articles

molecular pharmaceutics

Mechanisms by Which Moisture Generates Cocrystals

Adivaraha Jayasankar, David J. Good, and Naír Rodríguez-Hornedo*

Department of Pharmaceutical Sciences, University of Michigan,
Ann Arbor, Michigan 48109-1065

Received January 14, 2007; Revised Manuscript Received April 6, 2007; Accepted April 10, 2007

Abstract: The purpose of this study is to determine the mechanisms by which moisture can generate cocrystals when solid particles of cocrystal reactants are exposed to deliquescent conditions (when moisture sorption forms an aqueous solution). It is based on the hypothesis that cocrystallization behavior during water uptake can be derived from solution chemistry using models that describe cocrystal solubility and reaction crystallization of molecular complexes. Cocrystal systems were selected with active pharmaceutical ingredients (APIs) that form hydrates and include carbamazepine, caffeine, and theophylline. Moisture uptake and crystallization behavior were studied by gravimetric vapor sorption, X-ray powder diffraction, and on-line Raman spectroscopy. Results indicate that moisture uptake generates cocrystals of carbamazepine−nicotinamide, carbamazepine−saccharin, and caffeine or theophylline with dicarboxylic acid ligands (oxalic acid, maleic acid, glutaric acid, and malonic acid) when solid mixtures with cocrystal reactants deliquesce. Microscopy studies revealed that the transformation mechanism to cocrystal involves (1) moisture uptake, (2) dissolution of reactants, and (3) cocrystal nucleation and growth. Studies of solid blends of reactants in a macro scale show that the rate and extent of cocrystal formation are a function of relative humidity, moisture uptake, deliquescent material, and dissolution rates of reactants. It is shown that the interplay between moisture uptake and dissolution determines the liquid phase composition, supersaturation, and cocrystal formation rates. Differences in the behavior of deliquescent additives (sucrose and fructose) are associated with moisture uptake and composition of the deliquesced solution. Our results show that deliquescence can transform API to cocrystal or reverse the reaction given the right conditions. Key indicators of cocrystal formation and stability are (1) moisture uptake, (2) cocrystal aqueous solubility, (3) solubility and dissolution of cocrystal reactants, and (4) transition concentration.

Keywords: Cocrystallization; molecular complex; cocrystal stability; deliquescence; phase transformation; hygroscopicity

Introduction

The effects of moisture on drug stability are of central importance for the development of pharmaceutical products. Water can cause chemical instability and solid phase transformations that will compromise product safety and bioavailability. Relative humidity dependent phase transformations are well-documented and include anhydrous to hydrate,[1−6] polymorphic[7] and amorphous to crystalline transformations.[8,9] Recent studies from our laboratory demonstrated that amorphous regions mediate transformations of solid reactants to cocrystal and that moisture enhances reactivity.[10,11] These studies showed that the mechanism involves increased molecular mobility and is associated with the plasticizing effects of water.[10,12]

---

* Corresponding author. Mailing address: College of Pharmacy, 428 Church St., Ann Arbor, MI 48109-1065. Phone: 734-763-0101. Fax: 734-615-6162. E-mail: nrh@umich.edu.

(1) Salameh, A. K.; Taylor, L. S. Physical Stability of Crystal Hydrates and Their Anhydrates in the Presence of Excipients. *J. Pharm. Sci.* **2006**, *95*, 446−461.

(2) Kesavan, J. G.; Peck, G. E. Solid-State Stability of Theophylline Anhydrous in Theophylline Anhydrous-Polyvinylpyrrolidone Physical Mixtures. *Drug Dev. Ind. Pharm.* **1996**, *22*, 189−199.

10.1021/mp0700099 CCC: $37.00

Moisture sorption by hygroscopic materials can also lead to deliquescence. This process refers to the formation of an aqueous solution by the absorption of water vapor at a characteristic relative humidity or deliquescent relative humidity (DRH).[13] DRH is a function of the chemistry of a solid, solid phase composition, and temperature.[14−20] It is well-established that the presence of a second solid component decreases the DRH. Materials used in pharmaceutical formulations that exhibit deliquescence include sugars and organic and inorganic salts.[16,21−23] Deliquescence dependent phase transformations for hydrates[4] and deliquescence mediated chemical degradation have also been published.[16,24,25] Although cocrystals have been shown to prevent formation of hydrated API during storage at high RH,[26−29] various cocrystals have shown RH dependent transformation to hydrated API.[28,29] Therefore, it appears that identifying the mechanisms for cocrystal formation and stability would be of practical importance if cocrystals are to be developed as pharmaceutical products.

The research reported here is based on the premise that deliquescence can lead to cocrystal nucleation and growth because cocrystal solubility and thermodynamic stability are dependent on solution chemistry. Earlier reports from our laboratory have shown that cocrystal solubility is a function of the cocrystal components in solution and is described by solubility product and solution speciation.[26,30,31] This means that cocrystal solubility decreases as the liquid becomes richer in one of the cocrystal components. The important implication of this mechanism is that supersaturation with

---

(3) Airaksinen, S.; Karjalainen, M.; Kivikero, N.; Westermarck, S.; Shevchenko, A.; Rantanen, J.; Yliruusi, J. Excipient Selection Can Significantly Affect Solid-State Phase Transformation in Formulation During Wet Granulation. *AAPS PharmSciTech* **2005**, *6*, E311−E322.

(4) Otsuka, M.; Matsuda, Y. The Effect of Humidity on Hydration Kinetics of Mixtures of Nitrofurantoin Anhydride and Diluents. *Chem. Pharm. Bull.* **1994**, *42*, 156−159.

(5) Kaneniwa, N.; Yamaguchi, T.; Watari, N.; Otsuka, M. Hygroscopicity of Carbamazepine Crystalline Powders. *Yakugaku Zasshi* **1984**, *104*, 184−190.

(6) Pirttimaki, J.; Laine, E. The Transformation of Anhydrate and Hydrate Forms of Caffeine at 100-Percent RH and 0-Percent RH. *Eur. J. Pharm. Sci.* **1994**, *1*, 203−208.

(7) Yoshinari, Y.; Forbes, R. T.; York, P.; Kawashima, Y. Moisture Induced Polymorphic Transition of Mannitol and Its Morphological Transformation. *Int. J. Pharm.* **2002**, *247*, 69−77.

(8) Andronis, V.; Yoshioka, M.; Zografi, G. Effects of Sorbed Water on the Crystallization of Indomethacinfrom the Amorphous State. *J. Pharm. Sci.* **1997**, *86*, 346−351.

(9) Tong, P.; Zografi, G. Effects of Water Vapor Absorption on the Physical and Chemical Stability of Amorphous Sodium Indomethacin. *AAPS PharmSciTech* **2004**, *5*, Art. No. 26.

(10) Jayasankar, A.; Somwangthanaroj, A.; Shao, Z. J.; Rodríguez-Hornedo, N. Cocrystal Formation During Cogrinding and Storage Is Mediated by Amorphous Phase. *Pharm. Res.* **2006**, *23*, 2381−2392.

(11) Seefeldt, K.; Miller, J.; Alvarez-Núñez, F.; Rodríguez-Hornedo, N. Crystallization Pathways and Kinetics of Carbamazepine-Nicotinamide Cocrystals from the Amorphous State by in-Situ Thermomicroscopy, Spectroscopy and Calorimetry Studies. *J. Pharm. Sci.*, in press.

(12) Hancock, B. C.; Zografi, G. The Relationship between the Glass-Transition Temperature and the Water-Content of Amorphous Pharmaceutical Solids. *Pharm. Res.* **1994**, *11*, 471−477.

(13) Campen, L. V.; Amidon, G. L.; Zografi, G. Moisture Sorption Kinetics for Water-Soluble Substances I: Theoretical Considerations of Heat Transport Control. *J. Pharm. Sci.* **1983**, *72*, 1381−1388.

(14) Kontny, M. J.; Zografi, G. Moisture Sorption Kinetics for Water-Soluble Substances IV: Studies with Mixtures of Solids. *J. Pharm. Sci.* **1985**, *74*, 124−127.

(15) Salameh, A. K.; Taylor, L. S. Deliquescence in Binary Mixtures. *Pharm. Res.* **2005**, *22*, 318−324.

(16) Salameh, A. K.; Taylor, L. S. Role of Deliquescence Lowering in Enhancing Chemical Reactivity in Physical Mixtures. *J. Phys. Chem. B* **2006**, *110*, 10190−10196.

(17) Salcedo, D. Equilibrium Phase Diagrams of Aqueous Mixtures of Malonic Acid and Sulfate/Ammonium Salts. *J. Phys. Chem. A* **2006**, *110*, 12158−12165.

(18) Wexler, A. S. Second-Generation Inorganic Aerosol Model. *Atmos. Environ.* **1991**, *25A*, 2731−2748.

