

Kinetics of Moisture-Induced Hydrolysis in Powder Blends Stored at and below the Deliquescence Relative Humidity: Investigation of Sucrose–Citric Acid Mixtures

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Previous studies have shown that deliquescent organic compounds frequently exhibit chemical instability when stored in environmental conditions above their deliquescence relative humidity (RH). The goal of the current study was to investigate the effect of atmospheric moisture on the long-term chemical stability of crystalline sucrose–citric acid mixtures following storage at RHs at and below the mutual deliquescence relative humidity (MDRH). Interestingly, it was found that sucrose hydrolysis can occur below the MDRH of 64% and was observed for samples stored at 54% RH. However, hydrolysis was not seen for samples stored at 33 or 43% RH. The rate of sucrose hydrolysis could be modeled by taking into account the rate and extent of moisture uptake, which in turn was dependent on the composition of the powder and the storage RH. A reaction mechanism initiated by capillary condensation and involving additional deliquescence lowering by the degradation products formed as a result of sucrose hydrolysis (glucose and fructose) was proposed.

KEYWORDS: Deliquescence lowering; chemical stability; relative humidity; crystalline solids; capillary condensation

INTRODUCTION

The chemical stability of organic solids is of critical importance, in particular for food, pharmaceutical, and bioactive compounds, agricultural products, explosives, and other fine chemicals. It is well-known that moisture can promote instability in organic solids (1–5). Moisture can interact with organic solids via a number of different mechanisms, as described by Zografi (6, 7). Of the various types of water–solid interactions, deliquescence is one of the most potentially deleterious phenomena because a phase transformation occurs (2, 3, 8), affecting both chemical and physical stability.

Deliquescence is a first-order phase transition process whereby a substance dissolves in atmospheric moisture when the relative humidity (RH) reaches a certain critical value. This RH is termed the deliquescence RH (DRH), and the crystalline substance forms a saturated solution at this RH. Below the DRH, a deliquescent solid adsorbs only a minimal amount of water (9). When the ambient RH reaches the DRH of a solid, water begins to condense on the surface of the solid and the solid starts to dissolve in the condensed moisture. The water activity is lowered by the presence of the dissolved solute, and further absorption of water occurs until a saturated solution forms (10). If there is more than one deliquescent substance present in a mixture, the DRH is lower than the lowest DRH of the individual substances (11). This phenomenon is called deliquescence lowering, and the DRH of this mixture is termed the mutual DRH (MDRH) (8, 11).

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Many inorganic and organic substances relevant to numerous industries, for example, food and pharmaceutical industries, can undergo deliquescence. Examples include sodium chloride, sucrose, fructose, citric acid, ascorbic acid, some drug hydrochloride or sodium salts, etc. (1, 2, 8, 12, 13). Because many food and pharmaceutical products, among others, are deliberately formulated as solid products to achieve long shelf lives, it is important to understand how the presence of water can trigger detrimental effects. For instance, water can cause caking or agglomeration of powders and affect flowability (14). Water can also react with a bioactive ingredient or active pharmaceutical ingredient (API), resulting in a loss of biological activity and producing unwanted or harmful side products (15).

In this research study, the effect of moisture on the chemical stability of solid state mixtures of sucrose and citric acid anhydrous was studied to better understand how moisture triggers chemical instability, using a model system with a well-established mode of degradation. Sucrose is used as a sweetener in both the food and pharmaceutical industries (16). Citric acid is used as a preservative and flavoring agent in food products and as a buffering agent in pharmaceutical formulations (16). Sucrose and citric acid are coformulated in a wide range of food products. Sucrose is chemically labile and can undergo hydrolysis in the presence of an acid in solution to form fructose and glucose, both of which are reducing sugars. The kinetics and mechanism of this reaction have been well studied in the solution phase (17–25). However, the kinetics of the reaction in powders stored at various RHs has received less attention. Shalaev et al. investigated degradation kinetics in amorphous freeze-dried sucrose–citric

acid systems (26). Salameh and Taylor probed degradation kinetics for binary crystalline blends above and below the MDRH, over relatively short time frames (12). The goal of this research was to better understand the kinetics of this reaction in the solid state as a function of RH, concentrating on the effects of exposure to RH values just below the MDRH for the blend. In principle, a chemically labile blend should be stable to moisture-induced degradation below the MDRH because no dissolution should occur. However, if the degradation products decrease the value of MDRH, chemical instability could be potentially induced. The hypothesis to be tested in this study is that the formation of minute amounts of glucose and fructose via the acid-catalyzed hydrolysis of sucrose will promote moisture sorption and result in observable degradation at RHs below the MDRH of the sucrose–citric acid blend.

The MDRH of a sucrose–citric acid anhydrous mixture is 64% RH and is independent of the sucrose–citric acid ratio (13). However, the MDRH for this mixture decreases with time (12) because sucrose hydrolyzes to produce fructose and glucose, both of which are also deliquescent. On the basis of the prediction of the Ross equation, the MDRH of the quaternary system should be around 36% RH (13, 27). Therefore, from a theoretical perspective, hydrolysis of sucrose may occur at RHs as low as 36% RH if both glucose and fructose are present or can be formed during storage. In this study, we investigated the chemical stability of sucrose in sucrose–citric acid blends, stored in RH conditions at and below the MDRH of the sucrose–citric acid anhydrous mixture, and probed the kinetics and mechanism of the hydrolysis reaction.

EXPERIMENTAL METHODS

Materials. All chemicals used in this research were of reagent grade. D-(–)fructose and citric acid anhydrous were obtained from Sigma Aldrich (St. Louis, MO). Sucrose and D-glucose were obtained from Mallinckrodt (Paris, KY). Diphosphorus pentoxide, used to maintain a RH environment of 0% RH, was obtained from Alfa Aesar (Ward Hill, MA). Magnesium chloride hexahydrate (Sigma Aldrich), potassium carbonate (Alfa Aesar), magnesium sulfate hexahydrate (Alfa Aesar), and cobalt chloride hexahydrate (Sigma Aldrich) were used to prepare saturated salt solutions to maintain desiccators at 33, 43, 54, and 64% RH, respectively.

