associating with themselves the oxygen "lone pair" electrons generally act as Lewis Bases, while the O-H groups act as Lewis Acids to form the O·····H-O hydrogen bond. The strong tendency of water to form such bonds is demonstrated by the existence of a significant amount of water dimers, $(H_2O)_2$, in the vapor state[5]. A useful model to depict the major factors giving rise to the structure of water in the condensed state is the Bjerrum "four point charge" model, where the oxygen is at the center of a regular tetrahedron and the partial positive and negative charges are placed at vertices of the tetrahedron. Indeed, in various forms of ice each water molecule forms an O-H·····O hydrogen bond in a tetrahedral arrangement with four other water molecules; each water molecule donates 2 hydrogens and accepts 2 hydrogens. In the liquid state of water a local preference for tetrahedral geometry persists, but there is a large proportion of broken hydrogen bonds, as well as strained bonds in various three-dimensional networks. Theoretical analysis has shown that the average number of hydrogen bonds per molecule in liquid water is about two[5]. Studies concerned with the radial distribution of water molecules in the liquid state indicate that each molecule "senses" an ordered structure with other water molecules out to about 3 molecular diameters. The strength of the hydrogen bond in ice or liquid water has been estimated to be about 15 to 25 KJ (3-6 Kcal) per mole of hydrogen bonds.

Thermodynamic Properties of Liquid Water

In assessing changes in the properties of water which might take place when it is associated with a solid, it is convenient to begin by evaluating any changes which might occur in its chemical potential because of the solid. If we consider, for example, liquid water at temperature, T, to be in equilibrium with its vapor, we may express the chemical potential, μ, of pure water as:

$$\mu = \mu^o + RT\ln p_o \tag{1}$$

where p_o is the vapor pressure, R is the gas constant and μ^o is the standard chemical potential.

If we have an aqueous solution at temperature, T, with a vapor pressure, p_s, which is less than p_o, we can express the chemical potential of the solution as, μ_s, and the change in chemical potential, $\mu_s - \mu$, as:

$$\mu_s - \mu = RT\ln(\frac{p_s}{p_o}) \qquad (2)$$

Hence, the chemical potential of water in the solution has been reduced to a fraction of that of pure water in proportion to the fractional change in vapor pressure, p_s/p_o, generally expressed as the relative pressure, or water activity (note that p_s/p_o times 100 is generally taken as relative humidity). It is the ability of water associated with water-soluble solids to produce a film of saturated solution having $p_s < p_o$, and hence a lowered thermodynamic activity relative to pure water, which provides the basis for the deliquescence process, i.e., dissolution of the solid when the environmental water vapor pressure is greater than p_s[6].

Another situation where the activity of a liquid can be altered is when the surface of the liquid is constrained to be highly curved, as in a pore or capillary, with a radius, r. Here, the vapor pressure of the pure liquid will change from p_o to p_r as described by the Kelvin equation:

$$\ln(\frac{p_r}{p_o}) = -\frac{(2\gamma V_m)}{(rRT)} \qquad (3)$$

where γ is the surface tension of the liquid, and V_m is its molar volume. This behavior is responsible, for example, for the ability of a vapor to condense as a liquid in a solid pore below its normal value of p_o, i.e., capillary condensation. Such phenomena also play a role in the occurrence of the vapor adsorption/desorption hysteresis noted with microporous solids. The Kelvin equation, recently tested directly using cyclohexane and water adsorbed to mica, has been shown to be applicable down to a value of r equal to 0.4 nM and 5 nM, respectively, when using the bulk liquid values of γ and V_m[8]. Limitations in the equation appear to occur as the dimensions of the space into which a liquid is confined become very small, i.e., approaching the dimensions over which intermolecular forces can operate. Indeed, even on an uncurved surface, as with thin films having such dimensions, it is possible to observe deviations in the properties of a liquid and to define a "disjoining pressure, π, the force per unit area at equilibrium required to remove a small increment of thickness from the bulk liquid[9], where:

$$\pi = \frac{\{RT\ln(\frac{p_d}{p_o})\}}{V_m} \qquad (4)$$

and p_d is the vapor pressure in equilibrium with the thin film.