(19) Carroll, S.; Craig, L.; Wolery, T. J. Deliquescence of NaCl-$NaNO_3$, KNO_3-$NaNO_3$, and NaCl-KNO_3 Salt Mixtures from 90 to 120 Degrees C. *Geochem. Trans.* **2002**, *6*, 19−30.

(20) Brooks, S. D.; Wise, M. E.; Cushing, M.; Tolbert, M. A. Deliquescence Behavior of Organic/Ammonium Sulfate Aerosol. *Geophys. Res. Lett.* **2002**, *29*, Art. No. 1917.

(21) Salameh, A. K.; Mauer, L. J.; Taylor, L. S. Deliquescence Lowering in Food Ingredient Mixtures. *J. Food. Sci.* **2006**, *71*, E10−E16.

(22) Salameh, A. K.; Taylor, L. S. Deliquescence-Induced Caking in Binary Powder Blends. *Pharm. Dev. Technol.* **2006**, *11*, 453−464.

(23) Parsons, M. T.; Mak, J.; Lipetz, S. R.; Bertram, A. K. Deliquescence of Malonic, Succinic, Glutaric and Adipic Acid Particles. *J. Geophys. Res.* **2004**, *109*, Art. No. D06212.

(24) Carstensen, J. T.; Attarchi, F.; Hou, X.-P. Decomposition of Aspirin in the Solid-State in the Presence of Limited Amounts of Moisture. *J. Pharm. Sci.* **1985**, *74*, 741−745.

(25) Teraoka, R.; Otsuka, M.; Matsuda, Y. Effects of Temperature and Relative-Humidity on the Solid-State Chemical-Stability of Ranitidine Hydrochloride *J. Pharm. Sci.* **1993**, *82*, 601−604.

(26) Rodríguez-Hornedo, N.; Nehm, S. J.; Jayasankar, A. Cocrystals: Design, Properties and Formation Mechanisms. In *Encyclopedia of Pharmaceutical Technology*, 3rd ed.; Swarbrick, J., Ed.; Taylor and Francis: New York, 2006; pp 615−635.

(27) Rodríguez-Spong, B. Enhancing the Pharmaceutical Behavior of Poorly Soluble Drugs through the Formation of Cocrystals and Mesophases. Ph.D. Thesis, University of Michigan, Ann Arbor, 2005.

(28) Trask, A. V.; Motherwell, W. D. S.; Jones, W. Physical Stability Enhancement of Theophylline Via Cocrystallization. *Int. J. Pharm.* **2006**, *320*, 114−123.

(29) Trask, A. V.; Motherwell, W. D. S.; Jones, W. Pharmaceutical Cocrystallization: Engineering a Remedy for Caffeine Hydration. *Cryst. Growth Des.* **2005**, *5*, 1013−1021.

(30) Nehm, S. J.; Rodríguez-Spong, B.; Rodríguez-Hornedo, N. Phase Solubility Diagrams of Cocrystals Are Explained by Solubility Product and Solution Complexation. *Cryst. Growth Des.* **2006**, *6*, 592−600.

(31) Rodríguez-Hornedo, N.; Nehm, S. J.; Seefeldt, K. F.; Pagán-Torres, Y.; Falkiewicz, C. J. Reaction Crystallization of Pharmaceutical Molecular Complexes. *Mol. Pharmaceutics* **2006**, *3*, 362−367.

respect to cocrystal can be generated by dissolving nonequivalent amounts of its components. Supersaturation is dependent on solution composition, and for a binary cocrystal AB is expressed by[31]

$$\sigma = \left(\frac{[\mathrm{A}][\mathrm{B}]}{K_{\mathrm{sp}}}\right)^{1/2} \qquad (1)$$

Hence, if the required supersaturation for cocrystal nucleation is attained, then cocrystals are formed. Evidence has been presented to show increase in cocrystal formation rates with increasing solution concentration of the more soluble reactant.[31,32]

The thermodynamic stability of a cocrystal relative to pure API crystal has been demonstrated to vary with the concentration of reactants in solution.[30,31] Moreover, in solvents where cocrystal is more soluble than pure API, there is a reactant transition concentration (C_{tr}) at which the cocrystal solubility is equal to the solubility of pure API or API solvate. At this concentration, both crystalline forms are at equilibrium. Above the C_{tr}, cocrystal solubility is below that of API, and therefore cocrystal is the thermodynamically stable form. Rapid transformation of API to API cocrystal has been shown in aqueous media for API that readily transforms to API hydrate in pure water, e.g., carbamazepine (CBZ) to carbamazepine−nicotinamide (CBZ−NCT) cocrystal.[31]

The present study is based on the hypothesis that cocrystals are produced when solid reactants are exposed to deliquescent conditions, since dissolution of cocrystal reactants in the sorbed moisture can generate the supersaturation necessary for nucleation and growth of cocrystals. Cocrystal systems were selected from previously reported pharmaceutical cocrystals with APIs that form hydrates.[28,29,33] This initial report presents results of cocrystal formation at constant RH in (1) binary blends of cocrystal reactants (CBZ/NCT) and (2) ternary blends of cocrystal reactants with a deliquescent additive that is not consumed by the reaction (CBZ/NCT, CBZ/SAC, caffeine/dicarboxylic acids, theophylline/dicarboxylic acids with sucrose or fructose). The influence of deliquescent additive, solid blend composition, and RH on the transformation rate to cocrystal was studied by on-line Raman spectroscopy during deliquescence. To our knowledge this is the first report on cocrystal formation induced by deliquescence and on the indicators of cocrystal stability under deliquescence processes.

Experimental Section

All chemicals were obtained from Sigma Chemical Company (St. Louis, MO) and were of USP grade. Chemicals were used as received without further purification. All chemicals were characterized prior to use by X-ray powder diffraction (XRPD) and infrared spectroscopy. XRPD of carbamazepine and theophylline agreed with the Cambridge Structural Database (CSD) simulated XRPD pattern of form III monoclinic CBZ (CSD refcode: CBMZPN01) and anhydrous theophylline (CSD refcode: BAPLOT01). The pattern of caffeine agreed with form II anhydrous caffeine.[6]

Table 1. List of the Materials Used To Study Moisture Uptake and Phase Stability

APIs	cocrystal formers/ligands	deliquescent additives
carbamazepine	*nicotinamide*	fructose
theophylline	saccharin	sucrose
caffeine	*oxalic acid*	
sulfadimidine	*glutaric acid*	
	malonic acid	
	maleic acid	
	anthranilic acid	
	salicylic acid	

All samples were sieved to collect particle size fractions of 45−63 μm and 106−125 μm. Large crystals were hand ground prior to sieving. Samples were annealed and characterized again by XRPD and FTIR prior to their use in our studies. These fractions were used in preparing samples to study deliquescence by gravimetric sorption analysis and cocrystal formation in bulk samples at constant RH. The composition of the deliquescent additives is expressed on a weight percent basis unless otherwise specified.

Within the scope of this paper we can define the materials used as APIs, cocrystal formers or ligands, and deliquescent additives as listed in Table 1. The term reactant refers to cocrystal components, i.e., API and ligand. The deliquescence behavior of some of the cocrystal formers (shown in italics in Table 1) and additives has been published.[20,21,23]

Gravimetric Vapor Sorption. Vapor sorption studies were conducted to determine DRH or to monitor the progress of moisture sorption toward equilibrium under constant RH and temperature. Both types of gravimetric vapor sorption studies use samples of 5−10 mg with particle size of all components between 45 and 63 μm unless otherwise noted. All studies were done on an SGA-100 symmetrical gravimetric analyzer from VTI Corp. (Hialeah, FL). The instrument uses a microbalance (CI Electronics, Wiltshire, U.K.) to monitor sample weight and a chilled dew point analyzer (Edgetech, Milford, MA) to detect and control humidity in the sample chamber. Temperature is controlled to within 0.01 °C, and the instrument RH resolution is ±1%. All experiments were conducted at 25 °C.

The DRH for single components and binary blends was determined using a nonequilibrium sorption method. This is an isothermal method that ramps RH by 2% increments. The relative humidity is increased incrementally when the sample changes weight by less than 0.036% in 15 min or 240 min whichever comes first at constant RH. While the samples only adsorb small levels of moisture below the DRH, a large weight increase from moisture absorption is observed once the DRH is reached.

---

(32) Jayasankar, A.; Nehm, S. J.; Rodríguez-Hornedo, N. The Use of Raman Spectroscopy for Real-Time Monitoring of Cocrystal Formation During Wet Granulation. *AAPS J.*, in press.

(33) Fleischman, S. G.; Kuduva, S. S.; McMahon, J. A.; Moulton, B.; Walsh, R. D. B.; Rodríguez-Hornedo, N.; Zaworotko, M. J. Crystal Engineering of the Composition of Pharmaceutical Phases: Multiple-Component Crystalline Solids Involving Carbamazepine. *Cryst. Growth Des.* **2003**, *3*, 909−919.

The time course of moisture sorption, and desorption in some instances, at fixed temperature and humidity was also studied for a variety of sample compositions. In these studies constant RH and temperature were maintained over the course of several days until the sample reached an equilibrium moisture sorption level.