Sample Preparation and Reaction Kinetics Monitoring. Both sucrose and citric acid anhydrous were ground using a ball mill (Paul O. Abbé Inc., Bensenville, IL) and sieved (Fisher Scientific, Pittsburgh, PA) to have the same size distribution (300–500 μm). Ground particles were stored in desiccators equilibrated at different RHs (54 and 64% RH for citric acid anhydrous and sucrose, respectively) for at least 5 days to recrystallize any amorphous materials induced by grinding (28). After this treatment, samples were stored over diphosphorus pentoxide (P_2O_5) for at least 5 days to remove any adsorbed moisture. Two sets of mixtures, 50:50 and 95:5 sucrose–citric acid anhydrous, were prepared to study the effect of citric acid concentration on the kinetics of the sucrose hydrolysis reaction. The total mass of each mixture was approximately 2.0 g. The mixtures were held in 20 mL scintillation vials (Research Products International, Mount Prospect, IL) and stored at room temperature ($24 \pm 2^\circ\text{C}$) under four different RH conditions (33, 43, 54, and 64% RH) to compare the effect of environmental moisture on the chemical stability of these mixtures. Three mixtures from each RH condition were taken out at various time intervals for mass measurement and quantitative analysis of each of the four components using Fourier transform infrared spectroscopy (FT-IR). The laboratory RH was monitored and was < 50% RH at all times.

Fourier Transform Infrared Spectroscopy. Quantitative analysis of each component (sucrose, glucose, fructose, and citric acid) was performed by analyzing samples with a FT-IR spectrometer (Nexus 670, Thermo Scientific, Verona, WI) equipped with a diamond crystal attenuated total

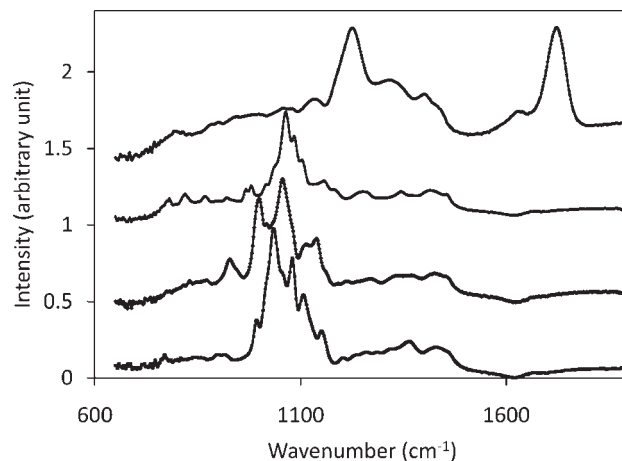


Figure 1. Infrared spectra of individual components present in the sucrose–citric acid blends, including the hydrolysis products glucose and fructose. Concentration = 40 g/L. From top to bottom spectra show citric acid, fructose, sucrose, and glucose.

Table 1. Experimental and Calibration Parameters of the PLS Model Developed Using FT-IR Spectra for Monitoring Sucrose, Citric Acid, Glucose, and Fructose Concentrations in Powder Blends

component	no. of factors	concn range (g/L)	correl coeff	RMSEC ^a	RMSECV ^b	RMSEP ^c
sucrose	5	0–80	0.9998	0.564	0.663	0.795
glucose	8	0–80	0.9998	0.530	0.739	0.840
citric acid	7	0–40	0.9997	0.330	0.417	0.434
fructose	6	0–80	0.9998	0.491	0.700	0.735

^a RMSEC, root mean square error of calibration. ^b RMSECV, root mean square error of cross validation. ^c RMSEP, root mean square error of prediction.

reflectance (ATR) accessory device (Smart diamond ATR, Thermo Scientific). Each mixture was dissolved and diluted to 25.00 mL with 18 M Ω ·cm water before being subjected to analysis. Spectra (4000–750 cm^{-1} , 4 cm^{-1} resolution, 256 scans) were collected with the aid of Omnic software (version 8.0.342, Thermo Scientific).

Data Analysis. Collected spectra were preprocessed and analyzed using the TQ Analyst software (version 8.0.1.30, Thermo Scientific). Individual spectra of pure components showed severe overlapping (Figure 1); hence, partial least-squares (PLS) regression was used for the quantification of the four components. A calibration set was needed to perform a PLS regression; hence, 61 calibration samples and 21 validation samples that contained select concentrations of the four components were used. Details of the experimental and calibration parameters are summarized in Table 1. All other data analyses including curve fitting and kinetic modeling were performed using EXCEL (Microsoft Corp., Redmond, WA) and MATLAB (The Mathworks, Inc., Natick, MA).