Contributions to π arise from various intermolecular forces operating within the liquid and at the solid-liquid interface, including bulk intermolecular forces and those due to any electrical double layer effects[9]. The direct effects of the solid on the thermodynamic properties of water located within its vicinity, e.g., freezing temperature, have been difficult to assess, but they appear to occur out to about 1 nM from the solid surface, which is on the order of about 3 molecular diameters. In a recent study with well-defined finely porous zeolites, for example, it has been shown that aggregates of water containing less than about 5 molecules exhibit no phase transition, i.e., freezing at 0°C, whereas those with 10-30 molecules exhibit such a phase transition. However, this still occurs with a reduced heat of fusion, presumably because of a dimensional constraint on the structure of ice which can form[10].

Adsorption of Water on Crystalline Solids

Measuring adsorption to surfaces of well-defined crystalline solids such as, metals, semiconductors, metal oxides, and alkali halides under ultrahigh vacuum conditions has provided many insights into the general properties of water at solid surfaces[11]. The tendency for any molecule in the vapor state to be adsorbed at a solid surface is strongly dependent on the vapor pressure, the temperature, and the binding energies between solid and vapor. For nonpolar gases, such as nitrogen or oxygen with binding energies of about 4-8 KJ per mole, very low temperatures, approaching the boiling point of the adsorbing substance (e.g., 78°K for nitrogen) are required to offset the unfavorable entropy change associated with vapor adsorption and to observe significant amounts of physisorption. At such low temperatures and at high enough pressures, it is also possible to observe condensation of adsorbing molecules to form multimolecular layers. In the case of water molecules adsorbing on more polar surfaces, such as metals or metal oxides, overall binding energies are generally in the range of 40-60 KJ per mole since a minimum of two hydrogen bonds occur per water molecule[11]. This reflects binding energies on the borderline between physisorption and chemisorption. In situations at the lower end of this range, water may be completely desorbed at room temperature, while at the upper end, as with many metal oxides, adsorption can persist to above room temperature. In the case of silicon dioxide, it is interesting to note that strong hydrogen bonding with water occurs at sites covered with silanol groups, but little binding occurs with the dehydroxylated siloxane groups[12]. In view of this, it is not surprising that water at room temperature shows little tendency to adsorb to nonpolar surfaces such as carbon or polytetrafluoroethylene (Teflon) or other relatively hydrophobic organic solids and much more so to polar solids, such as alkali halides and sugars.

Since hydrogen bond strengths between water molecules in ice and liquid water are typically 15-25 KJ per mole, not too different than the energy of one hydrogen bond between the solid and water, it also is not surprising that clustering of water molecules can occur even before a complete monolayer has formed, leading to the formation of multilayered networks beyond the first layer. Such clustering below monolayer coverage also suggests that there is significant lateral diffusion along the surface, despite the relatively strong hydrogen bonding with the surface.

Continuation of such clustering to form many "condensed" layers beyond the first layer occurs as the pressure is increased and more molecules adsorb.

The simplest model for such adsorption is described by the "2-state" BET equation[13]:

$$w = \frac{w_m C_b (\frac{p}{p_o})}{\{1-(\frac{p}{p_o})\}\{(1-(\frac{p}{p_o}) + C_b(\frac{p}{p_o})\}} \qquad (5)$$

where w is the weight of water adsorbed per unit weight of dry solid at a relative pressure of p/p_o, w_m is the weight of water adsorbed corresponding to monolayer coverage, and C_b is a constant related to the equilibrium constant for the process. Here, the assumption is that the influence of the solid on the enthalpy and entropy of the adsorbed species extends only to the first layer and that the rest of the adsorbed molecules making up the multilayered portion have properties which are the same as in the bulk phase. The general lack of fit of most adsorption data to the BET equation above a p/p_o of about 0.35, in part, reflects the inadequacy of this assumption and suggests that perhaps more than two thermodynamic states exist. Many other models have been developed for such systems, but in the context of this discussion, a useful equation is an extension of the BET equation, developed by deBoer[14] and Guggenheim[15]. It assumes 3 thermodynamic states for the adsorbed species by introducing one with intermediate properties to those assumed in the BET model:

