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Water–solid interactions in amorphous maltodextrin-crystalline sucrose binary mixtures

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Abstract

Amorphous and crystalline solids are commonly found together in a variety of pharmaceutical and food products. In this study, the influence of co-formulation of amorphous maltodextrins (MDs) and crystalline sucrose (S) on moisture sorption, deliquescence, and glass transition (T_g) properties of powder blends was investigated. Individual components and binary mixtures of four different molecular weight MDs with sucrose in 1:1 w/w ratios were exposed to various relative humidity (RH) environments and their equilibrium and dynamic moisture contents were monitored. The deliquescence point (RH_0) and dissolution behavior of sucrose alone and in blends was also monitored by polarized light microscopy and second harmonic generation imaging. In S:MD blends, the deliquescence RH of sucrose was lower than the RH_0 of sucrose alone, and synergistic moisture sorption also occurred at RHs lower than the RH_0 . Intimate contact of sucrose crystals with the amorphous MDs resulted in complete dissolution of sucrose at $RH < RH_0$. When blends were stored at conditions exceeding the T_g of the individual MDs (25 °C and 60%, 49% and 34% RH for MD21, MD29 and MD40, respectively), the T_g of the blends was lower than that of individual MDs. Thus, co-formulation of amorphous MDs with crystalline sucrose sensitizes the blend to moisture, potentially leading to deleterious changes in the formulation if storage conditions are not adequately controlled.

Keywords

Amorphous; deliquescence; glass transition temperature; relative humidity; sucrose

Introduction

The interaction of water with solids has a significant implication for pharmaceutical and food products as it can lead to physical instabilities including phase separation and crystallization^{1–3}, caking and agglomeration^{4,5} or chemical degradation^{6,7}. Numerous

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Declaration of interest

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studies have investigated water-solid interactions in amorphous materials, especially polymers, whether as single components^{8,9} or in blends^{1,10,11}. The amorphous solids used in the pharmaceutical and food industries are typically more hygroscopic than their crystalline counterparts, and have a tendency to sorb water even when stored at a low relative humidity (RH). The glass transition temperature (T_g) is highly dependent on the amount of moisture sorbed¹²; water exerts a strong plasticizing effect due to its low T_g value (-135°C). The resultant lowering of T_g upon moisture sorption is often described by Gordon and Taylor (G-T) equation^{13,14}:

$$T_{g(\text{mix})} = \frac{[w_1 T_{g1}] + (kw_2 T_{g2})}{[w_1 + (kw_2)]}, \quad (1)$$

where w_1 and w_2 are the weight fractions, and T_{g1} and T_{g2} are the T_g s of components 1 and 2, respectively. The constant k is considered the ratio of the free volume of the two components under any set of conditions and can be estimated from the densities of the two components (ρ_1 and ρ_2) using the Simha Boyer equation¹⁵:

$$k = \frac{\rho_1 \cdot T_{g1}}{\rho_2 \cdot T_{g2}}. \quad (2)$$

For simple heterogeneous blends of two amorphous components, additive moisture sorption is typically seen. Miscible binary blends of amorphous materials can also exhibit moisture sorption isotherms that can be predicted from the weight averaged sum of the moisture sorbed by each of the individual components in some instances^{12, 16}. However, in other cases, moisture sorption is non-additive, and in extreme instances absorbed moisture can induce phase separation, leading to the appearance of two T_g events^{10,17}.

Non-hydrate forming crystalline materials interact with water differently from amorphous solids whereby only a minimal amount of moisture is adsorbed to the crystalline surface. If the crystalline compound is deliquescent, then at a critical RH value, known as the deliquescence point (RH_0), the amount of surface-adsorbed moisture is enough to induce surface dissolution of highly water-soluble crystals to form a film of saturated solution around the crystals. The solution formed has a partial water vapor pressure lower than that of pure water, thus more moisture is uptaken to maintain the same RH¹⁸. As a result of the added moisture, more of the crystalline material is dissolved and the process continues until the entire solid is dissolved. Deliquescence is a first order phase transformation that depends on the aqueous solubility of the crystalline material at a given temperature. Therefore, materials with higher aqueous solubility usually have lower RH_0 , and RH_0 varies with temperature changes when the temperature influences solubility^{19,20}. The kinetics of deliquescence tend to increase as the RH increases above RH_0 ^{21–23}. Numerous pharmaceutical excipients and some drugs, typically salts, are known to exhibit deliquescence¹⁸.

Deliquescence in binary mixtures of deliquescent crystalline powders happens at a RH ($RH_{0\text{mix}}$) that is lower than the RH_0 s of the two components. This RH_0 lowering occurs only when the two materials are in intimate contact with each other²⁴. The $RH_{0\text{mix}}$ of a mixture

can be calculated from the water activity of this mixture (a_w), which in turn is estimated to be the product of water activities above saturated solutions of each of the components, $(a^0)_n$, as described by the Ross equation:

$$a_w = (a^0)_1 \cdot (a^0)_2 \cdot (a^0)_3 \cdots \quad (3)$$

where

$$RH_{0mix} = a_w \times 100. \quad (4)$$

The Ross equation assumes that the difference between the solute activity coefficient in a mixture and a simple solution is insignificant and can be neglected²⁵. Although the RH_{0mix} is related to the RH_0 of the individual components, it is independent of their ratio as dissolution of these components at RH_{0mix} occurs according to their eutonic composition¹⁸.

