Role of Water in the Physical Stability of Solid Dosage Formulations

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ABSTRACT: The interaction of moisture with pharmaceutical solids is highly crucial to an understanding of water-based processes, for example, manufacturing processes or prediction of solid dosage form stability and shelf life. Both the active pharmaceutical ingredient (API) and excipients in the formulation have different moisture sorption properties that can result in unexpected processing-induced phase transitions and they can affect solid-state phase transitions in the final dosage forms. The character of excipient effects on the stability of formulation. Phase transformations in formulations can lead to instability in physicochemical, biopharmaceutical, and processing properties of products. The aim of the present study was to investigate the water sorption properties of different excipients, model the sorption isotherms, examine the phase transitions, and identify differences of excipients in solid dosage form stability using dynamic vapor sorption analysis, near-infrared spectroscopy, and X-ray diffraction methods. The thermal processing was carried out with a variable temperature X-ray powder diffractometer to compare the dehydration behavior of wet excipients and evaluate solid-state properties during heating. These results showed that despite some limitations, moisture sorption isotherms of excipients are useful in predicting solid-state stability, interactions at early stages of formulation development, and effects of moisture on physicochemical properties of the final dosage forms. © 2005 Wiley-Liss, Inc. and the American Pharmacists Association J Pharm Sci 94:2147–2165, 2005

Keywords: dynamic vapor sorption; excipients; near-infrared (NIR) spectroscopy; phase transition; sorption isotherms; X-ray powder diffraction

INTRODUCTION

Pharmaceutical solids may come in contact with water during manufacturing processes and some moisture could remain as the residual water from processing in solid oral dosage forms. Moreover, they may be exposed to water during storage at high relative humidity (RH) or in a dosage form consisting of materials that contain water and are capable of transferring it to other ingredients.1 The physical and chemical properties of pharmaceutical solids are critically dependent on the presence of moisture, for example, flow, compaction, dissolution, stability, storage, processing into formulations, and final product packing.2 The association between moisture and solid materials was described as one in which the moisture is adsorbed as monolayers or multilayers or may be present as condensed water at the surface.3 Water can interact with crystalline solids by
adsorption of moisture on particle surfaces, crystal hydrate formation, deliquescence, and capillary condensation. In contrast, amorphous materials have a high capacity for water vapor sorption, that is, the amount of water absorbed is greater than what could be accounted for only by surface adsorption and thus the bulk properties of the solid can be significantly altered. The amount of water that is sorbed is dependent on the chemical properties and polarity of the compound, as well as on the RH, temperature, and particle-size distribution, specific surface area, and deliquescence, structure of the sorbent surface, and porosity of the material. For these reasons information on the sorption mechanism of water on powder surfaces is required. This information can often be obtained from the shape of the vapor sorption isotherm. Moisture sorption isotherms characterize the amount of vapor adsorbed or desorbed at different equilibrium concentrations in the gas phase. Isotherm equations are useful for predicting the water sorption properties of excipients, but not even one equation gives results accurate throughout the entire range of water activities. The BET equation (Brunauer-Emmett-Teller’s multilayer adsorption theory) was developed based on the fact that sorption occurs in two distinct thermodynamic states—a tightly bound portion and multilayers having the properties of bulk free water. The classical BET model of adsorption is used only in the range of RH up to about 30%–40%. The GAB (Guggenheim-Andersen-de Boer) monolayer sorption theory model introduces a third state of sorbed species intermediate with the tightly bound and free states. Even though the GAB model does not always truly describe the moisture sorption phenomenon, this equation offers considerable practical utility in fitting isotherms for pharmaceutical materials to compare them with each other over the entire RH range.

The physical adsorption isotherms may be classified into six major types (I–VI) according to the IUPAC classification (International Union of Pure and Applied Chemistry). Types I, III, V, and VI isotherms are not commonly observed. Type III isotherms appear when all the sorption occurs according to a multilayer mechanism throughout the pressure range and indicate weak adsorbent-adsorbate interactions. Type II isotherms (sigmoid or S-shaped) are the normal form of isotherms, that are usually obtained with nonporous or macroporous adsorbents. This isotherm represents unrestricted monolayer-multilayer sorption. In type II isotherms multilayer sorption occurs at high water vapor pressures, whereas monolayer adsorption occurs at low pressures. The equilibrium conditions are slightly different if attained from adsorption rather than desorption processes and the moisture content is lower for sorption. The difference between adsorption and desorption isotherms is termed hysteresis, which occurs in the capillary condensation region of the sorption isotherms for ranges of different adsorbate-adsorbent pairs.

A pharmaceutical dosage form generally consists of an active pharmaceutical ingredient (API) combined with a varying number of excipients that have been added to the formulation to define the responsibility of formulating a product that is physically and chemically stable, manufacturable, and bioavailable. Dalton and Hancock found that the behavior of the formulations varied considerably depending on the large differences in the water sorption behavior of the excipients. The excipients also significantly affected the phase transitions of the API, as previously reported. These studies indicated that crystalline excipients in the formulation could even accelerate and amorphous excipients could delay the polymorphic transformations of APIs. Many factors related to moisture may induce unexpected phase transformations with new properties in the solid state and therefore the solid-state properties of API as well as the excipients must be understood in order to ensure consistent dosage form. Phase transformations of nitrofurantoin anhydrate with α-lactose monohydrate (LMH) or microcrystalline cellulose (MCC) under high humidity conditions were reported earlier by Otsuka et al. They found that the hydrate formation of nitrofurantoin was accelerated by LMH in the formulation but not by MCC.