Bulk Sample Studies in RH Chambers. The effects of DRH, storage RH, particle size, and the amount of deliquescent materials on the rate of cocrystal formation were studied using ternary mixtures of CBZ (III), with NCT or saccharin (SAC), and a deliquescent additive (fructose or sucrose). In these studies the cocrystal reactant ratio in the solid phases was held constant at equimolar concentrations and the composition of the deliquescent additive was varied. Raman spectroscopy has been shown to be valuable for real-time monitoring of cocrystal formation[31,34] and was used to study cocrystal formation at constant RH and temperature.

Desired RH conditions during storage at 25 °C were generated in glass desiccators with appropriate saturated salt solution: NaCl for 75%, KCl for 85%, and K_2SO_4 for 98%.[35] An aluminum plate with holes was suspended above the solution to hold samples, and a 1/8 in. thick quartz glass lid was used to seal the chamber. The relative humidity in the chambers was confirmed using a HydroClip SC05 RH probe from Rotronics (Huntington, NY). Probe accuracy is ±1.5% RH/±0.2 °C.

Solid blends were stored at 0% RH in a P_2O_5 desiccator and analyzed by XRPD and IR prior to introduction into RH chambers. Quartz cuvettes containing 30-60 mg of 45−63 μm (unless otherwise specified) crystalline blends were introduced into the RH chambers. Phase transformation in the blends was monitored by Raman spectroscopy. A noncontact fiber optic probe was used to collect Raman spectra through the quartz chamber lid. Spectra were collected frequently over random areas of the sample for several days. A time course of the change in spectral features was used to monitor cocrystal formation. HoloReact software, from Kaiser Optical Systems (Ann Arbor, MI), was used for multivariate curve resolution to plot the change in spectral features correlating to reactants and cocrystal. The analysis region for CBZ−NCT systems was 924−1182 cm^{-1} and CBZ−SAC was 225−300 cm^{-1}. Samples were promptly analyzed by XRPD and IR once removed from the chamber. The masses of the blends before and after storage were also noted to determine the amount of moisture sorbed.

Slurry Studies. Screening for cocrystals was carried out according to methods published earlier.[30,31] Cocrystal reactants were added to aqueous solutions such that nonstoichiometric reactant concentrations would favor cocrystal formation. The slurries were placed in a 25 °C recirculation water bath and stirred continuously. No nucleating seeds were added to these samples. Once removed from the water bath the slurries were dried by vacuum filtration and promptly analyzed by XRPD.

Raman Spectroscopy. Raman spectra of solid phases were collected with an RXN1 Raman spectrometer equipped with a 785 nm laser from Kaiser Optical Systems, Inc. (Ann Arbor, MI). Crystallization in bulk samples was monitored in situ with a fiber optic noncontact probe. Crystallization was also monitored in microscale using a Leica DMLP (Wetzlar, Germany) Raman microscope. Acquisition conditions were optimized so that the spectra collected for bulk studies had maximum intensity around 30−40k counts. The spectra collected had a spectral resolution of 4 cm^{-1} and were collected between 100 and 3200 cm^{-1}.

X-ray Powder Diffraction (XRPD). XRPD was used to identify crystalline phases and phase transformations after exposure to various storage conditions. XRPD patterns of solid phases were recorded with a Rigaku MiniFlex X-ray diffractometer (Danvers, MA) using Cu Kα radiation (λ = 1.54 Å), a tube voltage of 30 kV, and a tube current of 15 mA. The intensities were measured at 2θ values from 2° to 40° at a continuous scan rate of 2.5 deg/min. Samples, prior to and after RH storage experiments, were analyzed by XRPD. Results were compared to diffraction patterns reported in literature or calculated from crystal structures reported in the Cambridge Structural Database (CSD).

Attenuated Total Reflectance Fourier Transform Infrared Spectroscopy (ATR-FTIR). IR spectra of solid phases were collected on a Bruker Vertex 70 FT-IR (Billerica, MA) unit equipped with a DTGS detector. Samples were placed on a zinc selenide (ZnSe) attenuated total reflectance (ATR) crystal accessory, and 64 scans were collected for each sample at a resolution of 4 cm^{-1} over a wavenumber region of 4000−600 cm^{-1}.

Polarized Optical Light Microscopy Studies. Particles of cocrystal reactants and deliquescent additives were placed in contact with each other on a slide and introduced into a variable relative humidity microscope stage from Surface Measurement Systems (VGI 2000M, Middlesex, U.K.). This stage provides temperature and humidity control capability during optical microscopy studies. The stage is computer controlled and receives a flow of dry nitrogen that is saturated in situ with water to the appropriate extent as monitored by internal sensors. Water uptake, deliquescence, dissolution, and crystallization were visually monitored with a Leica DMPL polarizing optical microscope (Wetzlar, Germany). Images were collected with a Spot Insight FireWire 4 Megasample Color Mosaic camera controlled with Spot software (Diagnostics Inc, Sterling Heights, MI). Solid phases were identified by Raman microscopy.

Results

Microscopy Study. Figure 1 shows optical microscopy images of deliquescence-induced cocrystal formation of an initially dry ternary system of cocrystal reactants and a sugar. CBZ, NCT, and sucrose crystals were arranged on the controlled RH microscope stage as shown in Figure 1A and

---

(34) Rodríguez-Hornedo, N.; Nehm, S. J.; Jayasankar, A. Process Analytical Technologies to Analyze and Control Cocrystallization. *Am. Pharm. Rev.* **2007**, *10*, 46−55.

(35) O'Brien, F. E. M. The Control of Humidity by Saturated Salt Solutions. *J. Sci. Instrum.* **1948**, *25*, 73−76.

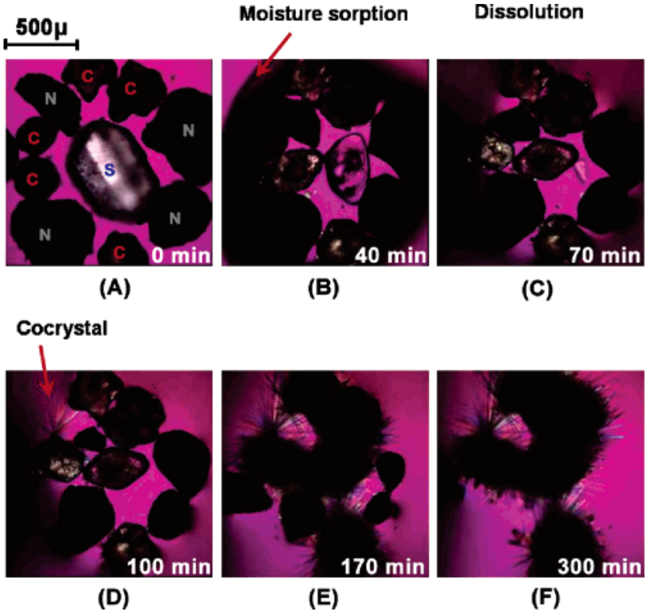


Figure 1. Optical microscopy images showing moisture sorption, deliquescence, dissolution, and cocrystallization in CBZ/NCT/sucrose system at 25 °C and 95% RH. Symbols C, N, and S represent CBZ, NCT, and sucrose, respectively.

exposed to 95% RH. These images illustrate the sequence of events that lead to cocrystal formation: moisture uptake, dissolution, and crystallization.

The first stage in the formation of cocrystals is the formation of a liquid phase as moisture is sorbed and deliquescence proceeds as shown by the liquid domain in Figure 1B. This is followed by dissolution of sucrose and cocrystal reactants as indicated by the change in size and shape of particles. NCT dissolves faster than CBZ as expected based on their different aqueous solubilities. A new phase is observed to crystallize from solution (Figure 1D) near the surface of CBZ crystals. This new phase was determined to be CBZ−NCT cocrystal by Raman microscopy.

Cocrystallization in Bulk Samples. The microscopy results presented above suggest that cocrystal formation can occur in solid blends of cocrystal reactants exposed to deliquescence conditions. In this section we present results on the moisture uptake behavior of bulk samples, and the factors that determine cocrystal formation by monitoring solid phase changes by spectroscopic and XRPD analysis.

DRH of Single Components and Binary Blends. To determine the DRH of blends composed of cocrystal reactants and deliquescent additives, moisture sorption isotherms were obtained under nonequilibrium conditions while the RH was ramped (Figure 2). DRHs were determined for pure components and binary mixtures of a deliquescent additive (sucrose or fructose) with the most water soluble cocrystal reactant (nicotinamide or saccharin) and are shown in Table 2. The weight percent of deliquescent additive in all the binary mixtures listed would be 50% if 1 molar equiv of CBZ were added. The weight ratios of SAC blends are lower than those of NCT blends because SAC has a higher molecular weight.

