molecular pharmaceutics

BRIEF ARTICLE

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Unintended Water Mediated Cocrystal Formation in Carbamazepine and Aspirin Tablets

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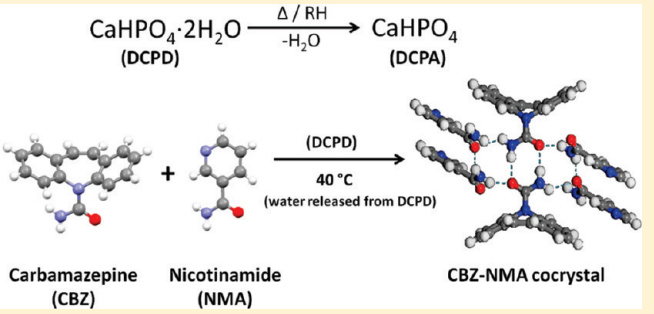
ABSTRACT: The water of crystallization released during dehydration of dibasic calcium phosphate dihydrate (DCPD) mediated the cocrystal formation between carbamazepine (CBZ) and nicotinamide (NMA) in intact tablets. The dehydration of DCPD, the disappearance of the reactants (CBZ and NMA) and the appearance of the product (CBZ−NMA cocrystal) were simultaneously monitored by quantitative powder X-ray diffractometry. In a second model system, the water of crystallization released by the dehydration of DCPD caused the chemical decomposition of aspirin. Salicylic acid, one of the decomposition products, reacted with CBZ to form CBZ−salicylic acid cocrystal in tablets. This is the first report of cocrystal formation in intact tablets, demonstrating water mediated noncovalent synthesis in a multicomponent matrix. While the potential implications of such transformations, on both the mechanical and biopharmaceutical properties, can be profound, their characterization, using conventional solution based analytical techniques, can be challenging.



KEYWORDS: cocrystal, crystal growth, dibasic calcium phosphate dihydrate, excipients, hydrates, phase transformations, X-ray diffractometry

INTRODUCTION

A large fraction of drugs are administered orally as tablets or capsules. It is well recognized that the physical form (polymorphic form, hydration state, crystallinity) of the active pharmaceutical ingredient (API) can influence the processing as well as the performance of the dosage form.[1,2] Cocrystallization is a long known[3] but recently applied strategy to customize API properties.[4] A pharmaceutical cocrystal[5] is a multiple component crystal wherein the components, in their pure form, are solids under ambient conditions. There is a stoichiometric ratio between the API and the cocrystal formers. The versatility and power of the cocrystallization approach stems from the wide array of cocrystal formers. Compounds with GRAS (generally regarded as safe) status as well as EAFUS (everything added to the food in the United States) list of substances are potential cocrystal formers. Cocrystals of numerous APIs have been prepared with these cocrystal formers, and their potential to enhance bioavailability has been documented.[6]

In addition to the API, a solid dosage form often contains several excipients. Each excipient has a specific functionality and serves as a binder, lubricant, diluent, disintegrant, sweetener etc.[7] Since tablet manufacturing typically involves numerous unit operations, there is a potential for physical and occasionally chemical transformations, of both the API and the excipients, during processing.[1,2,8] This discussion will be restricted to salt and cocrystal formation. For example, AMG517, a compound under development for the treatment of acute and chronic pain, formed a cocrystal with sorbic acid, a preservative in the formulation. The consequent enhancement in aqueous solubility caused a pronounced increase in bioavailability.[9] Likewise, transformations can occur during product storage, sometimes with serious consequences. A classic example is a pediatric formulation of midazolam hydrochloride with saccharin as a sweetener. During storage, midazolam saccharinate with a lower solubility than the hydrochloride salt precipitated, resulting in a product recall.[10] An unusual and fatal consequence of *in vivo* cocrystal formation is exemplified in a major pet food recall following the death of animals. The ingestion of the contaminated pet food resulted in the crystallization of melamine−cyanuric acid cocrystals in the kidneys leading to tubular blockage.[11]

A significant fraction of pharmaceuticals occur as hydrates, wherein water is incorporated, usually stoichiometrically, in the crystal lattice.[12] Dehydration of hydrates can occur, either during processing or storage. The liberated water, in addition to having the potential to bring about physical (crystallization) and chemical (decomposition) changes, can also affect the functionality (for example, compromise disintegrant function) of excipients.[13] Dibasic calcium phosphate is extensively used as a diluent in tablet dosage forms. Dibasic calcium phosphate can exist either as an anhydrate (DCPA: $CaHPO_4$) or as a dihydrate (DCPD: $CaHPO_4 \cdot 2H_2O$), with a stoichiometric water content of *ca.* 20.9% w/w. Dehydration of DCPD, under a variety of pharmaceutically relevant

Received: January 27, 2011
Accepted: May 6, 2011
Revised: April 5, 2011
Published: May 06, 2011

