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Research Article

Water Vapor Sorption of Water-Soluble Substances: Studies of Crystalline Solids Below Their Critical Relative Humidities

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Water vapor sorption on unground and ground samples of sodium chloride and sodium salicylate at relative humidities below RH_0, that at which deliquescence is initiated, has been measured. Sorption isotherms, expressed as the amount sorbed per unit area of solid surface, were different for unground and ground samples. Measurement of specific surface area for samples previously exposed to various relative humidities revealed no change with unground samples but a significant reduction with ground samples beyond about 20% relative humidity. Correcting isotherms for this change in area brings the results with ground and unground samples into closer agreement. These studies reveal that relatively low levels of water vapor sorption on crystalline water-soluble solids, below RH_0, can give rise to some form of "surface dissolution" when the solid has been subjected to various forms of mechanical disturbance.

KEY WORDS: water vapor sorption; deliquescence; surface dissolution; sodium chloride; sodium salicylate.

INTRODUCTION

Previous studies from this laboratory (1–4) investigated the underlying mechanisms responsible for water vapor uptake by water-soluble crystalline solids above their critical relative humidity, RH_0, the relative humidity of a saturated solution of the crystalline solid. It was shown theoretically and experimentally that the uptake of water to produce deliquescence for both single- and multiple-component systems first occurs above RH_0 for the system, with the maintenance throughout the process of a saturated solution in the liquid film surrounding the solid. Further, the kinetics of this process were shown to be governed by vapor diffusion and heat transport rates.

What is less clearly understood is under what conditions exposure to water vapor below RH_0 might cause hydration and dissolution of these crystalline solids so as to produce enough mobility of surface atoms or molecules to cause a change in their physical and chemical properties. From a bulk-phase thermodynamic perspective, the dissolution of a crystalline solid into its sorbed water would not be expected to occur below RH_0 since the chemical potential of the water associated with the surface must be equal to that in the vapor state at equilibrium. As such, if solid dissolves, the water activity (approximated by vapor pressure) in the vapor phase must equal the water activity above the saturated solution at equilibrium (vapor pressure and, by definition, RH_0). It is important to note that vapor pressure, a colligative property, will be lowest for a saturated solution relative to all other less concentrated solutions. However, despite this, significant evidence exists to show that sorbed water below RH_0 is capable of influencing such solid properties as the specific surface area, surface conductivity, and tendency to cake and to flow (5–7). Rees and Shotton (8), Lordi and Shiromani (9), and Down and McMullen (10) have attributed hardness increases observed for compacts of sodium chloride exposed to relative humidities below RH_0 to solubilization and subsequent recrystallization of the sodium chloride. Down and McMullen (10) have suggested that such behavior arises because of a disruption in the surface structure of sodium chloride by the compaction process, which permits enough water vapor sorption to produce a metastable state of dissolved sodium and chloride ions. This then recrystallizes upon standing and drying to produce a greater bond. These conclusions were based on earlier suggestions by Hüttenrauch (11) that various pretreatments of solids, such as mechanical trituration and compaction, can "activate" solid surfaces to higher states of disorder and, hence, higher free energies. This in turn can bring about enhanced vapor sorption and chemical reactivity. These ideas were developed by Hüttenrauch (11,12) from the recognition that amorphous forms of water-soluble solids, e.g., sucrose (13,14), can take up relatively large amounts of water below RH_0 and can form metastable solutions which recrystallize on standing or with drying. This has also been reported to occur with various cephalosporins made amorphous by grinding or freeze drying (15,16). Consequently, it is possible that the effects observed by various workers when crystalline solids are exposed to water vapor below RH_0 may arise because of subtle states of disorder at the surface brought about by their prior treatment.

In this study, we have systematically measured the sorption of water vapor by well-defined samples of crystal-

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Table I. Surface Area, Critical Relative Humidity, and Water Solubility for Sodium Chloride and Sodium Salicylate

Solid	Specific surface area (m^2/g)	Critical relative humidity, RH_0	Water solubility (molal)
Sodium chloride	0.0875	75	6.14
Sodium salicylate	1.97	79	6.25

line sodium chloride and sodium salicylate as a function of relative humidity before and after mechanical trituration. We have sought to obtain quantitative evidence for an understanding of the occurrence or absence of water vapor effects below RH_0 under various conditions.

EXPERIMENTAL

Materials

Solids. Sodium chloride (Columbus Chemical Industries) and sodium salicylate (Matheson, Bell and Coleman) were chosen as examples of an inorganic and organic water soluble salt, respectively. The sodium chloride was recrystallized by the procedure of Barraclough and Hall (17), while the sodium salicylate was used as received to maintain maximum specific surface area. Both samples were shown by X-ray powder diffraction studies (Phillips Instruments) to exhibit a high degree of crystallinity, with the expected characteristic peaks (18,19). Table I reports the specific surface area of each solid, as determined by BET gas adsorption using high-purity krypton–helium gas mixtures (Matheson Co.). Also included in Table I are the values of RH_0, the relative humidity of an aqueous saturated solution, obtained by a procedure described previously (4), and the aqueous solubilities of sodium chloride and sodium salicylate (20).

