molecular pharmaceutics

articles

Screening for Pharmaceutical Cocrystal Hydrates via Neat and Liquid-Assisted Grinding

Shyam Karki,[†] Tomislav Friščić,[†] William Jones,*[,†] and W. D. Samuel Motherwell[‡]

Pfizer Institute for Pharmaceutical Materials Science, Chemistry Department, University of Cambridge, Lensfield Road, Cambridge CB2 1EW, United Kingdom, and Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, United Kingdom

Received January 10, 2007; Revised Manuscript Received March 19, 2007; Accepted March 27, 2007

Abstract: The formation of cocrystal hydrates represents a potential route to achieve molecular materials with improved properties, particularly stability under conditions of high relative humidity. We describe the use of neat and liquid-assisted grinding for screening for hydrated forms of pharmaceutical cocrystals. In the case of liquid-assisted grinding, water is present in the reaction mixture as a liquid, whereas in the case of neat grinding, it is introduced by employing crystalline hydrates as reactants. The ability to form a cocrystal hydrate by either of the two methods appears to be variable, depending on the choice of cocrystal components. Theophylline readily forms a cocrystal hydrate with citric acid. This contrasts with the behavior of caffeine, which provides only an anhydrous cocrystal ("caffeine citrate") even when both reactants are crystalline hydrates. The preference of theophylline to form a cocrystal hydrate is qualitatively explained by similarity between crystal structures of the products and reactant hydrates. Overall, liquid-assisted grinding is less sensitive to the form of the reactant (i.e., hydrate or anhydrate) than neat grinding. For that reason liquid-assisted grinding appears to be a more efficient method of screening for cocrystal hydrates, and it is also applicable to screening for hydrates of APIs.

Keywords: Neat grinding; liquid-assisted grinding; pharmaceutical cocrystal; hydrate

Introduction

Cocrystals, or multicomponent molecular crystals,[1] have recently attracted significant interest as functional materials with potential applications as pharmaceutical[2] or electronic materials,[3] as well as in synthetic organic chemistry.[4] In part, this interest results from an ability to select the components of the cocrystal, thereby facilitating the fine-tuning of the physical properties of the solid.[5,6] Cocrystals are especially

* Author to whom correspondence should be addressed. Mailing address: Pfizer Institute for Pharmaceutical Materials Science, Chemistry Department, University of Cambridge, Lensfield Road, Cambridge CB2 1EW, U.K. E-mail: wj10@cam.ac.uk. Tel: +44-(0)1223-336468. Fax: +44-(0)1223-762829.

[†] University of Cambridge Chemistry Department.

[‡] Cambridge Crystallographic Data Centre.

(1) Aakeröy, C. B.; Salmon, D. J. Building co-crystals with molecular sense and supramolecular sensibility. *CrystEngComm* **2005**, *7*, 439−448.

(2) Vishweshwar, P.; McMahon, J. A.; Peterson, M. L.; Hickey, M. B.; Shattock, T. R.; Zaworotko, M. J. Crystal engineering of pharmaceutical co-crystals from polymorphic active pharmaceutical ingredients. *Chem. Commun.* **2005**, 4601−4603.

(3) Sokolov, A. N.; Friščić, T.; MacGillivray, L. R. Enforced Face-to-Face Stacking of Organic Semiconductor Building Blocks within Hydrogen-Bonded Molecular Cocrystals. *J. Am. Chem. Soc.* **2006**, *128*, 2806−2807.

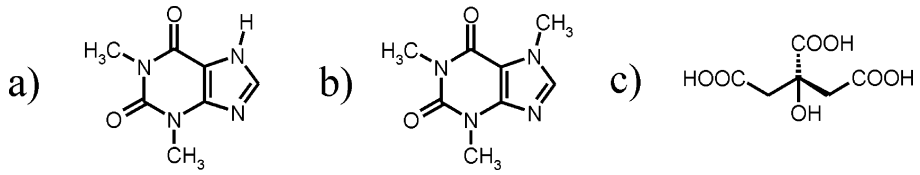
(4) Friščić, T.; MacGillivray, L. R.. Reversing the code of a template-directed solid-state synthesis: a bipyridine template that directs a single-crystal-to-single-crystal [2+2] photodimerisation of a dicarboxylic acid. *Chem. Commun.* **2005**, 5748−5750.

