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Mechanistic Insight into Caffeine–Oxalic Cocrystal Dissociation in Formulations: Role of Excipients

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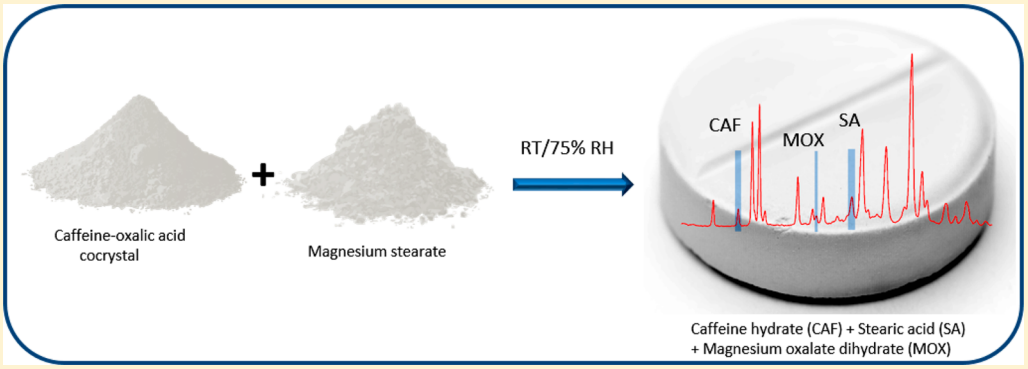
Supporting Information



ABSTRACT: Caffeine–oxalic acid cocrystal, widely reported to be stable under high humidity, dissociated in the presence of numerous pharmaceutical excipients. In cocrystal–excipient binary systems, the water mediated dissociation reaction occurred under pharmaceutically relevant storage conditions. Powder X-ray diffractometry was used to identify the dissociated products obtained as a consequence of coformer–excipient interaction. The proposed cocrystal dissociation mechanism involved water sorption, dissolution of cocrystal and excipient in the sorbed water, proton transfer from oxalic acid to the excipient, and formation of metal salts and caffeine hydrate. In compressed tablets with magnesium stearate, the cocrystal dissociation was readily discerned from the appearance of peaks attributable to caffeine hydrate and stearic acid. Neutral excipients provide an avenue to circumvent the risk of water mediated cocrystal dissociation.

KEYWORDS: *pharmaceutical cocrystals, dissociation, excipients, formulations, powder X-ray diffractometry*

INTRODUCTION

Pharmaceutical cocrystals have been prepared with the goal of improving the physicochemical, mechanical, and/or biopharmaceutical properties of active pharmaceutical ingredients (API).[1−3] This approach is of particular interest for class II and class IV drugs in the Biopharmaceutical Classification System.[4] For example, the bioavailability of a danazol–vanillin cocrystal was about an order of magnitude higher than that of danazol.[5] The cocrystal strategy has advanced from an early development option (support preclinical studies) to marketed drug products, for example, Entresto (valsartan–sacubitril) by Novartis[6] and Suglat (iproglifozin–L-proline) by Astellas Pharma.[7] In addition, an ertugliflozin–L-pyroglutamic acid cocrystal formulation by Pfizer is under late stage development.[8] There have been enormous advancements in the design, synthesis, and characterization of pharmaceutical cocrystals. However, two important areas remain largely unaddressed: large-scale synthesis of cocrystals[9,10] and their formulation into dosage forms. Since cocrystals are typically sustained by hydrogen bonds, in the presence of competing excipients, there is potential for hydrogen bond disruption leading to dissociation.

In order to develop a cocrystal into a pharmaceutical dosage form (for example, tablets), it is necessary to assess cocrystal stability under three conditions: (i) "as is", (ii) in the presence of excipients or additives, and (iii) during various processing steps (milling, granulation, compression) in the manufacture of solid dosage form. The stability of as is cocrystals has been the subject of numerous investigations. For example, heating caffeine–theophylline cocrystal to ∼150 °C resulted in dissociation followed by the crystallization of caffeine and theophylline.[11] The combined effects of temperature and water vapor pressure were comprehensively investigated in pyrazine–phthalic acid cocrystal.[12] An elevation in temperature or water vapor pressure accelerated cocrystal dissociation. The dissociation mechanism was postulated to be dissolution of the

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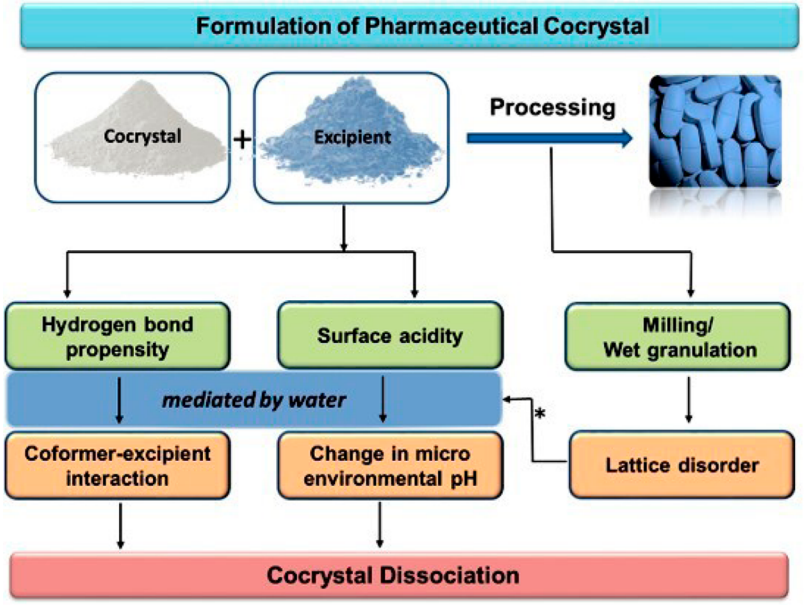
Scheme 1. Potential for Cocrystal Dissociation in Tablets: Effect of Formulation and Processing[a]



[a](*) The role of lattice disorder is discussed in the text.