RESULTS AND DISCUSSION

The kinetic profile of each component in the treated sucrose–citric acid blends is shown in Figures 2 and 3. Sucrose and citric acid are presented as the mass fraction remaining in the mixture as a function of time, whereas glucose and fructose are presented as the mass fraction generated with time, calculated on the basis of the initial amount of sucrose. Over the experimental period, significant chemical changes were observed in mixtures stored at 64 and 54% RH but not at 43 and 33% RH (Figures 2 and 3), although there were differences in physical appearance. For samples stored at 33% RH, no changes in powder properties were observed, with samples appearing “dry” and free-flowing. For the 43% RH samples, the samples started to agglomerate

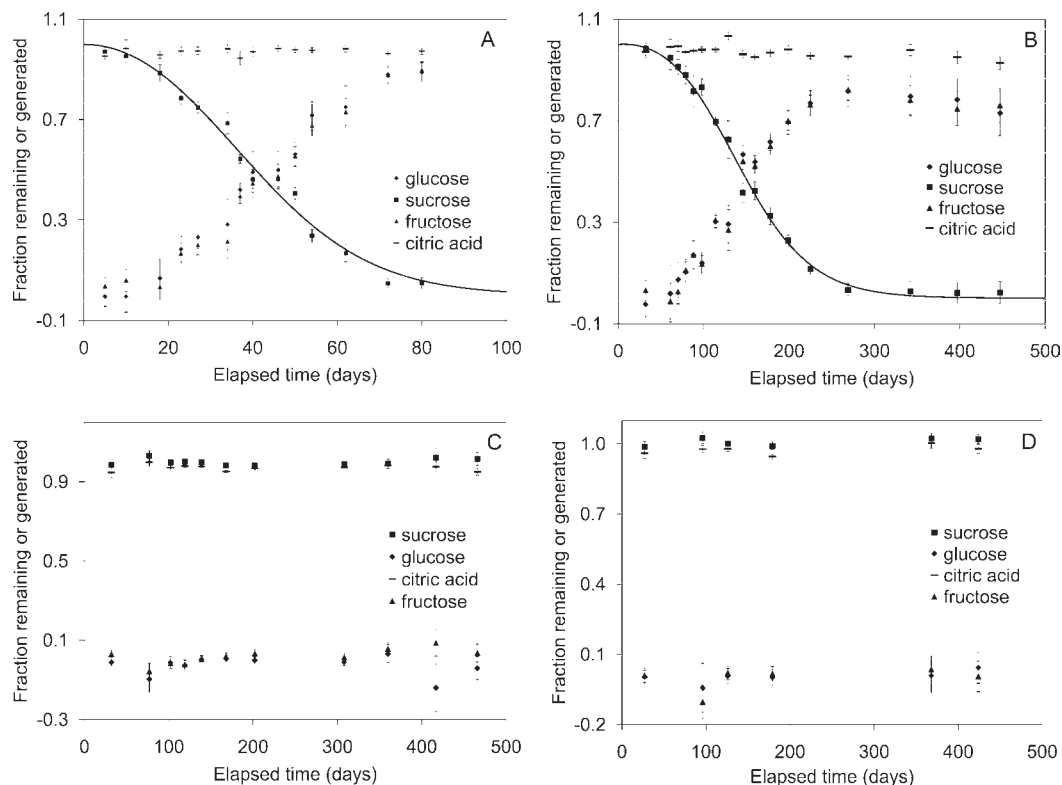
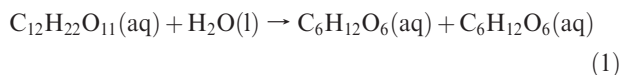


Figure 2. Kinetic profiles of all components in the 50:50 sucrose–citric acid blends: (A) 64%; (B) 54%; (C) 43%; (D) 33% RH. Symbols represent experimental data, and solid lines are fits to the models described in the text. Each error bar represents the standard deviation of a set of triplicate samples or the average uncertainty evaluated from the PLS model for these samples, whichever is larger.

after ~300 days, especially the 50:50 mixtures. The observation that degradation can occur following storage below the MDRH is important and to the best of our knowledge has not been reported previously. As discussed above, minimal water absorption would theoretically be predicted for a mixture of two crystalline materials stored below MDRH. The net moisture gain as a function of time is shown for each component in **Figure 4**, where it is clear that samples stored at 54% RH acquired non-negligible amounts of water. Because the total molecular weight of glucose and fructose is not equal to the molecular weight of sucrose, the water gain was corrected by the amount of glucose and fructose generated to yield the net water gain. Despite the change in physical appearance of the 43% RH samples, no significant moisture gain was detected for these samples (**Figure 4**). For the 54 and 64% RH samples, the moisture sorption profiles resemble sigmoidal curves in that they all appear to have reached equilibrium at the end of the experiment.

Theoretical Basis for Sucrose Hydrolysis. The overall equation for sucrose hydrolysis in solution is



The kinetics of this reaction is pseudo-first-order with respect to sucrose because water is a solvent and therefore in excess in the solution. Hence, the water concentration and pH can be approximated as being constant throughout the reaction (17), and the rate equation can be written as

$$-\frac{d[\text{suc}]}{dt} = k[\text{suc}] \quad (2)$$

where [suc] is the sucrose concentration, k is the rate constant, and t is time.

The integrated form of this rate equation is

$$[\text{suc}]_t = [\text{suc}]_0 e^{-kt} \quad (3)$$

where $[\text{suc}]_0$ is the initial sucrose concentration.

Equation 3 holds true if water is in excess in the system as for a solution phase. However, in this study this is not the case (**Figure 4**). The water content of the solid mixtures changed due to continuous moisture sorption by the systems until the water activity in the solid/solution mixture was the same as that of the surrounding environment. Thus, the amount of sucrose dissolved at any time and available to undergo hydrolysis varies with the mass of water in the system. Therefore, the quantity of water in the system needs to be accounted for when the reaction kinetics are described (29). The amount of water taken up varies as a function of time and resembles a sigmoidal function for systems with significant moisture sorption (namely, those stored at 54 and 64% RH). It can be described by the following empirical equation as

$$W = \frac{A}{1 + e^{-a(t-c)}} - B \quad (4)$$

where W is the mass of water gained relative to the initial mass of sucrose at a given time, t , and the kinetic parameters of moisture sorption A , a , c , and B are constants obtained by fitting the experimental data (**Table 2**). A is related to the maximum amount of water at equilibrium; a is the starting point of the linear part of the curve; c is the midpoint of the curve; and B is a correction factor related to the lag time. Rate constants for powder samples are typically extracted from plots of the fractional degradation of the total amount of reaction as a function of time even if the degradation most likely occurs in localized regions of solution or disorder (29–32). Such an approach was followed in this study