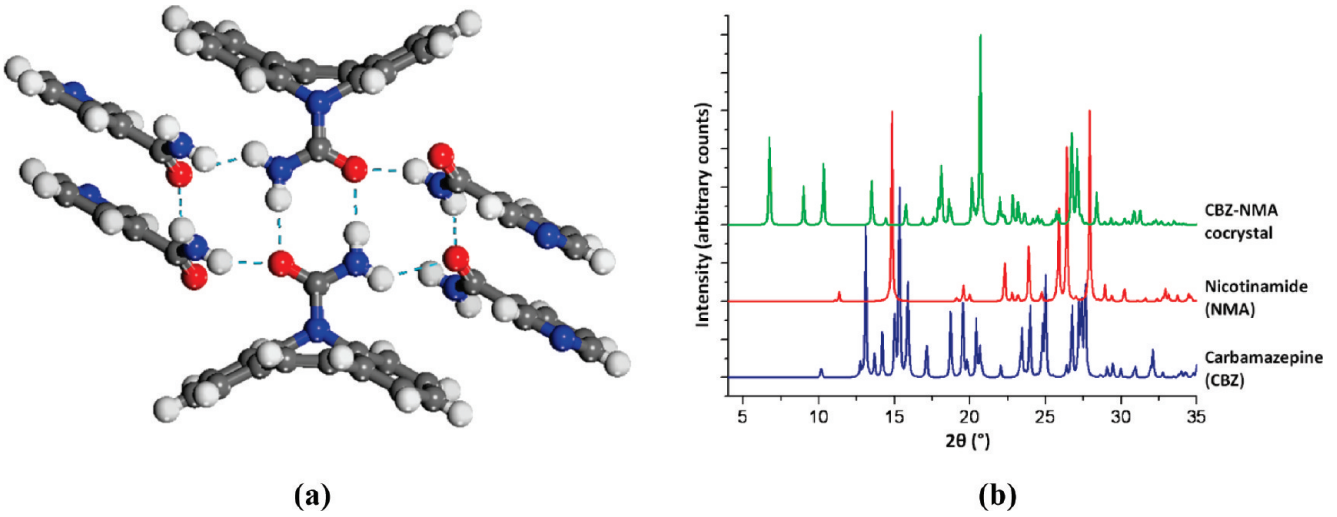


Figure 1. (a) Molecular recognition in 1:1 cocrystal of carbamazepine (CBZ) with nicotinamide (NMA). (b) Calculated powder patterns of CBZ, NMA and CBZ−NMA cocrystal from Cambridge Structural Database.[17]

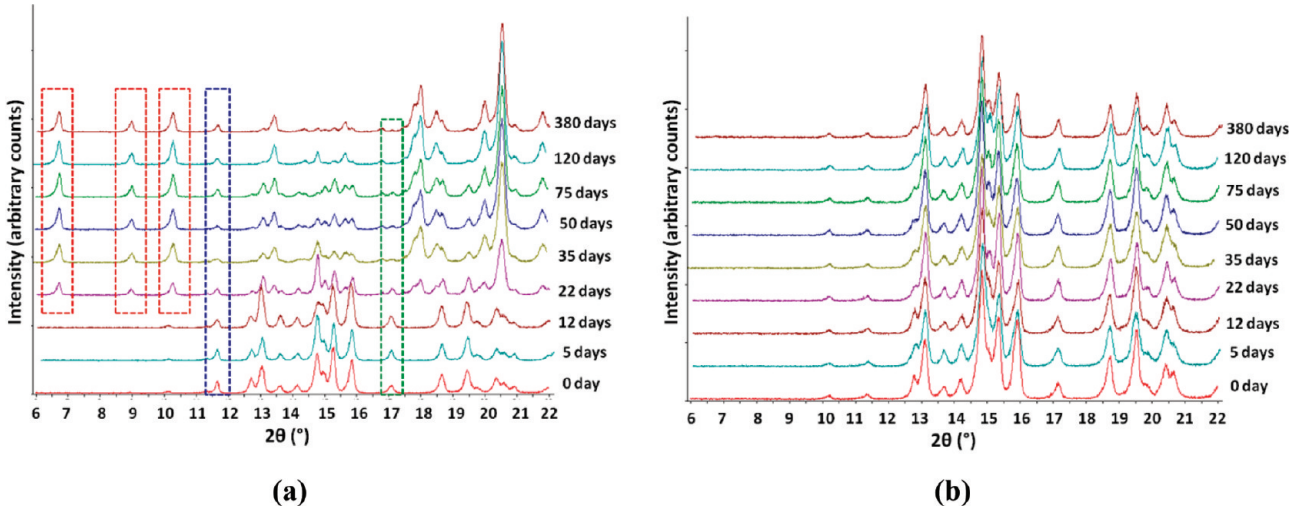


Figure 2. (a) X-ray diffraction patterns of (a) CBZ−NMA−DCPD (test) and (b) CBZ−NMA (control) tablets as a function of time. The tablets were stored at 40 °C in sealed Mylar pouches. The colored boxes are described in the text.

storage conditions, has been reported.[14a] While it is well recognized that dehydration of DCPD can have serious consequences, it finds widespread use as an excipient in tablet formulations in light of its desired mechanical and physicochemical properties. The dehydration behavior of DCPD is known to be influenced by its particle size distribution, DCPA content (present as an impurity), and the storage temperature and water vapor pressure (expressed as relative humidity, RH) above the sample.[14b]