cocrystal in sorbed water followed by crystallization of the individual components. This formed the basis for the aqueous slurry method, which was developed to quickly assess the stability of several caffeine and theophylline cocrystal systems.[13] Using this approach, partial dissociation in caffeine−adipic acid cocrystals was observed while caffeine−oxalic acid (CAFOXA) cocrystals were stable.[14] The stability of cocrystals has been evaluated in the presence of additives.[15] Abourahma et al. investigated the stability of theophylline *p*-hydroxybenzoic acid cocrystal in the presence of a variety of coformers. The cocrystal was stable in the presence of additives with carboxylic acid, amide, and phenol functional groups. However, in the presence of salicylic acid and 3,5-dinitrobenzoic acid, the hydrogen bonds in the cocrystal were disrupted due to competition with relatively strong hydrogen bond donors (pK_a of *p*-hydroxybenzoic acid, 4.6; salicylic acid, 3.0; and 3,5-dinitrobenzoic acid, 2.8).[16] The effect of milling on caffeine−glutaric acid cocrystal stability was reported by Chow et al.[17] The authors proposed that, during ball milling, the temperature on the particle surface exceeded the polymorphic transition temperature leading to form conversion. The cocrystal physical instability in solution/suspension formulations was recently reviewed.[18]

Once the API cocrystal is determined to be stable, the next step will be its formulation into a pharmaceutical dosage form. The current research is focused on stability of cocrystals in the presence of excipients used to manufacture tablets, the most widely used dosage form. Tablet formulations can contain several excipients including diluent, disintegrant, and lubricant, each of which can hydrogen bond or ionically interact with API. Such a reaction between the API and excipient (or two APIs) led to the unexpected cocrystal formation in intact tablets of aspirin, carbamazepine, and theophylline.[19,20] In each case, cocrystal formation was mediated by the water released from the lattice of either the drug (theophylline monohydrate, carbamazepine dihydrate) or excipient (dicalcium phosphate dihydrate). It is therefore interesting and relevant to evaluate the reverse process, i.e., cocrystal dissociation in solid formulations, which is also expected to be mediated by water. When cocrystals are formulated into tablets, water will be available for interaction during unit operations such as wet granulation and film coating. More commonly, the formulation components can sorb water from the atmosphere and the dissociation reaction can be initiated at the interface of cocrystal and excipient particles. To date, there is only one report on cocrystal dissociation in the presence of excipients in a prototype tablet environment.[21] The authors discussed the dissociation of compound A into amorphous free form and coformer under high humidity conditions. The microenvironmental acidity of the excipient as well as its hygroscopicity facilitated cocrystal dissociation in tablets. The cocrystal dissociation was mitigated by coating the cocrystal particles with hydrophobic excipients to reduce interaction with water and addition of buffering agents to control acidity.[22] Scheme 1 outlines the possible routes of cocrystal dissociation in solid formulations. In this water-mediated reaction, both the physicochemical nature of the excipients and the processing conditions can bring about instability. In spite of the widespread interest in formulating cocrystals, there are no formal published reports on excipient−coformer interactions leading to cocrystal dissociation in tablets. In order to design and manufacture robust dosage forms, it is necessary to have a mechanistic understanding of excipient induced cocrystal dissociation. Such an insight will not only enable rational excipient selection but also aid in developing strategies to mitigate cocrystal dissociation. We believe that this report is an important advancement toward the development of cocrystal formulations, and details the mechanistic basis for excipient-induced cocrystal dissociation in solid dosage forms.

Caffeine−oxalic acid cocrystal (CAFOXA), stoichiometry of 2:1, was selected as the model compound since it is reported to be robust, i.e., physically stable at high water vapor pressures.[23] The cocrystal exhibited no dissociation even after storage at 98% relative humidity (RH) at room temperature (RT) for 7 weeks. The objectives are to (1) develop a rapid screening method to evaluate CAFOXA cocrystal stability in the presence

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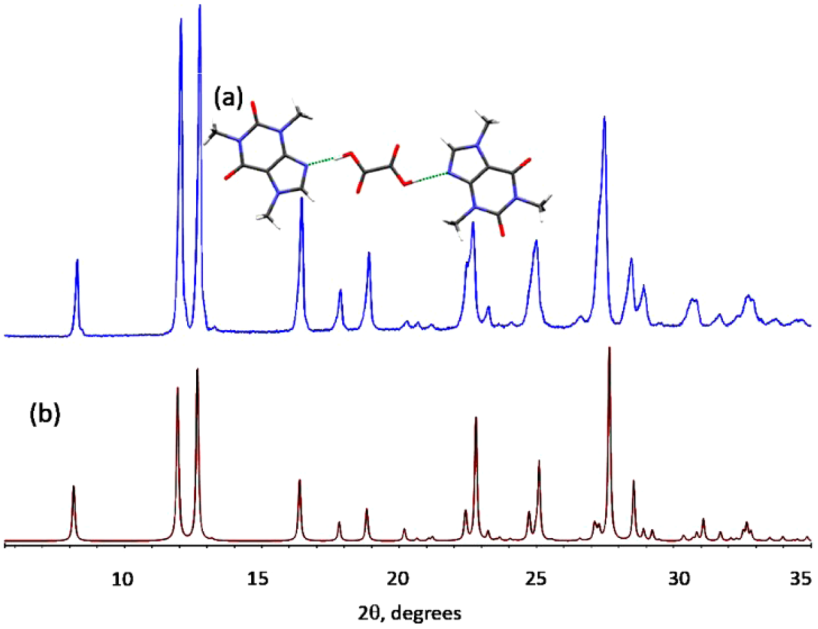

Figure 1. (a) Illustration of O−H···N hydrogen bond in caffeine−oxalic acid cocrystal. (b) Overlay of calculated PXRD pattern of caffeine−oxalic acid cocrystal from Cambridge Structural Database (bottom) and experimental pattern obtained from slurry cocrystallization (top).

of excipients, (2) gain a mechanistic understanding of the cocrystal dissociation brought about by excipients, and (3) develop the basis for rational excipient selection so as to formulate cocrystals into stable solid dosage forms.

EXPERIMENTAL SECTION

Materials and Preparation. Caffeine (CAF, Sigma-Aldrich), oxalic acid (OXA, Sigma-Aldrich), magnesium stearate (MgSt, Fischer Scientific Company), poly(ethylene oxide) (PEO, Dow Chemical Company), crospovidone (CPD, ISP Pharma Technologies), sodium starch glycolate (SSG, JRS Pharma), croscarmellose sodium (CCS, FMC BioPolymer), dicalcium phosphate dihydrate (DCPD, JRS Pharma LP), dicalcium phosphate anhydrous (DCPA, Rhodia Pharma Solutions), sodium stearyl fumarate (SSF, JRS Pharma), sodium citrate (SCT, Archer Daniels Midland Company), and calcium stearate (CaSt, Spectrum Chemicals and Laboratory Products) were used as received. Caffeine−oxalic acid cocrystal (CAFOXA) cocrystal was prepared by the aqueous slurry method.[14]

Thermogravimetric Analysis (TGA). In a thermogravimetric analyzer (model Q50 TGA, TA Instruments, New Castle, DE), 5−10 mg of sample was heated in an aluminum pan from RT to 300 °C at 10 °C/min under dry nitrogen purge (75 mL/min). The TGA data were analyzed using commercial software (Universal Analysis 2000, TA Instruments, New Castle, DE).