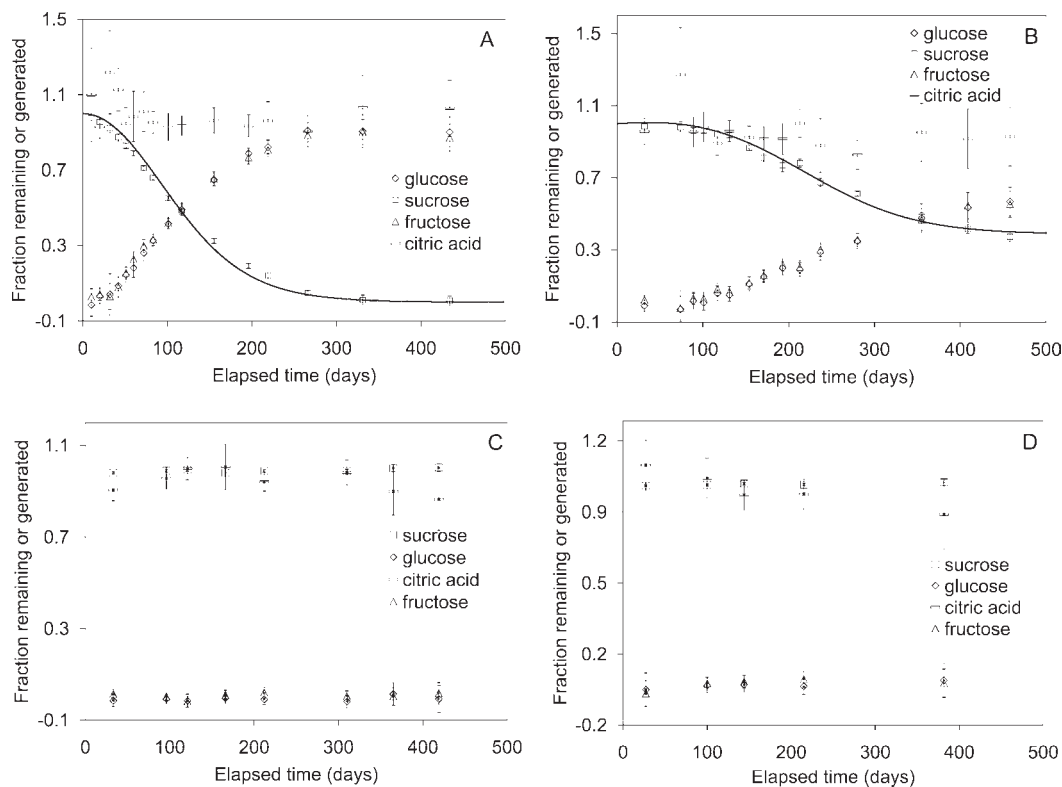


Figure 3. Kinetic profiles of all components in the 95:5 sucrose—citric acid blends: (A) 64%; (B) 54%; (C) 43%; (D) 33% RH. Symbols represent experimental data, and solid lines are fits to the models described in the text. Each error bar represents the standard deviation of a set of triplicate samples or the average uncertainty evaluated from the PLS model for these samples, whichever is larger.

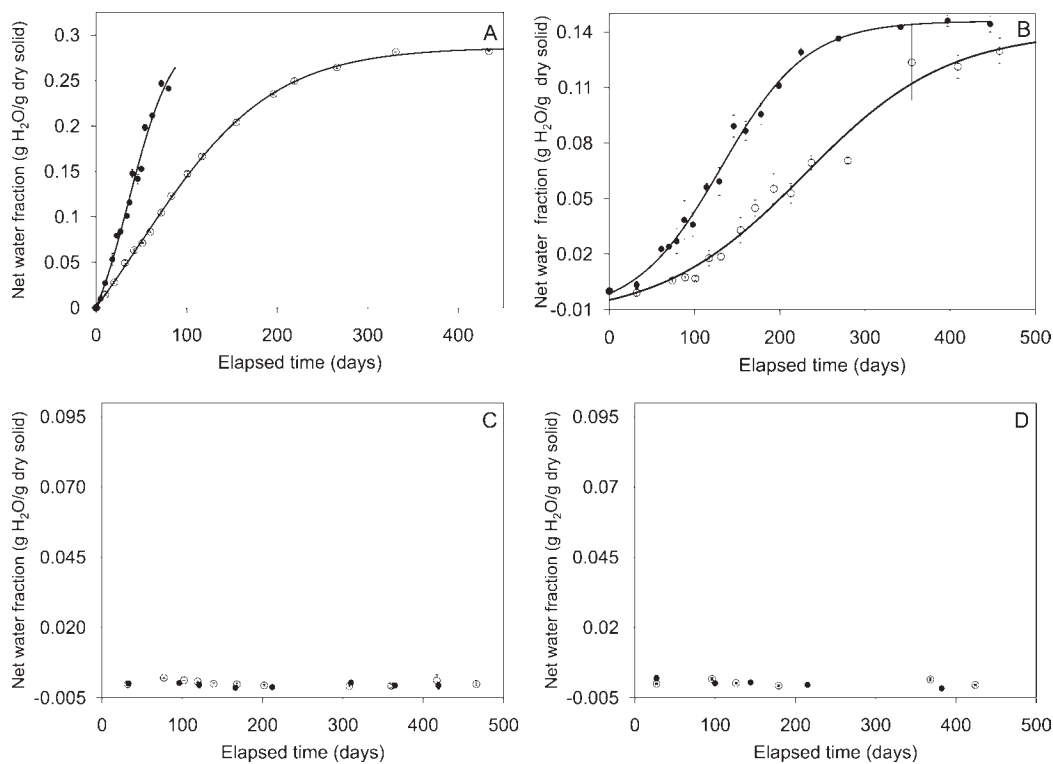


Figure 4. Moisture sorption profiles of the sucrose—citric acid blends as a function of time: (A) 64%; (B) 54%; (C) 43%; (D) 33% RH. Symbols represent experimental data, and solid lines are fits to the models described in the text. Solid and open symbols represent 50:50 and 95:5 samples of sucrose—citric acid, respectively. Each error bar represents the standard deviation of a set of triplicate samples.

where the fraction of total sucrose (i.e., in both solution and solid form) remaining as a function of time was measured experimentally.