(5) Friščić, T.; MacGillivray, L. R. Modularity in organic solid state and supramolecular chemistry. *Croat. Chem. Acta* **2006**, *79*, 327−333.

(6) Aakeröy, C. B.; Beatty, A. M.; Helfrich, B. A. "Total synthesis" supramolecular style: design and hydrogen-bond-directed assembly of ternary supermolecules. *Angew. Chem., Int. Ed.* **2001**, *40*, 3240−3242.

10.1021/mp0700054 CCC: $37.00
Published on Web 05/12/2007

Scheme 1. Schematic Representations of a) Theophylline, (b) Caffeine, and (c) Citric Acid



attractive as pharmaceutical solids, providing a method of achieving new solid forms of active pharmaceutical ingredients (APIs) with tailored properties (e.g., enhanced dissolution rates, thermal stability, or mechanical properties).[7,8] In that context, we have recently demonstrated that cocrystal formation can enhance the hydration stability of the model APIs theophylline[9] and caffeine (Scheme 1a,b).[10] While our previous studies encountered pharmaceutical cocrystals[11] that either were stable toward different relative humidity conditions or decomposed into hydrated components,[10] we now wish to address the specific issue of cocrystals that contain water as a part of the cocrystal structure. Such cocrystal hydrates[12] are interesting for at least two reasons. First, they might be resistant upon exposure to high relative humidity levels. Second, the formation of such a cocrystal hydrate upon storage is an attractive alternative to the decomposition of an anhydrous cocrystal to its components under conditions of high relative humidity.

In order to screen for possible cocrystal hydrate formation we have turned to mechanochemical methods of neat[13−15] and liquid-assisted grinding.[16,17] These two methods have already been proven significantly more efficient than conventional crystallization from solution for screening and synthesis of cocrystals and cocrystal inclusion compounds.[17] In particular, we suggest that the two methods can provide alternative paths to cocrystal hydrate synthesis. In the case of liquid-assisted grinding, the water can be introduced to the reaction as a liquid phase. In the case of neat grinding, water can be introduced by using hydrated forms of the cocrystal components as solid reactants. Consequently, it was important for the purpose of our study to select cocrystal components that can independently form hydrates. For that reason, we have selected caffeine and theophylline as suitable target molecules for cocrystallization (Scheme 1a,b). Theophylline and caffeine form a stoichiometric and a nonstoichiometric hydrate, respectively, and have previously been used as model APIs in cocrystal formation. We decided to explore citric acid[18] as the cocrystal former in our hydrate formation studies, since it forms a stable monohydrate at room temperature.[19,20] In addition, citric acid is an attractive pharmaceutical cocrystal former due to physiological acceptability and the presence of four hydrogen bond donor sites.[21] In principle, each site could be utilized to form a hydrogen bond to a different API molecule. Citric acid might therefore be more efficient than cocrystal formers with fewer hydrogen-bonding sites (e.g., acetic acid, oxalic acid) to organize multiple API molecules and provide a high API-to-cocrystal former ratio.[22,23] We now reveal the results of neat and liquid-assisted grinding experiments that suggest

(7) McNamara, D. P.; Childs, S. L.; Giordano, J.; Iarriccio, A.; Cassidy, J.; Shet, M. S.; Mannion, R.; O'Donnel, E.; Park, A. Use of a Glutaric Acid Cocrystal to Improve Oral Bioavailability of a Low Solubility API. *Pharm. Res.* **2006**, *23*, 1888−1897.

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

(9) Trask, A. V.; Motherwell, W. D. S.; Jones, W. Physical stability enhancement of theophylline via cocrystallization. *Int. J. Pharm.* **2006**, *320*, 114−123.