Differential Scanning Calorimetry (DSC). A differential scanning calorimeter (model Q2000, TA Instruments) equipped with a refrigerated cooling accessory was used. The instrument was calibrated with indium. Between 5 and 10 mg of sample was hermetically sealed in an aluminum pan. All measurements were performed at a heating rate of 10 °C/min under nitrogen purge (50 mL/min).

Polarized Light Microscopy. A polarized light microscope (Eclipse E200 POS; Nikon, Tokyo, Japan) equipped with a DS-Fi1 microscope digital camera was used to capture the digital images. CAFOXA cocrystal was suspended in silicone oil and dispersed between a slide and a coverslip. Prior to observation, the coverslip was gently rubbed against the slide to render good dispersion of the particles.

Powder X-ray Diffractometry (PXRD). Data was collected in a diffractometer (model D8 ADVANCE; Bruker AXS, Madison, WI) using Cu Kα radiation (40 kV × 40 mA) over an angular range of 5−35° 2θ with a step size of 0.0196° and a dwell time of 0.5 s. The instrument was equipped with a variable-temperature stage (TTK 450; Anton Paar, Graz-Straßgang, Austria) and a silicon strip one-dimensional detector (LynxEye, Bruker AXS, Madison, WI, USA). For the variable temperature experiment, the sample was rapidly heated to 80 °C and the XRD pattern was collected.

Two-Dimensional X-ray Diffractometry (2D-XRD). Intact tablets were exposed, at room temperature, to Co Kα radiation (1.78 Å; 45 kV × 40 mA) in a two-dimensional X-ray diffractometer (D8 Discover 2D, Bruker with a 140 mm diameter window VÅNTEC-500 detector). The center of the tablet was exposed to X-rays, using a 0.8 mm collimator set at a 6° angle of incidence and an area detector (angular range 30°) set at an angle of diffraction of 18° 2θ. The irradiated area can be described by an ellipse with a major axis of 3.4 mm and minor axis of 0.96 mm. Data analyses were performed using commercially available software (JADE Materials Data, Inc., Livermore, CA).

Water Sorption Analysis. The water sorption profiles of CAFOXA cocrystal, physical mixtures (cocrystal with each MgSt and DCPA), were obtained using an automated water sorption analyzer (DVS-1000 Advantage, Surface Measurement Systems, Middlesex, U.K.). Approximately 15.0 mg of powder was placed in a quartz sample pan and equilibrated at 0% RH (25 °C) for 1 h under a nitrogen flow rate of 200 mL/min. The RH was then increased to 75% RH and held for up to 96 h.

Preparation of Tablets. Tablets of binary physical mixtures (1:1 w/w; total weight is 200 mg) containing cocrystal and excipient (DCPA and MgSt) were prepared. Each mixture was filled into a tablet die, held in place with a flat-faced lower punch, and compressed in a hydraulic press

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Table 1. Excipients Used and Their Physicochemical Properties[24−26]

sample no.	excipient	excipient type	pK_a of acid in excipient	dissociation	pH of solution/slurry (1.0 g excipient in 20 g of water)	"hygroscopicity"
1	magnesium stearate (MgSt)	lubricant	4.9	y	9.2	hydrophobic
2	poly(ethylene oxide) (PEO)	binder		n	8.9	hydrophilic
3	crospovidone (CPD)	disintegrant		n	6.2	hygroscopic
4	sodium starch glycolate (SSG)	disintegrant	3.3[27]	y	6.3	very hygroscopic
5	croscarmellose sodium (CCS)	disintegrant	4.3[28]	y	5.4	hygroscopic
6	dicalcium phosphate dihydrate (DCPD)	diluent	pK_{a1} = 2.0, pK_{a2} = 7.1, pK_{a3} = 12.3	y	7.8	nonhygroscopic
7	dicalcium phosphate anhydrate (DCPA)	diluent	pK_{a1} = 2.0, pK_{a2} = 7.1, pK_{a3} = 12.3	y	5.4	nonhygroscopic
8	sodium stearyl fumarate (SSF)	lubricant	3.6[29]	y	8.3 for 5% w/v aq soln at 90 °C	hydrophilic[30]
9	sodium citrate (SCT)	alkalizing and emulsifying agent	pK_{a1} = 3.1, pK_{a2} = 4.7, pK_{a3} = 6.4	y	8.6	slightly deliquescent in moist air
10	calcium stearate (CaSt)	lubricant	4.9	y	not found in lit.	hydrophobic[31]

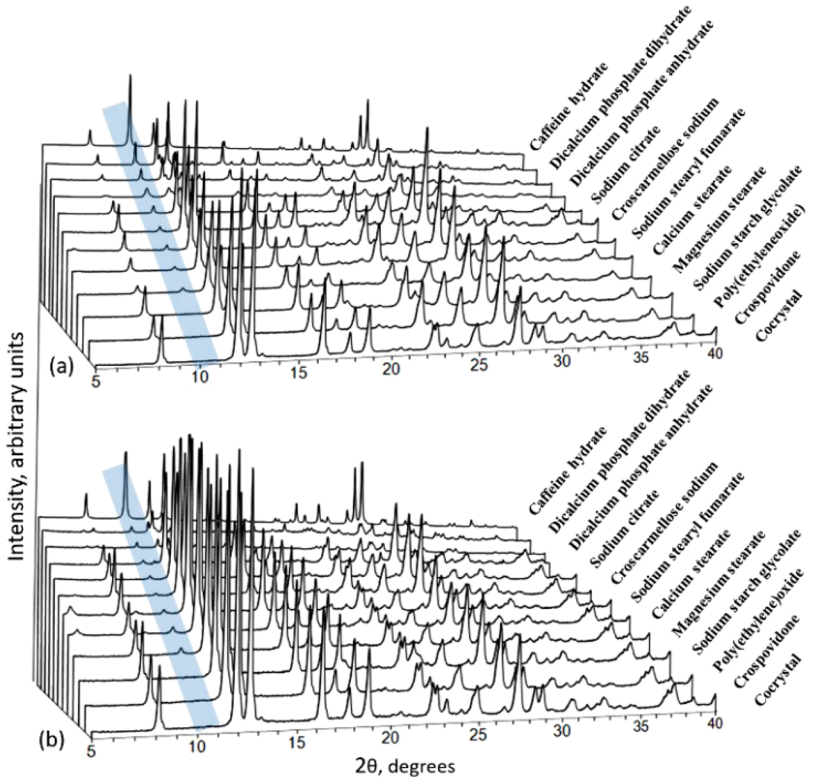

Figure 2. Powder X-ray diffraction patterns of binary mixtures of CAFOXA with each excipient following (a) the addition of 30.0% w/w water and (b) storage at RT/75% RH for 1 week. The characteristic peak of caffeine hydrate (10.6° 2θ) is highlighted.