Expressing the rate of degradation in terms of fraction of sucrose remaining and taking into account the varying water contents of

Table 2. Kinetics Parameters of Moisture Sorption and Sucrose Degradation (See Equations 4–7)

sample composition ^a	storage RH (%)	A (g of H ₂ O/g of sucrose)	a (day ⁻¹)	c (day)	B (g of H ₂ O/g of sucrose)	RMSE ^b	R ^{2b}	D (g H ₂ O/g sucrose · day)	k _{obs} (g of sucrose/g of H ₂ O · day ⁻¹)	RMSE ^c	R ^{2c}
50:50	54	0.3151	0.02010	131.6	0.02332	0.0093	0.993	-42.54	0.07993	0.027	0.995
95:5	54	0.3093	0.01188	229.0	0.02857	0.014	0.980	-72.49	0.02333	0.064	0.909
50:50	64	0.7684	0.03928	36.21	0.1484	0.022	0.985	-32.05	0.1365	0.039	0.986
95:5	64	0.8738	0.01362	47.23	0.2998	0.0047	0.9995	-68.37	0.03726	0.031	0.993

^a Ratio of sucrose–citric acid anhydrous. ^b Root mean square errors and correlation coefficients for the moisture sorption fitting. ^c Root mean square errors and correlation coefficients for the sucrose degradation fitting.

the powder as a function of time, the observed overall rate of sucrose degradation is given by

$$-\frac{d(mf_{\text{total}})}{dt} = k_{\text{obs}} \times mf_{\text{total}} \times W \quad (5)$$

where mf_{total} is the overall mass fraction of sucrose remaining at a given time and k_{obs} is the experimentally observed rate constant. Hence

$$mf_{\text{total}} = \frac{m_{\text{suc(s)}} + m_{\text{suc(aq)}}}{m_{\text{initial}}} \quad (6)$$

where $m_{\text{suc(s)}}$ is the mass of sucrose in solid form, $m_{\text{suc(aq)}}$ is the mass of sucrose that is dissolved, and m_{initial} is the initial mass of sucrose. Equation 5 predicts an S-shaped degradation profile, because at the beginning of the experiment there is no sucrose in solution and no water sorbed (i.e., $W = 0$), whereas at the end of the experiment, the mass fraction of sucrose in solution will decrease due to consumption by the reaction process without any solid phase to replenish that consumed by hydrolysis and the water content reaches steady state. This fits the experimental profiles shown in **Figures 2** and **3**.

The integrated form of eq 5 is

$$mf_{\text{total}} = (mf_{\text{total}})_0 e^{-k_{\text{obs}}(f(t))} \quad (7)$$

where

$$f(t) = A \left[t + \frac{1}{a} \ln(1 + e^{-a(t-c)}) \right] - Bt + D$$

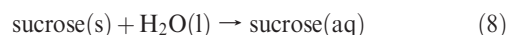
D is an integration constant (**Table 2**). Because the concentration of sucrose was expressed as the fraction of total sucrose remaining in the mixture, $(mf_{\text{total}})_0$ was unity. The rate constant k_{obs} was determined by fitting the experimental data to eq 7 (**Table 2**).

The fitting parameters (**Table 2**) indicate that this model is suitable for all samples with the exception of the 95:5 samples stored at 54% RH. This system had a lower correlation coefficient (0.909) for fitting of the aforementioned model. It is thought that this exception arises due to the limited amount of water acquired by this system. According to the moisture sorption profile (**Figure 4**), pseudoequilibrium of moisture sorption was reached at the end of the experiment; hence, the 95:5 system stored at 54% RH does not appear to be capable of absorbing additional moisture, even though the reaction is incomplete. Any sucrose remaining in the solid phase will be resistant to hydrolysis, and it appears that not enough water is absorbed by this system to dissolve all of the crystalline sucrose; that is, water is the limiting reagent. In fact, only about half of each 95:5 mixture at 54% RH appeared to be dissolved by the end of the experiment on the basis of visual observation. A possible reason for this was the insufficient physical contact between certain regions of sucrose and citric acid to initiate the processes of moisture uptake, deliquescence lowering, and subsequent hydrolysis of sucrose. This was not the case for the 50:50 samples kept at 54% RH, for which

enough water was absorbed to dissolve all of the crystalline sucrose, enabling the complete conversion of sucrose to fructose and glucose.

This issue can also be understood mathematically by examining eq 5. If the left-hand side of this equation (the rate) is 0, either mf_{total} or W should be 0. The only time when $W = 0$ is at the beginning of the experiment. On the other hand, $mf_{\text{total}} = 0$ only at the end of the experiment, that is, after all of the crystalline sucrose has been dissolved and converted into fructose and glucose. This model is correct for the other three sets of samples, but not so for the 95:5 samples at 54% RH because mf_{total} was not 0 at the end of the experiment (**Figure 3**). Therefore, a modified model is needed to better describe the degradation kinetics for these conditions.

In this model, the dissolution of sucrose is thus also considered:



The experimental rate equation for the appearance of sucrose solution can be written as

$$-\frac{d(mf_{\text{total}})}{dt} = k_{\text{diss}} \times W \quad (9)$$

where k_{diss} is the observed experimental rate constant for the dissolution process.