The excipients used in this study are widely used for solid dosage forms and have different water sorption properties—two crystalline, three partially amorphous, and two amorphous well-known excipients were selected. The aim of present study was to investigate the water sorption properties of different excipients, model the sorption isotherms, examine the phase transitions, identify differences of the excipients in solid dosage form stability as well as to compare the dehydration behavior of wet excipients and evaluate solid-state properties during heating. It is advantageous if the moisture sorption isotherm of a formulation can be predicted at an early stage of formulation development.
MATERIALS AND METHODS

Materials

A total of 13 different excipients were used in this study (Table 1). The excipients studied were divided into three groups based on their crystallinity:

- crystalline excipients,
- partially crystalline excipients,
- amorphous excipients.

Water Sorption-Desorption Isotherms by DVS Method

The water sorption-desorption isotherms were measured using an accurate humidity- and temperature-controlled microbalance system, Dynamic Vapor Sorption (DVS 1, Surface Management Systems, Ltd., 3 Warple Mews, Warple Way, London, UK). The 10–20 mg sample was predried at 25°C by flowing dry nitrogen. The relative humidity (RH) was raised in steps from 0% to 95% and back to 0%. The equilibration condition at each step of the RH for the rate of change in mass with time ($\frac{dm}{dt}$) was selected for each material separately. The mass changes were calculated with respect to the mass of the dried sample.

Data Analysis

The experimental monolayer water values were determined from the sorption isotherms, using BET equations and GAB equations for modeling the moisture sorption isotherms.

Water Sorption with the Desiccator Method

Each excipient was dried on trays at 45°C and 70–75 mbar for 24–48 h in a vacutherm (Heraeus VT 6025, Kendro Laboratory Products GmbH, 63450 Hanau, Germany) and then dried further at 22°C in the vacuum desiccator (Nalgene desiccator, Nalge Company, Rochester, NY) at RHs of 0% for 5 days. The moisture sorption properties of the excipients (~500 mg/sample) were determined gravimetrically before and after storage at 22°C under conditions of differing RH (0%–95% RH). The various RH conditions were achieved in vacuum desiccators using saturated salt solutions. The relative humidities were 0% RH (silica gel), 11% RH (lithium chloride), 23% RH (potassium acetate), 33% RH (magnesium nitrate), 43% RH (potassium carbonate), 52% RH (magnesium nitrate), 59% RH (sodium bromide), 75% RH (sodium chloride), 85% RH (potassium chloride), 95% RH (disodium hydrogen phosphate), and all the salts were of reagent grade. Samples in triplicate in open glass vials were allowed to equilibrate in the vacuum desiccator and were stored for 2 weeks.

X-Ray Powder Diffractometry (XRPD)

The X-ray diffraction patterns were measured as previously described. The sorption samples were measured at room temperature after a 2-week storage under conditions of differing RH (0%–95% RH) in the desiccators.

The thermal processing samples were measured using a variable-temperature X-ray powder diffractometer (VT-XRPD) theta–theta diffractometer (Bruker axs D8, Bruker AXC GmbH, Karlsruhe, Germany). Both dry and wet masses at different water contents for each excipient (Table 1 and Fig. 5) were placed into the holder of an XRPD. The wet masses were performed with a mortar and pestle to simulate the early stages of preformulation. Each sample was heated at increments of 10°C from 25°C to 180°C–270°C (depending on the melting temperature) and maintained at the target temperature for 15 min. The heating rate was 0.2°C/s, angular range was 5°–40°, with increments of 0.1°, and the measuring time was 1 s/step (3° (2θ)/min). The variable-temperature diffraction patterns of the wet masses were measured 24 h after addition of water to ensure a uniform distribution of water. This method enabled us to follow the phase transformations of each excipient during the thermal processing. Estimation of the crystallinity was calculated as previously described.

Near Infrared Spectroscopy

Offline near-infrared (NIR) spectra were measured as previously described. The sorption samples were measured at room temperature after a 2-week storage under conditions of differing RH (0%–95% RH).

Specific Surface Area

The specific surface area was measured using the nitrogen-adsorption technique based on the BET theory (TriStar 3000, Micromeritics, Inc., Norcross, GA). The samples were outgassed under vacuum at 40°C for 1200 min. The specific surface area was calculated based on three points of the relative pressure 0.1, 0.2, and 0.3 in accordance with the current United States Pharmacopoeia (USP) version. The acceptance criteria for
**Table 1.** Physical Properties of Excipients Used in the Study