(Carver model C laboratory press, Menomonee Falls, WI) to a compression pressure of 177 MPa. Tablets were compressed under ambient conditions (25 °C; 35% RH) with a dwell time of 10 s. The tablet diameter was 8.0 mm with a thickness of 3.0 mm.

RESULTS AND DISCUSSION

The PXRD pattern of the CAFOXA cocrystal prepared by aqueous slurry method showed an excellent agreement with the calculated pattern (Figure 1). Differential scanning calorimetry and thermogravimetric analysis served as complementary characterization techniques (Figures S2 and S3).

Ten common excipients, with wide structural diversity, used in tablet formulations as diluent (DCPA and DCPD), disintegrant (SSG, CCS, and CPD), binder (PEO), buffer (SCT), and lubricant (MgSt, CaSt, and SSF), were selected to determine their ability to cause CAFOXA dissociation. The relevant physicochemical properties of the excipients are provided in Table 1.

Binary mixtures (1:1 w/w) of CAFOXA with each excipient were prepared. Water (30% w/w) was added to each composition, and the sample was ground for 5 min using a mortar and pestle and then subjected to PXRD. This procedure is substantially similar to the mechanochemical synthesis of pharmaceutical cocrystals. Liquid assisted grinding is known to

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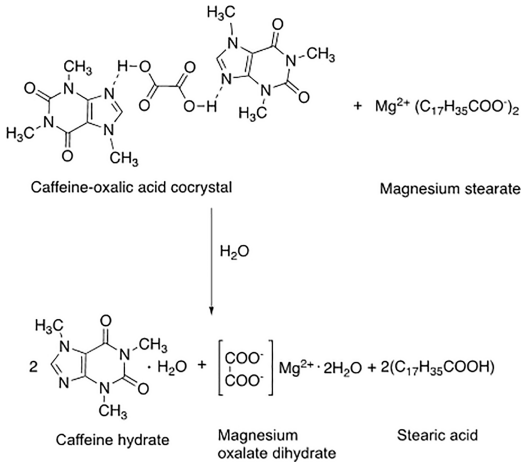
substantially accelerate cocrystal formation.[32] In our study, the addition of bulk water (30.0% w/w) provided an avenue to rapidly assess the potential for excipient-induced cocrystal dissociation. The dissociation of CAFOXA will result in the formation of caffeine and oxalic acid. In the highly humid environment, caffeine is expected to exist as a hydrate (0.8 mol of water per mole of $C_8H_{10}N_4O_2$; referred to simply as caffeine hydrate throughout the manuscript) and can be readily identified from its characteristic peak at 10.6° 2θ.[33] The presence of caffeine hydrate was evident in eight out of the 10 compositions (Figure 2a). CAFOXA appeared to be stable only in the presence of poly(ethylene oxide) and crospovidone. From a practical viewpoint, it is important to evaluate cocrystal stability at temperatures and water vapor pressures reflecting manufacturing and storage conditions. Therefore, a second set of cocrystal−excipient mixtures were stored at RT/75% RH for a week. In spite of the absence of bulk water, the dissociation behavior was consistent and caffeine hydrate was detected in eight out of the 10 compositions (Figures 2a and 2b). In order to assess the potential role of water, the mixtures were also stored at RT/0% RH for 1 week. The PXRD patterns revealed no instability, indicating that the excipient-induced cocrystal dissociation was water mediated (Figures S5 and S6).

Typically, cocrystals are useful when the API is nonionizable and salt formation is not a viable option. For a given neutral API, a coformer could be neutral, acidic, or basic. It is possible to draw a parallel between salt disproportionation and cocrystal dissociation specifically when either the API or the coformer molecule is ionizable. Both salts and cocrystals exhibit pH dependent solubility with maximum solubility at pH_{max}.[34,35] In the case of cocrystals of an ionizable API, the extent of ionization of the coformer and API will be pH dependent. Alternatively, for cocrystal of neutral API, the ionization of only the coformer will be pH dependent and would dictate the stability of the cocrystal as a function of pH. For example, in the system under consideration (CAFOXA), the ionization behavior of oxalic acid (pK_{a1} = 1.3 and pK_{a2} = 4.3), the coformer, is strongly pH dependent. Since some of the excipients used in the present study create a basic microenvironment,[26] the potential effect of excipient(s) on cocrystal stability warrants consideration. A rational basis for excipient selection will be enabled if a mechanistic understanding of cocrystal dissociation is known. Though our preliminary studies revealed dissociation in the presence of numerous ionic excipients, for detailed investigation and to elucidate plausible mechanism, MgSt was used as a representative example.

When the CAFOXA−MgSt mixture is allowed to interact with water (either bulk water or exposure to RT/75% RH), dissociation is likely to be initiated at the points of contact of cocrystal and excipient particles. It is well-known that there can be processing-induced lattice disorder, sometimes pronounced, in the surface region of particles.[36] Thus, the interface of cocrystal and excipient particles can be visualized as a poorly crystalline (or amorphous) region. This region will have a much higher tendency to interact with water than the crystalline regions, i.e., the interior of the particles. The sorbed water can act as a plasticizer, lower the glass transition temperature, and increase molecular mobility and thereby facilitate reactions.[37] Following the dissolution of CAFOXA and MgSt in the sorbed water, this aqueous layer can serve as the medium for excipient−coformer interaction. It can contain caffeine, oxalic acid, oxalate (or hydrogen oxalate), stearate anions, and magnesium cations. Proton transfer (generated by the ionization of oxalic acid) to stearate anion resulted in stearic acid while the magnesium cations (Mg^{2+}) reacted with oxalate anion to yield magnesium oxalate dihydrate (Scheme 2).