In tablet dosage forms, the influence of lattice water released during dehydration of DCPD on the chemical stability of APIs has been investigated.[15] Interestingly, the potential for the liberated water to bring about cocrystallization in tablets has not been explored. Carbamazepine−nicotinamide[16] (Figure 1) cocrystal formation was induced by grinding powder blends followed by storage at elevated temperature and relative humidity.[18] Cocrystal formation occurred even in the absence of mechanical activation, but at a slower rate.[18b] The authors demonstrated that cocrystal formation is a spontaneous process (the free energy of CBZ−NMA cocrystal formation in the solid state is −4.8 kJ/mol at 25 °C). They reported cocrystal formation following storage of powder blends of CBZ and NMA at 45 °C/0% RH for 2 months. The reaction also occurred at room temperature and was facilitated by water vapor pressure in the atmosphere (75% RH at 25 °C). However, it is of interest to study such transformations in solid dosage forms such as compressed tablets. If lattice water, through dehydration of an excipient, becomes available in tablets, can it facilitate cocrystal formation? This study was therefore carried out with two objectives. (i) In tablets, explore the potential for moisture-induced *in situ* cocrystal formation and (ii) monitor cocrystal formation, by simultaneously quantifying the disappearance of the reactant and appearance of the product (i.e., cocrystal) phases as a function of time. Two model systems were evaluated. In the first, the lattice water released by dehydration of an excipient mediated the *in situ* cocrystal formation. In the second system, the released water first caused chemical decomposition of the API followed by cocrystal formation.

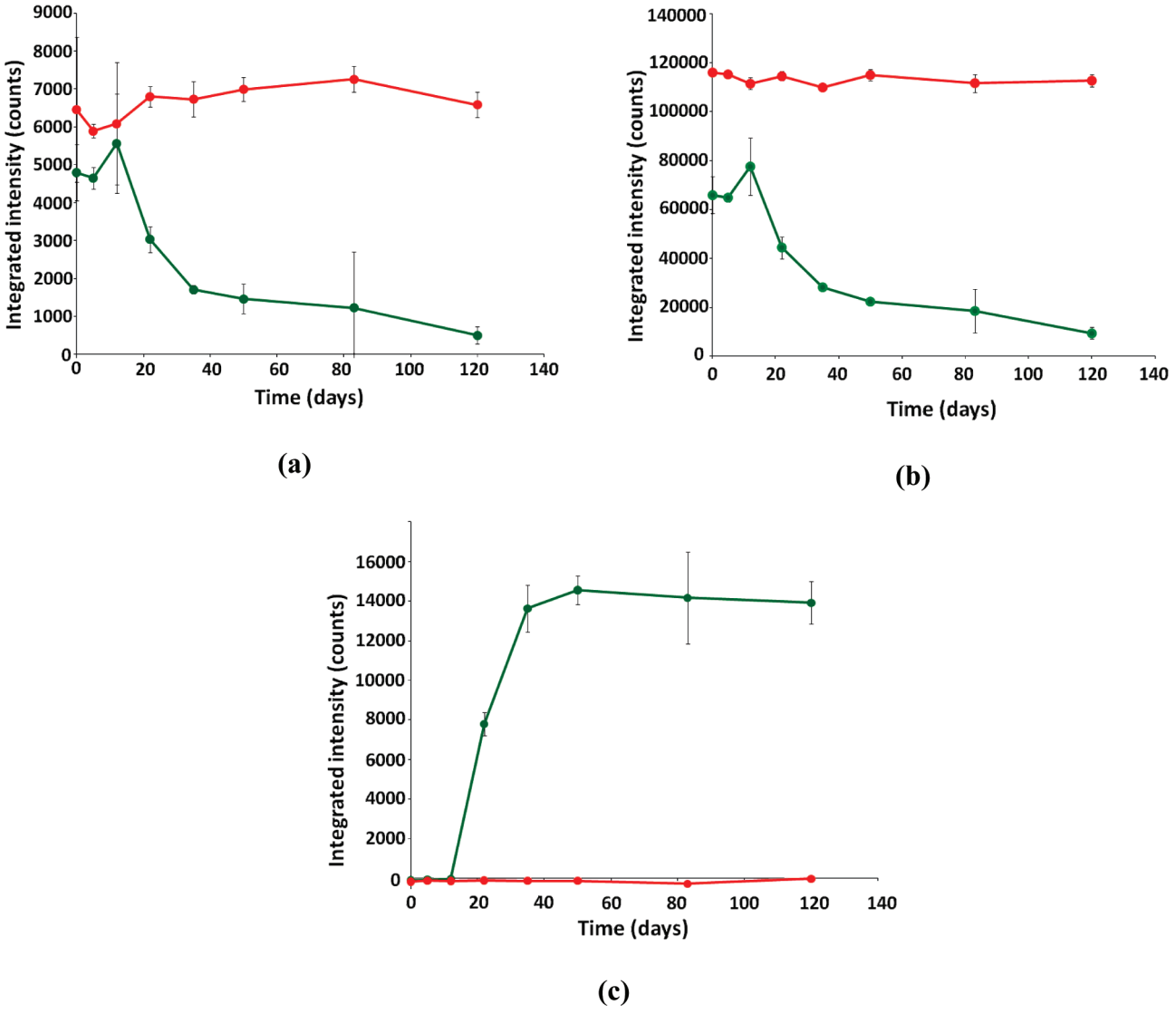


Figure 3. Intensities of the characteristic peaks of (a) CBZ (5.2 Å), (b) CBZ (5.8 Å) + NMA (6.0 Å), and (c) CBZ−NMA cocrystal (13.1 Å) in test (green) and control (red) tablets as a function of time. The tablets were stored at 40 °C in sealed Mylar pouches. Data is shown only up to 120 days of storage. No measurable changes were observed when stored up to 380 days (error bars represent standard deviation; $n = 3$).