Both solids were also pretreated by grinding in a mortar for 15 min using a hand-held pestle. Powder diffraction X-ray analysis revealed no change in X-ray patterns from that observed with unground samples. The reduction in particle size produced specific surface areas of 0.348 and 8.01 m^2/g, respectively, for the ground sodium chloride and sodium salicylate samples.

Water Vapor Sorption

Apparatus. The water vapor sorption apparatus used in this study is schematically depicted in Fig. 1. Important features of the setup include a vacuum down to about 10^{-7}

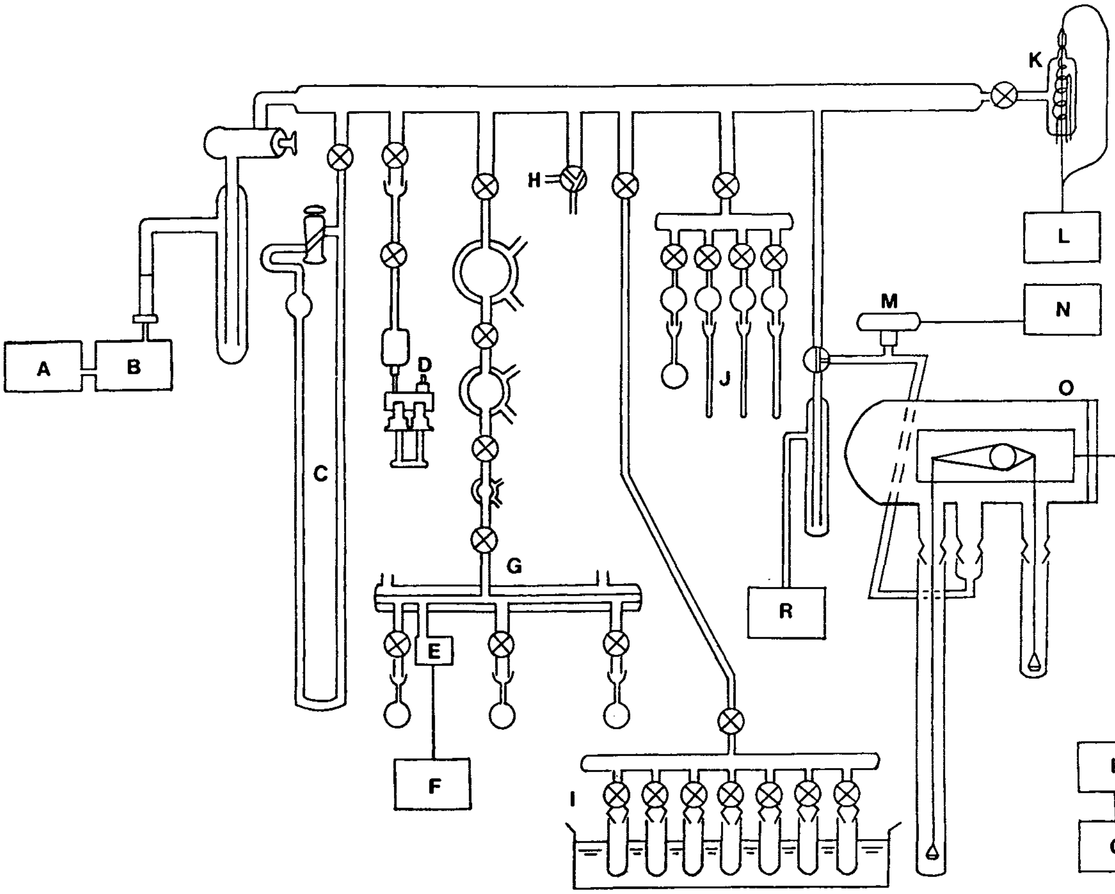

Fig. 1. Water sorption apparatus. Components: forepump 1 (A); oil diffusion pump (B); oil manometer (C); surface area equilibration port (D); pressure transducer (E); electronic manometer (F); volumetric sorption apparatus (G); connection to pure helium gas (H); temperature-controlled saturated salt solution chambers (I); NMR equilibration ports (J); ionization gauge (K); ionization gauge controller (L); convectron gauge (M); convectron gauge controller (N); electrobalance (O); electrobalance control unit (P); recorder (Q); forepump 2 (R).

Torr, the capability of measuring water vapor sorption isotherms both volumetrically (E, F, G) and gravimetrically (O, P, Q), thermostated saturated solutions to provide constant relative humidity over a wide range (I), direct measurement of this relative humidity (C), and various ports for pretreating samples before making such measurements as surface area (D) and NMR (J). Details have been presented elsewhere (21).

Procedures. Because of its relatively low specific surface area, it was necessary to study the sorption of water vapor by sodium chloride volumetrically, using a sample size of approximately 20 g. Such a large sample size, and hence high total surface area, precluded the need to correct sorption data for any water sorbed to the apparatus. Sample pretreatment consisted of heating to 220°C under a vacuum of less than 10^{-6} Torr. Following reequilibration of the sample cell to 20°C the cell was isolated from the dosing chamber and the appropriate dosing volume was equilibrated with water vapor of selected vapor pressure. Water vapor from the dosing volume was then expanded into the sample cell volume, with the pressure in the system again being monitored until a new equilibrium was attained. The second and subsequent isotherm points were obtained by repeating this procedure, always beginning each determination with the sample isolated in vacuum. It was shown that this procedure greatly enhanced the sensitivity of the method and reduced the cumulative effect of experimental error in determining the amount sorbed. This procedure required approximately 3 days per data point: 1 day for each equilibration and 1 day of vacuum/heat drying.