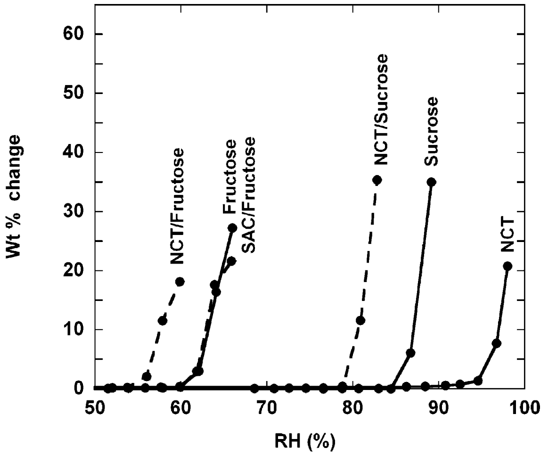


Figure 2. Moisture sorption isotherms of single components and binary blends.

Table 2. Deliquescent RH of Single Components and Binary Blends (SD = ±0.3)

deliquescent components and blends	wt ratio	mol ratio	DRH (%) at 25 °C
sucrose			86.1
fructose			62.0
nicotinamide			94.5
NCT/sucrose	1.0:2.9	1.0:1.1	80.0
NCT/fructose	1.0:2.9	1.0:2.0	55.3
SAC/fructose	1.0:2.3	1.0:2.3	61.5

The DRH values of the pure components are in good agreement with those available in the literature. The reported DRH for fructose and sucrose is 62% and 85% respectively.[16,21] Slight differences between the reported DRH values and those observed in this study for sucrose may be due to instrument accuracy of 1% RH and the specific conditions used for ramping RH as listed in the Experimental Section. The DRH of a pure substance is decreased by the addition of a second deliquescent component. Similar deliquescence behavior has been observed in binary and ternary systems with inorganic and organic components[15,17,20,21] and is explained by the effect of solute composition on the water activity of solutions. While in this study we report the DRH of blends at only one composition for the purpose of investigating transformation to cocrystal, the dependence of DRH on composition is currently being investigated.

The DRH of binary mixtures was determined to avoid rapid cocrystal formation associated with ternary mixtures containing CBZ since transformation to cocrystal can affect the resolution of DRH measurements. Furthermore, the low solubility of CBZ in water means it should have negligible impact on the DRH and water activity of solutions with sugar and NCT or SAC. The DRH of ternary blends is not expected to change in the presence of CBZ. Indeed CBZ exhibits no

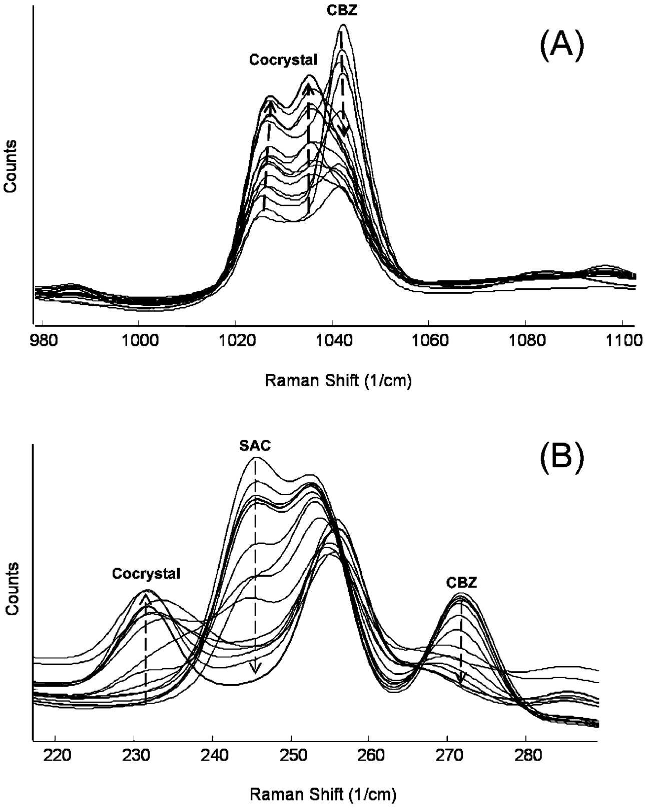


Figure 3. Raman spectra showing cocrystal formation and CBZ depletion in (A) CBZ/NCT/50% sucrose and (B) CBZ/SAC/50% fructose at 85% RH.

deliquescence as anticipated from its low solubility.[27,36] Consequently, ternary blends of CBZ with cocrystal former in equimolar ratios and 50% deliquescent additive referenced in the next section can be assumed to have the same DRH as blends listed in Table 2.

Cocrystallization in Ternary Blends. Figure 3A shows the changes in the Raman spectra as CBZ−NCT cocrystal formation proceeds in CBZ/NCT/50% sucrose. Peaks at 1026.5 and 1035.0 cm^{-1}, characteristic of CBZ−NCT cocrystal, are observed as cocrystal formation occurs. This is accompanied by a decrease in the intensity of the peak characteristic of CBZ at 1041.5 cm^{-1}. Figure 3B shows the changes in Raman spectra as CBZ−SAC cocrystal formation occurs in CBZ/SAC/50% fructose blends at 85% RH. A peak at 231.7 cm^{-1}, characteristic of CBZ−SAC cocrystal, is observed as cocrystal formation occurs. A decrease in peak intensity for peaks characteristic of SAC and CBZ at 246.0 cm^{-1} and 272.5 cm^{-1} respectively is also observed with cocrystal formation. These changes in the spectra were used to measure cocrystal formation in ternary blends during storage as a function of ambient RH and deliquescent additive.

The progress of cocrystal formation in CBZ/NCT/sugar (fructose or sucrose) blends at 75% and 85% RH was monitored over a 2 day period by Raman spectroscopy. The initial composition of sugar in these blends was 10%, 20%, or 50% while the cocrystal reactant molar ratio (CBZ/NCT) was constant at 1:1. A control sample without sugar is included at 85% RH for reference.

It is evident from Figure 4 that deliquescence generates cocrystals. Significant cocrystal formation was observed in CBZ/NCT/sugar blends above their DRH, while no cocrystal formation was detected in mixtures below their DRH. For instance, cocrystal formation occurred in ternary blends with sucrose or fructose at 85% RH. In contrast, neither the control sample at 85% RH nor the ternary mixtures with sucrose at 75% RH transformed to cocrystal during the course of the study because RH was below DRH. The DRH for NCT is greater than 85% and for NCT/sucrose is greater than 75% as shown in Table 2.

The rate and extent of cocrystal formation appears to be dependent on the sugar, the percentage of sugar, and the ambient RH as shown in Figure 4. At 85% RH the fructose blends transformed faster than sucrose blends. Faster rate of cocrystal formation was also observed in fructose blends stored at 85% RH than those stored at 75% RH. It can be seen that the rate of transformation decreases with time. Time intervals at the beginning of the transformation have rapid cocrystal formation followed by a slow conversion period or plateau region. Samples with less deliquescent additive (sugar) exhibit a more gradual conversion to cocrystal as shown by the 10% fructose at 75% RH. After the initial interval of rapid conversion producing a small fraction of cocrystal, the progress of transformation is slow, as indicated by the slope of the plateau region. In contrast, higher sugar compositions experience faster and extensive transformation to cocrystal during the initial time interval. This behavior is also observed with increasing ambient RH farther above DRH as seen by comparing the 75% and 85% RH fructose samples.

Lower rates of cocrystal formation at low sugar composition may be associated with small volumes of water uptake and small domains of supersaturation leading to isolated regions of cocrystal formation in the bulk of the sample. In fact, the curves in Figure 4 have jagged features corresponding to the nonuniform distribution of cocrystal nucleation and growth sites throughout the bulk of the sample. To resolve this spatial distribution of transformation sites, spectra were randomly collected from different regions of the samples. Together the spectra collected represent the average level of transformation in the bulk.

The data in Figure 4 has been shown over a 2 day time frame to highlight the dependence of cocrystal formation rates as a function of blend composition and RH. Transformation was monitored over a longer period by Raman until full conversion to cocrystal was achieved, at which point the samples were analyzed by XRPD. Figure 5 compares the XRPD patterns of CBZ and NCT blends containing 20% sugar (fructose or sucrose) before and after storage at 85%

---

(36) Murphy, D.; Rodríguez-Cintrón, F.; Langevin, B.; Kelly, R. C.; Rodríguez-Hornedo, N. Solution-Mediated Phase Transformation of Anhydrous to Dihydrate Carbamazepine and the Effect of Lattice Disorder. *Int. J. Pharm.* **2002**, *246*, 121−134.