EXPERIMENTAL SECTION

Carbamazepine, nicotinamide, and aspirin were purchased from Sigma Aldrich. DCPD (Emcompress, batch # 7089X) and DCPA (Emcompress, batch # 2049X) were obtained from JRS Pharma (Patterson, NY). For the first system, carbamazepine (CBZ) and nicotinamide (NMA) were selected as the model APIs in light of their ability to form cocrystals. DCPD, with a propensity to dehydrate and liberate the water of crystallization, was the model excipient. Tablets containing CBZ (120 mg, 0.50 mM), NMA (60 mg, 0.50 mM), and DCPD (20 mg, 0.10 mM) were compressed at room temperature and at low controlled RH (<10% RH; 25 °C). The CBZ:NMA molar ratio was 1:1, and the excipient constituted 10% w/w of the dosage form. There were two controls: tablets containing (i) CBZ (132 mg, 0.55 mM) and NMA (68 mg, 0.55 mM), and (ii) CBZ (120 mg, 0.50 mM), NMA (60 mg, 0.50 mM), and DCPA (20 mg, 0.15 mM). The tablets were immediately sealed in Mylar blister packs and stored at 40 °C. At selected time points, three tablets (for each test and control) were subjected to (i) powder X-ray diffractometry and (ii) scanning electron microscopy. They were discarded after analyses. Since NMA is known to be hygroscopic, water sorption from the atmosphere during tablet preparation can lead to cocrystal formation even in control tablets. Therefore the entire tablet manufacture was carried out under low RH (<10%) conditions.

Powder X-ray Diffractometry. Intact tablets (200 mg) were placed in specially fabricated aluminum holders and exposed, at room temperature, to Cu Kα radiation (1.54 Å; 45 kV × 40 mA) in a powder X-ray diffractometer (Bruker D5005). For the CBZ−NMA system, the angular range was 6 to 22° 2θ, with a step size of 0.01° 2θ. For the CBZ−aspirin system, the angular range was 5 to 40° 2θ, with a step size of 0.05° 2θ. In both cases, the counts were accumulated for 1 s at each step. Data analyses were performed using commercially available software (JADE Materials Data, Inc., Livermore, California).

Scanning Electron Microscopy. The tablets were placed on aluminum stubs using a double-sided carbon tape, coated with platinum (50 Å), and viewed in a scanning electron microscope (Jeol 6500 F microscope Hitachi, Japan).

Tablet Preparation. The powder mixture (200 mg) was filled in a circular stainless steel holder (10 mm diameter; flat face beveled edge) and compressed in a hydraulic press (Carver Model C Laboratory press, Menomonee Falls, WI) to a pressure of ~115 MPa and held for 1 min. The tablets were prepared at room temperature under controlled RH (<10% RH; 25 °C). No phase transformations were detected following the compression.

Headspace Humidity Measurement. A digital humidity sensor (EK-H4, Sensirion AG, Switzerland) was connected through an interface to the computer. It was used to simultaneously record, in real time, the relative humidity and temperature in the headspace above the tablet within a sealed Mylar pouch.

RESULTS AND DISCUSSION

X-ray diffractometry provided direct and unambiguous evidence of *in situ* cocrystal formation. In tablets containing DCPD, CBZ and NMA, the first evidence of DCPD dehydration was observed after 12 days of storage based on the decrease in the intensity of the 11.7° 2θ (7.6 Å) peak (qualitatively evident in Figure 2a, blue box). However, there was no evidence of cocrystal formation. Upon continued storage (22 days), there was a further decrease in the intensity of the 7.6 Å peak of DCPD (Figure 2a). In addition, the decrease in the intensity of the 17.1° 2θ (5.2 Å) peak of CBZ also became discernible when plotted as a function of time (Figure 2a, green box; Figure 3a, green profile). Unfortunately, the change in the intensity of the second reactant, NMA, could not be plotted since no unique (diagnostic) peak of NMA was available. Therefore, the intensities of two overlapping peaks unique to each CBZ (5.8 Å) and NMA (6.0 Å) were integrated as one peak and the intensity was plotted as a function of time (Figure 3b). Again, after 22 days of storage, several characteristic peaks of CBZ−NMA cocrystal, for example with *d*-spacings of 13.1 (6.7° 2θ), 9.8 (9.0° 2θ) and 8.6 Å (10.3° 2θ), appeared (Figure 2a, red boxes). Since the dehydration of DCPD preceded the cocrystal formation, the reaction appears to be mediated by released water. The intensity of the 13.1 Å peak, selected as a representative example for the cocrystal phase, plotted as a function of time, reveals rapid cocrystallization (Figure 3c). With increase in storage time, the most pronounced decrease in the reactant concentration as well as the increase in the product concentration (measured by the X-ray peak intensity) occurred up to 35 days. Thereafter, the reaction appeared to progress at a much slower rate.