It is common to have formulations containing both hydrophilic amorphous and deliquescent crystalline materials. Examples of hydrophilic amorphous excipients include carbohydrate-based polymers, whereas hydrophilic crystalline materials of interest include sugars, sugar alcohols, organic acids and salts. However, there are limited studies on the interaction of water with amorphous and crystalline blends and the influence of such interaction on the T_g and RH_0 of amorphous and deliquescent crystalline materials, respectively. Hence, the objective of this study was to examine the influence of amorphous maltodextrin (MD) on the dissolution/deliquescent behavior of crystalline sucrose (S). This model system represents the typical saccharide blend used in orodispersible tablet formulations, which are often moisture sensitive^{26–28}. It was also of interest to evaluate the impact of the deliquescent crystalline material on the T_g of MDs as a function of RH.

Materials and methods

Materials

Four different MDs, Glucidex IT 6 (MD6), Glucidex 21 D (MD21), Glucidex IT 29 (MD29) and Glucidex 40 (MD40) were obtained from Roquette (Lestrem, France) with the average dextrose equivalent (DE), weight average molecular weight (M_w), number average molecular weight (M_n) and degree of polymerization (DP) characteristics reported in Table 1. Sucrose (S) obtained from Mallinckrodt-Baker (Philipsburg, NJ) was ground in a coffee grinder and screened through mesh sieve # 60 to reduce its particle size to a comparable size with the MDs, thus avoiding potential segregation in the blends. The ground S was annealed for 3 d to crystallize any amorphous material generated during milling. Annealing was performed at ambient temperature by storing the ground S samples for 3 d in a desiccator maintained at 75%RH by a saturated solution of sodium chloride.

Particle size analysis

Mean particle sizes (μm) were determined in triplicate for the amorphous MDs (“as is” from the supplier) and the crystalline sucrose (after grinding) using a Malvern Mastersizer 2000 with a Scirocco 2000M dry powder feeder (Malvern Instruments Ltd., Worcestershire, UK).

Five thousand snaps of background and sample measurements were taken within 5 s and the instrument lower and upper obscuration limits and alarm were set at 0.5% and 8%, respectively. Data are reported in Table 1.

Preparation of binary mixtures

Physical mixtures of S with each of the MDs were prepared by mixing the annealed crystalline S with the amorphous MDs in the ratio of 1:1 w/w. All samples were stored in desiccators over Drierite desiccant (W. A. Hammond Drierite Co., Ltd., Xenia, OH) for at least 2 weeks before determination of the initial moisture content and further use.

Polarized light microscopy

The effect of moisture uptake by MD40 on the dissolution/ deliquescence of S at an RH below the RH_0 was evaluated by monitoring the behavior of two crystals of the sugar, one in contact with MD40 while the other was isolated. The particles were exposed to 80% RH at 25 °C using a VGI 2000M microscope stage (Surface Measurement Systems Ltd, London, UK) and observed under a Nikon E600 polarizing microscope over time.

Moisture sorption, water activity and deliquescence behaviors

The initial moisture content (%MC) of the MDs and S were determined from the weight change after oven drying 1 g (three replicates) of each at 135 °C for 2 h. The %MC of S, MD6, MD21, MD29 and MD40 was 0.02%, 1.71%, 1.75%, 1.92% and 1.88%, respectively (Table 1).

Water activity meter—The water activity (a_w) of saturated aqueous solutions of sucrose at 25 °C was measured by a Decagon Aqualab 4TE instrument (Decagon Devices, Inc., Pullman, WA) and was used to calculate the RH_0 of sucrose.

Desiccator equilibrium moisture uptake—Equilibrium moisture sorption profiles were collected for all samples in a desiccator moisture uptake study. Samples (1 g) of MDs, annealed S and binary mixtures (1:1 w/w) of S:MDs were placed in plastic water activity cups (Decagon Devices) and stored in RH controlled desiccators. The RHs were 44%, 54%, 63%, 75% and 85% RH controlled using saturated solutions of potassium carbonate, magnesium chloride, cobalt chloride, sodium chloride and potassium chloride, respectively, at 22°C. The samples were weighed at different time intervals until an equilibrium weight, defined as 0.1% change over a period of 1 week, was attained. This required 3 weeks to 2 months depending on the %RH. The percent equilibrium moisture content (%EMC) was then calculated on a dry basis from the initial moisture content and the moisture present at equilibrium. Equilibrium desiccator moisture sorption profiles were then plotted and trends were compared.