Scheme 2. Proposed Mechanism of Water Mediated CAFOXA Cocrystal Dissociation in the Presence of Magnesium Stearate



Ambient temperature PXRD provided direct evidence of cocrystal dissociation and the formation of caffeine hydrate, stearic acid, and magnesium oxalate dihydrate (Figure 3). Variable temperature PXRD further confirmed the presence of stearic acid (Figure 4). Cocrystal dissociation was observed in all the binary mixtures prepared with ionic excipients. It is important to note that the pK_a value of the free acid form (for example, stearic acid; pK_a = 4.9) of each salt (MgSt) excipient is higher than the pK_{a1} of oxalic acid. Therefore, in each excipient, there is a driving force for the salt to free acid conversion by accepting protons from oxalic acid. When a CAFOXA−MgSt was ground in the absence of water, there was no evidence of dissociation, confirming that the MgSt−oxalic acid interaction was water mediated. Thus, the data suggests that the mechanism of cocrystal dissociation in the presence of ionic excipients involves water sorption followed by dissolution of cocrystal and excipient in the sorbed water layer. The subsequent proton transfer from oxalic acid to anion (for example to carboxylate in CaSt and phosphate in DCPA) and formation of metal salt will drive the cocrystal dissociation. The formation of reaction products in selected systems was confirmed by PXRD (Supporting Information; Figures S8 and S9). Interestingly, a similar water-mediated reaction between methanesulfonic acid (from delavardidine mesylate) and carboxyl group in croscarmellose sodium was believed to be the mechanism of the salt disproportionation reaction.[38]

In contrast, when binary mixtures of CAFOXA with each PEO and CPD were exposed to bulk water (30% w/w) or to high RH (75% at RT), the cocrystal was stable with no evidence of dissociation (Figure 5). The cocrystal stability could be attributed to the absence of (i) anions to accept the protons from oxalic acid and (ii) metal cations to react with oxalate or hydrogen oxalate anions. Thus, neutral excipients provide an avenue to circumvent the risk of water mediated cocrystal dissociation. There is an interesting parallel between cocrystal formation and dissociation. Cocrystal formation by grinding was attributed to grinding-induced amorphization of reactant particles leading to their interaction.[39,40] In the current

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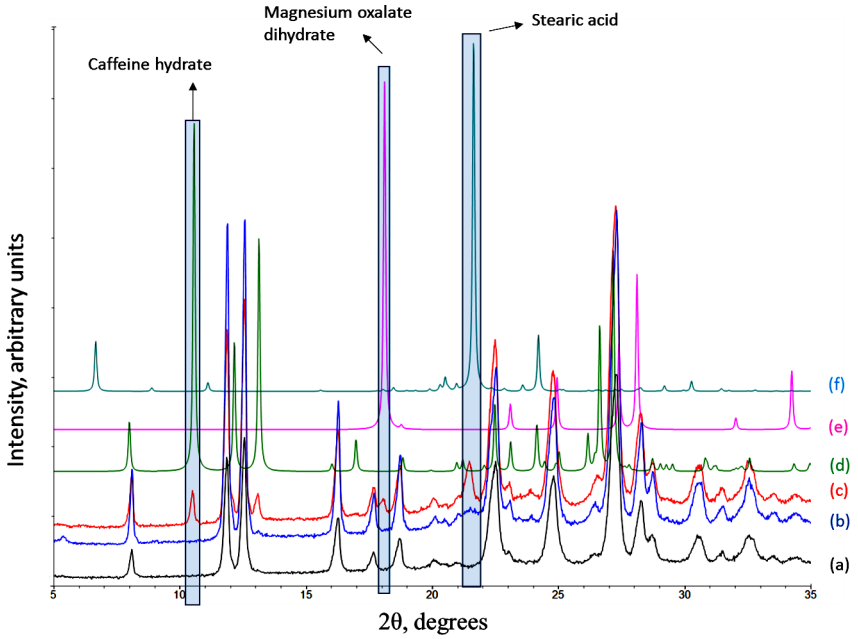

Figure 3. Overlay of PXRD patterns of (a) "as is" cocrystal, (b) obtained after grinding cocrystal−magnesium stearate physical mixture in the absence of water and (c) in the presence of water. The calculated patterns of (d) caffeine hydrate, (e) magnesium oxalate dihydrate, and (f) stearic acid are also presented. The formation of caffeine hydrate, magnesium oxalate dihydrate, and stearic acid was evident in the "wet ground" mixture.

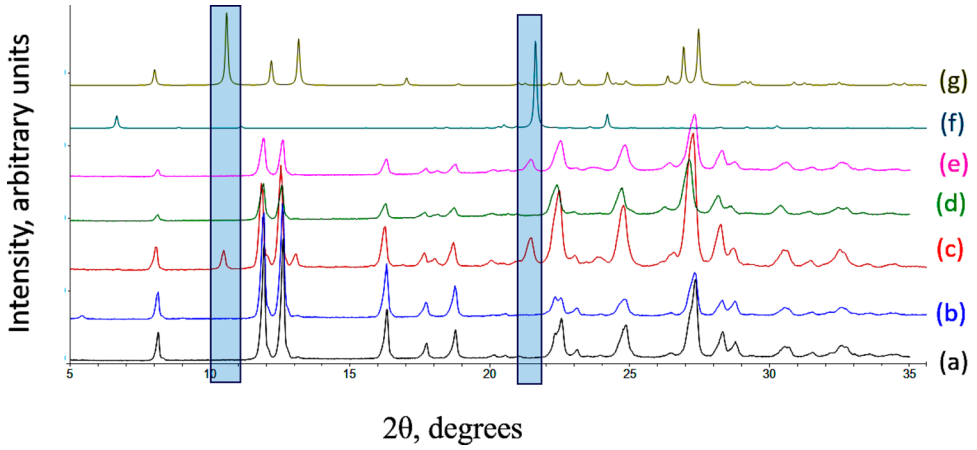

Figure 4. Overlay of PXRD patterns (from bottom to top) of physical mixture of caffeine−oxalic acid cocrystal with magnesium stearate (1:1 w/w). (a) "As is" caffeine−oxalic acid cocrystal. (b) Physical mixture at "zero" time. (c) Physical mixture ground in the presence of water. The grinding was done manually in a mortar and pestle for 30 min. (d) Sample c heated to 80 °C. A characteristic stearic acid peak (21.6° 2θ) disappeared since the melting point of stearic acid is ∼69 °C. (e) Sample d cooled to 25 °C. The stearic acid peak reappeared. The two highlighted regions are the angular ranges for a characteristic peak of caffeine hydrate (peak at 10.6° 2θ) and stearic acid (21.6° 2θ). The calculated patterns of (f) stearic acid and (g) caffeine hydrate are also included.

system, the opposite process, cocrystal dissociation, is brought about by water-mediated interaction in the disordered cocrystal−excipient particle interfaces. While investigation of the reaction kinetics was outside the scope of this study, it is expected to be dependent on numerous factors including surface area of contact between cocrystal and excipient particles, and the reactivity of the components. Although cocrystal dissociation was water mediated, the reaction kinetics appeared to be independent of the water sorption potential of the excipient (Figures S10, S11, and S12). With both MgSt (hydrophobic) and DCPA (nonhygroscopic), the dissociation was rapid. It was much slower with SSG and CCS, two hygroscopic excipients.