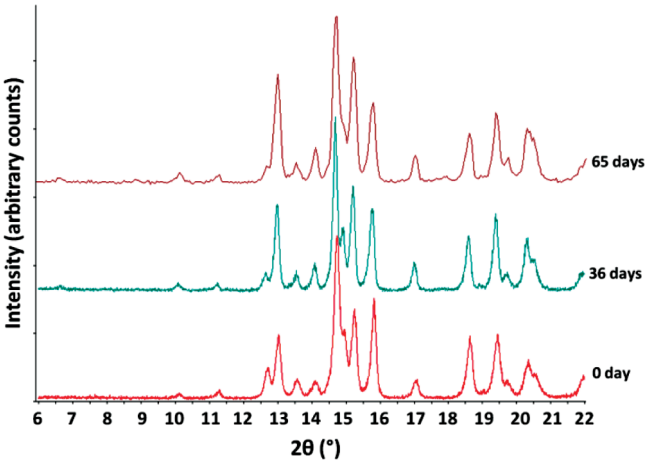


Figure 4. X-ray diffraction patterns of DCPA−CBZ−NMA (second control) tablets stored at 40 °C in sealed Mylar pouches.

As mentioned earlier, the first set of control tablets consisted only of CBZ and NMA. The characteristic peaks of the cocrystal (13.1, 9.8, and 8.6 Å) were not observed even after 380 days of storage (Figure 2b). The intensities of the characteristic peaks of CBZ, (CBZ + NMA) and CBZ−NMA cocrystal, as a function of time in the control tablets, have also been plotted (Figure 3; red profiles). There was no measurable decrease in the intensities of the characteristic peaks of the reactant phases and no evidence of the appearance of the cocrystal phase (Figure 3c). This was strong evidence of the role of water released by the dehydration of DCPD on cocrystal formation.

Since the water released by the dehydration of DCPD was believed to mediate the cocrystal formation, a second set of control tablets were prepared using the anhydrous form of dibasic calcium phosphate (DCPA). Therefore, compositionally, this system was close to the test tablets except that DCPD was

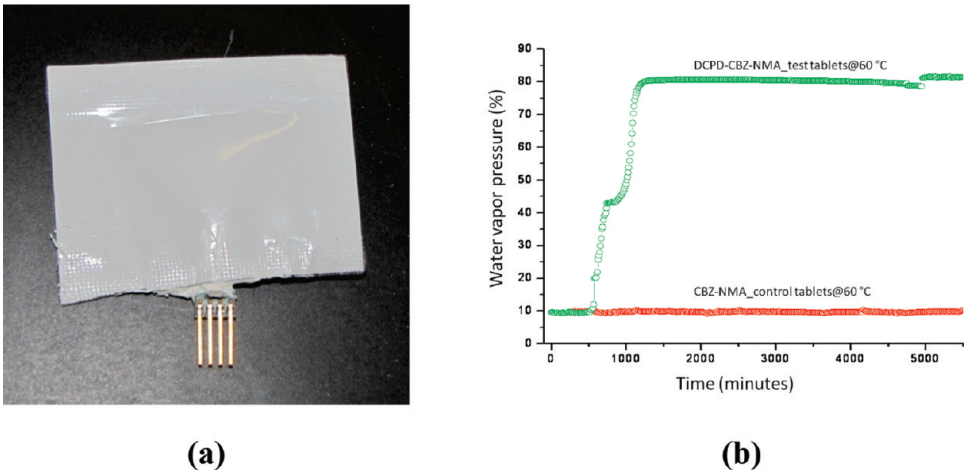


Figure 5. (a) Photograph of tablet and humidity sensor sealed in a Mylar pouch. (b) Comparison of head space relative humidity (RH) of DCPD−CBZ−NMA (test) and CBZ−NMA (first control) tablets stored at 60 °C in sealed Mylar pouches with RH sensor.