Because of its much greater specific surface area, the water vapor sorption of sodium salicylate could be studied gravimetrically using a Cahn electrobalance Model RG-HV situated in the vacuum system as schematically shown in Fig. 1. Samples were vacuum dried at 100°C and sequentially equilibrated with water vapor at increasing relative humidities, while the sample weight was continuously monitored. With this procedure each data point required about 1 day for equilibration.

Effects of Water Vapor Sorption on Surface Area

Since in previous studies some changes in specific surface area had been noted when water-soluble salts were exposed to relative humidities below RH_0 (5,6), such experiments were carried out in this study with unground and ground sodium chloride and sodium salicylate. The specific surface area of each sample was measured initially using a Quantasorb system (Quantachrome Corp.), then dismounted from the Quantasorb and attached to the vacuum assembly (see Fig. 1, component D). After thorough drying under vacuum, it was exposed to the desired relative humidity for at least 24 hr, the time required for sorption equilibrium. This sample was then vacuum dried and reattached to the Quantasorb for final surface area measurement. A sample holder, described in detail previously (22), that could facilitate attachment to both the vacuum assembly and the Quantasorb system without exposing the sample to ambient conditions was employed to conduct these experiments.

Pulsed NMR Studies

Sample Treatment. Up to 1-g samples of unground and ground sodium chloride and sodium salicylate were filled into 5-mm NMR tubes and attached to the sorption apparatus. A small amount of glass wool was inserted into the upper portion of the tubes to prevent sample loss during vacuum drying. Select samples were dried to less than 1×10^{-6} Torr and 320°C to obtain baseline spectra for each dry material. Other samples were subjected to vacuum drying (1×10^{-4} Torr) at ambient temperature prior to equilibration at specific relative humidities. Upon the attainment of equilibrium, the external surface of the glass tube was heated at a point between the solid and the glass wool to produce a sealed equilibrated sample that could be used for subsequent pulsed NMR analyses.

Pulsed NMR Procedure. Pulsed NMR measurements were carried out using Brucker Model HX-90 and Nicolet Corp. Model 1280 NMR spectrometers, with field strengths of 2.1139 and 4.6975 tesla, respectively. Studies carried out using the 2.1139-tesla-field strength instrument consisted of coaxially inserting the 5-mm sample tube into a 10-mm tube containing d_6-benzene diluted in carbon tetrachloride. With the instrument centered on the water frequency, an inversion recovery pulse sequence was employed to reduce the incidence of anomolous peaks that were apparent in the viewing frequency range. Between 300 and 1000 scans were taken for samples in proton studies using this instrument.

^{23}Na NMR studies using 23.8-MHz rf pulses required only a single pulse (i.e., no inversion recovery sequence was necessary). With the viewing frequency centered on the sodium frequency range, approximately 500–5000 scans were conducted on these samples.

Proton and sodium studies carried out on the higher-field strength instrument were run unlocked, as the field was quite stable. An inversion recovery sequence was not necessary. Experiments run using this instrument employed about 300 scans.

Following collection of the individual "free induction decay" signals, a computer summed and Fourier transformed the data from a time-domain to a frequency-domain function. Further data analysis allowed estimation of the state of sorbed water in these systems.

RESULTS

Water Vapor Sorption Isotherms

Sorption isotherms at 20°C below RH_0 for unground and ground sodium chloride samples, expressed as the amount sorbed per unit area of previously unexposed sample, are presented in Fig. 2. The results obtained with the unground sample are in excellent agreement with those reported by Barraclough and Hall (17) on a similarly prepared sample. In Fig. 2, it can be seen that the ground sodium chloride sample sorbs considerably more water than the unground sample at lower relative humidities, even though the two sets of data are expressed on a per unit area basis. On the other hand, with increasing relative humidity, the sorption of water vapor on the ground sample is distinctly less than that for the unground sample.

A comparison of sorption isotherms for sodium salicylate in Fig. 3 shows that up to about 54% relative humidity there is less apparent difference between sorption on a per unit area basis than that observed for sodium chloride. However, as with sodium chloride, at higher relative humidities, but still below RH_0, the unground sample exhibits signifi-