Finally, the potential for cocrystal dissociation in intact tablets was evaluated. A binary mixture of CAFOXA with MgSt was prepared. The mixture was compressed into tablets, stored at RT/75% RH for 35 days, and subjected to 2D-XRD. This technique was used since compression can induce preferred orientation. The cocrystal dissociation in tablets could be readily discerned from the appearance of peaks attributable to caffeine hydrate and stearic acid (Figure 6, I). Cocrystal dissociation (appearance of caffeine hydrate peak) was first evident after 5 days. There was a progressive increase in the intensities of characteristic peaks of caffeine hydrate (10.6° 2θ) and stearic acid (21.6° 2θ) up to 35 days (Figure 6, II).

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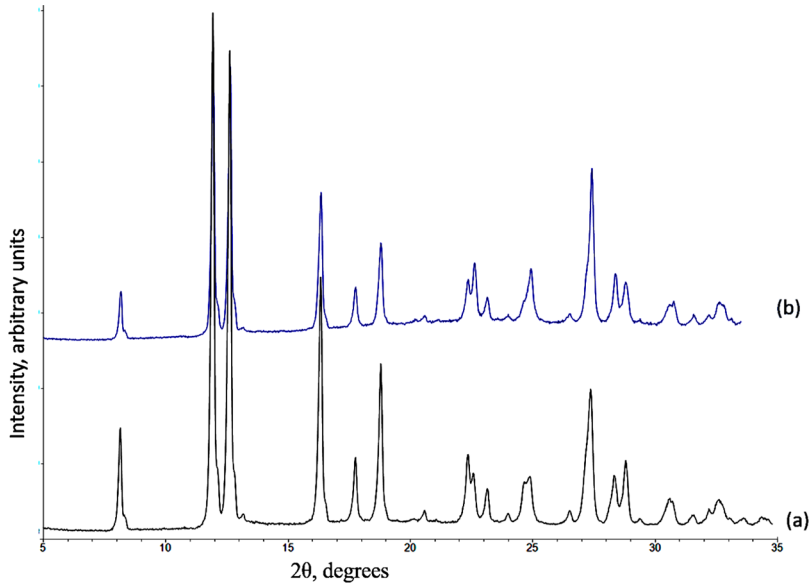

Figure 5. Overlay of PXRD patterns of (a) "as is" cocrystal and (b) physical mixture of cocrystal and crospovidone, slurried with water.

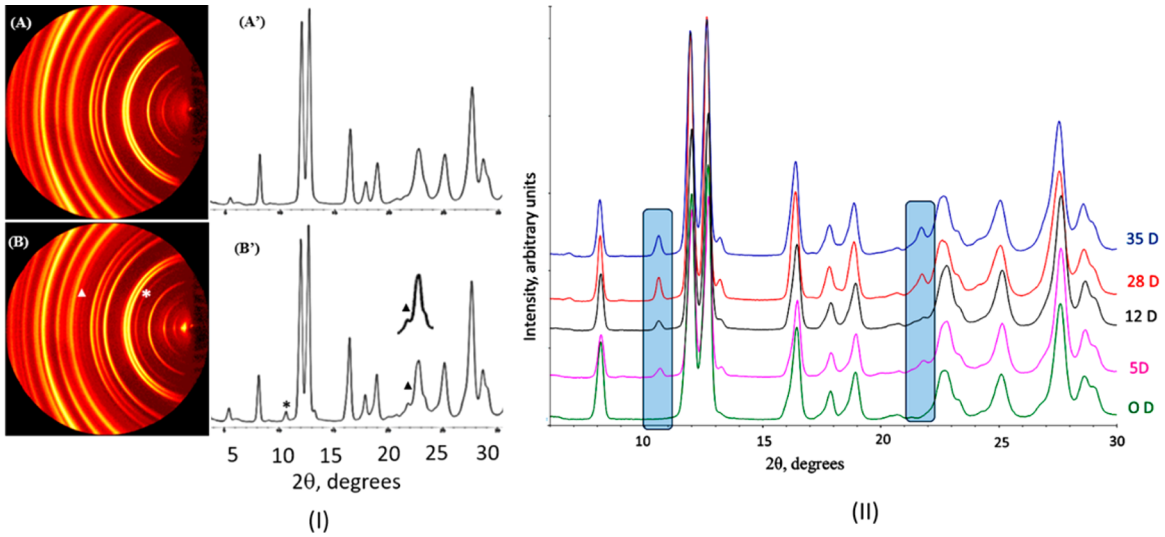

Figure 6. (I) Two-dimensional XRD patterns (obtained using Co Kα radiation) of (A) tablet containing cocrystal and MgSt (95 and 5% w/w) at time zero and (B) after 5 days at RT/75% RH. To facilitate visualization, the corresponding one-dimensional XRD patterns (A′, B′) are also presented (converted to Cu Kα radiation). The appearance of the peak at 10.6° 2θ (*), attributed to caffeine hydrate, is a consequence of cocrystal dissociation. The appearance of a peak at 21.6° 2θ (▲) is attributed to the formation of stearic acid. The peak is separately drawn for clarity. (II) Overlay of PXRD patterns revealing the formation and progressive increase in the concentrations of caffeine hydrate and stearic acid in tablets. The two highlighted regions are the angular ranges for a characteristic peak of caffeine hydrate (peak at 10.6° 2θ) and stearic acid (21.6° 2θ).