<table>
<thead>
<tr>
<th>Excipient (Manufacturer)</th>
<th>Brand Name</th>
<th>Average Particle Size $d_{50}$ (d10–d90) ($\mu$m)</th>
<th>Specific Surface Area (m$^2$/g)</th>
<th>BET g H$_2$O/100 g d.m.</th>
<th>GAB g H$_2$O/100 g d.m.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low substituted hydroxypropylcellulose (LHPC) (Shin-Etsu Chemicals Co., Tokyo, Japan)</td>
<td>Grade LH-11 (LHPC1)</td>
<td>57 (13–173)</td>
<td>0.99</td>
<td>5.41</td>
<td>6.58</td>
</tr>
<tr>
<td></td>
<td>Grade LH-21 (LHPC2)</td>
<td>54 (12–136)</td>
<td>0.97</td>
<td>5.46</td>
<td>6.73</td>
</tr>
<tr>
<td></td>
<td>Grade LH-30 (LHPC3)</td>
<td>18 (4–54)</td>
<td>1.93</td>
<td>5.29</td>
<td>6.36</td>
</tr>
<tr>
<td>$\alpha$-Lactose monohydrate (DMV International, Veghel, Netherlands)</td>
<td>Pharmatose® 200M (LMH)</td>
<td>43 (5–127)</td>
<td>0.52</td>
<td>0.0074</td>
<td>0.0071</td>
</tr>
<tr>
<td>Corn starch (Maydis amylum, Cerestar, Scandinavia)</td>
<td>(STA)</td>
<td>17 (9–35)</td>
<td>1.00</td>
<td>5.55</td>
<td>7.87</td>
</tr>
<tr>
<td>D-Mannitol (Roquette freres, Lestrem, France)</td>
<td>Mannitol® 60 (MANN)</td>
<td>46 (9–135)</td>
<td>0.33</td>
<td>0.0110</td>
<td>0.0050</td>
</tr>
<tr>
<td>Microcrystalline cellulose (FMC International, Cork, Ireland)</td>
<td>Avice1® PH 101 (MCC1)</td>
<td>57 (18–127)</td>
<td>1.21</td>
<td>2.69</td>
<td>3.46</td>
</tr>
<tr>
<td></td>
<td>Avice1® PH 102 (MCC2)</td>
<td>113 (31–209)</td>
<td>1.24</td>
<td>2.77</td>
<td>3.56</td>
</tr>
<tr>
<td></td>
<td>Avice1® PH 200 (MCC3)</td>
<td>196 (52–330)</td>
<td>1.17</td>
<td>2.69</td>
<td>3.41</td>
</tr>
<tr>
<td></td>
<td>Emcocl® 50 (MCC4)</td>
<td>63 (21–133)</td>
<td>1.37</td>
<td>2.80</td>
<td>3.71</td>
</tr>
<tr>
<td>Silicified microcrystalline cellulose (JRS Pharma, Nastola, Finland)</td>
<td>ProSolv® 50 (SMCC1)</td>
<td>56 (18–121)</td>
<td>5.63</td>
<td>2.71</td>
<td>3.45</td>
</tr>
<tr>
<td></td>
<td>ProSolv® 90HD (SMCC2)</td>
<td>121 (38–207)</td>
<td>6.48</td>
<td>2.67</td>
<td>3.39</td>
</tr>
<tr>
<td>Starch, pregelatinized (Colorcon, Indianapolis, IN, USA)</td>
<td>Sta-rx® 1500 (FGSTA)</td>
<td>72 (17–157)</td>
<td>0.26$^a$</td>
<td>5.39</td>
<td>7.27</td>
</tr>
</tbody>
</table>

$^a$Handbook of pharmaceutical excipients.43
the correlation coefficient was at least 0.9975. The masses of the samples were calculated by weighing first the empty sample tube and stopper assembly and the tube with the dried sample plugged by the stopper after drying before analysis.

**Scanning Electron Micrographs (SEMs)**

The morphology of the samples was presented based on micrographs taken with a SEM (Scanning electron microscope JSM-840A, Jeol, Tokyo, Japan). The sample preparation for electron microscopy was done according to the current USP version (an acceleration voltage of 4.5 kV).

**Particle Size Distribution**

The volume particle size distribution was determined using a method based on laser light diffraction (Laser Diffraction Particle Size Analyzer LS13 320, Beckman Coulter, Inc., Miami, FL). The samples were measured using air as the medium and were prepared by dispersing powder in the unique Tornado Dry Powder System.

**RESULTS**

**Characterization of Starting Materials**

The characteristic XRPD diffraction patterns of all 13 excipients were observed using XRPD in the angular range of 5°–40° (2θ) and by NIR spectroscopy. Fig. 1 presents the XRPD diffraction patterns measured for the samples of crystalline material (LMH and MANN), partially amorphous (MCC2, SMCC1, and STA), and amorphous material (LHPC2, PGSTA). The detailed information for starting material is presented in Table 2.

**Moisture Sorption**

The moisture sorption isotherms, crystallinity and morphology of each sample were studied, and the results of the sample excipients are presented in Fig. 2. The specific surface area values and size distribution parameters of the sample excipients are presented in Table 1 and Fig. 2.

**Crystalline Excipients**

The water adsorption isotherms of the crystalline excipients (MANN and LMH) approached the type III in behavior in the IUPAC classification. The adsorption-desorption isotherm of crystalline LMH and MANN showed no significant hysteresis. The monolayer was determined from experimental water sorption isotherm data with the BET and GAB equations. The BET and the GAB values for LMH and MANN are presented in Table 1. The mean crystallinity of LMH or MANN after storage at 0%, 85%, and 95% RH are presented in Table 2. The morphology of the crystalline excipients was examined using a SEM. The shape of the LMH particles was similar to that of the MANN particles, but LMH had more fine particles on the surfaces of larger particles and the particle-size distribution appeared wide, as seen in Figure 2A. The MANN particles showed smooth and plate like layers with narrow particle-size distribution. MANN had lower specific surface area than LMH (Table 1), due to the presence of small particles.

**Partially Crystalline Excipients**

The water isotherm curves of the partially crystalline excipients (SMCC1 and STA) showed the typical type II behavior described in the IUPAC classification (Fig. 2C and D), with a distinct “knee” for each isotherm curve a low RH. The MCC and SMCC showed wider hysteresis gaps than STA, especially at high RH. The BET and GAB values for SMCC1 and STA are presented in Table 1. The mean crystallinities of them after storage at 0%, 85%, and 95% RH are presented in Table 2.
Table 2. Summarized the Changes in Crystal Structure Determined by XRPD