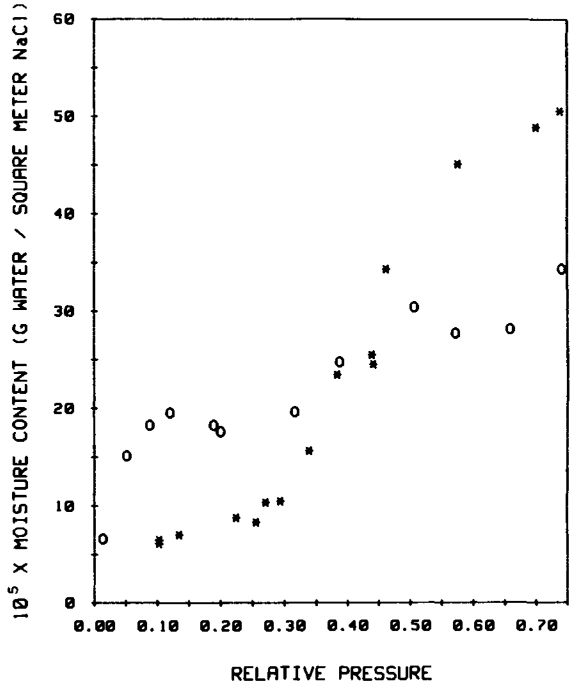

Fig. 2. Water sorption isotherms for unground (*) and ground (O) sodium chloride plotted per square meter of the previously unexposed sample at 20°C.

cantly greater water vapor sorption. It must be stressed that Figs. 2 and 3 represent equilibrium water uptake data and not kinetic effects.

Effects of Water Vapor on Surface Area

Figures 4 and 5 present data which show the effect on specific surface area from exposure to relative humidities below RH_0 for both sodium chloride and sodium salicylate, unground and ground. A convenient way to represent any change is to plot the surface area ratio of a sample exposed to water vapor to that prior to exposure. In Figs. 4 and 5,

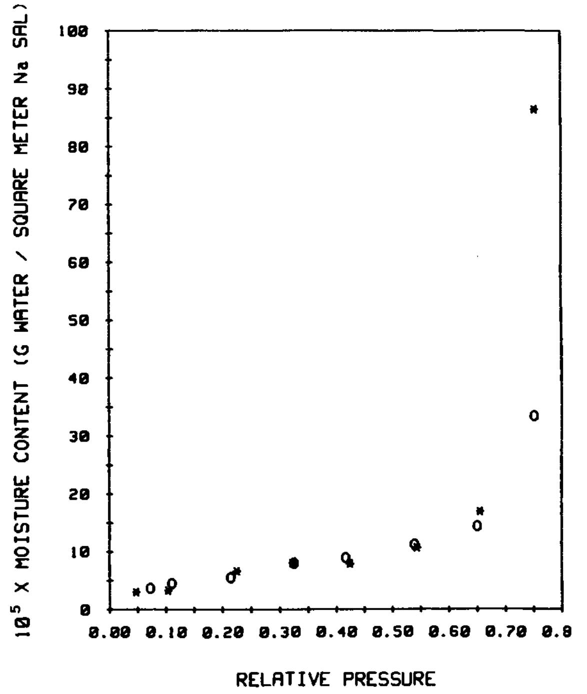

Fig. 3. Water sorption isotherms for unground (*) and ground (O) sodium salicylate plotted per square meter of the previously unexposed sample at 20°C.

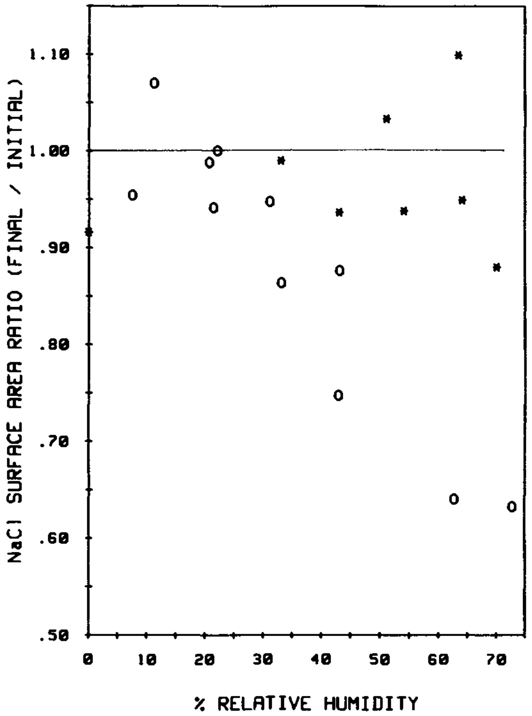

Fig. 4. Ratio of final surface area (following equilibration) to initial surface area as a function of relative humidity of equilibration for unground (*) and ground (O) sodium chloride.

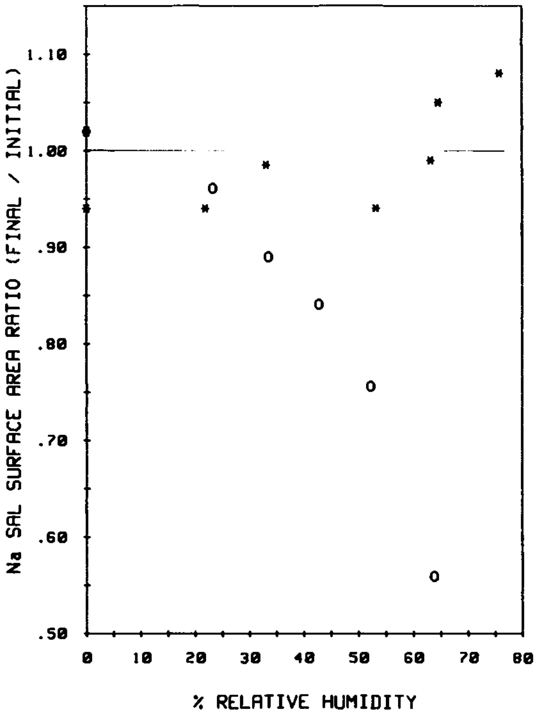

Fig. 5. Ratio of final surface area (following equilibration) to initial surface area as a function of relative humidity of equilibration for unground (*) and ground (O) sodium salicylate.