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

(11) Vishweshwar, P.; McMahon, J. A.; Bis, J. A.; Zaworotko, M. J. Pharmaceutical co-crystals. *J. Pharm. Sci.* **2006**, *95*, 499−516.

(12) Shaameri, Z.; Jones, W. Molecular complexes between 2,2′-biphenyldicarboxylic acid and phenazine: anhydrous and hydrated forms. *Mol. Cryst. Liq. Cryst.* **2001**, *356*, 131−142.

(13) Trask, A. V.; Jones, W. Crystal engineering of organic cocrystals by the solid-state grinding approach. *Top. Curr. Chem.* **2005**, *254*, 41−70.

(14) Batchelor, E.; Klinowski, J.; Jones, W. Crystal engineering using co-crystallisation of phenazine with dicarboxylic acids. *J. Mater. Chem.* **2000**, *10*, 839−848.

(15) Jayasankar, A.; Somwangthanaroj, A.; Shao, Z. J.; Rodriguez-Hornedo, N. Cocrystal Formation during Cogrinding and Storage is Mediated by Amorphous Phase. *Pharm. Res.* **2006**, *23*, 2381−2392.

(16) Friščić, T.; Fábián, L.; Burley, J. C.; Jones, W.; Motherwell, W. D. S. Exploring cocrystal-cocrystal reactivity via liquid-assisted grinding: assembling of racemic and dismantling of enantiomeric cocrystals. *Chem. Commun.* **2006**, 5009−5011.

(17) Friščić;, T.; Trask, A. V.; Jones, W.; Motherwell, W. D. S. Screening for Inclusion Compeounds and Systematic Construction of Three-Component Solids by Liquid-Assisted Grinding. *Angew. Chem., Int. Ed.* **2006**, *45*, 7546−7550.

(18) A search of the 2006 Cambridge Structural Database (version 5.27) for structures of organic compounds of citric acid revealed three structures, CCDC reference codes: CITARC, CITRAC10, XOBHIF.

(19) Melia, T. P. Dissociation pressures of citric acid monohydrate. *Trans. Faraday Soc.* **1964**, *60*, 1286−1288.

(20) Chappel, F. P.; Hoare, F. E. Heat of combustion of citric acid monohydrate. *Trans. Faraday Soc.* **1958**, *54*, 367−371.

(21) The cocrystal of caffeine and citric acid is probably the "caffeine citrate" used in treatment of apnea: Bhatia, J. Current options in the management of apnea of prematurity. *Clin. Pediatr.* **2000**, *39*, 327−336.

(22) Shan, N.; Jones, W. Identification of supramolecular templates: design of solid-state photoreactivity using structural similarity. *Tetrahedron Lett.* **2003**, *44*, 3687−3689.

(23) Shan, N.; Bond, A. D.; Jones, W. Crystal engineering using 4,4′-bipyridyl with di- and tricarboxylic acids. *Cryst. Eng.* **2002**, *5*, 9−24.