$$w = \frac{w_m C_g K(\frac{p}{p_o})}{\{1-K(\frac{p}{p_o})\}\{1-k(\frac{p}{p_o}) + (C_b K(\frac{p}{p_o})\}} \qquad (6)$$

where a second equilibrium constant, K, is introduced to account for the intermediate state. This, too, is very oversimplified mechanistically, but it produces excellent fit over almost the entire adsorption isotherm in many cases of interest, and is consistent with the idea that the solid can affect water a few molecular diameters away from the surface.

Experimental studies of adsorbed species on well-defined crystalline surfaces, using techniques such as infrared and raman spectroscopy, as well as nuclear magnetic resonance and dielectric relaxation, indicate that adsorption of water directly to the surface most generally occurs with the water oxygen acting as a Lewis base and the solid site as the Lewis Acid[11]. Bonding via the hydrogens of water, acting as a Lewis Acid, however, also has been observed. In all cases, adsorbed molecules exhibit significant alteration in vibrational, rotational, and translational properties relative to bulk water, out to about three molecular diameters from the solid surface[1]. Beyond this distance, such molecular properties remain constant and similar to that of bulk water.

In the discussion so far, we have assumed that the adsorbing species is molecular water. This, indeed, is generally the case; however, it has been shown that with some solid binding sites, and at certain temperatures, it is possible for water to dissociate into the highly reactive H and OH radicals, where the oxygen of the OH radical can act as an even stronger Lewis Base. Thus, in some cases, the very first layer of adsorbed water can contain a much more reactive chemical species than molecular water. This may be of some importance in situations where water directly causes chemical changes in a drug molecule.

Studies with single crystals of pure solids have made it possible to show how the chemical differences between different atoms in a solid lead to differences in the amount of adsorption and in the binding energies[11]. For example, for water adsorption on zinc oxide at the zinc-rich (001), and oxygen-rich (001) faces, as well as at the (100) face, where both zinc and oxygen atoms are well exposed, water adsorbs in the molecular form and interacts more strongly with zinc than with oxygen, e.g., no desorption occurs up to 340°K with zinc and up to only 190°K with oxygen. Other studies with single crystals of titanium dioxide[16] reveal that, whereas water adsorbs at the titanium site as the intact molecule on the (110) and (100) faces, it dissociates upon adsorption at the (001) face.

Another important factor in such studies is that these solids, and most others encountered, are not perfect crystals, i.e., they contain defects and impurities. Defects can act as high energy sites for adsorption and can even promote dissociation of water. Zinc oxide powder, for example, which contains a mixture of exposed crystal faces and a considerable number of crystal defects, exhibits dissociative adsorption of water, in contrast to single crystals of zinc oxide, as discussed above. This leads to a general conclusion that with powders of the type normally encountered in practice, adsorption of water will be influenced by defects, impurities, and the polycrystalline nature of the sample. This should result in adsorption in the first layer with a range of binding energies rather than a single value expected if all of the binding sites are identical. The first molecules adsorbing should be attached to the higher energy sites with a progressively decreasing energy as monolayer coverage increases to completion. This is reflected in an isosteric heat of adsorption which also progressively decreases to the value of condensed water as coverage increases[17].