The overall rate equation for the hydrolysis reaction can be obtained by combining eqs 5 and 9:

$$-\frac{d(mf_{\text{total}})}{dt} = k_{\text{obs}} \times mf_{\text{total}} \times W - k_{\text{diss}} \times W \quad (10)$$

The integrated form of eq 10 is

$$mf_{\text{total}} = \frac{k_{\text{diss}}}{k_{\text{obs}}} - \frac{k_{\text{diss}} - k_{\text{obs}}}{k_{\text{obs}}(e^{f(t) \cdot k_{\text{obs}}})} \quad (11)$$

where

$$f(t) = A \left[t + \frac{1}{a} \ln(1 + e^{-a(t-c)}) \right] - Bt + D \quad (12)$$

k_{obs} and k_{diss} were determined by fitting all experimental data to eq 11 (**Table 3**). The other constants are the same as for eq 7. The fitting parameters (**Table 3**) and the resultant curve (**Figure 3**) using eq 11 show that this is a better model to describe the 95:5 samples stored at 54% RH.

The kinetic profiles shown in **Figures 2** and **3** indicate that the fraction of citric acid remained constant throughout the experiment for all samples. This suggests that citric acid was not involved in the rate equation because of the excess quantities present. However, the overall rate of sucrose hydrolysis was related to the initial amount of citric acid in the mixtures. For the 64% RH samples, the reaction reached equilibrium about 3 times more rapidly for the 50:50 samples than for the 95:5 samples. It is well-known from solution studies that a source of

protons catalyzes the hydrolysis reaction (17–19). However, for these samples the concentration of citric acid in solution should be a constant (certainly at the beginning of the reaction) and equivalent to the solubility. The difference in the reaction rate between the 50:50 and 95:5 samples can thus be attributed to the difference in the amount of citric acid present in the mixtures in terms of the local environment of the sucrose particles. Thus, the probability of a sucrose particle being in contact with a citric acid particle is higher for the 50:50 samples than the 95:5 samples. This increase in contact probability will create the required acidic microenvironment on dissolution to cause sucrose hydrolysis and hence increase the overall reaction rate.

The 95:5 samples at 64% RH initially degraded more quickly than the 50:50 samples at 54% RH (Figure 5). However, the

Table 3. Kinetics Parameters of Sucrose Degradation Using Alternative Model (See Equations 10 and 11)

sample composition ^a	storage RH (%)	k_{obs}	k_{diss}^b	RMSE ^c	R^2
95:5	54	0.06678	0.02568	0.026	0.987

^a Ratio of sucrose–citric acid anhydrous. ^b Unit of k_{diss} : g of sucrose/g of H₂O·day. ^c Root mean square error.

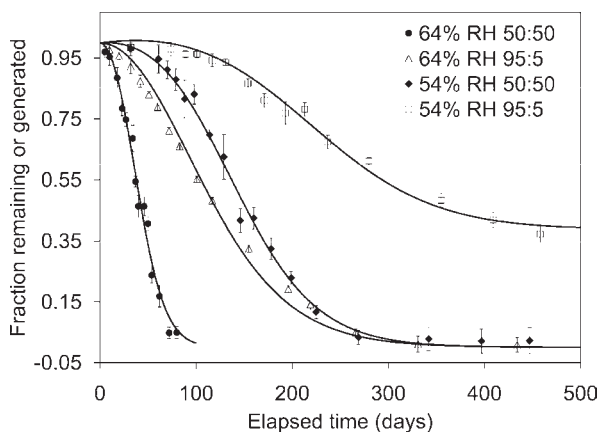


Figure 5. Comparison of sucrose degradation among the blends of sucrose and citric acid stored at 54 and 64% RH. Symbols represent experimental data, and solid lines are fits to the models described in the text. Each error bar represents the standard deviation of a set of triplicate samples or the average uncertainty evaluated from the PLS model for these samples, whichever is larger.

degradation rate of the 54% RH samples became similar to that of the 64% RH samples after approximately 100 days, and both sets of samples reached equilibrium at approximately the same time (~350 days). This suggests that the amount of moisture within the system is important for the initialization of the reaction, as there was more water in the 95:5 samples (64% RH) than in the 50:50 samples (54% RH) at any given moment. However, the amount of citric acid present also appears to be important, particularly during the latter part of the degradation process; there was 10 times as much citric acid in the 50:50 samples as in the 95:5 samples.

The 50:50 samples stored at 54% RH acquired less water than the 50:50 samples stored at 64% RH at equilibrium but took longer to reach equilibrium. These results are consistent with the higher water vapor pressure in the 64% RH environment compared to the 54% RH condition. According to the kinetic model described above, the overall rate will increase with more water in the system. Hence, the 50:50 samples stored at 64% RH reached equilibrium before the 54% RH counterparts.

Reaction Mechanism and Thermodynamics. In this section, a reaction mechanism between sucrose and citric acid is proposed, and the detailed reasoning and thermodynamics behind each step are illustrated.

The amount of moisture sorbed by the various systems as a function of time is clearly a key parameter, as demonstrated by the models described above. To understand the difference in the moisture sorption profiles of the various systems, the effects of composition on both the MDRH and the kinetics of moisture sorption have to be considered. The MDRH of the initial mixture (sucrose + citric acid anhydrous) is 64% RH at 25 °C. When the ambient RH is below the MDRH, only a limited amount of water vapor can be adsorbed on the surface of the solid particles (9). Once the ambient RH reaches the MDRH, water vapor can condense onto the surface of heteroparticles that are in physical contact and both sucrose and citric acid start to dissolve until a saturated solution is formed. The extent of dissolution will depend on the composition of the blend relative to the eutonic composition, which is estimated to be approximately 56% w/w sucrose and 44% w/w citric acid (12). Thus, the 50:50 blend is near the eutonic composition and can potentially undergo a significant extent of dissolution. The dissolved sucrose molecules will be in the same solution phase as the dissolved citric acid molecules and will undergo hydrolysis due to the acidic environment (17, 19), producing glucose and fructose in solution. The presence of glucose and fructose in solution triggers further moisture sorption to satisfy the Gibbs–Duhem equation (11), thereby diluting the