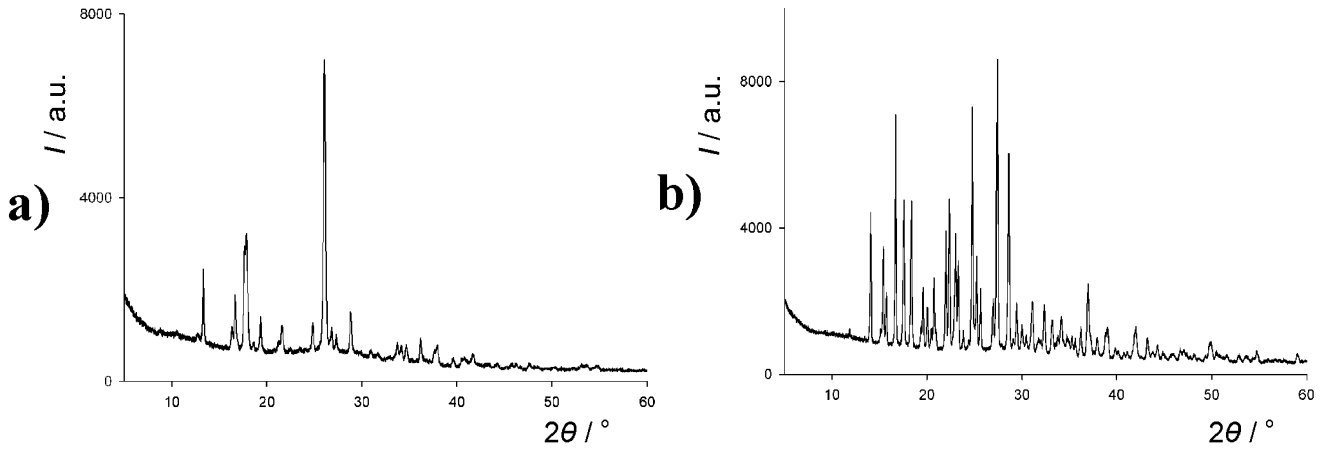


Figure 1. X-ray powder diffraction patterns of theophylline products: (a) **1** and (b) **2**.

that theophylline can form an anhydrous cocrystal (**1**), as well as a cocrystal hydrate (**2**) with citric acid. In contrast, experiments involving caffeine yielded only an anhydrous cocrystal (**3**). In addition, hydrates of caffeine, theophylline, and citric acid have readily been synthesized, in a quantitative fashion, by liquid-assisted grinding of the anhydrous compound with water.[24]

Experimental Section

Anhydrous theophylline, caffeine (β-form), and citric acid were commercially available from Sigma-Aldrich Chemical Co. and used without purification. Neat grinding experiments were performed by placing 0.150 g of solid mixtures of an equimolar combination of the model API (theophylline, theophylline hydrate, caffeine, or caffeine hydrate) with the pharmaceutical cocrystal former (citric acid or citric acid monohydrate) into a 25 mL stainless steel grinding jar. The mixture was then ground in a Retsch MM200 mixer mill for 20 min (1 h in the case of anhydrous theophylline and citric acid mixture), using two stainless steel grinding balls 7 mm in diameter. Measuring the temperature of the grinding jar contents immediately after grinding revealed that the overall temperature of the reaction mixture remained below 35 °C. Liquid-assisted grinding experiments were performed in a similar manner, but with the addition of two drops of water to the mixture in the grinding jar before grinding.

Caffeine and theophylline hydrates were synthesized from solution following previously described procedures.[25,26] The two hydrates were also quantitatively synthesized by liquid-assisted grinding of anhydrous reactants in the presence of water. Citric acid hydrate was obtained by crystallizing commercial anhydrous citric acid from water, as well as by grinding of the anhydrous acid with water.

Single crystals of the hydrate of the cocrystal of citric acid and theophylline were serendipitously obtained by slow evaporation (1 week) of a solution of theophylline (0.18 g) and citric acid (0.19 g) in a 1:1 (v/v) mixture of methanol and acetonitrile (5 mL) at ambient conditions. Single crystals of the anhydrous cocrystal of citric acid and caffeine were obtained by slow cooling and evaporation of a solution of a 1:1 mixture of caffeine and citric acid (0.40 g) in a 1:1 (v/v) mixture of methanol and nitromethane (2 mL).

X-ray powder diffraction patterns were recorded on a Philips X'Pert Pro diffractometer equipped with an X'celerator RTMS detector, using Ni-filtered Cu Kα radiation. Single-crystal X-ray diffraction data were collected on a Nonius Kappa CCD diffractometer equipped with an Oxford Cryosystems cryostream, using Mo Kα radiation.