To illustrate the important role of defects in influencing the interaction of water with crystalline solids, we have examined the adsorption of water on freshly crystallized sodium chloride before and after grinding the samples to introduce crystal defects[18]. Whereas the freshly crystallized sample exhibited reversible adsorption/desorption isotherms right up to the deliquescence point, i.e., a relative pressure of 0.76, the ground sample exhibited a number of different behaviors. Below a relative pressure of 0.2 water uptake per unit area was greater for the ground sample than for the unground sample, whereas at higher

p/p_0 much less adsorption occurred with ground samples. Adsorption/desorption hysterisis also occurred. After exposure of both samples to relative pressures of water vapor below 0.2, no change was noted in their respective specific surface areas. However, above 0.2 the ground sample showed a significant decrease in surface area, which became greater as the relative pressure was increased to values still below 0.76. No change, however, was noted with the unground sample. It was concluded that water vapor was taken up in greater amounts by the ground sample because of defects introduced into the sodium chloride crystal by grinding. Presumably water is able to exist at a defect site in a higher metastable thermodynamic state than that in the crystalline sample and to create enough mobility in the sodium and chloride ions to allow recrystallization, e.g., "surface sintering". This, in turn, can cause a reduction in the specific surface area of the solid. Such behavior correlates very well with the increase noted in the hardness of sodium chloride compacts after exposure to relative pressures above about 0.2, but below 0.76, presumably due to surface recrystallization[19]. It appears that the compaction process introduces surface defects at the points of particle contact, which then act as sites for the metastable uptake of water vapor and subsequent recrystallization.

Crystal Hydrates

One of the more important aspects of water-solid interactions encountered in pharmaceutical systems is the ability of water and solids to form crystal hydrates. This is so because the level of moisture present per unit mass of solid is generally very high and because the formation of a crystal hydrate often produces a significant change in the thermodynamic properties of the molecules involved. Whether or not a crystal hydrate has formed may be determined by asking two questions: 1) does the water molecule occupy regular positions within the crystal lattice with respect to other molecules; and 2) does a specific stoichiometry exist between water and the other molecule? To address these questions definitively, it is desirable to carry out a number of different measurements using single crystals. Such measurements might include X-ray and neutron diffraction, thermal analysis, polarizing microscopy, infrared spectroscopy, and solid-state NMR.

For the type of crystal hydrate which occurs with many well studied systems, e.g., copper sulfate, the formation of hydrates from an anhydrous form occurs as a first order phase transition between two distinct thermodynamic phases. The strength of the interaction between water and the other molecule will generally be on the order of other noncovalent interactions involving water, i.e., hydrogen bonding or ion-dipole interactions. However, the geometric arrangements allowed by the size and shape of the molecules involved can lead to extremely strong bonding at multiple sites. This is particularly true for interactions involving water and many ionic species. In some cases, as with caffeine and theophylline[20], water molecules may assume positions in the crystal lattice in a regular pattern but with relatively weak interactions and with more of a space-filling role. In such situations, upon heating or exposure to the atmosphere, water molecules have been observed to move out of the solid via "tunnels" between the main crystal lattice without affecting the lattice[20]. Because of this, many of the sites expected to contain water often will be empty and the stoichiometry may often appear to be incomplete. There are some situations, as with erythromycin[21], where the method of removing the waters of hydration can lead to collapse of the lattice into a metastable amorphous form. In all cases, since large amounts of water per unit mass of solid are generally present, it is important to know whether or not this water has the potential to be released from the solid under a given set of conditions. This will not only change the properties of the solid with which it was originally associated, but it also can allow large amounts of released water to interact with other solids in a mixture which originally contained the hydrate.

Water Interactions With Amorphous Solids

The last situation to be considered is the uptake of water by solids that exhibit amorphous structures. These solids may be polymeric materials, used as dosage form excipients and packaging materials, or they may be small molecules, ordinarily crystalline, but rendered amorphous by processing operations such as comminution, thermal treatments, lyophilization, wet granulation, and spray drying. Typical polymers of pharmaceutical interest are starches, celluloses, proteins, and synthetic hydrogels. Water interactions with such solids are characterized by significant uptake into the solid structure, far in excess of what would be predicted for adsorption to the dry external surface area and independent of specific surface area. This is termed, absorption or sorption, to differentiate it from adsorption. In such cases there is usually a significant hysteresis between the sorption and desorption isotherms.