<table>
<thead>
<tr>
<th>Excipient</th>
<th>Identification of Starting Material</th>
<th>Average Crystallinity (±10%) After Storage at 0–85–95% RH</th>
<th>Changes in Crystal Structure After Storage at 0%–95% RH</th>
<th>Changes in Crystal Structure During Thermal Processing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crystalline excipients:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>α-Lactose monohydrate (LMH)</td>
<td>Monoclinic monohydrate (27–1947, ICDD(^a))</td>
<td>80–80–75%</td>
<td>At 95% RH: features of the diffraction patterns for anhydrous β-lactose</td>
<td>At 150°C crystalline water dehydrated, at 180°C changed and remained to anhydrate</td>
</tr>
<tr>
<td>d-Mannitol (MANN)</td>
<td>β form(^{21,22})</td>
<td>75–75–75%</td>
<td>At 75% RH: ratios of some intensities changed because of preferred orientation of the crystals</td>
<td>At 160°C transformed to amorphous form, after cooling transformed to crystalline polymorph α form</td>
</tr>
<tr>
<td>Partially crystalline excipients:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Silicified microcrystalline cellulose (SMCCI)</td>
<td>Diffraction reflections at about 15.2, 18, 20.2, 23.1° (2θ)</td>
<td>45–45–45%</td>
<td>No changes in crystal structure</td>
<td>No permanent changes in crystal structure</td>
</tr>
<tr>
<td>Corn starch (STA)</td>
<td>Diffraction reflections at about 15, 16.5, 22.6, 34.7° (2θ)</td>
<td>25–45–55%</td>
<td>At 75%–95% RH: recrystallization</td>
<td>Some recrystallization</td>
</tr>
<tr>
<td>Amorphous excipients:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Starch, pregelatinized (PGSTA)</td>
<td>Wide diffraction reflections at around 19° (2θ)</td>
<td>0–25–30%</td>
<td>At 75%–95% RH: recrystallization</td>
<td>Some recrystallization</td>
</tr>
<tr>
<td>l-hydroxypropylcellulose LH-21, (LHPC2)</td>
<td>Wide diffraction reflections at around 21° (2θ)</td>
<td>No possible to determine</td>
<td>Transformed more amorphous</td>
<td>No changes, remained amorphous</td>
</tr>
</tbody>
</table>

\(^a\)ICDD; International Center for Diffraction Data, Newtown Square, PA, USA.)
The SMCC1 showed typical cellulose structure with different sizes and shapes of particles (Fig. 2C), whereas STA had nearly spherical particles (Fig. 2D). The MCC did not have much higher specific surface area than STA (Table 1). The specific surface area of SMCC was much higher compared with that of any other excipient, because the SiO2 treatment increases the specific surface area.

Amorphous Excipients

The water isotherm of the amorphous PGSTA was type II according to the IUPAC classification (Fig. 2E). At low RH the isotherm curve showed a distinct “knee” and a hysteresis gap remained over the entire RH range. The BET and the GAB values for PGSTA and LHPC2 are presented in Table 1. Average crystallinity of PGSTA after storage at 0%, 85%, and 95% RH is presented in Table 2. It was not possible to determine the crystallinity of LHPC2 (Fig. 2F). The water isotherm of the amorphous LHPC remained at type II curve, showing high moisture absorption at high RH; the LHPC2 showed no significant hysteresis. The PGSTA particles showed porous aggregates together with small particles (Fig. 2E). In contrast, the LHPC2 was composed of fibrous (rodlike particles) and relatively large particles with various shapes (Fig. 2F). The PGSTA had lower surface area than LHPC (Table 1).

X-Ray Diffraction

The effect of moisture sorption on all 13 excipients was investigated with XRPD after a 2-week
storage under conditions of differing RH (0%–95% RH) and major changes in crystal structure and in crystallinity are summarized in Table 2.

At a 95% RH, some additional features of the LMH diffraction patterns were identified, which closely reminded features of the diffraction patterns for anhydrous β-lactose (Fig. 3A). At 75% RH some additional features of the MANN diffraction patterns were also identified (Fig. 3A) and the ratios of some intensities changed. None of the MCC and SMCC samples showed any difference in crystal structure or crystallinity after storage at 0%–95% RH (Fig. 3B). At RH levels from 75% to 95% the STA diffraction patterns included features of recrystallization—reflections at about 15°–24° (2θ) became more clear (Fig. 3C). Wide reflections of the characteristic diffraction pattern for all LHPC samples were observed at 18°–23° (2θ). The widths and intensities of all three LHPC sample diffraction patterns decreased gradually with increase in humidity and transformed a more amorphous form (Fig. 3B). PGSTA, like STA, included features of recrystallization diffraction patterns after storage at RH from 75% to 95% (Fig. 3C). In case of PGSTA, the diffraction pattern of the recrystallized form was reminiscent of the STA diffraction pattern at 0% RH. Wide reflections of the characteristic diffraction pattern of PGSTA (13°–24° (2θ)) disappeared totally at 95% RH and new reflections for the diffraction patterns were observed at 15°, 17°, and 23° (2θ) (Fig. 3C).

Near-Infrared Spectroscopy

The effect of moisture sorption on all 13 excipients was investigated with NIR spectroscopy after a 2-week storage under conditions of differing RH (0%–95% RH). Distinct absorption maxima of
water were identified in the 1900–2000-nm region. The water bands for the crystalline excipients were identified with NIR spectroscopy and are shown in Fig. 4A. The crystalline water of LMH was seen as a distinct absorption maximum at 1933 nm and it was seen as an increasing absorption maximum after storage at 75% RH (Fig. 4A). The NIR spectra of MANN did not change after storage at 0%–85% RH, but at 95% RH free water showed an absorption maximum at around 1900 nm (Fig. 4A).

The water related to partially crystalline excipients celluloses and starches was seen as a wide band at lower wavelengths of around 1920 nm. The water bands for SMCC1 at 0%–85% RH showed that a gradually increasing absorption maximum formed at 1920 nm and for STA at 1925 nm (Fig. 4B). At 95% RH free water showed an absorption maximum at around 1900 nm.

The same water bands at 1900–2000 nm were identified with NIR from the amorphous excipients present after moisture sorption. The sorbed water was seen for LHPC2 and PGSTA as an increasing absorption maximum at 1920–1925 nm at 0%–85% RH (Fig. 4B and C). At 95% RH the sorbed moisture was observed as free water, and thus as an increased absorption maximum at around 1900 nm.