Different relative humidity experiments were performed by keeping prepared materials for 7 days in desiccators containing either phosphorus pentoxide or a saturated solution of either potassium carbonate, sodium chloride, or potassium sulfate, corresponding to relative humidity levels of 0%, 43%, 75%, and 98%, respectively. Changes to any of the samples were monitored by recording an X-ray XRPD pattern of each sample on the first, third, and seventh day of the experiment.

Results and Discussion

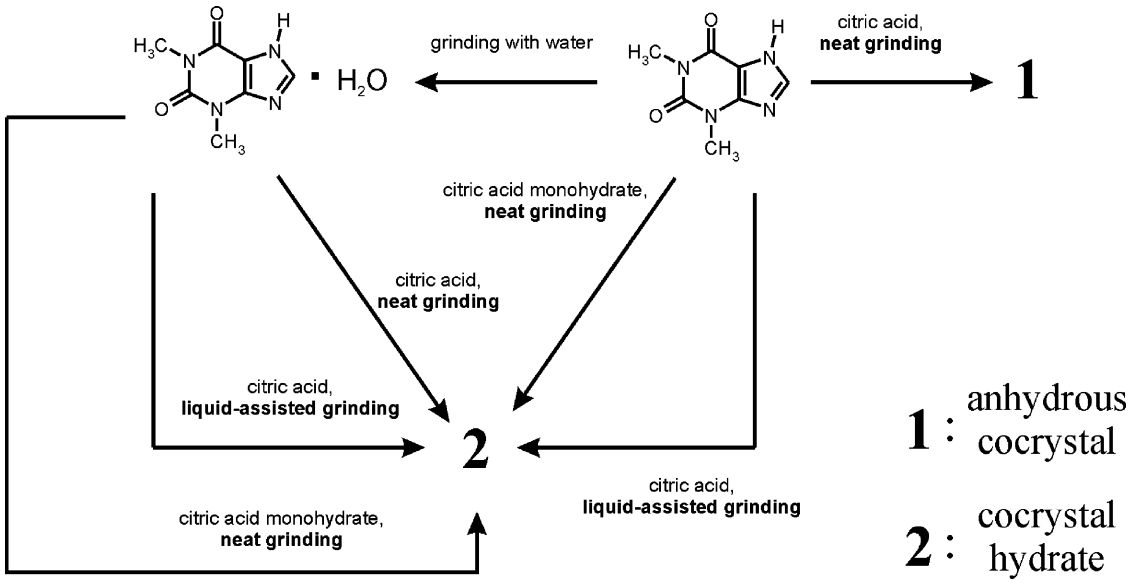
Theophylline as the Model API. The results of grinding experiments involving theophylline are depicted in Scheme 2. Neat grinding of anhydrous theophylline with citric acid provided a new crystalline solid, as evidenced by an X-ray powder diffraction (XRPD) pattern that did not contain any reflections belonging to the starting materials (Figure 1a). Exploration of different stoichiometric ratios of the two reactants during grinding suggests that the product is a cocrystal composed of theophylline and citric acid in a 1:1

(24) The mechanochemical formation of caffeine and theophylline hydrates has been previously reported during wet granulation of corresponding anhydrates: Jorgensen, A.; Rantanen, J.; Karjalainen, M.; Khriachtchev, L.; Raesaenen, E.; Yliruusi, J. Hydrate Formation During Wet Granulation Studied by Spectroscopic Methods and Multivariate Analysis. *Pharm. Res.* **2002**, *19*, 1285−1291.

(25) Edwards, H. G. M.; Lawson, E.; de Matas, M.; Shields, L.; York, P. Metamorphosis of caffeine hydrate and anhydrous caffeine. *J. Chem. Soc., Perkin Trans.* **1997**, *2*, 1985−1990.

(26) Sun, C.; Zhou, D.; Grant, D. J. W.; Young, V. G., Jr. Theophylline monohydrate. *Acta Crystallogr.* **2002**, *E58*, o368−o370. CCDC reference code: THEOPH01.