Sorption/desorption isotherms generally can be fitted reasonably well to a variety of gas adsorption equations, including equation 6, the "3-state" extension of the BET equation described above, often called the GAB equation[22]. In Table 1 are given w_m values at 25°C obtained by fitting water vapor sorption data for a variety of polymers to equation 6. For gas adsorption, w_m is the amount of vapor either adsorbed directly on the available solid surface, or to available surface binding sites, which produces a complete monolayer. With water vapor absorption, it is less clear what this parameter might mean in physical terms , but it generally has been interpreted to be the amount of water that directly hydrates the solid[23]. In this context, it is interesting to note that for various starches and proteins, the values of w_m in Table 1 give a ratio for moles of water interacting per mole of monomer unit (anhydroglucose and amino acid, respectively) of about 0.8 to 1.0, or about a 1:1 molar stoichiometry. This is also true for various celluloses after one accounts for the fact that water is not taken up into the crystalline regions[22]. In the case of hy-

TABLE 1

Water Vapor Sorption Data for Various Polymeric Solids at 25°C

Solid	w_m* (g/g)	Reference
corn starch	0.083	22
potato starch	0.085	34
microcystalline cellulose	0.035	22
gelatin	0.087	35
wool	0.066	35
p(HEMA)	0.040	24

* amount of water vapor sorbed at saturation from equation 5 or 6 in the text.

drogels, such as p(HEMA), and some of its copolymers, however, the values of w_m center around 0.3 moles of water per monomer unit[24]. Whether these possible stoichiometric relationships are chemically meaningful is not clear at the present time.

Another way in which the process of vapor absorption into amorphous solids and the value of w_m might be viewed is reflected in the "dual sorption" theory[25]. Here, it is assumed that water and other gases initially are taken up by 2 mechanisms: 1) by dissolving into the solid, as predicted by Henry's law; and 2) by a simultaneous filling up of micropores in the "glassy" amorphous structure of the solid. Saturation at the equivalent of w_m, is believed to occur when these microvoids become saturated, although the possibility that the saturation may be due to other mechanisms also has been suggested[25].

As a result of various physical chemical measurements, such as freezing point, NMR, dielectric relaxation, and self diffusion, it has been suggested further that there may be two forms of "bound" water, one involving specific hydration directly to the molecules of the solid, as reflected in w_m, and the other, a more nonspecific intermediate type of binding out to about 3-5 times w_m[22-24,26].

At higher moisture contents, water molecules are believed to be able to cluster and to begin the process of forming "solvent-like" water, very much like that which occurs with multilayer adsorption on crystalline surfaces[11]. Using simple solution thermodynamics, for example, it has been shown that such clustering can give rise to the significantly sharp rise in water sorption exhibited in most sorption isotherms as the relative pressure increases beyond a certain point[27]. Thus, as in the case of adsorption of water to crystalline solid surfaces, the idea that "bound" and "solvent-like" exist in the structure of an amorphous solid containing water, along with perhaps an intermediate state of "bound" water, has been widely advocated.

An expanded perspective on this problem has recently been developed in the work of Levine and Slade[3], who have expressed concern for the fact that little attention has been given to changes which occur in the properties of the solid during water sorption and desorption and to how such changes, in turn, can influence the properties of water in these systems. For example, the fact that some polymers visibly swell at very high relative pressures and that they exhibit sorption/desorption hysteresis is a clear indication that absorbed water can alter the conformations of polymer chains in the solid state[28].