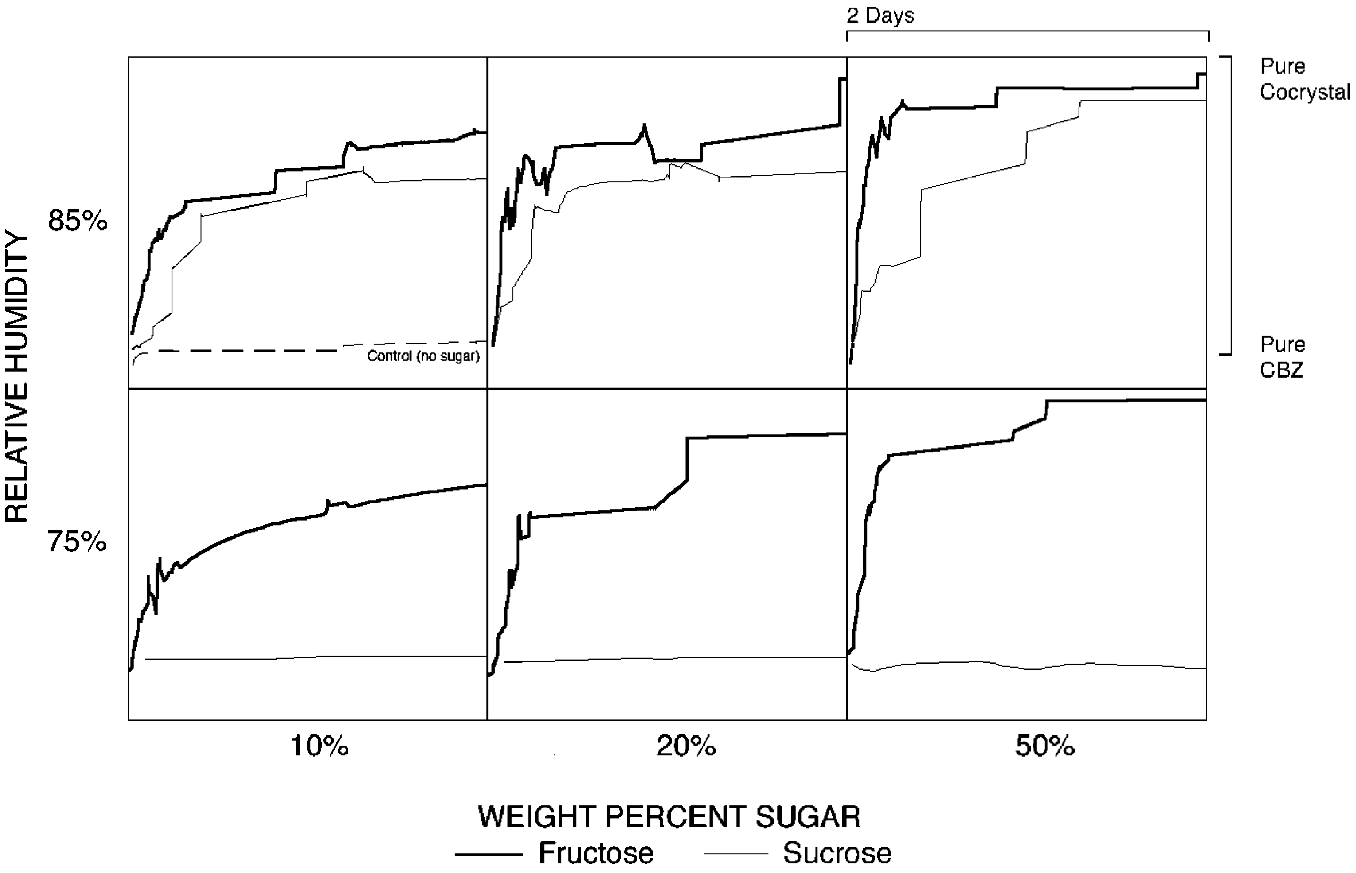


Figure 4. Effect of RH and sugar composition on CBZ−NCT cocrystal formation in CBZ/NCT/sugar blends. Six separate panes corresponding to two relative humidity conditions and three different sugar compositions are shown. Each pane has the same time and composition axis scaling presented for the top right pane. The maximum of the *y*-axis corresponds to pure cocrystal, while the minimum corresponds to pure reactants.

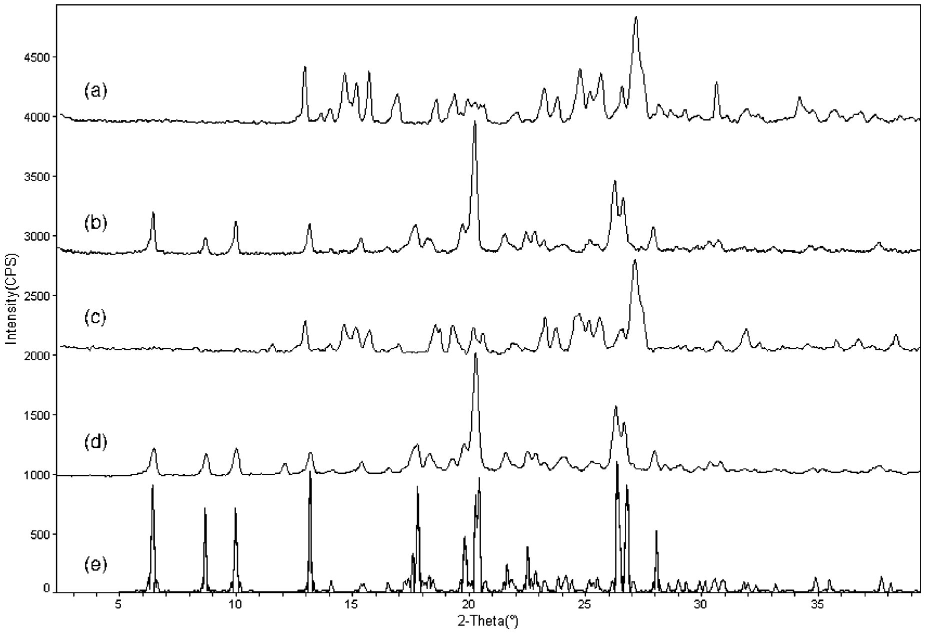


Figure 5. XRPD of CBZ/NCT/20% sugar blends confirms cocrystal formation after storage at 85% RH: 20% fructose (a) before storage and (b) after storage; 20% sucrose (c) before storage and (d) after storage; (e) CBZ−NCT calculated from CSD.

RH with the CBZ−NCT cocrystal XRPD pattern calculated from CSD. XRPD pattern homology between the stored blends and the cocrystal indicate cocrystal formation during storage. XRPD patterns of blends containing 10% and 50%

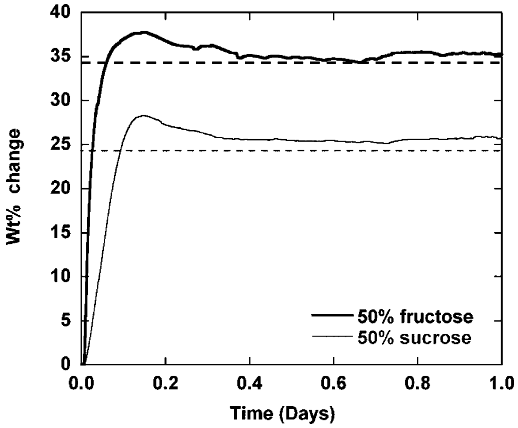


Figure 6. Moisture sorption in CBZ/NCT/50% sugar (fructose or sucrose) at 85% RH. Dashed horizontal lines indicate equilibrium moisture sorption level of pure sugars scaled to the percent in the blends.

sugars similarly showed evidence for cocrystal formation during storage.

The moisture sorption behavior of reactive blends was investigated since water uptake is an important factor affecting solution composition, supersaturation, and consequently cocrystal formation. Figure 6 shows the moisture sorption behavior of CBZ and NCT blends containing 50% sucrose or fructose at 85% RH. An increase in weight due to water uptake through deliquescence is observed for both blends. Moisture sorption is faster in the fructose blend than the sucrose blend. Both curves are characterized by a maximum in the moisture sorption behavior followed by desorption and leveling off. Desorption correlates with the depletion of NCT from solution as it is consumed by cocrystal formation. Previous moisture uptake studies of pure CBZ−NCT cocrystal indicate very low moisture uptake (<1%) compared to NCT (>50%) at 98% RH.[27]

Comparison with the progress of cocrystal formation in these blends (Figure 4) indicates that moisture sorption and cocrystal formation begin quickly and occur simultaneously. Both systems shown in Figure 6 achieved an equilibrium level of water sorption in about half a day, indicating that phase transformation to cocrystal has reached a steady state or is mostly complete. The time frame within which this plateau is attained agrees with that shown in Figure 4 for transformation in bulk samples with 50% sugar stored at 85% RH, and corresponds to a high level of conversion to cocrystal. Analysis of the ternary blends by XRPD and FTIR after exposure to 85% RH in the vapor sorption analyzer confirmed cocrystal formation.

The final water content in the ternary blend containing fructose is ∼35% while that containing sucrose is ∼25% (Figure 6). The equilibrium water content at 85% RH for pure sugar scaled to the amount in each blend is shown by a horizontal dashed line in Figure 6. Thus the final water content in the ternary blends is proportional to the amount of sugars in these blends and the equilibrium moisture content of the sugars at 85% RH.