Scheme 2. Theophylline as the Model API[a]



[a] A summary of neat and liquid-assisted grinding experiments involving combinations of anhydrous and hydrated forms of theophylline and citric acid. All liquid-assisted grinding experiments were performed using water as the liquid phase.

stoichiometric ratio. All attempts to grow single crystals of the cocrystal have been unsuccessful so far, hindering the structural characterization of the material.

Using theophylline hydrate as a reactant instead of anhydrous theophylline resulted in an XRPD pattern different from that of **1** (Figure 1b). Furthermore, the new XRPD pattern coincided with the patterns of product obtained either via neat grinding of theophylline anhydrate with citric acid monohydrate or via liquid-assisted grinding of theophylline and citric acid in the presence of liquid water. The product was established to be cocrystal hydrate **2**, as evidenced by comparison of its XRPD pattern with the one simulated from the crystal structure of **2**. Crystal structure of **2** was determined using a single crystal serendipitously obtained by evaporation of a solution of theophylline and citric acid.

Crystal structure analysis revealed that the stoichiometric ratio of all three components in **2** is 1:1:1, with the asymmetric unit containing one molecule of each component (Figure 2). Within the cocrystal, the citric acid molecule adopts a conformation similar to that found in pure citric acid and citric acid hydrate.[27,28] In contrast to previously reported cocrystals of carboxylic acids and theophylline,[9] citric acid is not hydrogen bonded to the imidazole nitrogen atom of theophylline. Instead, theophylline and citric acid form a hydrogen bond of the O−H···O type (O8^{i}···O2 separation, 2.75 Å; symmetry operator *i*, $2 - x$, $y + {}^{1}/_{2}$, $-z - {}^{1}/_{2}$) and the nitrogen atom is bonded to a water molecule via an O−H···N hydrogen bond (O1W···N1 separation, 2.75 Å), similar to theophylline hydrate.[26] The water molecule is further hydrogen bonded to a citric acid molecule. The cocrystal structure may best be described in terms of consecutive layers of theophylline and layers of citric acid and water. Each layer of theophylline is made up of juxtaposed chains of theophylline molecules, held together by N−H···O (N2···O1^{ii} separation, 2.74 Å; symmetry operator *ii*, $1 - x$, ${}^{1}/_{2} + y$, $-{}^{3}/_{2} - z$) hydrogen bonds.

The layers of citric acid and water are composed of four-membered centrosymmetric rings held together by O−H···O hydrogen bonds. Each ring comprises two water molecules and two molecules of citric acid (Figure 3a). The rings arrange by way of O−H···O hydrogen bonds in a herringbone manner to provide layers parallel to the crystallographic *bc*-plane (Figure 3b). The structure of layers of citric acid and water in **2** is similar to the structure of citric acid monohydrate. Distorted, non-centrosymmetric rings of water and citric acid also appear in citric acid hydrate, arranged in a herringbone fashion (Figure 3c). In contrast to the rings in **2**, one water molecule in each ring acts as both a hydrogen bond donor and acceptor, whereas the second one is held in the ring by acting as a 2-fold hydrogen bond acceptor.

The layers of citric acid and water in **2** are connected to layers of theophylline through pairs of hydroxyl functionalities belonging to water and citric acid molecules (Figure 4). The two functionalities are 7.3 Å apart and belong to a sequence of two citric acid molecules and one water molecule, held by O−H···O hydrogen bonds. The sequence acts as a binding site for theophylline that attaches through an O−H···N and an O−H···O hydrogen bond (Figure 4a). A motif analogous to this theophylline binding site is also found in the crystal structure of citric acid monohydrate, but with a somewhat longer separation (7.6 Å) between corresponding hydroxyl groups (Figure 4b).

(27) Roelofsen, G.; Kanters, J. A. Citric acid monohydrate, $C_6H_8O_7 \cdot H_2O$. *Cryst. Struct. Commun.* **1972**, *1*, 23−6. CCDC reference code: CITARC.