How water causes such changes to occur is best understood in the context of the well known ability of certain molecules to act as plasticizers when added to polymers or other amorphous solids[29]. Amorphous solids below their glass transition temperature, Tg, exist in a "glassy" or "vitreous" state, having less than 3% free volume and viscosities greater than about 10^{13} poise[29]. As the temperature is increased the molar volume increases to a small extent until Tg is reached and the "rubbery" state forms. Eventually, this "rubbery" amorphous solid state will change into a liquid without major discontinuities. Any crystalline forms present, of course, will exhibit a melting temperature. In the "glassy" and liquid states, the changes in molar volume of the substance will change with temperature according to the Arrhenius equation. However, in the "rubbery" state, this change will be exponential with temperature, resulting in significant change in a number of properties related to the free volume. From the equation of Williams, Landel and Ferry[30], it is possible to estimate the change in viscosity and other properties reflective of free volume as a function of temperature, T, for a wide range of polymers in the "rubbery" region by simply knowing Tg and the viscosity, η_g at Tg. Expressing the viscosity in S.I. units of Pa·s, where 1 Pa·s equals 10 poise, and assuming that the viscosity at Tg is 10^{12} Pa·s, we can express this equation as follows :

$$\ln \eta = \ln \eta_g - \frac{40.2\ (T - Tg)}{51.6 + (T - Tg)} \qquad (7)$$

This tells us is that where we are in relation to Tg can significantly affect the viscosity of the solid, and, hence, the mobility of the molecules or polymer chain segments. For example, 10^4 poise is reported to be the viscosity of a polymer film which will just be "dry to the touch", while 10^7 poise is the viscosity where the film will just retain the impression of a standard weight placed on its surface, i.e., no visible viscoelastic flow under higher stress[31]. To go from 10^{13} poise at Tg to 10^4 poise, requires an increase of temperature above Tg of about 54°C, while an increase of only 4°C is required to go to 10^7 poise. The main point here is that physical properties of the solid determined by the extent of free volume, e.g., viscosity, elastic modulus, nuclear magnetic relaxation, and dielectric relaxation, will be very greatly affected by where the operating temperature is relative to the Tg of the solid.

Water molecules, because of their polarity and their small size can penetrate into an amorphous solid structure and significantly increase its free volume. This, in turn, will decrease its apparent Tg, as would any plasticizer. The simplest equation used to describe this effect is[32]:

$$\frac{1}{Tg} = \frac{1}{Tg_1} - w_2\{\frac{(Tg_1 Tg_2}{(Tg_1 + Tg_2)}\} \qquad (8)$$

where Tg_1, Tg_2, and Tg are the glass transition temperatures, in degrees Kelvin, of the polymer (1), water (2), and mixture of the two, respectively, and w_2 is the weight fraction of water in the solid.

As an example of what this might mean quantitatively, let us consider the polymer, hydroxypropyl cellulose, containing 5% water, where Tg_1 is 283°K, Tg_2 is 134°K and w_2 is 0.05, and calculate the viscosity of the system at 25°C (298°K). From equation 8, the Tg for the mixture would be expected to be about 268°K, while from equation 7, the viscosity of such a system at 25°C, would have decreased from 10^9 poise in the absence of water to a value of 10^7 poise in the presence of 5% water.

The critical message being conveyed here is that the absorption of water into amorphous solids is quite unlike monolayer and multilayer adsorption at crystalline solid surfaces. As soon as water penetrates into the amorphous solid structure, it acts as a plasticizer and reduces Tg. Hence, each point on the sorption isotherm reflects the physical state of both the water and the solid and how each have influenced one another under a given set of conditions. Therefore, although the temperature of the experiment might be constant, the differences between this temperature and the glass transition temperature will be different for different amounts of absorption. This indicates that measurement of the apparent thermodynamic activity of water in such systems cannot be interpreted without considering the contributions of the solid to the phenomena being examined. It is also important to recognize that the property being measured reflects kinetic effects of the solid on water as well as any thermodynamic effects. For example, the lack of freezing of water, the difficulty in removing water by thermal means, and the changes in nuclear magnetic resonance and dielectric relaxation times, used to detect "bound" water may have less to do with any "bound" thermodynamic state than with the fact that the solid at low levels of moisture is in its "glassy" state with viscosities in excess of 10^{13} poise, i.e., where the mobility of water molecules is very small. Water in amorphous solids may cluster into condensed states beyond a certain level of uptake to give "solvent-like" properties because of a saturation of binding sites or a lack of affinity between it and the solid relative to itself, as predicted from thermodynamic considerations[27]. However, it also must be realized that as water is taken up and the solid approaches its "rubbery" state because of the plasticizing effect of water, the mobility, and hence the diffusion of the water molecules will increase exponentially, also giving rise to the appearance of "solvent-like" properties. In all cases, of course, such "solvent-like" water never attains exactly the same properties of liquid water; in starch, for example, "solvent-like" water exhibits diffusion constants on the order of 100 times less than that of liquid water[26].