Automated moisture sorption isotherm measurement—To further investigate moisture sorption behavior below the deliquescence RH of sucrose, moisture sorption isotherms for a subset of samples (single components and S blends with MD29 and MD40) were generated using an automatic multi-sample moisture sorption analyzer SPS-x with 23 sample-handling tray (Projekt Messtechnik, Ulm, Germany) at 25 °C. Samples of 250– 400

mg were evenly spread into 30 mm diameter aluminum dishes, transferred to the SPS-x analyzer, and equilibrated overnight at 0% RH prior to initial weight measurement. A moisture sorption study was then conducted by equilibrating the samples in a closed chamber at 25 °C and exposing them to a number of ascending RHs (35, 36.5, 38, 40, 41, 42, 44, 47, 49, 50, 51, 52, 53, 62, 64, 66, 68, 70, 75%RH) with the time between weighing cycles set at 15 min, and the equilibration end point criteria at each RH set at <0.01% change in weight within 60 min. A maximum resident time of 500 hours was allowed at each %RH before moving to the next programmed RH. From the moisture isotherm of individual crystalline S, the point of intersection of the two extrapolated regression lines of data collected before and after the inflection point of moisture uptake was considered the deliquescence point (RH_0)²⁹. For binary mixtures, the RH_0 of S was determined from sorption profiles derived by subtracting each MD sorption curve, after being multiplied by its fraction in the mixture, from its corresponding binary mixture sorption curve. The result of this subtraction was then divided by the fraction of S present in order to obtain a subtracted curve that could be overlaid and compared with that of the pure sugar. Equilibrium moisture sorption profiles were then plotted and trends were compared.

Dynamic dewpoint sorption—Moisture sorption profiles were generated for all samples using a dynamic technique that is different from the method described above in that it did not wait for moisture equilibration to be achieved between the atmosphere and the sample prior to changing RH. This technique can be useful to pinpoint dramatic moisture-induced changes such as deliquescence³⁰. The dynamic dewpoint sorption (DDS) experiments were conducted using an Aquasorb Isotherm Generator (AIG) (Decagon Devices, Inc., Pullman, WA) at 25 °C, an air flow rate of 80 ml/min, and 1 g of sample. The principle of the AIG is that it provides an inlet flow of wet or dry air (for sorption or desorption, respectively) over the sample and every few minutes shuts the air flow and simultaneously measures the a_w and weight (as a reflection of moisture uptake or loss). Dynamic DDS moisture sorption profiles were plotted and trends were compared.

The deliquescence point (RH_0) of pure crystalline S was calculated using the curve obtained from pure sucrose from the intersection of the extrapolated straight lines obtained by linear fitting of the data points before and after the abrupt change in moisture uptake. For binary mixtures, calculated curves for the crystalline components were derived by subtraction of the data of the MD curves multiplied by its fraction in the mixture from those of their corresponding binary mixtures. The result of this subtraction was then divided by the fraction of the crystalline material, in order to be able to overlay the subtracted curve with that of the pure S. The RH_0 of S in the mixture was determined from the calculated curve of S using the aforementioned procedure described for the pure crystalline sugar.

Differential scanning calorimetry

The T_g of MDs were measured from the second scan of the samples using a TA Q2000 differential scanning calorimetry equipped with a refrigerated cooling accessory (TA Instruments, New Castle, DE) and are reported as the onset T_g values. Prior to analysis, individual MDs and MD:S blends were pre-equilibrated in desiccators (at controlled RHs 43, 54, 64, 75 and 85%RH) at $23 \pm 2^\circ\text{C}$, then three replicates of each sample (5–10 mg) were

prepared in hermetically sealed pans. The samples were first scanned at a rate of 20 °C/min to about 20 °C above the T_g to erase thermal history resulting from aging. The samples were then cooled to -90 °C at a rate of 10 °C/min before being scanned for the second time at a rate of 20 °C/min. After the run, sample pans were weighed to ensure that no moisture loss occurred during the experiment. The difference in T_g between the material “as is” first scan and its second scan was approximately 5–10 °C for storage at RH conditions resulting in a T_g above the equilibration temperature. At high RH, where T_g was reduced to below the equilibration temperature, the difference between the two scans was negligible.

An estimate of the RH required for the T_g of individual MDs to reach the storage temperature (%RH_{25°C}) was interpolated from the two T_g data points encompassing this RH. Plots of T_g against the weight fraction of water sorbed by the binary mixtures and individual MDs at each %RH were fitted to the G–T equation (Equation 1). The k constant values used in the G–T model were determined from the Simha-Boyer rule (Equation 2) using a reported density of 1.5093 g cm⁻³ for MDs³¹ and an assumed density of 1 g cm⁻³ for water. The T_g of water used in the calculation was -135 °C^{32,33}, and the T_g of dry MDs measured after drying samples over phosphorus pentoxide for 2 weeks was 134, 115 and 86 °C for MD21, MD29 and MD40, respectively (Table 1).