The rates of moisture sorption and reactant dissolution depend on surface area and hence particle size of the components in the blend. A decrease in cocrystal formation rate was observed in blends of larger particles (106−125 μm; results not shown).

Cocrystallization in Binary Blends. The preceding section showed that deliquescence generates cocrystals in ternary blends containing a deliquescent additive (sugar) and cocrystal reactants. However, cocrystal formation can also occur in binary blends if one or both cocrystal reactants are deliquescent. Figure 7A shows the moisture sorption behavior for an equimolar CBZ/NCT blend at 98% RH. An increase in weight is observed due to deliquescence of NCT (DRH = 94.5%) until a maximum is achieved, after which desorption dominates as CBZ−NCT cocrystal (nonhygroscopic) forms. This behavior is similar to that of ternary blends with sugars shown in Figure 6. Beyond the maximum, the weight of the binary blend decreases continuously due to depletion of NCT (hygroscopic) from solution. XRPD after storage of the binary blend for 4 days at 98% RH confirmed cocrystal formation (Figure 7B).

Effect of Reactant Properties on Cocrystal Formation. The effect of cocrystal reactant properties on moisture sorption and cocrystal formation was studied by replacing NCT with SAC as the cocrystal reactant. NCT is highly hygroscopic and water soluble while SAC is nonhygroscopic, is ionizable ($pK_a = 1.8$),[37] and has lower aqueous solubility than NCT. The DRH of the SAC/fructose blend shown in Table 2 is similar to that of pure fructose. This is due to the nonhygroscopic nature and low aqueous solubility of SAC.

Figure 8 compares CBZ−NCT and CBZ−SAC cocrystal formation rates at 85% RH in ternary blends of CBZ/50% fructose and NCT or SAC. Clearly the rate of CBZ−SAC cocrystal formation is slower than that of CBZ−NCT. This may be a result of cocrystal solubilities, reactant dissolution rate, and ionization in the sorbed moisture.

Figure 9A shows the CBZ−SAC cocrystal formation in ternary blends of CBZ/SAC with fructose at 85% RH. Cocrystal formation is more extensive and faster in blends with higher sugar level. Figure 9B compares cocrystal formation rates during storage of CBZ/SAC/50% fructose blends at 75% and 85% RH. These results are similar to those of CBZ/NCT/sugar blends where cocrystal formation rate increases with storage RH and sugar composition.

Cocrystal Formation via Deliquescence Is Broadly Applicable to Other Compounds. Based on the above findings, transformation to cocrystal induced by deliquescence was studied with caffeine and theophylline systems. These APIs have been reported to form cocrystals from organic solvents and by cogrinding.[28,29] Our studies show that the cocrystals in Table 3 are generated both by slurrying the reactants in aqueous solutions and by storing ternary

---

(37) Zubair, M. U.; Hassan, M. M. A. Saccharin. In *Analytical Profiles of Drug Substances*; Florey, K., Ed.; Academic Press: New York, 1984, p 487.

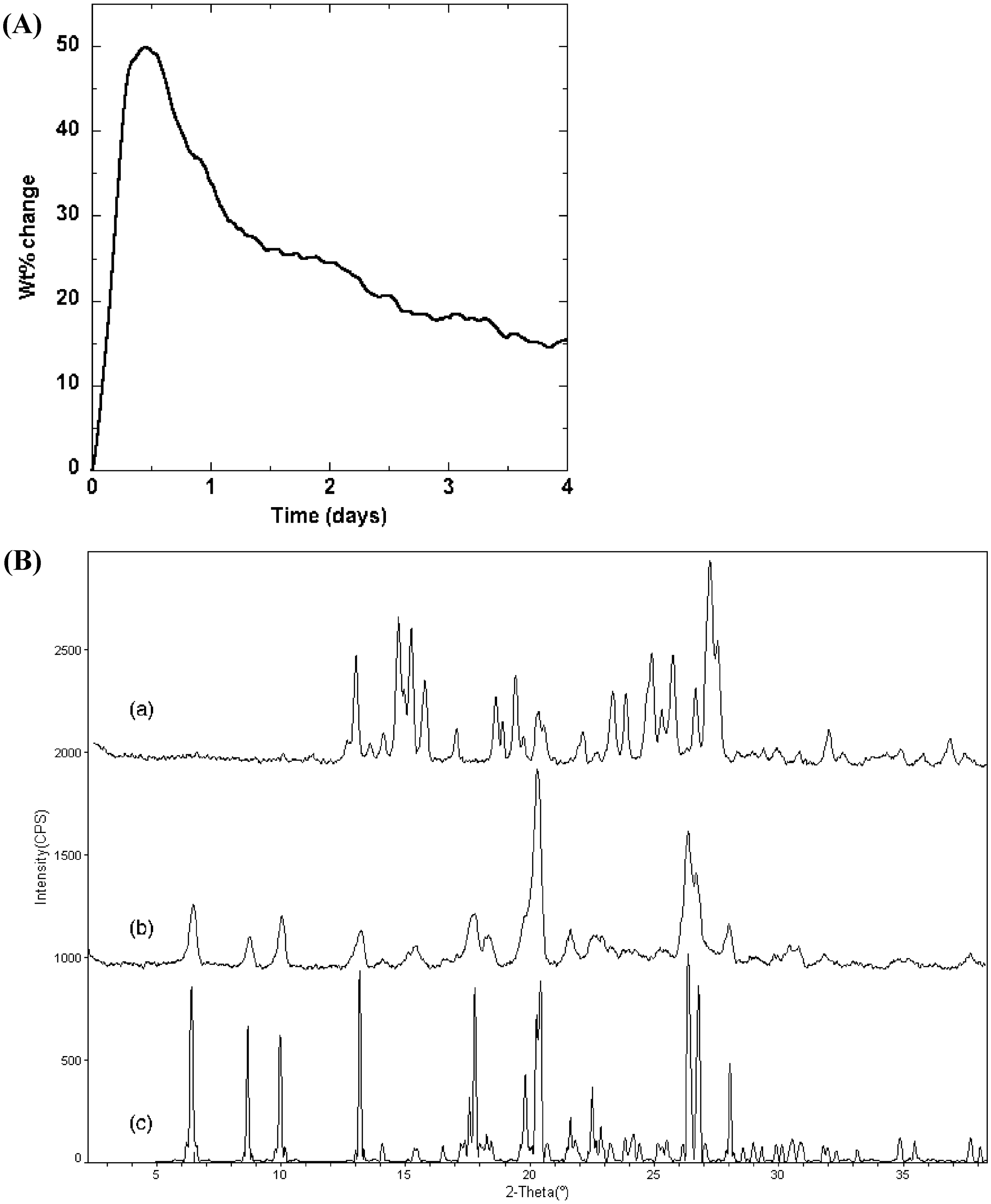


Figure 7. (A) Moisture sorption behavior of equimolar CBZ/NCT blend at 98% RH. (B) XRPD confirms CBZ−NCT cocrystal formation in CBZ/NCT blend after storage at 98% RH: CBZ/NCT blend (a) before storage and (b) after storage; (c) CBZ−NCT cocrystal calculated from CSD.

blends with 20% fructose above the DRH. All cocrystals have equimolar composition except theophylline−maleic acid, theophylline−oxalic acid, caffeine−malonic acid, and caffeine−oxalic acid, which have the cocrystal reactants in a 2:1 (API:ligand) molar ratio. Cocrystal formation was confirmed by XRPD analysis. These results illustrate broad applicability of the concepts presented to other APIs with a variety of cocrystal components. The kinetics of deliquescent mediated cocrystal formation in these systems is currently being investigated in our laboratory.

Discussion

The results of this study indicate that cocrystals can form spontaneously when solid mixtures with cocrystal reactants deliquesce. The mechanism for deliquescence-induced cocrystal formation involves three important processes as revealed by microscopy studies (Figure 1) and illustrated in Scheme 1: water uptake, dissolution of cocrystal reactants, and crystallization of molecular complex. Several factors that determine transformation kinetics are nucleation rate, growth rate, and the density and distribution of nucleation sites.

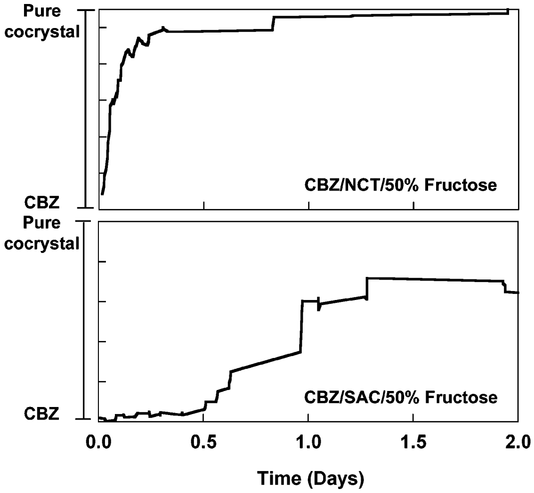


Figure 8. Comparison of CBZ−NCT and CBZ−SAC cocrystal formation rates at 85% RH.