Evaluation of Thermal Processing Induced Phase Transformation

To compare the dehydration behavior of wet excipients, to evaluate solid-state properties during heating and to determine the changes in crystal structure induced by high temperature the thermal processing was carried out with a VT-XRPD under ambient conditions. The amount of water...
added to the excipients varied, depending on the sorption properties of the material (amounts of water added in Fig. 5). The diffraction patterns of the wet excipients heated at temperatures ranging from 25°C to 180°C–260°C and cooled back to 25°C are shown in Fig. 5. Major changes in crystal structure during thermal processing are summarized in Table 2.

The crystalline LMH, after addition of 0.1 g/g water, showed dehydration behavior beginning at 150°C, at which temperature the water of crystallization of LMH dehydrates. Some features of the diffraction patterns for anhydrous β-lactose could also be identified during the thermal processing at 150°C–170°C, in accord with previous reports.20 The crystal structure of LMH changed and remained in anhydrous at 180°C (Fig. 5A). The diffraction pattern of MANN, after addition of 0.1 g/g water, transformed from the crystalline to the amorphous form at 160°C (Fig. 5B). After cooling back to 25°C, the polymorphic β form of MANN transformed to the new form, which remained in the polymorphic α form shown previously.21–23

The thermal processing of partially amorphous SMCC1, after addition of 0.3 g/g water, showed no difference after heating from 50°C to 260°C or after cooling back to 25°C (Fig. 5C). The position of the reflection at about 22° (2θ) shifted to smaller scattering angles as a function of temperature indicating that the heating had increased the distance of the lattice planes. The partially amorphous STA, after addition of 1.5 g/g water, began to transform to a more amorphous form at about 160°C, transforming increasingly amorphous at 200°C–260°C, and finally becoming permanently amorphous even after cooling (Fig. 5D). After addition of 1.5 g/g water the amorphous PGSTA remained amorphous during heating to 260°C as well as after cooling (Fig. 5E). The diffraction curve for amorphous LHPC2 showed only normal evaporation of water during heating from 50°C to 260°C and cooling back to 25°C, despite addition of 4 g/g water (Fig. 5F).

Figure 3. X-ray powder diffraction patterns of excipients after a 2-week storage at 0%, 75%, and 95% RH. (A) Crystalline excipients: α-lactose monohydrate (LMH) and mannitol (MANN) (B) Low-substituted hydroxypropylcellulose (LHPC2) and silicified microcrystalline cellulose (SMCC1) (C) Corn starch (STA) and pregelatinized starch (PGSTA).
DISCUSSION

Water sorption properties may be affected by time-dependent phenomena, due to structural transformations and phase transitions. The water sorption isotherm relates the equilibrium amount of water sorbed onto a solid and the water activity at constant temperature and pressure. The general shape of the isotherm, specific surface area of the sample, reversibility of moisture uptake, presence and shape of a hysteresis loop provide information on the manner of interaction of the solid with water. The shape of a sorption isotherm is dependent on the interaction between the vapor molecules and the solid sample and allows for conclusions regarding the sorption mechanism. The water sorption isotherms of biological materials often follow the shape of the sigmoid type II isotherm. Some crystalline materials, for example, sugars, may have a fairly low adsorption of water until deliquescence, at which point the sorption increases and follows the Type III isotherm. Hysteresis may result from condensation of water in the capillaries. The size and shape of the hysteresis loop itself can also give a useful indication of the predominant pore-filling or -emptying mechanisms. The hysteresis loops at high RH are often identified in highly porous materials and at low RH are often associated with swelling or some other type of interaction between the sorbate and sorbent in the bulk.

Water vapor onto porous solids differs from vapor uptake onto the surfaces of flat materials in that water will condense to a liquid in a pore structure. This is generally attributed to the increased attractive forces between adsorbate molecules that occur as surfaces become highly curved, such as in a pore or capillary.

Moisture Adsorption by Crystalline Solids

Crystalline excipients are nonhygroscopic and there is no monolayer formation, but delayed multilayering occurs. At low RH water is adsorbed onto the surface of crystalline material. As RH increases, the water molecules become attached at the sugar-vapor interface by weak interaction forces, for example, van der Waals forces. Water primarily interacts with the polar groups on the crystalline surface. This is a surface effect and thus surface area, particle size, and size distribution are crucial for the ability to adsorb moisture as a function of RH. As the RH is increased, some tendency for multilayer sorption is
expected. At high humidity (generally more than 65% RH) solid water-soluble sugar molecules at the particle surfaces begin to dissolve in adsorbed water vapor and form a saturated sugar solution. This will eventually lead to a deliquescence of the solid or sugar. Because a solution is being created, the moisture content rises dramatically.

At a characteristic RH a complete monolayer of water molecules will be formed on the surface of the crystalline solid particles and measurement of this point may be useful in estimating the isotherms of solid sorbate. Since most crystalline solids have low specific surface areas (<1 m²/g), they will adsorb much less than 0.1% (w/w) water vapor even at very high humidities and low temperatures.

The water sorption isotherms of LMH and MANN followed the shape of the type III isotherm. A type III isotherm shows very little moisture gain until water begins to dissolve the crystal surface. The shape of this curve is due to water interacting only via hydrogen bonds with the hydroxyl groups on the surface of the crystalline material. The adsorption-desorption isotherm of crystalline LMH and MANN showed no significant hysteresis. Many crystalline solids exhibit low hygroscopicity (anhydrous form) over a wide range; since the flow moisture point has been reached; the crystalline solid rapidly adsorbs large amounts of water vapor, causing it to deliquesce (hydrous form). Solids that form specific crystalline hydrates, for example, LMH, sorb small amounts of water onto their external surface below a characteristic RH. Crystalline hydrates are frequently formed because they represent a lower thermodynamic energy state than the anhydrous form and water molecules may not be removed without the application of a large amount of energy. Our results showed that the water content of the crystalline LMH remained relatively constant at all RH levels. LMH adsorbs very little moisture over low RH (0%–85%). At a point above 85% RH LMH adsorbs more moisture and the moisture content increases. The reason for the significant increase in moisture content at high RH is capillary condensation, the consequence of which is that at high RH the isotherm is only valid for packed beds of lactose powders, and a capillary size distribution of the powder may influence the shape of the isotherm curve. However, the critical relative humidity (RHₐ) for LMH is above 85% (~99% at 24°C) and the deliquescence of LMH could also explain the sorption behavior. It was also suggested that enhanced chemical and physical reactivity at the surface of crystals in the presence of water vapor may be due to plasticization of small disordered (amorphous) regions.