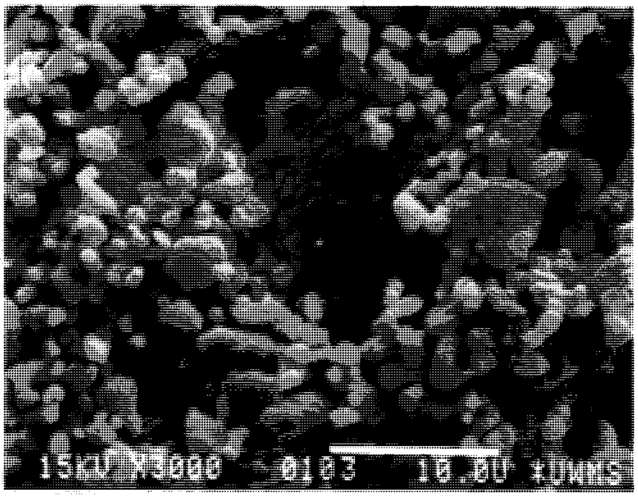

Fig. 6. Scanning electron photomicrograph of ground sodium chloride exposed to 0% relative humidity.

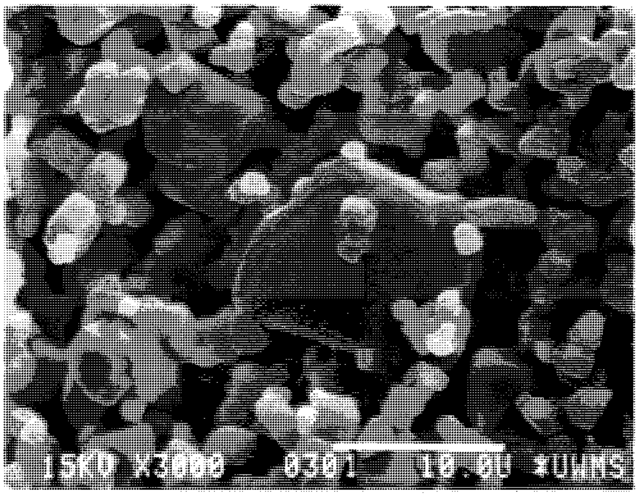

Fig. 8. Scanning electron photomicrograph of ground sodium chloride exposed to 64% relative humidity.

therefore, a ratio of one represents no change in surface area with exposure, whereas a value of less than one indicates a reduction in specific surface area. As seen in Figs. 4 and 5, the unground samples generally exhibit ratios within plus or minus 10% of 1.0, which is consistent with the experimental error associated with these BET surface area measurements. On the other hand, beyond about 20% relative humidity, with both solids, there is a significant decrease in specific surface area; this effect becomes greater with increasing relative humidity. As expected, beyond RH_0 deliquescence occurs with all samples.

To support these observations, various samples of sodium chloride and sodium salicylate, before and after exposure to different relative humidities, were subjected to scanning electron microscopic examination (JSM-35C, JEOL) to look for possible surface morphological changes. Figures 6, 7, and 8 show the surface morphology of ground sodium chloride exposed to 0, 11, and 64% relative humidity, respectively. Whereas there appears to be no change relative to 0% in the 11% sample, apparent smoothing and enlarging of crystals clearly can be seen for the sample exposed to 64% relative humidity. Figures 9 and 10 show micrographs for unground sodium chloride exposed to 0 and 70% relative humidity, respectively, with no apparent morphological difference being noted. Likewise, with sodium salicylate, a morphological change indicative of dissolution appeared to occur with the ground sample but not the unground sample. These findings are entirely consistent with the observations in Figs. 4 and 5.

NMR Studies

To ascertain whether any more direct evidence of surface structural change could be obtained, both proton and sodium pulsed NMR measurements were carried out on unground and ground samples exposed to different relative humidities and sealed in NMR tubes. Previous studies with polymeric excipients have been able to detect differences between "mobile" and "nonmobile" water associated with the solid (21). Although clear signals for mobile sodium ions

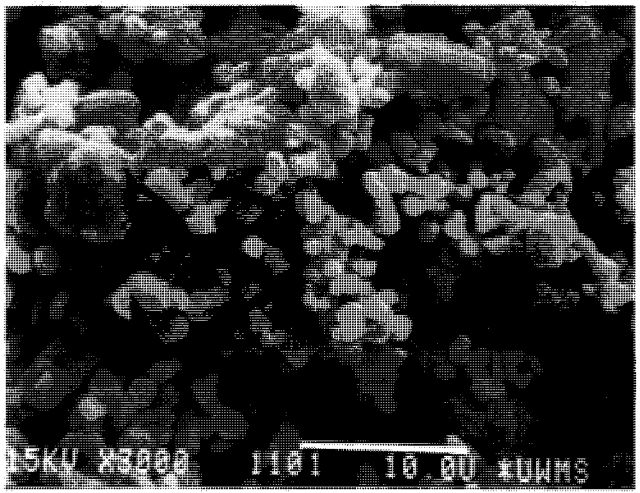

Fig. 7. Scanning electron photomicrograph of ground sodium chloride exposed to 11% relative humidity.