Second harmonic generation imaging via second order nonlinear optical imaging of chiral crystals

An experiment to monitor the deliquescence of S at 85% RH in the presence and absence of MD40 was conducted by second-order nonlinear optical imaging of chiral crystals (SONICC) utilizing second harmonic generation (SHG). The majority of chiral crystals, when in the presence of intense optical electromagnetic fields, will produce SHG, which is the frequency-doubling of the incident light³⁴. The custom-built SONICC instrument utilizes beam scanning with a resonant vibrating mirror (Electro-Optical Products, 8 kHz) on the fast-axis, and a galvanometer (Cambridge Technologies) for slow-axis scanning, significantly reducing the possibility of laser-induced photo-damage³⁵. The instrument was configured to acquire 200 sweeps per line with the laser for four fields of view via an automated xyz stage (Prior Scientific OptiScan). The incident beam was generated with a Spectra-Physics Mai Tai HP Ti:Sapphire laser (150 fs, 80 MHz, operating at 800 nm). The frequency-doubled SHG signal was collected with photomultiplier tubes (Burle VD189) in both the epi and transmission directions, utilizing dichroic mirrors and filters in the beam path, both centered around 400 nm, rejecting the incident light, but allowing the SHG signal to pass through. The signals were amplified with Ortec 9305 amplifiers, directed into photon-counting cards (PMS-400A, Becker and Hickl GmbH). The acquisition software utilized Labview, and the images acquired were analyzed using ImageJ software^{35,36}. Five z-planes were acquired for each field of view of 600 × 600 μm with a 10×objective (Nikon 0.3 NA).

A sample of either crystalline S alone or a 1:1 w/w binary mixture of S/MD40 was placed on a slide, and a puff of compressed air was used to reduce aggregation of particles. The slide was then placed in the middle of a slide box with a window, on its upper and lower side, covered with silicon-sealed transparent slide. A saturated salt solution of potassium chloride

was placed in the box to generate a RH of 85% RH. The box was then placed on the automated xyz instrument stage for analysis. The number of crystals present and their total at any time point was normalized with respect to initial number of crystals and their total volume at time 0 in order to eliminate the variation due to the difference in initial number of crystals present and their volume.

Statistical analysis

A Tukey Kramer HSD test was performed for the comparison of RH_0 and the onset of higher-than-expected moisture uptake among the different binary systems and individual components using JMP® Software version 8 (SAS Institute Inc., Cary, NC).

Results

Polarized light microscopy

A simple polarized light microscopy experiment at a controlled RH below the RH_0 of sucrose provided evidence that the presence of an amorphous MD could enhance the dissolution of crystalline sucrose (Figure 1). Contact between MD40 and S induced complete dissolution of the S crystals in less than 140 min whereas the isolated S crystals did not undergo deliquescence or show any sign of dissolution (Figure 1a). Under the same environmental conditions, it can be clearly seen from Figure 1(b) that two crystals of S in contact with each other remained intact throughout the time frame of the experiment. In contrast, pure MD40 powder alone sorbed water and took on a liquid like appearance under the same conditions as shown in Figure 1(c).

Equilibrium moisture uptake

Monitoring the moisture uptake of single ingredients and binary blends at 22 °C also provided evidence that the co-formulation of crystalline S with amorphous MD altered the moisture sorption behavior and that this moisture sorption was synergistic (Figure 2). Following equilibration at low RHs (54% RH), there was a good correlation between the experimental results and the predicted %EMC based on an additive model of moisture sorption. However, at higher RHs, between 64% and 85%RH (the RH_0 for S), a remarkable positive divergence between actual and predicted moisture uptake was observed for three S:MD binary mixtures (MD 21, 29 and 40). The extent of the higher-than-expected moisture sorbed (%EMC) by the MDs at 64%RH based on the additive model was 2%, 3% and 7% for the S:MD21, S:MD29 and S:MD40 blends, respectively. A divergence of moisture sorption by the S:MD6 blend also occurred but not until 85% RH (Figure 2). At 85%RH the %EMC was 3.8%, 22.1%, 23.1% and 19.1% for the S:MD6, S:MD21, S:MD29 and S:MD40 blends, respectively. Therefore, it appears that there is a threshold RH above which synergistic moisture sorption can occur in S:MD blends, but this threshold may vary by type of MD.

There also appears to be a trend for the moisture sorption that is related to the M_w of the MD whereby at 75%RH, the lower the M_w of MD present in the mixture the higher was the %EMC. Hence, mixtures with MD6 showed the lowest %EMC (7%) whereas mixtures with MD40 had the highest (19%). Binary S mixtures containing MD21 and MD29 had 12% and

15%EMC at 75%RH, respectively. At 85%RH this %EMC trend with MD M_w was not as noticeable. Although the S mixture with the highest M_w MD (MD6) maintained the lowest %EMC at 85%RH, the difference between the %EMC of S with the other three MDs was not significant at this RH (ranging from 35% to 38%).

To complement this larger desiccator study and narrow the focus to the RH region at which it appeared synergistic moisture sorption began, a subset of samples was analyzed using a SPS-x instrument to generate moisture sorption isotherms at 25 °C. The RH at which higher than expected moisture uptake began was found to be $61.4\% \pm 0.3\%$ RH for S:MD29 blends and $49.5\% \pm 0.0\%$ RH for S:MD40 blends, again demonstrating the sensitivity of the moisture sorption behavior to the MD M_w .

