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### Review Article

# The molecular basis of moisture effects on the physical and chemical stability of drugs in the solid state

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## Introduction

It is well recognized that residual water associated with drugs in the solid state can have significant effects on a variety of physical and chemical properties, such as chemical degradation, dissolution rate, flow and compactibility. Such residual water exists because of prolonged exposure to an atmosphere containing water vapor, or as a result of processing that involves the use of water, e.g. lyophilization, spray drying, aqueous film coating, wet granulation or recrystallization. To develop strategies that can be used to deal with such physical and chemical changes, or more importantly, to anticipate them, requires an understanding of the molecular events underlying such solid-state phenomena and of the means by which water molecules can influence these events. Consequently, in this brief review we have attempted to bring together a body of literature and concepts that we believe can provide the basis for addressing these important pharmaceutical problems less

empirically and with greater understanding. Emphasis will be placed on the role of water in affecting drug entities that are believed to exist predominantly in the crystalline state, in the absence and presence of excipients and other drugs in the formulation.

## Mechanisms of Water-Solid Interactions

It is convenient to think of water as being able to interact with crystalline solids in three major ways: adsorption of water vapor to the solid-air interface; crystal hydrate formation; and deliquescence. For solids containing microvoid spaces it is also possible for capillary condensation to occur at fairly low relative humidities, leading to occluded water (El-Sabaawi and Pei, 1977; Carstensen et al., 1980). Two of these processes, deliquescence and capillary condensation, lead to the formation of condensed or bulk water, capable of dissolving water-soluble components. Crystal hydrates are characterized by the penetration of water molecules into the crystal lattice, most often, but not always, in a well-defined molecular position within the unit cell, and hydrogen bonded to certain groups with a specific stoichiometry (Byrn,

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the water molecules and the strength of the interaction determine the extent to which such water can enter or leave the crystal unit cell under a given set of conditions. Water molecules adsorbed to the surface of the solid generally exist, as expected for physically adsorbed monolayers, with a first layer hydrogen bonded to the solid, and at most 2–3 additional molecular layers formed at the higher relative humidities. Such adsorption generally is readily reversed by small increases in the temperature or by small decreases in the relative humidity (Thiel and Madey, 1987).

Recognition of the various mechanisms by which water can interact with water-soluble drugs in the solid state has led to some important perceptions and misperceptions of how water affects the properties of such solids. Given, for instance, that condensed water is produced during deliquescence and that such water continues to dissolve the solid as long as a sufficiently high relative humidity is maintained, i.e. a relative humidity in excess of that for a saturated solution of the material, there is a general perception that small amounts of water below this point, somewhere in excess of a monolayer also can cause small amounts of 'surface dissolution' of the solid, which in turn, can trigger a variety of more subtle and slow physical and chemical changes. This, for example, is the basis for the model of Leeson and Mattocks (1958) for drug degradation in the solid state, where the drug is visualized to exist as a saturated solution around the solid particle and where the rate of degradation is determined by the aqueous solubility of the drug and the first-order solution rate constant. From a thermodynamic perspective it can be shown that dissolution of a crystalline water-soluble solid should not occur in any water present until the chemical potential of the water is equal to that of a saturated solution (Van Campen et al., 1983). Indeed, it is possible repeatedly to adsorb and desorb water vapor on freshly crystallized sodium chloride up to its critical relative humidity of 76% and observe no changes in the amounts of adsorbed water and no physical changes in the solid (Barracough and Hall, 1974; Kontny et al., 1987).

Related to this issue also is the common per-

cules associated with a solid is unavailable to 'dissolve' the solid and to cause changes in the system. Water, for example, present in crystal hydrates or adsorbed in the first surface layer in direct contact with the solid is often thought of as 'tightly bound' and unavailable for 'dissolution' or 'interaction', while more nonspecifically surface bound water, in excess of a monolayer, as discussed above, is thought of as being available to act as a solvent for dissolution and other changes in the solid. It is important in this context, however, to recognize that the degree of hydrogen bonding and the strength of hydrogen bonds between water and solid, under ambient conditions, can be very variable and that this variability can lead to many situations where under different conditions water molecules directly bound to the solid can be shown to be quite mobile and free to move around on a long time scale, either within the crystal lattice or along the solid surface (Jelinski et al., 1983; Zografis, 1988). Thus, one cannot assume that such water is absolutely 'frozen' into a static tightly bound state with no possible role to play in affecting solid properties. In the context of these observations, therefore, how do we explain the fact that adsorbed water associated with crystalline solids, in relatively low amounts, appears to promote chemical degradation or other types of physical changes, but that below a certain level of water these phenomena do not occur?