MANN is a nonhygroscopic crystalline solid that has several polymorphic forms. The sorption of water vapor onto crystalline MANN below RH₀ is dependent on the polarity of the surface and is proportional to the surface area. At 75% RH the ratios of the intensities changed, due to the preferred orientation. MANN adsorbs, as does LMH, very little moisture over a low range of RH (0%–85%). At above 85% RH MANN adsorbs more moisture than LMH and the moisture content increases more than in LMH. The RH₀ for MANN is ~80% at 25°C. The hydration of MANN increased at water contents of about 0.1 g/g and 0.25–0.3 g/g. The formation of a monolayer of water occurs at hydration levels that are much lower than that of the observed transition. It was suggested that these transitions were associated with different stages of microdissolution with increasing levels of hydration. NIR results of MANN showed that some of the water exhibits behavior as free water at 95% RH, which is consistent with previous findings. The GAB value of MANN is smaller (0.5 g/g) than that of LMH (0.7 g/g), because LMH has a larger specific surface area than MANN.

Figure 5. Thermal processing behavior by variable-temperature XRPD (VT-XRPD). Diffraction patterns of the wet excipients heated at temperatures ranging from 25°C (+water) to 180°C–260°C and cooled back to 25°C (b). Amount of water added to the excipients varied, depending on the sorption properties of the material. First XRPD patterns in the figures are without addition of water as controls. (A) VT-XRPD patterns of α-lactose monohydrate (LMH) after additions of 0.1 g/g water. (B) VT-XRPD patterns of mannitol (MANN) after additions of 0.1 g/g water. (C) VT-XRPD patterns of silicified microcrystalline cellulose (SMCC1) after additions of 0.3 g/g water. (D) VT-XRPD patterns of corn starch (STA) after additions of 1.5 g/g water. (E) VT-XRPD patterns of pregelatinized starch (PGSTA) after additions of 1.5 g/g water. (F) VT-XRPD patterns of low-substituted hydroxypropylcellulose (LHPC2) after additions of 4.0 g/g water.
Figure 5. (Continued)
Moisture Absorption by the Amorphous Part of Solids

**Microcrystalline Cellulose**

Water vapor is absorbed into the amorphous part of solids and not simply adsorbed onto the surface; thus the amount of water taken up is not directly related to the specific surface area of the solid. The amount of moisture sorbed by amorphous solids is typically much greater than that sorbed by nonhydrating crystalline solids below their critical relative humidity (RH). The chemical and physical properties of the sorbent (e.g., hydrophilicity), temperature and RH, strength and nature of any interactions between the water and the solid molecules, and the bulk properties of the sorbent (e.g., glass transition temperature, $T_g$) control moisture absorption by amorphous materials.

The adsorption and desorption isotherms for MCCs and starches retain a sigmoidal-shaped curve, thus reflecting a type II isotherm, which is in agreement with, for example, Al-Muhtaseb et al. Sigmoidal isotherms are typical of partially amorphous material. At low RH the isotherm curve showed a distinct “knee”, because adsorption is enhanced at low RH as a result of the polar nature of surfaces, as reported previously. Water vapor sorption by MCCs occurs by the same basic mechanism as with other types of celluloses and starches, and this appears to be described by the sorption of a single tightly bound water molecule at an anhydroglucose unit, followed by a second less tightly bound water molecule, with additional water sorbed in a more nonspecific manner, that is, free water. During water-cellulose interactions, water replaces the cross-linking hydrogen bonds between cellulose chains and loosens the structure of cellulose until capillary condensation occurs. In contrast to starch, water is only sorbed in the noncrystalline regions of celluloses and only a reduction in the degree of crystallinity is allowed more water vapor uptake. Water can act as a plasticizer for the amorphous parts of solids, thereby lowering the $T_g$ of amorphous material. At an RH of about 70%, a decrease is observed corresponding to an upward shift for the moisture sorption isotherm, indicating that a glass transition in the amorphous structure of MCC has occurred.

Absorption of significant amounts of water into the internal structure of a solid influences the properties of solid. This is apparent in the hysteresis observed between the sorption and desorption isotherms and this phenomenon becomes exaggerated to a greater extent for materials that consist of higher proportions of amorphous material. Material that absorbs water into its internal structure exhibits sorption at lower RH in much greater amounts than is expected based on the specific surface area of the material, and exhibits hysteresis over the complete range of RH. This type of hysteresis is generally explained by either kinetic effects or a change in the polymer-chain conformation caused by the plasticization effects of sorbed water. Sorption-desorption equilibria with starches and celluloses always give rise to hysteresis. MCC, SMCC, and STA showed hysteresis, which indicates that water condenses into the pores by capillary condensation but only desorbs from them at lower humidities than those required for condensation. The presence of hysteresis loops at low RH is associated with swelling or some other type of interaction between the sorbate and sorbent in the bulk. Type H4 hysteresis loops (IUPAC classification, after Sing et al.) do not close until the equilibrium pressure is at, or very close to, the saturation pressure. These H4 hysteresis loops, for example, in SMCC1, are often associated with narrow slit-shaped pores and the pore-size distribution is mainly in the micropore range. However, interpretation of the hysteresis loop for pore-size analysis is considered to be unreliable. SMCC1 showed hysteresis, which increased continuously until 95% RH and both hysteresis and the hysteresis loop were different in starches or LHPC2. A clearly evident characteristic is that the hysteresis remains over the entire humidity range and, unlike in crystalline hydrates, water uptake occurs continuously. Partially amorphous materials tend to exhibit considerable bulk absorption of water, which is a slow diffusion-controlled process and thus part of the nonequilibrium regime.