Cocrystal nucleation and growth rates will depend on supersaturation. Supersaturation is determined by how fast cocrystal reactants dissolve, and this in turn depends on the amount and rate of water uptake.

How dissolution of cocrystal reactants leads to supersaturation with respect to cocrystal is illustrated in Scheme 1ii and is explained by considering the solution and cocrystal chemistry.[30,31] As the reactants dissolve in the sorbed moisture, their concentrations increase in solution. Unequal reactant dissolution rates, due to different solubilities and/or surface areas, result in nonstoichiometric concentrations of reactants in the sorbed moisture. As the deliquesced solution becomes rich in one of the cocrystal components, the cocrystal solubility decreases leading to ever increasing supersaturated conditions where cocrystal is the least soluble phase as shown in Figure 10. Cocrystal formation will be initiated when the critical supersaturation for nucleation is achieved. The CBZ and NCT system is particularly interesting since their aqueous solubilities are so different. Due to the higher dissolution rate of the more soluble reactant (NCT), cocrystal nucleation occurs on the surface or in the vicinity of the less soluble reactant (CBZ) (Figure 1).

Cocrystal Stability. Our results show that deliquescence leads to cocrystal formation even with certain APIs that readily form hydrates during storage[1−6] or by slurry conversion in water.[36,38−41] Carbamazepine, caffeine, and theophylline spontaneously transformed to cocrystal when mixtures of cocrystal reactants with deliquescent additive were stored above the DRH of the dry mixtures. This indicates that cocrystal nucleation and growth rates were faster than the rate of hydrate formation under the conditions studied. The stability of cocrystal is also confirmed by the lack of transformation to single components or hydrates thereof.

Although the deliquescent systems reported here exhibited cocrystal formation and stability, a reversal can occur given the right conditions. Cocrystal can transform to single component crystal or hydrate of reactant when cocrystal solubility is higher than the solubility of a reactant or hydrate thereof. This situation arises when solution concentrations of reactants reach values below the transition concentration as indicated in the solubility diagram (Figure 10). Previous studies from our laboratory have shown that, although in pure water CBZ−NCT cocrystals transform to CBZ dihydrate within minutes, the transformation is reversed (CBZ to cocrystal) at high NCT solution concentrations.[31,32] CBZ cocrystals of NCT or SAC are not hygroscopic at 98% RH and have been shown to be stable.[26,27] CBZ cocrystal formation during deliquescence is thus explained by the relationship between solution composition and thermodynamic stability of reactant and cocrystal phases.

Caffeine and theophylline cocrystals shown in Table 3 formed during deliquescence of blends of API/ligand/fructose (as well as in highly concentrated aqueous solutions of ligand) even though some of these cocrystals have been reported to transform to hydrated API when exposed to moisture. Caffeine−maleic acid cocrystals and theophylline cocrystals with maleic acid, malonic acid, and glutaric acid have been reported to transform to hydrated API when exposed to 98% RH.[28,29] Caffeine−glutaric acid has been reported to transform to hydrated caffeine at 43% RH.[29] These results clearly indicate that for the direction of transformation to be reversed by aqueous solution composition there must be a transition concentration above which solubility of cocrystal is less than pure API and cocrystal formation is favorable. Therefore deliquescence will generate conditions of cocrystal stability or instability depending on solution chemistry including ionization and complexation processes.

Deliquescence and Cocrystal Formation. Previous studies on deliquescence and crystallization have shown hydrate formation in solid mixtures.[1,2,4] There are also reports of crystallization as a result of moisture loss and efflorescence due to changes in ambient RH or DRH as composition of solution changes.[22,42−44] It is important to note that in the

---

(38) Rodríguez-Hornedo, N.; Lechuga-Ballesteros, D.; Wu, H. J. Phase-Transition and Heterogeneous Epitaxial Nucleation of Hydrated and Anhydrous Theophylline Crystals. *Int. J. Pharm.* **1992**, *85*, 149−162.

(39) Rodríguez-Hornedo, N.; Murphy, D. Surfactant-Facilitated Crystallization of Dihydrate Carbamazepine During Dissolution of Anhydrous Polymorph. *J. Pharm. Sci.* **2004**, *93*, 449−460.

(40) Ticehurst, M. D.; Storey, R. A.; Watt, C. Application of Slurry Bridging Experiments at Controlled Water Activities to Predict the Solid-State Conversion between Anhydrous and Hydrated Forms Using Theophylline as a Model Drug. *Int. J. Pharm.* **2002**, *247*, 1−10.

(41) Zhu, H.; Yuen, C.; Grant, D. J. W. Influence of Water Activity in Organic Solvent + Water Mixtures on the Nature of the Crystallizing Drug Phase, 1. Theophylline. *Int. J. Pharm.* **1996**, *135*, 151−160.

(42) Parsons, M. T.; Riffell, J. L.; Bertram, A. K. Crystallization of Aqueous Inorganic-Malonic Acid Particles: Nucleation Rates, Dependence on Size and Dependence on the Ammonium-to-Sulfate Ratio. *J. Phys. Chem. A* **2006**, *110*, 8108−8115.

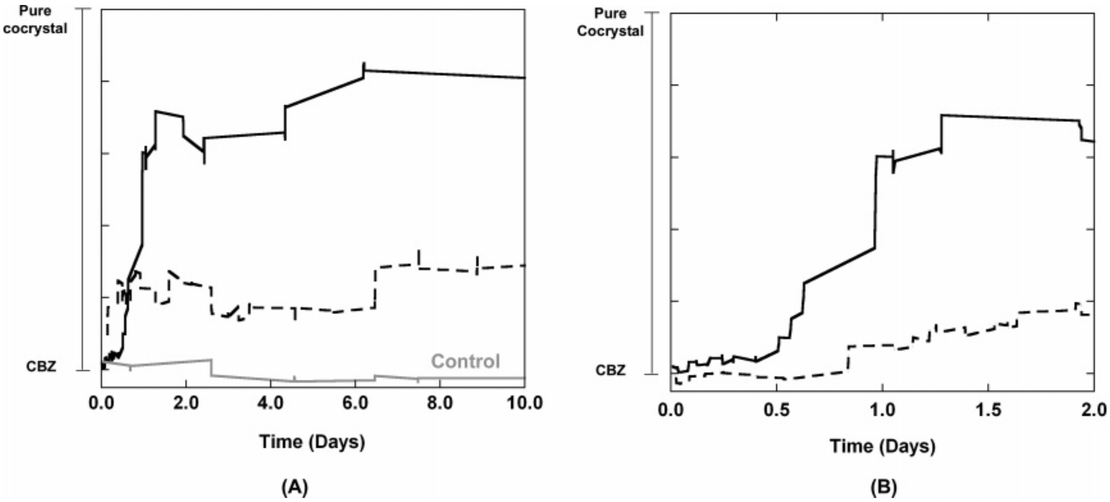


Figure 9. CBZ−SAC cocrystal formation rate dependence on (A) fructose composition in ternary blends exposed to 85% RH: control sample without sugar (gray solid line), 10% (dashed line), and 50% (black solid line) fructose, and (B) storage RH in CBZ/SAC/ 50% fructose blends at 75% RH (dashed line) and 85% RH (solid line).

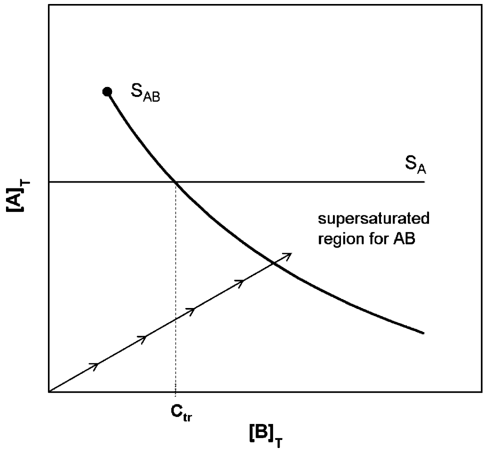


Figure 10. Schematic of solubility of cocrystal AB (S_{AB}) and pure component crystal A (S_A) as a function of ligand concentration B, showing the ligand transition concentration (C_{tr}) and a hypothetical cocrystallization pathway where supersaturation is generated by the unequal dissolution rates of reactant components A and B.

studies reported here there was no RH cycling and crystallization was a result of solution composition. To our knowledge this is the first report of cocrystal formation induced by deliquescence. This finding also makes apparent the opportunity for producing cocrystals by green chemistry methods. Aqueous media can generate cocrystals as illustrated for carbamazepine, caffeine, theophylline, and sulfadimidine systems.