### Water and Amorphous Solids

To put the issues raised so far for water and crystalline solids into a broader context, it will be helpful to review briefly a few concepts concerning the interactions of water with amorphous solids, where considerably more water is taken up, relative to the crystalline form of the same chemical entity (Nakai et al., 1977; Pikal et al., 1978). Here, because of the disordered state of the solid it is possible for *water to dissolve in the solid*. Thus, in contrast to adsorption, where the amount of water taken up depends on the available surface area, uptake by amorphous solids is predominantly determined by the total mass of amorphous

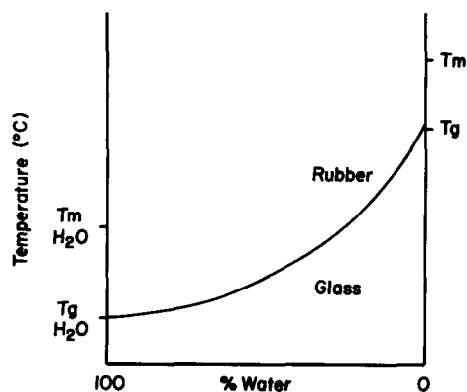


Fig. 1. Solute-water state diagram which illustrates the effect of water plasticization and its effect on  $T_g$ .

on solid properties is the fact that water dissolved in an amorphous solid, can act as a plasticizer to greatly increase the free volume of the solid by reducing hydrogen bonding between adjoining molecules of the solid, with a corresponding reduction in its glass transition temperature,  $T_g$  (Franks, 1982; Levine and Slade, 1987, 1988; Slade and Levine, 1988). In Fig. 1 is given a schematic representation of this change for a typical amorphous solid having very high water solubility and a high  $T_g$  in the dry state. Thus, water with a very low  $T_g$ ,  $-134^\circ\text{C}$ , increasingly and continually reduces the  $T_g$  of the solid system as its concentration in the solid increases. As with any completely miscible mixture, at low concentration of water, we can think of the system as a solution of water in an amorphous solid, whereas as the amount of water in the system increases we can think of this more as a solution of the solid in amorphous water. What is important here, is that the change in free volume occurring as one increases the temperature,  $T$ , above  $T_g$  (or by decreasing  $T_g$  below  $T$ ), has a profound effect on a number of properties related to it. Of particular interest to us are the significant changes which take place in the viscoelasticity of the solid as one passes from the glassy state below  $T_g$  to the rubbery state above  $T_g$ . For example, as shown from the WLF-equation (Williams-Landel-Ferry, 1955) for the viscosity of an amorphous rubber solid, going just  $20^\circ\text{C}$  above  $T_g$  will cause the viscosity to change from about  $10^{15}$  P at  $T_g$  to  $10^8$  P, with a

of the solid and water. Thus, the mixture of the two amorphous components, if kept below the  $T_g$ -line in Fig. 1, will remain as an extremely viscous immobilized glassy solution where water molecules in this highly immobilized state behave as if they were in a tightly bound state. If, however, the temperature of the system is allowed to go above the  $T_g$ -line a significantly less viscous rubbery state will be formed with greatly enhanced molecular mobility of both the solid and water.

The implications of this in terms of product stability are shown in Fig. 2 where a plot of  $T_g$  vs relative humidity exposed to the solid is given for the amorphous polymer poly(vinylpyrrolidone), PVP (Oksanen, 1989; Oksanen and Zografis, 1990). Here, we can see, for example, that a sample of PVP stored at  $25^\circ\text{C}$  and 80% relative humidity would have its  $T_g$  decreased to approx.  $10^\circ\text{C}$  and hence would have been converted from a glassy to a rubbery state. At  $40^\circ\text{C}$  such a conversion only would require storage at about 65% relative humidity. The increased mobility which occurs as  $T_g$  is reduced to values near and below the operating temperature has been shown to be sufficient to allow amorphous solids to readily undergo solid-state chemical reactions (Pikal et al., 1977) and to support the recrystallization of small molecules rendered amorphous through various types of processing, e.g. lyophilization, mechanical grinding or rapid precipitation (Makower, 1956; Palmer,