Dynamic dewpoint sorption

The RHs at which data could be collected for our systems in desiccators was limited by the range of available saturated salt solutions, while the SPS generation of moisture sorption isotherms for numerous samples was limited by the amount of time equilibration took at each RH step (up to 500 h at each RH) in the method and number of sampling cups in the instrument (23 cups). In order to characterize all of the systems over a wider variety of RHs than the desiccators and in a shorter amount of time than the SPS, a DDS study was also performed at a constant temperature of 25 °C. The DDS curve of the single component S is shown in Figure 3 and is characteristic of the moisture sorption profile of a deliquescent solid. The deliquescence point a_w of S determined from its DDS curve was 0.845 ± 0.006 , which was not significantly different from the a_w 0.849 ± 0.001 obtained by the a_w meter measurement (Table 2). These values were similar to those reported in the literature for S (0.850, 0.857 and 0.843), which were measured from equilibrium sorption isotherms and DDS curves as well as a_w measurements of saturated solutions of S^{3,30,37}. The moisture sorption profiles of the individual MDs are also shown in Figure 3.

Due to the number of data points generated in the DDS method, in particular the number of points that generate a near-vertical slope during deliquescence, it was hoped that this dynamic method could be a useful tool in providing insight into the influence of MDs on the deliquescence point (or dissolution behavior) of the crystalline S as well as the onset of synergistic moisture sorption. Moisture sorption profiles of the binary S:MD blends were collected, and the moisture sorption attributable to the MD component was subtracted to calculate the moisture sorption curve of the crystalline component as well as any synergistic events (Figure 4). This pattern was then compared with the actual moisture sorption profile of pure crystalline S to examine the effects of the amorphous MDs (Figure 4). From Figure 4, it is clear that synergistic moisture uptake started at RHs well below the RH_0 of S, and the near-vertical lines indicative of deliquescence also occurred at RHs below RH_0 in all of the S:MD blends. The higher moisture uptake reflects dissolution of S that was initiated before its deliquescence. The synergistic moisture sorption and likely dissolution of S in the binary mixtures started at a_w of 0.79, 0.68, 0.68 and 0.56 for S:MD6, S:MD21, S:MD29 and S:MD40, respectively (Figure 4, Table 3). Therefore, the a_w at which S dissolution commenced was generally lowered by reducing the M_w of the MD present in the mixture, although there was no significant difference between S:MD21 and S:MD29. The

deliquescence point of S, which was calculated from the sorption profile of the individual sugar to be at a_w of 0.845, was significantly shifted to lower values of 0.760, 0.781, 0.792 and 0.817 in the blends of S:MD40, S:MD29, S:MD21 and S:MD6, respectively (Figure 4, Table 3). Thus, all MDs significantly lowered the RH_0 of S.

Second harmonic generation

Crystalline materials that are composed of homochiral crystals (crystal units that are not mirror images of each other) such as S are typically capable of producing coherent SHG, while disordered amorphous or liquid materials do not produce SHG. Therefore, the technique was used to confirm the MD-induced dissolution of sucrose on exposure to RH by monitoring the change in the size and number of S crystals over time in the presence of MD40 at 85%RH/25 °C without the interference of the amorphous structure of the MD. In the S:MD40 binary mixture there was a rapid decrease in the number of crystals over time with a complete disappearance of the S crystals within the first 1000 min (Figure 5). The pure S sample showed slower decrease in number of crystals than the mixture within the first 1000 min. This loss of crystallinity subsequently became extremely slow such that a complete loss of crystals within the time frame of the experiment was not observed for S alone. These results illustrate the impact of amorphous MD on enhancing S deliquescence kinetics at RH_0 . The change in the total volume of S crystals was similar to the change in the number of crystals, and a complete loss of crystal volume occurred within 1000 min in the S:MD mixture but not in the S crystals alone.

A plot of the ratio of normalized total crystal volume to the normalized crystal number over time correlates with the rate of change in the size of the crystals relative to their number (v/n). There was an initial gradual rise in the v/n ratio for pure S within the first 1500 min, indicative of faster decrease in crystal number compared to size as a result of rapid dissolution of small sized crystals (Figure 6). After 1500 min, leveling-off of the v/n ratio might be due to the lack of change in the size and number of large crystals or a change that occur at a slow pace but at a similar rate for both.

In the S:MD40 blend, the v/n ratio of the S crystals increased initially but unlike the individual S it was more rapid within the first 200 min indicating a much faster rate of small crystals disappearance. After 200 min, a gradual decrease in the ratio occurred up to 900 min followed by sharp decrease before a plateau was reached at 1250 min. The decrease in the v/n ratio in the blend reflects dissolution/deliquescence of the medium and large size crystals with a rate of decrease in size greater than in number. Therefore, the presence of MD40 at the RH_0 of S promotes the dissolution/deliquescence of the larger sized crystals that appear to dissolve very slowly or not at all when no MD is present.

T_g of MD

Dry individual MDs had their T_g values in a descending order with decreasing M_w , where the values of T_g were MD6>MD21>MD29>MD40 (Table 1). The T_g of the individual MDs also decreased with an increase in storage RH (Figure 7). The RH required for the onset T_g of the individual MDs to reach the storage temperature of 25 °C (%RH_{25°C}) was 85%, 60%, 49% and 34%RH for MD6, MD21, MD29 and MD40, respectively (Table 4).