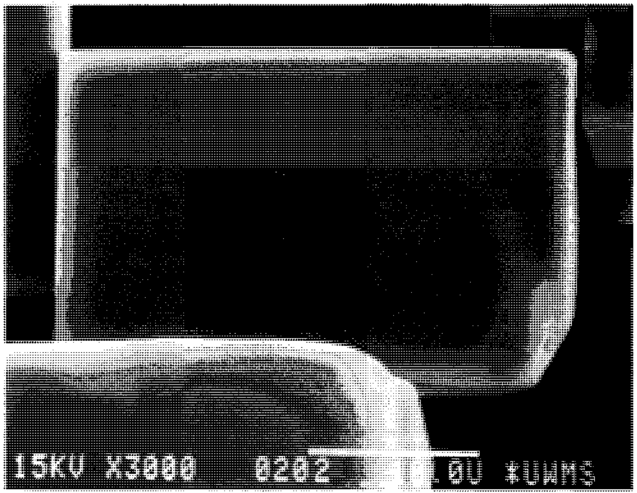

Fig. 9. Scanning electron photomicrograph of unground sodium chloride exposed to 0% relative humidity.

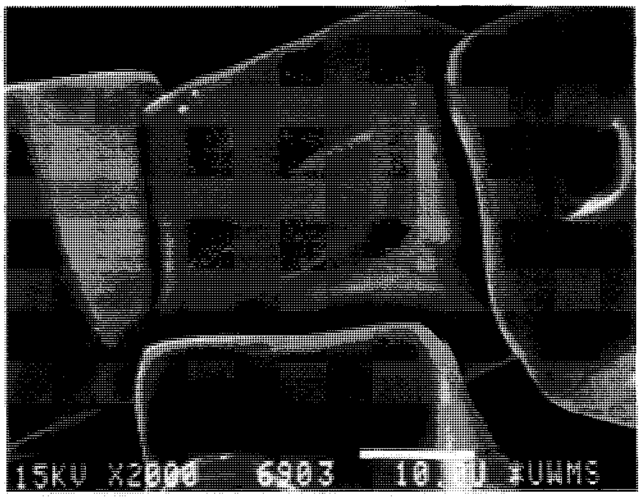

Fig. 10. Scanning electron photomicrograph of unground sodium chloride exposed to 70% relative humidity.

were observed after exposure to relative humidities just in excess of RH_0, where deliquescence occurs, no evidence for such "mobility" could be detected for any samples at field strengths of 2.1139 and 4.6975 tesla below RH_0. We believe, therefore, that either there are no mobile sodium ions below RH_0 or any small change in mobility which might have occurred is below the sensitivity of this measurement. Likewise, whereas mobile water could easily be detected above RH_0, no mobile water was detected below RH_0 except for sodium salicylate at a relative humidity of 75%. Again, we believe that the low total amount of water sorbed, particularly in the case of sodium chloride, precluded the detection of mobile water by NMR under the conditions available for study.

DISCUSSION

Sorption on Unground Samples

From Figs. 2 and 3 it can been seen that the sorption of water by the unground samples of sodium chloride and sodium salicylate on a per unit area basis is quite low in terms of percentage water uptake and fairly comparable for the two systems. From these data, up to about 35% relative humidity, it is possible to apply the BET equation (23) to estimate an apparent specific surface area. Table II lists the weight of water sorbed per square meter that is expected to be equivalent to the first layer of molecules, W_m, and the "apparent" specific surface area calculated by assuming this first layer to cover the surface completely at a closest-packing area of 12.5 Å^2 per water molecule (22). Also listed is the "true" surface area of these materials estimated using krypton gas and the ratio of apparent to true surface area. From these ratios it is clear that the sorbed water molecules represented by W_m cover only a fraction of the available surface area and, therefore, constitute less than complete monolayer coverage of the surface. This suggests that it is quite meaningless, as is often done, to speak in terms of number of layers as multiples of W_m obtained from water sorption studies, except as a point of reference (5,6). A number of workers have studied water vapor sorption of highly crystalline alkali halides and, likewise, have shown that W_m does not represent a completely covered monolayer (17,24,25). Isosteric heats of adsorption with these systems indicate that the water sorbed up to W_m is very tightly bound, while subsequently sorbed water is less tightly bound (17,25).