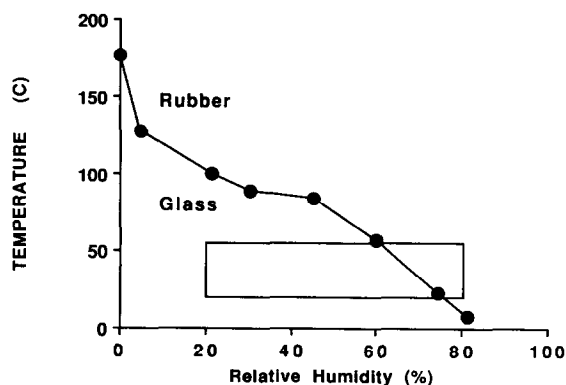


Fig. 2. Effect of relative humidity on the glass transition temperature of PVP K30. The box illustrates conditions normally in use during accelerated storage testing. (Data compiled

1956; Otsuka and Kaneniwa, 1983; Fukuoka et al., 1986, 1989). Thus, in these cases it is not surprising that water is often suggested, incorrectly, to have attained 'solvent-like' or 'unbound' properties when it produces such chemical and physical changes.

### Molecular Disorder in Crystalline Solids

It is well recognized that the regular and repeating arrangements of atoms and molecules in a crystalline state are most often altered by the presence of defects, imperfections or regions of amorphous structure. Such defects or imperfections, which give rise to local regions of molecular disorder, relative to that of the crystal structure, can arise from a variety of processes used in pharmaceutical development, including mechanical grinding, lyophilization, and other processes where rapid drying and recrystallization occur. Since the molecules located in such regions of local disorder can exhibit greater chemical reactivity (Hüttenrauch, 1978, 1983, 1988; Hersey and Krycer, 1980; Hüttenrauch et al., 1985) and 'solubility' (Waltersson and Lundgren 1985), they are often said to be in an 'activated state'. Such 'activation' arises from a combination of greater molecular mobility and the exposure of more reactive chemical groups. Taken to the extreme of a complete lack of long-range order in the solid state, the system will be completely amorphous, as described above. As in the case of amorphous solids, the regions of greater local disorder and reactivity, should exhibit an ability to take up more water than would ordinarily be adsorbed on the surface of the crystalline portions of the solid. If the amount of water taken up is sufficient to plasticize the local region to a point where  $T_g < T$ , molecular mobility can be high enough to support enhanced dissolution rates (Fukuoka et al., 1986) and chemical reactivity. Direct evidence for this plasticizing effect of water on alkali halide crystals comes from studies of surface electrical conductance as a function of exposure to various relative humidities (Asselmeyer and Zott, 1965; Knacke and Neuschütz, 1970). Here, it was shown that

cur near to, but still below, the critical relative humidity,  $RH_0$ , for deliquescence, at a level well below that of a saturated salt solution. The fact that the conductance near  $RH_0$  increases significantly but does not equal that of a saturated solution is consistent with an increasing ionic mobility due to plasticization as water dissolves in a metastable manner into the defects and other disordered regions of the crystal. In this regard, also, it is interesting to note that, whereas the maximum number of water molecules adsorbed on crystalline surfaces usually amounts to about three equivalent monolayers (Barraclough and Hall, 1974; Thiel and Madey, 1987; Kontny et al., 1987), in one study where NaCl crystals were subjected to mild comminution, as much as five equivalent monolayers were observed just below  $RH_0$  (Walter, 1971).

The role of energetic 'hot spots' on the particle surfaces or thin amorphous layers surrounding the particles in acting as sites for chemical degradation of solids particularly at higher temperatures has been extensively discussed (Prout and Tompkins, 1944; Ng, 1975; Hasegawa et al., 1975). What has not been considered is the fact that relatively small amounts of moisture absorbed into these hot spots can produce significant increases in molecular mobility at much lower temperatures by means of its plasticizing properties. Thus, rather than think of water as having solubilized the drug in order to influence chemical degradation rates, we can think of water as dissolving in the local regions of disordered molecules to produce enough mobility to support chemical reactivity. Therefore, in most chemical reactions in the solid state of pharmaceutical interest, e.g. hydrolysis or oxidation, water can act as both a plasticizer and a chemical reactant dissolved in the drug.