In the S:MD blends, the T_g value of MD6 overlapped with the melting endotherm of S and thus it was not detected in the binary mixture. In the other binary mixtures (S:MD21, S:MD29 and S:MD40), the T_g of the MDs was reduced by increasing the RH to which the mixtures were exposed (Figure 7). For the RHs where the T_g was higher than the storage temperature ($\%RH_{25^\circ C}$), T_g values in the binary mixtures were not significantly different from those of the individual MDs. However, above the $\%RH_{25^\circ C}$, i.e. where the samples were stored above T_g , the T_g values of the binary mixtures were lower than those of the individual MDs, except for S:MD40. Although the T_g value of MD40 in the binary mixtures was slightly lower than the single component MD T_g , the magnitude of this difference did not change by increasing the RH above $\%RH_{25^\circ C}$ (Figure 7c, Table 2). For MD21 and MD29 the magnitude of the difference in T_g between the binary mixtures and individual MDs increased with the RH above $\%RH_{25^\circ C}$ (Figure 7a, b, Table 2).

The magnitude of the T_g reduction at the RH_0 of S (85% RH), where all MDs were plasticized to above T_g , increased with increasing the M_w of MD (Table 2). The MD21 with a M_w of 7248 showed a 36 °C difference in T_g between the single component MD (with a T_g of -16 °C at 85% RH) and its binary mixture (with a T_g of -52 °C at this RH). This was higher than the 23 °C difference obtained for MD29 (with $M_w = 2297$ and T_g of -33 °C and -57 °C for the individual MD and the S/MD29 binary mixture at 85% RH, respectively). Accordingly, the difference for the two aforementioned MDs was higher than the 7 °C of MD40 ($M_w = 1322$ and T_g of -48 °C and -54 °C for the single component and binary mixture at 85% RH, respectively).

The G-T equation (Equation 1) was applied to the data for individual MDs using k values, calculated according to the Simha-Boyer rule, of 4.43, 4.22 and 3.93 for MD 21, 29 and 40, respectively. There was a fairly good fit between the G-T model predicted T_g s and the actual T_g s for individual MDs, based on the fraction of water sorbed, with R values of 0.844, 0.883 and 0.878 for MD 21, 29 and 40, respectively (Figure 8a-c). It was presumed that in binary blends, the reduction in T_g due only to plasticization by the synergistically sorbed extra moisture, would provide a similar fit to the G-T model as the individual MDs, while disregarding the crystalline component fraction. When the weight fraction of water sorbed was below 0.3 in the binary blends of S:MD, the G-T model appeared to fit the actual T_g values. However, significant deviation occurred when more water was sorbed (Figure 8a-c).

Discussion

Crystalline and amorphous solids interact with water differently, as is apparent from their moisture sorption isotherms. Moisture sorption isotherms of hygroscopic amorphous materials such as MDs often show type II or type III profiles according to Brunauer et al. classification, with some moisture uptake occurring at low RHs^{12,16,17,38,39}. When the RH is increased to a level whereby the solid is sufficiently plasticized by the absorbed moisture so that the T_g occurs at the experimental temperature, an increase in the moisture uptake occurs as a result of the greater molecular mobility^{9,40}. In contrast, moisture sorption isotherms of deliquescent crystalline solids exhibit an abrupt increase in moisture content only at and beyond RH_0 where a great amount of moisture up-take is involved and complete dissolution of the solid occurs^{18,24} to form a solution phase. Below RH_0 , crystalline materials tend to

sorb only minute amount of moisture via surface adsorption and capillary condensation⁴¹. These general trends were present in the moisture sorption profiles collected for the individual S and MDs studied (Figure 3). In the absence of synergistic interactions, a binary blend of amorphous and crystalline ingredients is expected to have moisture sorption patterns that are additive curves of the individual components at exactly the same %RH and with the same extent of moisture uptake. Since the crystalline component of the blend is not expected to sorb any significant amount of moisture below its RH_0 , moisture uptake below this RH is expected to occur as a function of the hygroscopic nature of the amorphous ingredient.

Synergistic moisture sorption

In the current study, the higher than expected moisture uptake by the S:MD binary mixtures at RHs lower than RH_0 suggests a synergistic effect induced by the presence of the crystalline and amorphous ingredients together. This moisture sorption synergy is contrary to the typical sorption behavior of either amorphous or crystalline blends. Moisture sorption by miscible amorphous binary blends, for instance, usually exhibit the additive uptake of individual components, or alternatively absorb less moisture than would be predicted based on the moisture sorption profiles of the individual amorphous components^{12,16,17,42,43}. On the other hand, crystalline binary blends do not sorb moisture below the deliquescence point of the mixture (RH_{0mix}), but this RH_{0mix} is lower than RH_0 of any of the single components^{24,44}. At RH_{0mix} the blends sorb sufficient moisture to dissolve the two components according to their eutonic composition (ratio of the molal solubilities in solution)¹⁸.