A good example of where this way of looking at the problem might be important is with small molecules in the amorphous state which spontaneously crystallize when exposed to a critical level of moisture. Although this might be thought of as arising from a small amount of "dissolution" of the solid by the water, it seems more reasonable to assume that such crystallization takes place as water molecules lower the value of Tg to the temperature of the system. Here, in the "rubbery" state the molecules start to attain sufficient mobility to crystallize[33].

SUMMARY

1. Water interacts with various crystalline solids at the surface primarily through its ability to hydrogen bond. The prop-

erties of water in the vicinity of a solid surface to which it is adsorbed, will appear to be different than that of bulk water out to about three molecular diameters away from the surface or when the space within which it is confined approaches these molecular dimensions, e.g., micropores and thin films. Binding of water in such cases, however, is quite easily reversed by raising temperatures and lowering the relative pressure of water vapor. Defects in a crystalline solid can act as high energy sites yielding a greater amount of water uptake than expected with a purely crystalline site. Since such uptake is metastable with respect to that which occurs with a crystalline solid, with water-soluble solids the possibility of reversion to lower energy forms through an increase in the mobility of ions or molecules, followed by surface crystallization, must be considered. If the relative humidity is kept high enough, such water uptake can lead to a saturated solution in a film around the solid and the initiation of deliquescence.

2. Water can assume regular positions in the lattice of crystalline solids with a specific stoichiometetry to form crystal hydrates. In some cases such hydrate formation leads to distinctly different solid phases from the anhydrous state, while in other cases no effect on the crystal structure of the anhydrous form by hydrate formation is observed. Generally, in the former case the water appears to strongly interact with the other molecule, while in the latter case water can easily be removed without altering the crystal structure.

3. The uptake of water into amorphous solids decreases the glass transition temperature, Tg, of the solid, acting as an efficient plasticizer. As the solid is plasticized, it undergoes a significant increase in free volume which greatly increases the mobility of molecules or segments of molecules in the system. This increase in mobility is reflected in a decrease in the viscosity of the solid which is particularly significant if the solid is made to change from the "glassy" state to the "rubbery" state

by the addition of water. Such changes are reflected in a number of physical measurements of water which have been interpreted to be changes in its thermodynamic state. This has led to the conclusion that water in amorphous solids can exist in both a "bound" and a "solvent-like" state, with, perhaps, two types of "bound" states. It can be shown, however, that these apparent changes in the thermodynamic state of water in amorphous solids include kinetic effects which reflect the overall change in the mobility of the molecules in the system; this is determined by the physical state of the solid, i.e., whether it is "glassy" or "rubbery." These kinetic phenomena help to explain the effects of moisture on a number of physical chemical processes of pharmaceutical interest involving amorphous solids and requiring molecular mobility, e.g., crystallization of lyophilized cakes, direct compaction properties, powder caking, permeability of coatings and packaging materials, and solid state chemical stability.

4. In considering situations where moisture will play a predominate role in affecting the properties of solids, three situations appear to be most critical because of the large amounts of water involved, the location of the water within the solid, and the metastable state of the system. These are: the formation of crystal hydrates, the absorption of water into amorphous solids, and the deliquescence that takes place with highly water-soluble solids at high relative humidities. Adsorption to solid surfaces will play a less important role, unless very high surface areas are involved, e.g., porous solids, or uptake into the crystal defects of water-soluble solids caused by comminution, which gives rise to metastability, greater mobility of ion and molecules, and the possibility of surface recrystallization.

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