To analyze these results further, it was of some interest to estimate any stoichiometric relationships that might exist between the number of molecules of water sorbed and the number of available sorption sites. Let us assume that the sorption site is a sodium chloride or sodium salicylate ion pair. The approximate number of pairs per unit area may be estimated by calculating the molar areas of these materials, A_m, from Eq. (1) (26):

$$A_m = fN^{1/3}(M/\rho)^{2/3} \tag{1}$$

where f is a packing factor assumed to be equal to 1.11 (27) (i.e., for a two-dimensional, hexagonal, close-packed surface layer), M is the molecular weight of the solid, and ρ is the density of the solid. Knowing the number of water molecules sorbed at W_m per square centimeter from Table II and the number of ion pairs of solid available per square centimeter as given in Table III, we can then calculate the expected ratio of water molecules per solid ion pair, as also given in Table III.

The ratio of water molecules per solid pair in Table III should correspond very closely to the ratio of apparent to true specific surface areas given in Table II since A_m and specific surface area are related if the sorption site is assumed to be a single salt pair, and the values for water in both tables are obtained from the W_m values from water sorption isotherms. The ratio for water and sodium chloride molecules in Table III corresponds quite closely to the ratio of the apparent to true specific surface areas given in Table II. However, although the ratio is still considerably less than unity, absolute agreement is not as good for sodium salicylate. This may indicate that the assumptions made in Eq. (1) concerning molecular geometry are not as good for the organic molecule as compared to sodium chloride. This anal-

Table II. BET Monolayer Values and Apparent and True Surface Areas for Sodium Chloride and Sodium Salicylate Unground Samples

Solid	BET "monolayer" value, W_m (g/m^2)	Specific surface area (m^2/g)		Surface area ratio, apparent/true
		Apparent	True	
Sodium chloride	7.6×10^{-5}	0.028	0.087	0.32
Sodium salicylate	6.0×10^{-5}	0.50	2.0	0.25

Table III. Comparison of the Number of Solid Molecules per Unit Surface Area with the Number of Water Molecules Sorbed per Unit Area at W_m[a]

			(Molecules/cm^2) × 10^{-14}		
Solid	MW	Density	Solid	Water	Ratio, water/solid
Sodium chloride	58.5	2.17[b]	7.1	2.3	0.32
Sodium salicylate	160	1.38[c]	2.7	2.0	0.74

[a] W_m corresponds to the completion of the BET monolayer of sorbed water vapor.

[b] From Ref. 28.

[c] Measured in this study using hexane.

ysis, therefore, lends further evidence that the tightly bound layer covers less than the maximum possible number of binding sites for both solids.

To summarize this section, we may conclude that for sodium chloride and sodium salicylate, a continuous layer of tightly bound water does not exist and that subsequent multiples of W_m do not represent distinct layers of water. More likely, water sorbed beyond W_m is sorbed directly to the solid surface via weaker bonding forces to form the more completed "first layer." In effect, an intermediate region of water is sorbed with a continually changing energy of sorption, ranging from slightly less than tightly bound water to that of bulk water. This intermediate region of sorbed water for sodium chloride and sodium salicylate should amount to about three to four times W_m before bulk water is formed, if stoichiometries of 0.32 and 0.25 water molecules per solid pair (see Table II) are assumed tightly sorbed, respectively, and bulk water is formed beyond a "complete" monolayer. It is interesting to note in Fig. 2 that a distinct step in the water sorption isotherm for unground sodium chloride occurs at three times W_m. This moisture content could correspond to that calculated for completion of the "true" monolayer.

Comparison of Sorption by Unground and Ground Samples

From Fig. 2 it is quite clear that the grinding of sodium chloride produces two interesting effects on water vapor sorption relative to that for the unground sample: (i) an enhanced extent of sorption per unit area at relative humidities below about 35% and (ii) a marked decrease in sorption for the ground sample at higher relative humidities. For sodium salicylate, which has a significantly greater specific surface area than sodium chloride, both unground and ground, we see no significant difference in water vapor sorption in Fig. 3 until 55% relative humidity, where the ground sample exhibits a markedly reduced extent of sorption. Since the data for sorption are expressed on a per unit area basis, the most plausible explanation for a higher extent of sorption for the ground sodium chloride sample is that the grinding process has in some way disrupted the surface structure to permit, in essence, a supersaturated state of sorbed water relative to that sorbed on the crystalline sodium chloride surface. This appears to be a clear experimental confirmation of the proposals previously presented by Hüttenrauch (11,12) and consistent with the observations of Down and McMullen with compacted sodium chloride samples (10). It is not exactly clear why we did not see a significant difference in water uptake for the ground and unground sodium salicylate samples at lower relative humidities, but we suspect that the larger total amounts of water taken up because of relatively high specific surface areas masked this rather subtle effect (small differences between large numbers).