**Low-Substituted Hydroxypropylcellulose**

The water sorption isotherm of LHPC2 followed the shape typical of type II isotherms and LHPC2 showed hysteresis, which was reminiscent of that for STA. The hysteresis of LHPC2 was maximum at 30% RH, whereas that of STA was maximum at 60% RH. These type II isotherms exhibit type H3 hysteresis loops (IUPAC classification, after Sing et al.), which exhibits no limiting sorption at high RH. LHPC is insoluble in water but swells when it comes into contact with water. Hysteresis at low RH may be associated with swelling of a nonrigid porous structure or with an irreversible chemical interaction of the adsorbate with the adsorbent.
Both the chemical binding and the effects of water on the structures of amorphous solids account for the presence of type II isotherms.\textsuperscript{38} The role played by water here is likely that of a plasticizer. In LHPC, the hydrogen bondings between the unsubstituted hydroxy groups are more firmly formed than the hydroxy groups of hydroxypropyl.\textsuperscript{39} The LHPC2 and starches absorbed more water than SMCC1, which is consistent with previous findings.\textsuperscript{39,40} Since the crystallinity of MCC is much higher than that of LHPC, there are few free hydroxyl groups in the MCC particles to undergo hydrogen bonding with the water molecule, compared with LHPC.\textsuperscript{39} The saturated amount of bound water with LHPC was larger than that with MCC, as was expected from the crystallinity. But the moisture contents (adsorbed water) of the MCC and LHPC stored at $<84\%$ RH were less than the saturated amounts of bound water. The amount of free water adsorbed to LHPC (LH11) and MCC (Avicel PH101) at 75\% RH was measured and it was determined that the water adsorbed with the MCC and LHPC was not free water, but water loosely bound with the particles.\textsuperscript{39} The NIR results of LHPC2 showed that free water had a gradually increasing absorption maximum at 95\% RH, but not at 75\% RH. The same phenomenon, but not as high as in LHPC2, was observed with SMCC1 and PGSTA. The swelling work and force of LHPC are higher than those of MCC and increased with increasing particle size and the degree of hydroxypropyl substitution, because the stronger intermolecular hydrogen bonding network in the MCC particles probably prevented the penetration of water into the particle in a manner independent of particle size.\textsuperscript{39} Swelling of LHPC attains saturation in a short time and LHPC is considered to be readily wettable (Shin-Etsu Chemical Co., Tokyo, Japan).

**Starches**

A similar mechanism of water uptake occurs in starches and the noncrystalline regions of cellulosics.\textsuperscript{2} Water molecules have a strong affinity for starch due to the combination of an abundance of hydroxyl groups and a relatively open conformation of the glucose monomers that comprise starch.\textsuperscript{42} The crystalline regions in starch granules are composed of partially crystalline amylpectin and the amorphous regions of linear amylase and branching points of amylpectin.\textsuperscript{41} STA is partially crystalline, due probably to the hydration of amylase, which fills in the distorted crystal lattices.\textsuperscript{5} Modified starch (PGSTA) is partially pregelatinized corn starch that contains soluble (gelatinized) and insoluble fractions.\textsuperscript{43} At low RH, water is bound directly to the available anhydroglucose units throughout the starch grain and in those amorphous regions of cellulose with a stoichiometry of one water molecule per anhydroglucose unit.\textsuperscript{5} At increasing RH, polymer--polymer hydrogen bonds break down, which allows water to begin binding to other water molecules already bound to anhydroglucose units. As the moisture content increases, the sorbed moisture causes a subsequent swelling of the biopolymer, the degree of crystallinity decreases, and there is an increasing availability of the polar groups to the water molecules.\textsuperscript{35} Finally, at high RH, water directly bound to one hydroxyl group per anhydroglucose unit as well as water can also bind to other water molecules such as free water. Although starch is able to take larger amounts of water into its internal structure, it was able to absorb less water than LHPC. The NIR results of STA showed that free water had a gradually increasing absorption maximum at 95\% RH, but less than with PGSTA. According to Delwiche et al.\textsuperscript{42} the NIR spectra of starch suggest that some multilayer water is present before the monolayer is completed.

The water sorption isotherms of STA and PGSTA were sigmoidally shaped type II, with the low- and high-RH end regions possessing the steepest slope for starches, as previously reported.\textsuperscript{42} The starch isotherm is attributable to hydrogen bonding of water molecules to the available hydroxyl groups of the substrate, that is, those in the amorphous regions and on the surfaces of the crystallites.\textsuperscript{35} Water affects the structure acting as a plasticizer of the amorphous regions. The hysteresis loop of PGSTA was the largest of all the excipients. This may have been due to the differing structure of the excipients including starches; the extent of hysteresis may reflect the structural and conformational rearrangements, which alters the accessibility of energetically favorable polar sites and thus may hinder the movement of moisture.\textsuperscript{35} It was shown that despite significant morphological differences between the various starches, the values of $W_m$ (weight sorbed corresponding to one water molecule per sorption site on the solid) from BET analysis were quite constant.\textsuperscript{5}

The crystallinity of STA increased as much as that of PGSTA (30\%) as a result of increased RH,
but at 95% RH the final crystallinity of STA (55%) was higher than that of PGSTA (30%). All amorphous sugars have a strong tendency to take up water vapor. At high RH sorption of water by an amorphous sugar may cause crystallization of that sugar, and this process can have significant consequences for the stability of pharmaceutical formulations. Crystallization is usually the limiting factor determining how much water vapor can be taken-up by low-molecularweight amorphous sugars.