Visualizing the role of water, in affecting the properties of 'crystalline' solids, in this manner, also helps to explain a number of other observations related to the physical stability of drugs. For example, it has been shown that many crystalline water-soluble solids after grinding or compaction, insufficient to produce measurable amorphous structure using powder X-ray diffraction, and exposure to relative humidities below the deliques-

area, due to what appears to be surface sintering and recrystallization (Chikazawa et al., 1972ab, 1976; Kaiho et al., 1973, 1974; Kontny et al., 1987; Ahlneck and Alderborn, 1989b). Such sintering, furthermore, has been shown to most likely be the cause of increased tablet hardness upon exposure to various relative humidities, (Lordi and Shirmani, 1983, 1984; Down and McMullen, 1985; Ahlneck and Alderborn, 1989ab) as well as the cause of decreased dissolution rates after storage at elevated temperatures and relative humidities (Danjo and Otsuka, 1988). Independent measurements of water uptake by such activated solids, indeed, reveal that they sorb more water per unit area than an untreated crystalline sample at low relative humidity (Kontny et al., 1987), and that above a certain point, local recrystallization or surface sintering is induced by the plasticizing effects of the absorbed water, just as described above for amorphous solids when  $T_g$  is brought down below  $T$ .

To put this discussion on a more quantitative basis, it would be useful to carry out some model calculations showing the extent to which a given total moisture content in a sample might cause physical or chemical changes to occur in a crystalline material. In Table 1 are given values of particle size and specific surface area of solid spheres along with the number of layers of water molecules required to cover these surfaces if 0.1% (0.001 g of water per g of solid) is adsorbed. Such a level of moisture is quite common in crystalline drugs. A cross-sectional area of 0.125 nm<sup>2</sup> per molecule of water is assumed for the purposes of this calculation. As seen in Table 1 for solids having particle sizes normally encountered in solid dosage

TABLE 1

*Specific surface area of sucrose spheres and theoretical number of water layers surrounding the spheres if 0.1% (w/w) moisture is adsorbed*

Particle size ( $\mu\text{m}$ )	$S_w$ ( $\text{cm}^2 \text{g}^{-1}$ )	Number of water layers
1	38000	1.1
10	3800	11
38	1000	42
100	280	110

TABLE 2

*Moisture content in the amorphous portion of sucrose and the glass transition temperature if a total of 0.1 or 0.5% moisture is taken up*

Amount of moisture (%)	Amount of amorphous material (%)	Moisture content in amorphous material (mg H <sub>2</sub> O/ 100 mg solid)	Glass transition temperature <sup>a</sup> (°C)
0.1	0.5	20	9
	1	10	27
	2.5	4	45
	5	2	49
0.5	0.5	100	-73
	1	50	-36
	2.5	20	9
	5	10	27

<sup>a</sup> Compiled from Slade and Levine (1988), assuming that the glass transition temperature of purely amorphous sucrose is 52°C.

forms, i.e. 10–100  $\mu\text{m}$ , the number of adsorbed layers of water is quite extensive and far beyond what one normally would expect for surface adsorption on such particles. Indeed, true surface adsorption of water at 25°C on well-defined solid surfaces has been shown to be orders-of-magnitude less than such a value (Kontny et al., 1987). What appears to be more likely is that, in addition to any occluded water that might be present in the crystal, a significant portion of this water is taken up and dissolved into the 'disordered regions', i.e. water is concentrated in these regions.

In Table 2, we have calculated the amount of water absorbed into the 'disordered' amorphous-like regions of sucrose for 0.1 and 0.5% total moisture content, assuming various percentages of amorphous structure between 0.5 and 5% of the total solid, and further assuming that essentially all of the water is preferentially taken up in these regions. As expected, depending on the amount of amorphous material present, there can be a considerable concentration of water for a given system, particularly as the fraction of amorphous material becomes quite small. To examine how such water contents might affect the  $T_g$  of



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