The existence of a "supersaturated" state of sorbed water is strongly supported by the marked reduction in water vapor sorption at higher relative humidities for ground samples relative to unground samples of sodium chloride and sodium salicylate. Such a reduction could arise if the disrupted solid surface in the presence of more moisture would be able to revert to a lower-energy, more crystalline form. Such a reversion would involve "recrystalization," or annealing, of surface atoms and molecules, leading to a re-

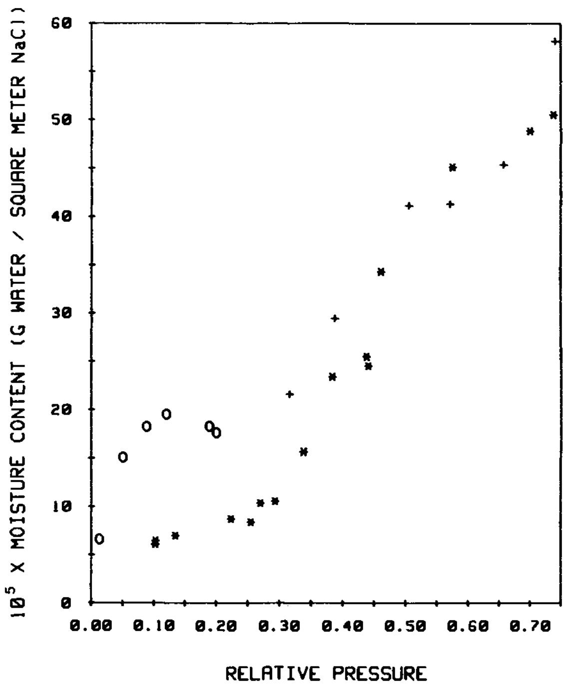

Fig. 11. Unground (*), ground noncorrected (O), and ground surface area-corrected (+) water sorption for sodium chloride.

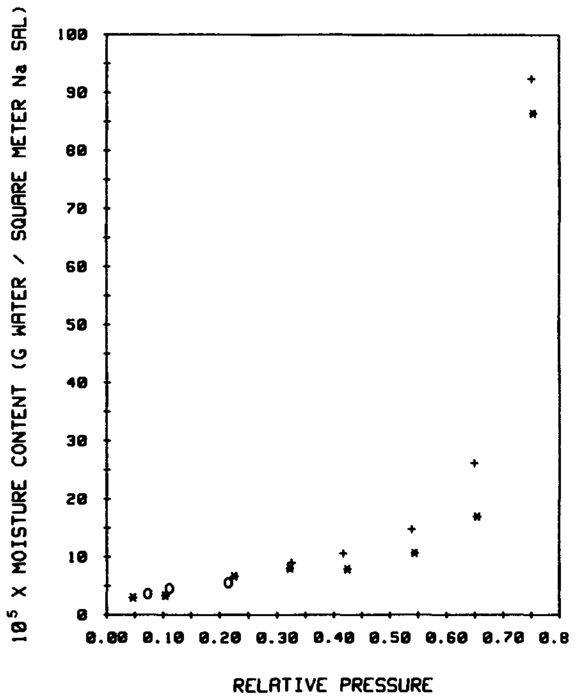

Fig. 12. Unground (*), ground noncorrected (O), and ground surface area-corrected (+) water sorption for sodium salicylate.

duced specific surface area. Since the surface areas of unexposed ground samples were used to estimate the amount sorbed per square meter, and since exposure to water vapor reduces the specific surface area of these samples, as seen in Figs. 4 and 5, it seems reasonable that the reduced water vapor sorption by the ground samples arises from the resultant reduction in specific surface area. Consequently, in Figs. 11 and 12, we have replotted the sorption isotherms of sodium chloride and sodium salicylate correcting for the surface area changes noted in Figs. 4 and 5. Comparison of Figs. 2 and 3 with Figs. 11 and 12 reveals that such a correction puts the sorption isotherms for ground and unground samples at higher relative humidities in much closer agreement with each other.

This analysis, therefore, suggests that there is a distinct amount of water sorbed above which sufficient surface ion mobility can occur to produce a reduction in specific surface area on standing or with drying. This metastable state of sorbed water and "dissolved" solid is induced by the grinding process. From the sorption isotherms of unground sodium chloride and sodium salicylate, the most tightly bound water, corresponding to W_m, should be completed near a relative humidity of 20%. As shown above, no change in specific surface area of ground samples occurs below this value. Hence, we can conclude that the exposure of these water-soluble solids to water vapor below RH_0 gives rise to surface changes only when the amount of water sorbed exists in excess of the most tightly bound fraction of water, W_m. Furthermore, these effects occur with less than one complete monolayer of water covering the solid surface.

Pharmaceutical Significance

These studies reveal that relatively low levels of water vapor sorption on crystalline water-soluble solid surfaces, i.e., less than complete coverage of the surface, can give rise to specific surface area changes, apparently caused by "surface dissolution." However, such effects are not seen with such solids unless a certain degree of disorganization is initiated at the surface. Thus water-soluble solids subjects to mechanical processing such as grinding, milling, micronization, and compaction can exhibit changes in their reactivity toward water vapor. The disturbing aspect from a pharmaceutical perspective is that subtle changes on the surface need only occur with relatively small amounts of sorption of water to produce significant changes. It suggests that many chemical and physical stability problems arising during the storage of solid dosage forms, particularly as they undergo variations in temperature and relative humidity, may arise from effects as subtle as those presented in this study. The lack of effect seen with the unground samples suggests that serious consideration be given to the pretreatment of all water-soluble crystalline materials used in formulations of solid dosage forms.

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