dx.doi.org/10.1021/mp200043u |*Mol. Pharmaceutics* 2011, 8, 982–989

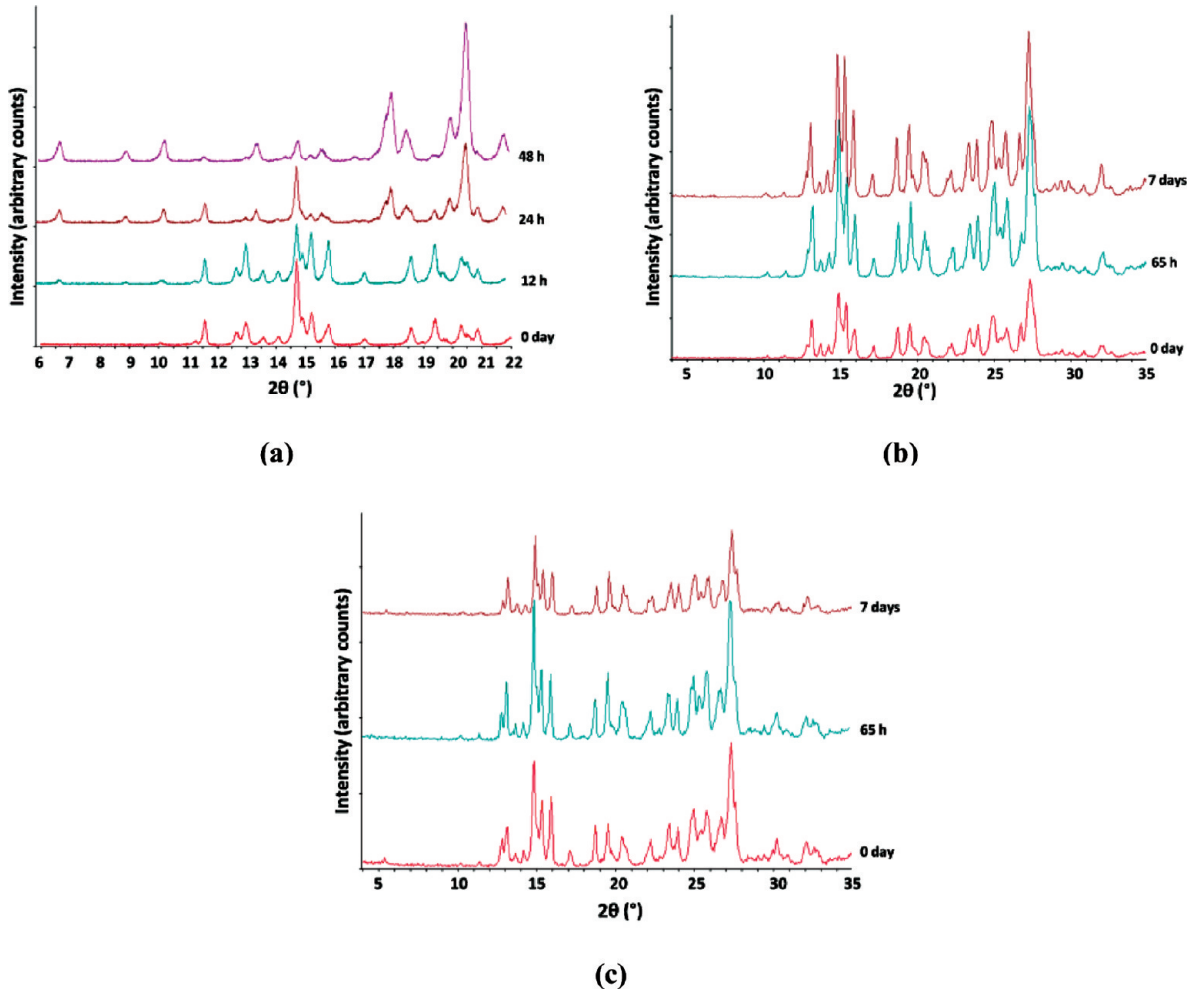


Figure 6. X-ray diffraction patterns of (a) DCPD−CBZ−NMA (test), (b) CBZ−NMA (first control) and (c) DCPA−CBZ−NMA (second control) tablets stored at 60 °C in sealed Mylar pouches with humidity sensors.

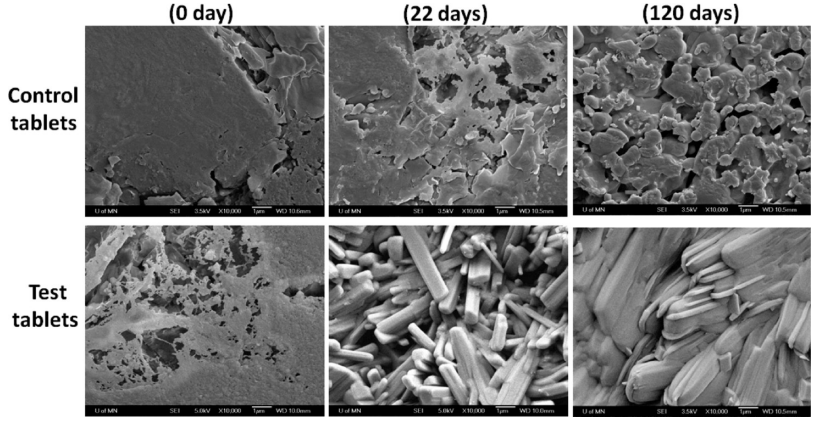


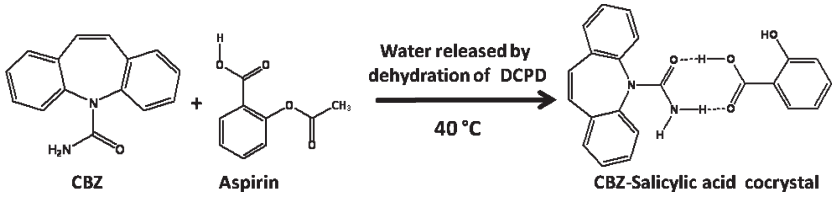
Figure 7. Scanning electron images of intact control (CBZ−NMA; top) and test (bottom) tablets stored at 40 °C.

replaced by DCPA. In this system, there was no evidence of cocrystal formation up to 65 days (Figure 4). Longer term stability studies are currently in progress.