Specific Surface Area by Water and Nitrogen Adsorption

Adsorption methods are usually used to characterize dispersed or porous solids in relation to their processing, for example, by adsorbent. The surface is subjected to adhering molecules and the extent of the surface and its structure are calculated by counting the molecules that are required to cover the surface or to fill a group of pores. The pore-size distributions calculated from the adsorption and desorption branches are substantially different. Problems appear if the pore structure varies due to influence of the adsorbate, for example by swelling. Highly polar molecules cause a hydrophobic or hydrophilic effect, depending on the chemical nature of the solid surface. The larger apparent discrepancy between the water vapor and nitrogen BET surface areas for excipients was observed and it was suggested that the term specific surface area should not be used when water vapor sorption is involved Zografi et al.

The amount of water that is sorbed into amorphous or partially amorphous substances (celluloses and starches) is larger than can be accounted for by surface adsorption. This is in contrast to adsorption in which the water taken up is dependent on the available surface area. The specific surface areas of MCCs and starches measured by water sorption were higher than those measured by nitrogen adsorption. However, the specific surface areas of MCCs measured by nitrogen adsorption were higher than those of starches. But the specific surface areas of MCC measured by water sorption were lower than the specific surface areas of starches. Differences in the apparent surface areas of celluloses and starches using nitrogen adsorption and water vapor sorption are not due to pre-existent pores, but instead to the penetration of water into the material and its specific interaction with individual anhydro-glucose units. Using pore analysis by nitrogen gas adsorption, it was shown that MCC does not contain the extent of intrinsic microporous structure that could account for the large apparent specific surface areas measured by water vapor sorption. Up to at least 6% moisture, sorbed water does not appear to influence the specific surface area of MCC and of STA up to about 10% moisture. Although water vapor sorption is reversible, the isotherm shows a hysteresis loop down to 0% RH. But then water often tends to exhibit type III behavior when adsorbed onto lowenergy surfaces, due to its strong intermolecular hydrogen bonding. Therefore it is not recommended that water be used as a probe molecule in BET surface determinations. Probe molecules of differing nature can show different adsorption mechanisms on the same solid surface. Water vapor is not suitable as a standard adsorbate for the investigation of surface structure, but the isotherms give additional and quite different information on adsorption properties from that given by nitrogen isotherms.

Thermal Processing Induced Phase Transformation

The drying phase is a critical step in many pharmaceutical processes. The strength of the water-solid interaction is dependent on the level of hydrogen bonding possible within the lattice. The crystalline water of LMH dehydrates at about 150°C during the thermal processing in a VT-XRPD. Some features of the diffraction patterns for anhydrous β-lactose could also be identified during the heating at 150°C–170°C, as shown previously. The wet mass of LMH was completely dried at 170°C and LMH was transformed and irreversibly attained anhydrous crystalline structure at 180°C. The MANN diffraction pattern transformed from a crystalline form to an amorphous form at 160°C, because this temperature is close to the melting point of MANN. Polymorphic transition from the β-form to the α-form of MANN was observed after heating and cooling back to room temperature.

The thermal processing of partially amorphous and amorphous celluloses showed no difference after heating up to 200°C or after cooling back to 25°C. It was observed that after evaporation of water, tightly cross-linked networks of LHPC would remain, suggesting that interchain binding may be sufficiently strong to produce crystalline like structure.
Undamaged native starch granules swell when they absorb water through hydrogen bonding with their free hydroxyl groups, but they still retain their order and crystallinity and then return to their original size on thermal processing. However, when these swollen starch granules are heated, the hydrogen bonding between adjacent glucose units is disrupted and the crystallinity is progressively destroyed. This process is referred to as gelatinization and typically occurs in the temperature range of 60°C–85°C.\textsuperscript{46} STA contains 28% amylose and the gelatinization temperature is 62°C–80°C. Leaching of amylose occurs during gelatinization, but some leaching of amylose occurs at temperatures below the gelatinization temperature due to its location in noncrystalline regions. Continued heating of starch granules in excess water results in further granule swelling, viscosity development, and additional leaching, primarily of amylose. During cooling or dehydration, some starch molecules begin to reassociate in an ordered structure, forming a precipitate or gel, or recrystallize slowly. This process is referred to as retrogradation or setback, which involves both amylose and amyllopectin with amylose undergoing retrogradation at a much more rapid rate than does amyllopectin alone.\textsuperscript{46} After heating and cooling in a VT-XRPD it appears that some amylose of both starches recrystallizes, despite that the crystallinity of starches remains low. Crystalization of amyllopectin in starch gels often occurs during storage at a rate depending on the water content and storage temperature, and crystalization can occur at temperatures above the \( T_g \).\textsuperscript{24}

CONCLUSIONS

The interaction of moisture with pharmaceutical solids is highly important for the understanding of water-based processes, for example, wet granulation, drying, or prediction of solid dosage form stability and shelf life. Excipients have different moisture sorption properties that can result in unexpected processing-induced phase transitions. Correspondingly, excipients can significantly affect solid-state phase transitions in the final dosage forms. The character of excipient effects on the stability of formulation. The more amorphous excipient used in the formulation the more water is absorbed into the structure of excipient. It is necessary to control, monitor, and understand the solid-state phase transformations occurring during processing and storage, because various solid phases have unique physical and chemical properties. Despite some limitations, moisture sorption information on excipients is useful in predicting the solid-state stability, interactions, and effects of moisture on physicochemical behavior of the final dosage forms.

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REFERENCES


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