SIGNIFICANCE

Cocrystal formation provides an avenue to modulate the properties of an active pharmaceutical ingredient. The advantages of a cocrystal may only be realized if it is physically stable during dosage form manufacture and the entire shelf life of the product. Our model compound, caffeine−oxalic acid cocrystal, dissociated in the presence of numerous pharmaceutical excipients, a reaction attributed to interaction between oxalic acid and salt excipients. The dissociation was facilitated by water, and, as a consequence, caffeine crystallized as caffeine hydrate. The reaction occurred under pharmaceutically relevant storage conditions (RT/75% RH). Many excipients used in formulations are salts and contain ions (for example, Na^+, Mg^{2+}, and Ca^{2+} cations; carboxylate anions). The anions can accept protons from acidic coformers to facilitate the disproportionation as is evident in the case of delavirdine mesylate salt.[38] In addition, the functionality of the lubricant may be affected by its interaction with coformer/drug. The reaction between oxalic acid and magnesium stearate resulted in the formation of stearic acid. The lubricant properties of the free acid and salt are different.[41] While the grinding method has been extensively used to prepare cocrystals,[39] we have extended it to evaluate the potential for cocrystal dissociation in the presence of excipients. The screening method used in this study (water-assisted grinding) can serve as a rapid evaluation tool to determine cocrystal stability in the presence of excipients.

CONCLUSION

In summary, we have demonstrated that caffeine−oxalic acid cocrystal, widely reported to be a physically robust crystalline

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solid form, dissociated in the presence of numerous pharmaceutical excipients. The reaction was water mediated and occurred very rapidly (<1 week) under pharmaceutically relevant conditions. Based on a mechanistic understanding of cocrystal dissociation, we propose the use of neutral excipients to successfully formulate this cocrystal into a robust solid dosage form. The potential for excipient-induced cocrystal dissociation exists for pharmaceutical cocrystals comprising acidic and basic coformers. The rapid screening approach provides an avenue to quickly evaluate the potential for cocrystal dissociation in formulations. Our subsequent studies will address the kinetics of caffeine−oxalic acid cocrystal dissociation in pharmaceutical compositions.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.molpharmaceut.7b00587.

PXRD, DSC, and TGA results and water sorption data (PDF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) Almarsson, Ö.; Zaworotko, M. J. Crystal engineering of the composition of pharmaceutical phases. Do pharmaceutical co-crystals represent a new path to improved medicines? *Chem. Commun.* **2004**, *17*, 1889−1896.

(2) Duggirala, N. K.; Perry, M. L.; Almarsson, O.; Zaworotko, M. J. Pharmaceutical cocrystals: along the path to improved medicines. *Chem. Commun.* **2016**, *52* (4), 640−655.

(3) Bolla, G.; Nangia, A. Pharmaceutical cocrystals: walking the talk. *Chem. Commun.* **2016**, *52* (54), 8342−8360.

(4) Shan, N.; Perry, M. L.; Weyna, D. R.; Zaworotko, M. J. Impact of pharmaceutical cocrystals: the effects on drug pharmacokinetics. *Expert Opin. Drug Metab. Toxicol.* **2014**, *10* (9), 1255−1271.

(5) Childs, S. L.; Kandi, P.; Lingireddy, S. R. Formulation of a Danazol Cocrystal with Controlled Supersaturation Plays an Essential Role in Improving Bioavailability. *Mol. Pharmaceutics* **2013**, *10* (8), 3112−3127.

(6) https://www.fda.gov/newsevents/newsroom/pressannouncements/ucm453845.htm; accessed 07-07-2017.

(7) https://www.astellas.com/en/corporate/news/detail/approval-of-suglat-tablets-a-s.html; accessed 07-07-2017.

(8) Bowles, P.; Brenek, S. J.; Caron, S.; Do, N. M.; Drexler, M. T.; Duan, S.; Dubé, P.; Hansen, E. C.; Jones, B. P.; Jones, K. N.; Ljubicic, T. A.; Makowski, T. W.; Mustakis, J.; Nelson, J. D.; Olivier, M.; Peng, Z.; Perfect, H. H.; Place, D. W.; Ragan, J. A.; Salisbury, J. J.; Stanchina, C. L.; Vanderplas, B. C.; Webster, M. E.; Weekly, R. M. Commercial Route Research and Development for SGLT2 Inhibitor Candidate Ertugliflozin. *Org. Process Res. Dev.* **2014**, *18* (1), 66−81.

(9) Ross, S. A.; Lamprou, D. A.; Douroumis, D. Engineering and manufacturing of pharmaceutical co-crystals: a review of solvent-free manufacturing technologies. *Chem. Commun.* **2016**, *52* (57), 8772−8786.

(10) am Ende, D. J.; Anderson, S. R.; Salan, J. S. Development and Scale-Up of Cocrystals Using Resonant Acoustic Mixing. *Org. Process Res. Dev.* **2014**, *18* (2), 331−341.

(11) Eddleston, M. D.; Lloyd, G. O.; Jones, W. Cocrystal dissociation and molecular demixing in the solid state. *Chem. Commun.* **2012**, *48* (65), 8075−8077.

(12) Arhangelskis, M.; Lloyd, G. O.; Jones, W. Mechanochemical synthesis of pyrazine: dicarboxylic acid cocrystals and a study of dissociation by quantitative phase analysis. *CrystEngComm* **2012**, *14* (16), 5203−5208.

(13) Eddleston, M. D.; Thakuria, R.; Aldous, B. J.; Jones, W. An investigation of the causes of cocrystal dissociation at high humidity. *J. Pharm. Sci.* **2014**, *103* (9), 2859−2864.

(14) Eddleston, M. D.; Madusanka, N.; Jones, W. Cocrystal dissociation in the presence of water: A general approach for identifying stable cocrystal forms. *J. Pharm. Sci.* **2014**, *103* (9), 2865−2870.

(15) (a) Caira, M. R.; Nassimbeni, L. R.; Wildervanck, A. F. Selective formation of hydrogen bonded cocrystals between a sulfonamide and aromatic carboxylic acids in the solid state. *J. Chem. Soc., Perkin Trans. 2* **1995**, No. 12, 2213−2216. (b) Remenar, J. F.; Peterson, M. L.; Stephens, P. W.; Zhang, Z.; Zimenkov, Y.; Hickey, M. B. Celecoxib: nicotinamide dissociation: using excipients to capture the cocrystal's potential. *Mol. Pharmaceutics* **2007**, *4* (3), 386−400. (c) Fischer, F.; Joester, M.; Rademann, K.; Emmerling, F. Survival of the Fittest: Competitive Co-crystal Reactions in the Ball Mill. *Chem. - Eur. J.* **2015**, *21* (42), 14969−14974. (d) Alsirawan, M. B.; Vangala, V. R.; Kendrick, J.; Leusen, F. J.; Paradkar, A. Coformer replacement as an indicator for thermodynamic instability of cocrystals: competitive transformation of caffeine: dicarboxylic acid. *Cryst. Growth Des.* **2016**, *16* (6), 3072−3075.