To confirm the role of water in cocrystal formation, test tablets were sealed in Mylar pouches and stored at 60 °C. By sealing an RH sensor into the pouch, it was possible to continuously monitor the headspace RH inside the tablet pouch (Figure 5a). There was an abrupt increase in the headspace RH after 8 h of storage, reflecting dehydration of DCPD in the tablets (Figure 5b).

The first clear evidence of cocrystal formation was observed after ∼12 h of storage (Figure 6a). Moreover, there was no

Scheme 1. Schematic Representation of *in Situ* Formation of CBZ−Salicylic Acid Cocrystal in Tablets[a]



[a] The scheme represents the predicted supramolecular heterosynthon (not yet experimentally verified).

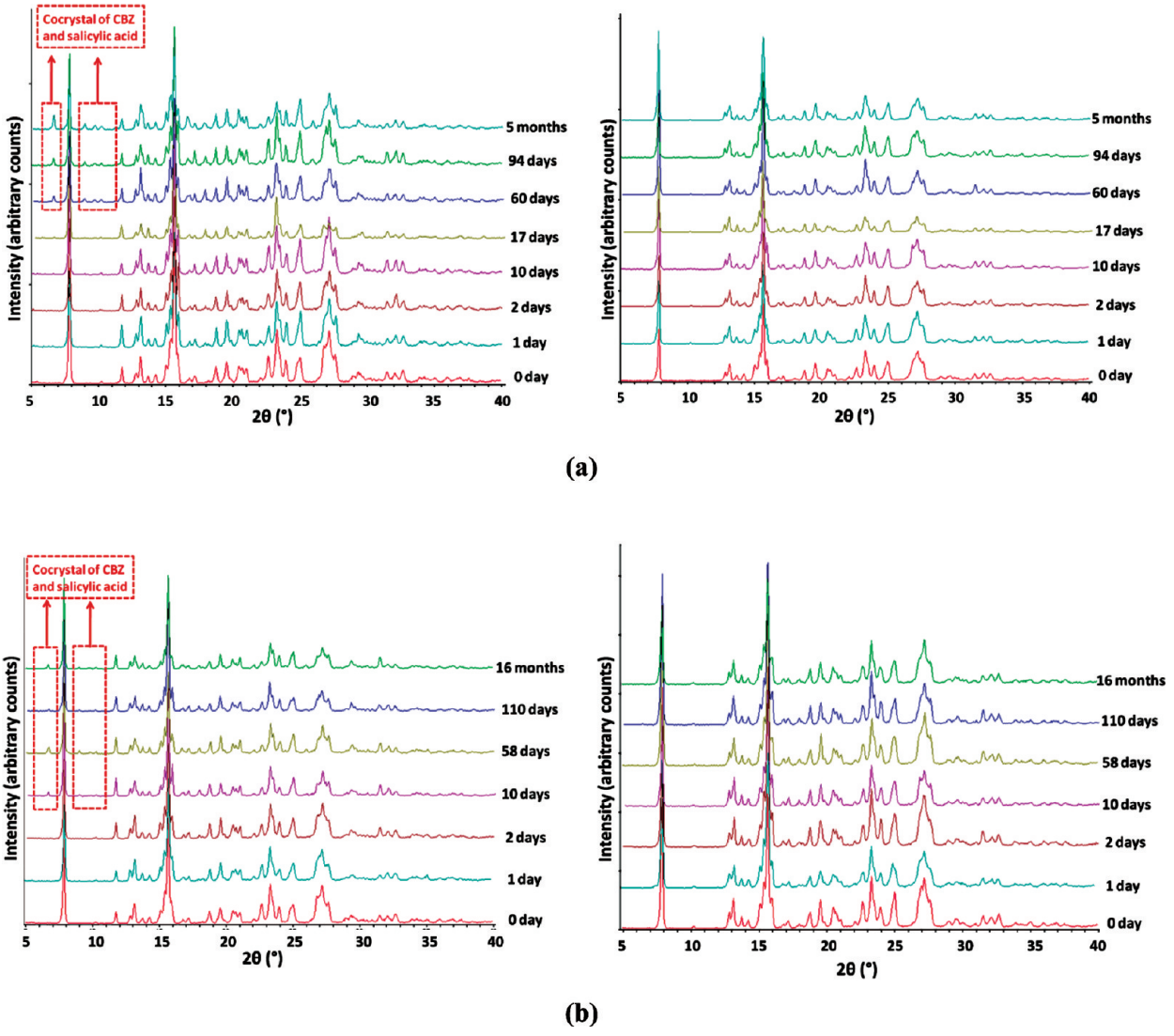


Figure 8. X-ray diffraction patterns of CBZ−aspirin tablets (left, test; right, control) as a function of storage time: (a) 50 and (b) 40 °C. The tablets were stored in sealed Mylar pouches.

evidence of cocrystal formation in both the controls during the entire storage period of 7 days (Figures 6b and 6c). In these controls, there was also no pronounced change in headspace RH.