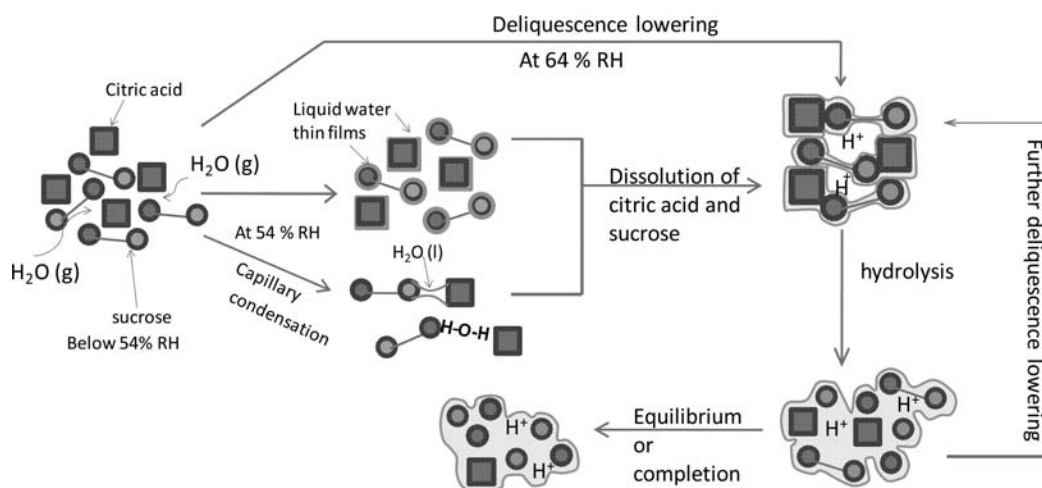


Figure 6. Proposed mechanism of sucrose hydrolysis in powder blends containing sucrose and citric acid stored at 64 and 54% RH.

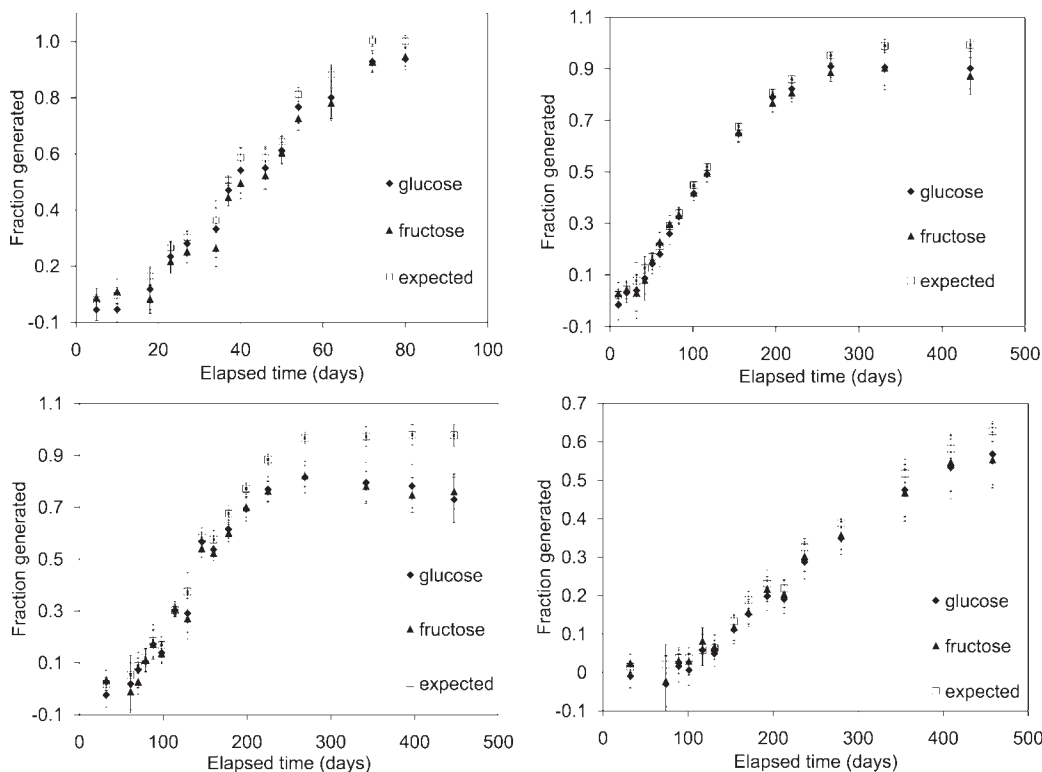


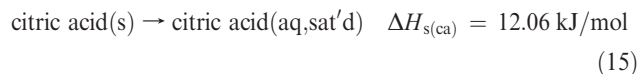
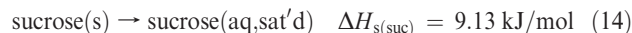
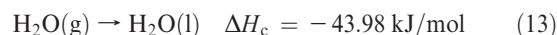
Figure 7. Comparisons between the expected products fraction and the real products fraction in sucrose—citric acid blends over time: (top) 64% RH; (bottom) 54% RH. Ratios of sucrose—citric acid were (left) 50:50 and (right) 95:5. Each error bar represents the standard deviation of a set of triplicate samples or the average uncertainty evaluated from the PLS model for these samples, whichever is larger.

solution and causing additional solid material to dissolve until saturation is reached, to re-establish equilibrium with the solid phases. The removal of sucrose through hydrolysis will also promote sucrose dissolution to re-establish the saturated solution. This cycle of water absorption, dissolution of sucrose and citric acid, and hydrolysis of sucrose continues until the system reaches equilibrium. At equilibrium, the activity of water in the mixture is equal to that of the surrounding environment. Following equilibrium, no additional water will be absorbed. Thus, when the storage RH is the same as MDRH for the sucrose—citric acid system, all of the sucrose should dissolve and hydrolyze, as long as there is sufficient citric acid present to supply enough protons for the reaction, and the citric acid in the initial powder achieves sufficient physical contact with the sucrose particles such that deliquescence lowering can be triggered. This is clearly the case for samples of both compositions stored at 64% RH, which undergo complete sucrose degradation.