Table 3. API and Corresponding Ligands That Formed Cocrystals by Both Slurrying in Water and Deliquescence

API	ligand
carbamazepine	nicotinamide
	saccharin
caffeine	oxalic acid
	maleic acid
	glutaric acid
	malonic acid
theophylline	oxalic acid
	maleic acid
	glutaric acid
	malonic acid
sulfadimidine	salicylic acid
	anthranilic acid

The ability of a deliquescent material to generate cocrystals depends on its potency for moisture uptake and on its ability to modify the mode and rate of nucleation. Blends stored below their DRH did not result in cocrystal formation during the course of the study as shown by binary blends of CBZ/NCT at 85% RH and ternary blends of CBZ/NCT/sucrose at 75% RH. Transformation to cocrystal was however associated with moisture uptake and storage RH above DRH as indicated by binary blends of CBZ/NCT at 98% RH and ternary blends of CBZ/NCT/sucrose at 85% RH.

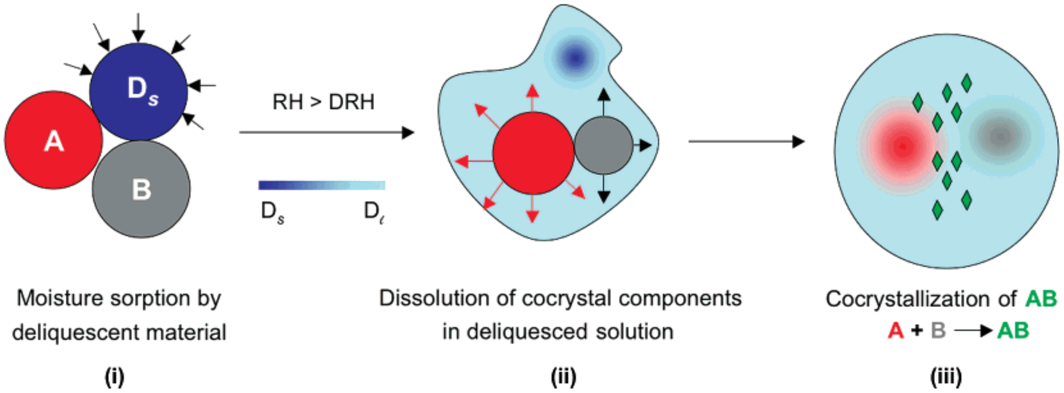
The interplay between moisture uptake and dissolution determines the liquid phase composition, supersaturation, and subsequent nucleation. This is shown by the rapid initial cocrystal formation rates of CBZ−NCT at both low and high sugar composition when stored at RH above DRH. Moreover, low small levels of moisture (<7%) are capable of producing the necessary cocrystal supersaturation to initiate nucleation as shown for the transformation to CBZ−NCT in blends with 10% sucrose or fructose at 85% RH. Deliquescent additives can also influence nucleation by their effects on solution viscosity, molecular associations that precede nucleation, and

---

(43) Braban, C. F.; Abbatt, J. P. D. A Study of the Phase Transition Behavior of Internally Mixed Ammonium Sulfate-Malonic Acid Aerosols. *Atmos. Chem. Phys.* **2004**, *4*, 1451−1459.

(44) Zhang, Y. H.; Hu, Y. A.; Ding, F.; Zhao, L. J. FTIR-ATR Chamber for Observation of Efflorescence and Deliquescence Processes of $NaClO_4$ Aerosol Particles on ZnSe Substrate. *Chin. Sci. Bull.* **2005**, *50*, 2149−2152.

Scheme 1. Illustration of the Moisture Uptake Process Leading to Deliquescence, Reactant Dissolution, and Cocrystal Formation[a]



[a] A and B are cocrystal reactants, D_S is solid deliquescent additive, and D_l is the solution phase created by deliquescence at RH greater than DRH.

to the extent that material surfaces serve as catalysts for nucleation.

Generally one expects the amount of moisture uptake to control the transformation rate based on its temporal and spatial distribution. Low levels of deliquescent additive and low moisture uptake will have the effect of reducing the regions of deliquescence. Consequently, small domains of supersaturation can develop in a liquid phase that is not uniformly distributed throughout the sample leading to isolated regions of cocrystal formation. In this case high supersaturations are initially achieved and transformation rate to cocrystal is initially fast, but the rate will slow or even level off before extensive conversion. This mechanism explains the transformation to CBZ−NCT cocrystal at the lower fructose composition (10%) and 75% RH.

High levels of moisture sorption allow for greater exposure of reactants to the crystallization medium and to larger extent of cocrystal formation during the initial time period, provided the kinetics and distribution of moisture sorption maintain adequate supersaturation for cocrystal formation. This behavior is observed with the CBZ/NCT/fructose at higher RH (85%) or higher fructose (20% and 50%) showing faster and more extensive conversion compared to the CBZ/NCT/fructose at 10% fructose and 75% RH. Similar behavior was observed with CBZ/SAC/fructose blends. These results clearly indicate that, for low fructose composition at low RH, the transformation is occurring at relatively low moisture uptakes where solute transport tends to be limited to small domains of liquid phase. Faster transformation rates with more deliquescent additive at RH above DRH were also observed for CBZ/NCT/sucrose and CBZ/SAC/fructose.

Quite a different situation arises when high amounts of moisture uptake lead to low supersaturation, saturation, or undersaturation with respect to cocrystal and consequently slow, prevent, or reverse the transformation to cocrystal. High moisture uptake levels are associated with the hygroscopic nature of the blend components, the amount of hygroscopic or deliquescent additive, and high RH values above DRH. A reversal in the transformation to cocrystal was observed at CBZ/NCT/50% fructose at 98% RH. CBZ dihydrate formed after initial formation of cocrystal (results not shown).

Moisture sorption and deliquescence of solid mixtures are a complex function of phase composition, relative humidity, and temperature.[17,18,20] The study presented here has focused on identifying the mechanism by which deliquescence induces cocrystal formation. Deliquescence and phase diagrams of composition and water activity (i.e., relative humidity) for the systems reported here are currently being investigated in our laboratory.

In this first report we have compared the transformation to cocrystal with the moisture uptake behavior and deliquescence under nonequilibrium conditions. Our results show that moisture uptake behavior is an indicator of cocrystal formation as shown by binary blends with deliquescent reactant (NCT) in Figure 7A and by ternary blends with deliquescent additive (sugars) in Figure 6.

Cocrystal formation during deliquescence is also dependent on the properties of cocrystal reactants, cocrystals, and solution chemistry. Reactant properties that increase solution concentrations in the sorbed moisture such as dissolution rate and solubility are expected to increase the rate of transformation to cocrystal as shown by the CBZ−NCT cocrystal formation rate relative to CBZ−SAC. In addition, particle size and solid-state form of reactants (amorphous, polymorphs and solvated forms) will influence the transformation rate to cocrystal when dissolution is the rate-limiting step.

The mechanisms for cocrystal formation reported here are valuable to design stable formulations and predict conditions that will preserve cocrystal. The amount of deliquescent additive required to prevent or reverse the transformation to cocrystal can in principle be estimated if one knows the moisture sorption of the blend at a given composition, temperature, and RH, and the C_{tr} in the sorbed moisture. For example, the C_{tr} in water at which the solubility of the CBZ−NCT cocrystal is equal to the solubility of CBZ dihydrate is around 1 m.[32] As a first approximation it is assumed that additives do not change C_{tr}. Consequently, levels of moisture sorption that lead to NCT concentrations above 1 m will favor cocrystal formation at adequate CBZ solution concentration as shown in Figure 10. Based on the results for the CBZ/NCT/50% fructose at 85% RH the moisture sorbed is about 35% and corresponds to moisture retained by fructose (70% for pure fructose at 85% RH). If one considers that NCT will fully dissolve in the sorbed moisture of the ternary blend, then the mass of water required to dilute NCT to the C_{tr} can be calculated. The percentage of fructose in the dry blend that will lead to the transition concentration at 85% RH was calculated to be 80%. Therefore if CBZ−NCT cocrystal is to be preserved in such a ternary blend, fructose compositions must be lower than 80% in the dry blend. Our results of cocrystal formation and stability in fructose blends are in agreement with this estimate.

Conclusions

This work demonstrates that moisture can generate cocrystals when particulate systems with cocrystal reactants are exposed to deliquescent conditions. Cocrystals of carbamazepine, caffeine, and theophylline were formed during deliquescence even when these APIs can form hydrates. The mechanisms responsible for cocrystal formation involve moisture uptake, dissolution of cocrystal reactants, cocrystal nucleation and growth. These mechanisms are important to design formulations and predict conditions that will preserve cocrystals. Cocrystal solubility dependence on aqueous solution composition and chemistry are good predictors of cocrystal formation and stability during deliquescence. Our findings have important implications for a green chemistry based approach in the use of aqueous media to produce cocrystals.

Acknowledgment. We acknowledge the Purdue/Michigan Consortium on The Study of Supramolecular Assemblies and Solid-state Properties for funding. We are also grateful to Boehringer Ingelheim for a research gift.

MP0700099