The electron micrographs permitted visualization of the cocrystals on the surface of test tablets (Figure 7). There was an increase in cocrystal particle size as a function of time. There was no morphological change, suggesting no phase transformation (i.e., formation of cocrystal) in the control tablets.

The mechanism of moisture mediated cocrystal formation in the CBZ−NMA system was investigated by Jayasankar et al.[19] For this purpose, a powder blend of CBZ, NMA and sucrose was stored at 85% RH (at 25 °C), which was above the deliquescence RH of NMA−sucrose binary mixture (80% RH). The proposed mechanism was the dissolution of cocrystal reactants in the sorbed water, followed by the nucleation and growth of the CBZ−NMA cocrystals. Interestingly, the same system, when

stored at 75% RH (25 °C), did not reveal cocrystal formation. These observations strongly support our postulate that the lattice water liberated by the dehydration of DCPD mediated cocrystal formation in tablets. The control tablets, which had been prepared under low (<10%) RH, did not reveal cocrystal formation even after storage for a year at 40 °C. While we recognize that CBZ−NMA cocrystal may eventually form in these tablets, the reaction rate is expected to be so slow as to not be of practical interest.

The second model system consisted of CBZ and aspirin as the APIs. In this formulation, the dehydration of DCPD led to the chemical decomposition of aspirin.[16] Salicylic acid, one of the decomposition products, reacted with CBZ to form CBZ−salicylic acid cocrystal (Scheme 1).

While, in the absence of DCPD (i.e., control), there were no discernible changes in the diffraction patterns, several new peaks were observed in the test tablets. These could not be attributed to CBZ−aspirin cocrystal,[20] since none of its characteristic high intensity peaks were observed. However, several of the new peaks (for example at 6.8, 9.8, 10.1° 2θ; red boxes in Figure 8) matched with those of CBZ−salicylic acid cocrystal.[21] Thus we believe that the water released by the dehydration of DCPD caused the hydrolysis of aspirin to yield salicylic acid. The interaction of CBZ and salicylic acid resulted in CBZ−salicylic acid cocrystal. As expected, the cocrystal formation was much more pronounced at 50 °C (Figure 8a). However, even at 40 °C (Figure 8b), which is a pharmaceutically relevant storage condition, cocrystal formation was evident after 58 days.

While one may take great care in selecting the appropriate physical forms of the various formulation components (active pharmaceutical ingredient (API) and excipients), it is instructive to recognize the potential for phase transformations. Such transformations can be brought about both by pharmaceutical processing steps and by the storage conditions of the finished product. We believe that this is the first report of unintentional cocrystal formation in tablets, mediated by the lattice water, released by excipient dehydration. Since a significant fraction of APIs are capable of forming hydrates (~30%),[12] cocrystal formation between formulation components can also be mediated by dehydration of the API in solid dosage forms.

In addition to the water released by dehydration, the broader implication is the potential role of moisture in facilitating cocrystal formation. Pharmaceutical dosage forms will be exposed to atmospheric water vapor, both during processing and during subsequent product storage. Thus moisture-induced cocrystal formation can occur not only at the time of manufacture but also during the entire shelf life of the product. The *in situ* cocrystal formation may have implication on product performance including pronounced alterations in dissolution behavior and bioavailability.[6]

Pharmaceutical products, both prescription and over-the-counter, manufactured or sold in the United States are required to meet the specifications set in the United States Pharmacopeia.[22] For tablet dosage forms, the dissolution rate of the drug and the drug content in each dosage unit (i.e., assay) are important quality control attributes. Liquid chromatography is a widely used analytical technique for this purpose, and this solution-based method requires dissolution of the analyte in a suitable solvent. Due to this sample preparation step, cocrystal formation may no longer be evident since the cocrystal, in solution, may disintegrate into the drug and the cocrystal former. Thus while *in situ* cocrystal formation may have implications on product performance, the conventional analytical methods may not even reveal cocrystal formation. Cocrystal formation in tablets will become evident only when the dosage form is analyzed directly, without dissolving or extracting the analyte in a solvent. The appropriate solid-state characterization technique should also be capable of revealing cocrystal formation in a complex, multicomponent dosage form.

■ CONCLUSIONS

In summary, we have demonstrated cocrystal formation in intact tablets which was mediated by the water released by a formulation component. While the detection of such *in situ* cocrystal formation can be analytically challenging, the potential implications on both the mechanical and biopharmaceutical properties can be profound.

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■ ACKNOWLEDGMENT

K.K.A. was partially supported by the William and Mildred Peters Endowment fund. N.G.T. gratefully acknowledges the financial support from Dane O. Kildsig Center for Pharmaceutical Processing Research. We thank Sunny Bhardwaj and Prakash Sundaramurthi for their comments. We also thank Dr. John Nelson for his help in recording SEM images. Parts of this work were carried out in the Characterization Facility, University of Minnesota, a member of the NSF-funded Materials Research Facilities Network (www.mrfn.org).

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