Interestingly, the moisture sorption synergy occurred only in the S:MD blends at RHs above the %RH_{25°C} that was required for the MDs to be above their T_g (i.e. in a higher mobility state than the glassy solid) (Tables 2 and 3). Therefore, having the MDs in a highly plasticized state seems to be important for the synergistic moisture sorption at RHs below RH_0 . Most likely, the decreased viscosity of the MDs following sufficient moisture sorption enables the material to flow, promoting contact and interaction with sucrose as seen in Figure 1. The more mobile MD-water system can then function as a “solvent” for crystalline S, resulting in some S dissolution. Thus it is not just the presence of water *per se* (since moisture is absorbed at low RHs, but no interaction with sucrose is seen), but also its impact on the MD viscosity which facilitates interaction between the components. A similar phenomenon has been observed with the polymer polyvinylpyrrolidone, which in a highly water-plasticized state was found to cause the dissolution of crystalline theophylline monohydrate⁴⁵. The dissolution of S then contributes to the moisture sorption synergy in S:MD21, S:MD29 and S:MD40 prior to 79%, 78% and 76%RH; having an additional dissolved species (particularly a hydrophilic one) will lead to more moisture sorption. The gradual increase in the synergistic uptake below these RHs is different from the near-vertical sorption characteristic of deliquescence⁴⁶ and the impact of the MD on the deliquescence transition will be discussed in more detail below.

Although there are limited literature reports of synergistic moisture sorption, the findings of this study are in accordance with those of Ortiz et al.⁴⁶, who reported synergistic moisture

uptake by binary blends of amorphous green tea powder with crystalline sucrose, citric acid and/or ascorbic acid. In the study, the synergistic moisture promoted catechin degradation, one of the active ingredients in green tea, in blends containing citric acid or ascorbic acid⁴⁷. This degradation was attributed to the low pH environment created by dissolution of the crystalline acids along with the depression of the green tea T_g in the blends.

Lowering of RH_0

In addition to the synergistic moisture sorption and dissolution of S at RHs lower than RH_0 , the presence of MD in the blend lowered the RH_0 of S (Table 3, Figure 4). This observation is consistent with a previous finding that blending sodium ascorbate with a MD lowered its RH_0 ⁴⁸. For the sodium ascorbate-MD system, the higher average DE MD (DE ~ 18) with the lower M_w seemed to reduce the RH_0 of sodium ascorbate to a greater extent than the MD with the lower DE (DE~10) and higher M_w . Similarly, in the current study, the RH_0 of S decreases more in the presence of a lower M_w MD (Table 3). The reduction in RH_0 was also demonstrated using polarized light microscopy where there was complete deliquescence of S in the presence of MD40 at an RH lower than RH_0 of sucrose (Figure 1). Moreover, the kinetics of deliquescence at the RH_0 of pure sucrose was faster in presence of MD40 as revealed by SHG (Figure 5), consistent with a reduced RH_0 value. In general, this unexpected decrease in RH_0 of a deliquescent crystalline ingredient by a hygroscopic amorphous component can be expected to impact both the chemical and physical stability of a formulation. The RH_0 of crystalline ranitidine was reported to be reduced in the presence of traces of amorphous degradant impurities and its rate of degradation was enhanced at RHs lower than its RH_0 ^{49,50}. However, interestingly, the chemical stability of crystalline sodium ascorbate increased when stored in a binary blend with MD for some storage conditions⁴⁸. This higher stability was attributed to the protective property of MD against oxidation of the ascorbate and its enhanced viscosity around and slightly above its T_g that limited the mobility and interaction of the reactants.

Lowering of T_g

The effect of MD and S on each other in the binary blends was mutual: as the MD reduced the RH_0 of S and initiated its earlier dissolution, S lowered the T_g of the MD once a threshold storage RH (or moisture content) was reached (Figure 7), presumably reflecting the point at which sucrose began to dissolve. For example, a decreased T_g was observed in the sucrose blends with MD21 and MD29 equilibrated at RHs above 64%RH, where the T_g of the MDs was lower than the experimental temperature (Figure 7a, b). The reduced viscosity of the MD above its T_g promoted synergistic moisture uptake as a result of water-sucrose interactions, leading to enhanced plasticization of the system. Numerous studies have reported the plasticization effect of moisture in reducing the T_g of amorphous ingredients^{10,12,33,43}. Therefore, the additional moisture sorbed in the S:MD blends in this current study provided additional plasticization to further reduce the T_g in the blend. This supposition was further supported by correlating the data to the G–T equation.

A good correlation was obtained between the plot of the T_g s of individual MDs against moisture weight fraction and the G–T model, with R^2 of 0.844, 0.883 and 0.878 for MD21, MD29 and MD40, respectively (Figure 8a – c). The T_g data of the binary mixtures also

closely followed the G–T model except at high moisture fractions, which corresponded to RH values at or above RH₀ of the blended sucrose – 75% for MD40 and 85% for both MD21 and MD29 (Figure 8a–c, Table 3). The agreement between the G–T model and the decrease in T_g with an increase in moisture fraction in blends indicated that lowering of their T_g below that of individual MDs was solely due to plasticization by the synergistically sorbed moisture. The higher than G–T model predicted T_g for blends equilibrated at RHs above the RH₀ of S can perhaps be attributed to an antiplasticizing effect of the now high concentration of sucrose in solution¹².