(16) Abourahma, H.; Urban, J. M.; Morozowich, N.; Chan, B. Examining the robustness of a theophylline cocrystal during grinding with additives. *CrystEngComm* **2012**, *14* (19), 6163−6169.

(17) Chow, P. S.; Lau, G.; Ng, W. K.; Vangala, V. R. Stability of Pharmaceutical Cocrystal During Milling: A Case Study of 1:1 Caffeine-Glutaric Acid. *Cryst. Growth Des.* **2017**, *17*, 4064.

(18) Bhardwaj, S.; Lipert, M.; Bak, A. Mitigating Cocrystal Physical Stability Liabilities in Preclinical Formulations. *J. Pharm. Sci.* **2017**, *106* (1), 31−38.

(19) Arora, K. K.; Tayade, N. G.; Suryanarayanan, R. Unintended water mediated cocrystal formation in carbamazepine and aspirin tablets. *Mol. Pharmaceutics* **2011**, *8* (3), 982−989.

(20) Arora, K.; Thakral, S.; Suryanarayanan, R. Instability in Theophylline and Carbamazepine Hydrate Tablets: Cocrystal Formation Due to Release of Lattice Water. *Pharm. Res.* **2013**, *30* (7), 1779−1789.

(21) Kong, A.; Arora, K. K.; Mehrens, S.; Nickerson, B.; Alstine, L. V.; Daddario, P.; Zhou, Y.; Grest, P.; Schmidt, H. F. AAPS. 2014: http://abstracts.aaps.org/Verify/AAPS2014/PosterSubmissions/T3202.pdf; accessed 07-07-2017.

(22) Arora, K. K.; Duggirala, N. K.; LaCasse, S.; Nickerson, B.; Zhou, Y.; Daddario, P.; Krzyzaniak, J. F. AAPS. 2015. http://abstracts.aaps.org/Verify/AAPS2015/PosterSubmissions/T2181.pdf; accessed 07-07-2017.

DOI: 10.1021/acs.molpharmaceut.7b00587
Mol. Pharmaceutics XXXX, XXX, XXX−XXX

(23) Trask, A. V.; Motherwell, W. D. S.; Jones, W. Pharmaceutical Cocrystallization: Engineering a Remedy for Caffeine Hydration. *Cryst. Growth Des.* **2005**, *5* (3), 1013−1021.
(24) Rowe, R. C.; Sheskey, P. J.; Weller, P. J. *Handbook of pharmaceutical excipients*; Pharmaceutical Press: London, 2006; Vol. *6*.
(25) Stahl, P. H., Wermuth, C. G., Eds. *Handbook of pharmaceutical salts: properties, selection and use*; Verlag Helvetica Chimica Acta: Zürich, 2002.
(26) Govindarajan, R.; Landis, M.; Hancock, B.; Gatlin, L. A.; Suryanarayanan, R.; Shalaev, E. Y. Surface Acidity and Solid-State Compatibility of Excipients with an Acid-Sensitive API: Case Study of Atorvastatin Calcium. *AAPS PharmSciTech* **2015**, *16* (2), 354.
(27) Instead of starch glycolic acid, glycolic acid pK_a is reported.
(28) Budavari, S. *The Merck Index*, 11th ed.; Merck & Co: Rahway, NJ, 1989.
(29) http://foodb.ca/compounds/FDB010281; accessed 07-07-2017.
(30) http://www.jrspharma.com/pharma-wAssets/docs/brochures/PRUV.pdf; accessed 07-07-2017.
(31) Li, J.; Wu, Y. Lubricants in pharmaceutical solid dosage forms. *Lubricants* **2014**, *2* (1), 21−43.
(32) Shan, N.; Toda, F.; Jones, W. Mechanochemistry and co-crystal formation: effect of solvent on reaction kinetics. *Chem. Commun.* **2002**, *20*, 2372−2373.
(33) Krzyzaniak, J. F.; Williams, G. R.; Ni, N. Identification of phase boundaries in anhydrate/hydrate systems. *J. Pharm. Sci.* **2007**, *96* (5), 1270−1281.
(34) Serajuddin, A. T. Salt formation to improve drug solubility. *Adv. Drug Delivery Rev.* **2007**, *59* (7), 603−616.
(35) Maheshwari, C.; André, V.; Reddy, S.; Roy, L.; Duarte, T.; Rodríguez-Hornedo, N. Tailoring aqueous solubility of a highly soluble compound via cocrystallization: effect of coformer ionization, pH max and solute−solvent interactions. *CrystEngComm* **2012**, *14* (14), 4801−4811.
(36) Ward, G. H.; Schultz, R. K. Process-induced crystallinity changes in albuterol sulfate and its effect on powder physical stability. *Pharm. Res.* **1995**, *12* (5), 773−779.
(37) (a) Ahlneck, C.; Zografi, G. The molecular basis of moisture effects on the physical and chemical stability of drugs in the solid state. *Int. J. Pharm.* **1990**, *62* (2−3), 87−95. (b) Koranne, S.; Govindarajan, R.; Suryanarayanan, R. Investigation of Spatial Heterogeneity of Salt Disproportionation in Tablets by Synchrotron X-ray Diffractometry. *Mol. Pharmaceutics* **2017**, *14* (4), 1133−1144.
(38) Rohrs, B. R.; Thamann, T. J.; Gao, P.; Stelzer, D. J.; Bergren, M. S.; Chao, R. S. Tablet dissolution affected by a moisture mediated solid-state interaction between drug and disintegrant. *Pharm. Res.* **1999**, *16* (12), 1850−1856.
(39) Hasa, D.; Jones, W. Screening for new pharmaceutical solid forms using mechanochemistry: A practical guide. *Adv. Drug Delivery Rev.* **2017**, DOI: 10.1016/j.addr.2017.05.001.
(40) Friščić, T.; Jones, W. Recent advances in understanding the mechanism of cocrystal formation via grinding. *Cryst. Growth Des.* **2009**, *9* (3), 1621−1637.
(41) Strickland, W. A.; Nelson, E.; Busse, L. W.; Higuchi, T. The physics of tablet compression IX. Fundamental aspects of tablet lubrication. *J. Am. Pharm. Assoc., Sci. Ed.* **1956**, *45* (1), 51−55.

DOI: 10.1021/acs.molpharmaceut.7b00587
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