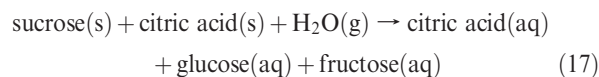
When the ambient RH is below the MDRH, that is, for the samples stored at 54% RH, no bulk dissolution should occur (12), and therefore it might be anticipated that no sucrose hydrolysis will occur. Obviously, that was not the case; experimental results showed that the mixtures can indeed undergo hydrolysis, albeit at a slower rate. The following mechanism can be proposed for these systems: The layer of surface water on sucrose and citric acid crystals in contact with one another contains mobile species of each compound that can react, producing initially minute quantities of fructose and glucose. The presence of fructose and glucose, which will lower the MDRH to around 36% RH, will cause more water to condense and initiate the cycle of dissolution and hydrolysis described above. The presence of a thin film of water containing mobile species on the surface of crystalline particles is well established (33–36). In addition, water could condense at interparticulate contacts as a result of capillary condensation. It has been demonstrated that capillary condensation can occur within a powder blend consisting of particle sizes of < 500 μm and is more

pronounced at higher RH (37). Capillary condensation provides bulk liquid water, which can then trigger the dissolution of solid sucrose and citric acid particles. A schematic of the reaction mechanism is presented in **Figure 6**.

Thermodynamically, the overall reaction can be separated into four steps. First, water vapor condensed onto the particle surface to form liquid water. Then the dissolution of the sucrose and citric acid solids occurred. Finally, the production of glucose and fructose via hydrolysis of sucrose in the solution medium completed the reaction. Each step and the overall reaction can be presented by the following chemical equations (25, 38–42):



$$\Delta H_{\text{h}} = -14.93 \text{ kJ/mol}$$



$$\Delta H = -37.72 \text{ kJ/mol}$$

On the basis of the heat of the overall reaction, the overall reaction is favorable enthalpically. As one can see from the

equations, the partial heat released (21.19 kJ/mol) from the condensation of water vapor and the hydrolysis of the sucrose is absorbed by the dissolution of the solid particles to further enhance solid dissolution. To determine the free energy of the overall reaction, entropy data are needed. However, the entropy data for the individual steps were not complete in the literature, so free energy cannot be determined for this reaction. The enthalpy change of the reaction should be similar for both the 50:50 and 95:5 samples. However, the entropy of mixing should be larger for the 50:50 samples than for the 95:5 samples. This enhancement should slightly decrease the overall free energy change for the 50:50 samples to make it more favorable.

Degradation of the Products. During the experiment, all of the mixtures except the 50:50 samples at 64% RH had developed various degrees of yellow color formation after about 150 days and continued to darken throughout the remainder of the experiment. By the end of the experiment, the 95:5 samples at 54 and 64% RH were pale yellow and the 50:50 samples at 54% RH were dark yellow. Color changes have been linked to degradation: 5-(Hydroxymethyl)-2-furaldehyde (HMF) is a brown-colored compound generated by dehydration of fructose or glucose under acidic conditions (43, 44). If every mole of sucrose consumed was converted into a mole of glucose and fructose, the expected amount of fructose or glucose generated could be obtained from quantifying the remaining sucrose. However, this was not the case for the 50:50 samples at 54% RH (Figure 7). The experimental amounts of glucose and fructose were lower than the expected amounts toward the end of the experiment for this set of samples. The discrepancy between the expected and the actual fraction of the products was probably caused by the degradation of the products, that is, to HMF and possibly other degradants. This degradation of the products is important because it demonstrated that the initial degradants may have a more compromised chemical stability and they may convert into undesired products, which could be toxic or in this case caused color change.

Implication for Powder Formulations. Published recommendations for storing products containing multiple deliquescent ingredients claim that stability can be maintained by storing the products at RHs below the MDRH (2, 3). However, in this study it is evident that a powder mixture of sucrose and citric acid can undergo hydrolysis not only at and over the MDRH but also below the MDRH, although at a slower rate. The formation of the hydrolyzed products caused further deliquescence lowering and favors the sorption of moisture and, consequently, the inversion of sucrose. This is a significant discovery because it shows that powder mixtures are susceptible to chemical degradation even below their MDRH if enough time is provided.

Conclusions. The chemical stability of a sucrose–citric acid powder system was investigated at various RHs (33–64% RH). Interestingly, hydrolysis of sucrose occurred not only at but also below the MDRH of the binary system, being observed at both 64 and 54% RH. Thus, it appears that moisture-induced instability in powder blends can occur below the MDRH over long time periods. Semiempirical kinetics models were established to predict the reaction rate of sucrose hydrolysis for the powder blends, and it was found that the rate of moisture uptake was the major factor dictating the reaction rate. The ratio of sucrose to citric acid was also important. Thus, the reaction rate was faster at 64% RH and for the 50:50 as compared to 95:5 sucrose–citric acid samples. It is speculated that the presence of a thin film of water below the DRH and capillary condensation at interparticulate contacts may initiate the reaction for samples stored at 54% RH. This study highlights the complex interplay of

atmospheric moisture with chemically heterogeneous blends and the subsequent implications for long-term chemical stability.

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