Conclusion

Blending amorphous MDs with crystalline sucrose induces synergistic moisture sorption, enhances dissolution of sucrose at RHs less than its deliquescence RH₀, and reduces the RH₀ of sucrose and the T_g of the MD. These fundamental changes that occur at RHs lower than expected can have detrimental impacts on the physical appearance and function of any formulations containing a hygroscopic amorphous excipient in combination with a deliquescent crystalline excipient (e.g. orodispersible dosage forms), as well as the chemical stability of the active pharmaceutical ingredient. Therefore, extra precautions may need to be taken with the packaging and storage environment of these formulations as they may be susceptible to moisture induced changes at lower than expected RH conditions.

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Figure 1.

Polarized light microscopy pictures showing the changes occurring to various samples over time when exposed to 80%RH and 25 °C: (a) crystals of S: (1) in contact with MD40 (lower right of pictures) and (2) isolated from MD (upper left of pictures); (b) two large crystals of S in contact with each other; (c) clusters of MD particles in contact with each other.

Figure 2.

Percent equilibrium moisture content (%EMC) of S/MD binary mixtures exposed to various %RH at 22 °C. Dashed lines represent predicted moisture uptake for binary mixtures where (---) S:MD6, (---) S:MD21, (---) :MD29 and (.....) S:MD40. Predicted moisture content was calculated using a weighted additive model and the moisture contents of the single components at the corresponding %RH.

Figure 3.
DDS-desorption curves of MDs and S.

Figure 4. Actual DDS curve of S and its predicted curves from its binary mixtures MD6, MD21, MD29 and MD40. Predicted curves were obtained by subtraction of curves of the individual MDs from their corresponding mixtures. Predicted data of S from its binary mixture with MD21 and MD29 are overlapping.

Figure 5. SHG measurement of the decrease in the number of S crystals during its deliquescence from pure S and S/MD40 (1:1w/w) binary mixture at 85%RH.

Figure 6.
Change in crystal volume relative to the number of crystals present.

Figure 7.

Onset T_g of MDs alone and in binary mixtures with deliquescent S pre-equilibrated at various %RH and 22°C for systems containing (a) MD21, (b) MD29 and (c) MD40.

Figure 8.

A plot of the change in T_g with the weight fraction of water present and fitting of data to G-T equation (dashed line) for systems with (a) MD21, (b) MD29 and (c) MD40.

Table 1

Physicochemical properties of the crystalline sucrose and amorphous MDs.

Material	DE	M _w	M _n	DP	Mean Particle size ^a (μm)	PSD range ^b (d _{0.1} –d _{0.9})	T _{g(dry)} ^c (°C)	% MC
Sucrose	–	180	–	–	631	292–967	–	–
Milled sucrose	–	180	–	–	115	10–260	–	0.02
MD6	4.2	81 000	3382	20.8	265	73–491	153.4 ± 1.5	1.71
MD21	21	7248	1030	6.3	108	10–241	134.3 ± 2.3	1.75
MD29	28	2297	737	4.6	159	94–308	115.3 ± 1.4	1.92
MD40	40	1322	504	3.1	114	10–250	85.7 ± 0.7	1.88

^aVolume weight mean.

^bRange in particle size distribution (PSD), where d_{0.1} and d_{0.9} represent the values below which 10% and 90% of volume of distribution occur, respectively.

^cT_g measured after drying under Drierite for more than 2 weeks.

Table 2

Magnitude of average T_g reduction ($^{\circ}\text{C}$) by equilibration of the crystalline sucrose with MDs at 22°C and various %RH.

%RH	T_g		
	S:MD21	S:MD29	S:MD40
43	2.04	0.46	6.91
53	0.00	2.05	7.83
64	-1.25	12.23	7.48
75	15.72	15.26	8.80
85	36.32	23.06	6.73

$$T_g = T_{g\text{MD}} - T_{g\text{mix}}$$

Table 3

Water activity for the deliquescence point of S and the onset of higher-than-expected moisture uptake by the binary sucrose: MD mixtures at 25 °C.

Amorphous component in the mixture	a_w for deliquescence of S			a_w for onset of higher-than-expected moisture uptake
	Single component		Binary mixture	
	a_w meter	DDS	DDS	
MD6	0.849 ± 0.000 ^a	0.845 ± 0.006 ^a	0.817 ± 0.015 ^b	0.791 ± 0.032 ^{bc}
MD21			0.792 ± 0.013 ^{bc}	0.675 ± 0.005 ^f
MD29			0.781 ± 0.011 ^{cd}	0.679 ± 0.029 ^f
MD40			0.760 ± 0.007 ^d	0.560 ± 0.018 ^g

Values having different letters are significantly different (Tukey–Kramer HSD test, $\alpha=0.05$).

Table 4Percent RH required for the T_g of MDs to reach 25 °C (%RH_{25°C}).

	MD			
	MD6	MD21	MD29	MD40
%RH _{25°C} based on onset T_g	84.7 ± 1.5	59.8 ± 3.7	49.4 ± 1.3	34.0 ± 0.4
%RH _{25°C} based on midpoint T_g	94.7 ± 0.7	65.9 ± 1.2	57.8 ± 0.5	46.8 ± 0.5