(28) Glusker, J. P; Minkin, J. A.; Patterson, A. L. X-ray crystal analysis of the substrates of aconitase. IX. A refinement of the structure of anhydrous citric acid. *Acta Crystallogr.* **1969**, *B25*, 1066−1072. CCDC reference code: CITRAC10.

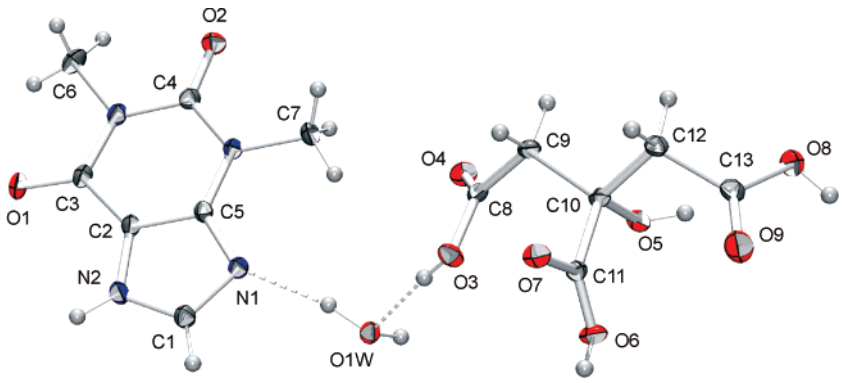


Figure 2. ORTEP representation of the asymmetric unit of **2**. Non-hydrogen atoms are shown as ellipsoids at the 50% probability level.

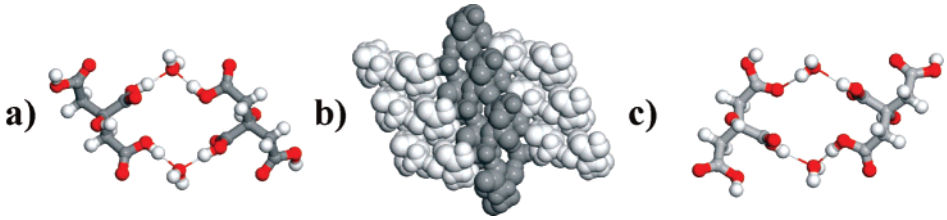


Figure 3. Representations of (a) the four-membered ring in **2**, (b) the herringbone arrangement of such rings in **2**, and (c) an analogous ring in citric acid monohydrate.

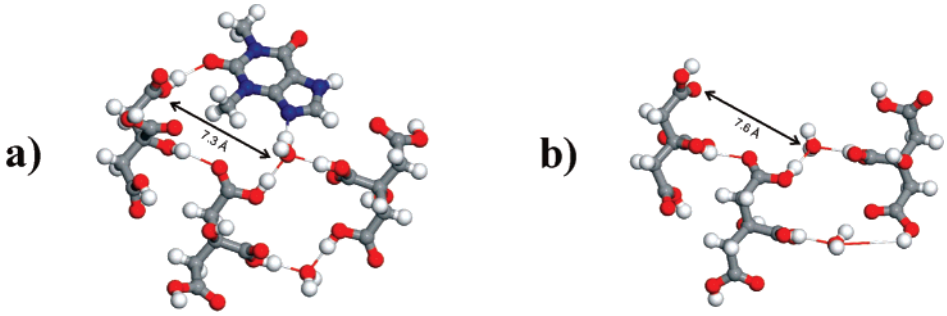


Figure 4. Representation of (a) the theophylline binding site in **2** and (b) an analogous site in citric acid monohydrate.

The similarity between the layers in **2** and citric acid monohydrate can be used to qualitatively explain the facile synthesis of the cocrystal hydrate via neat grinding. Namely, **2** is quantitatively obtained within 20 min in all grinding experiments that involved at least one hydrated reactant, whereas the quantitative formation of the anhydrous cocrystal using anhydrous reactants required an extended grinding time of 1 h. Structural similarity suggests the preservation of structural motifs of the reactant crystal upon formation of **2** from citric acid monohydrate or theophylline hydrate (or both). Presumably, the preservation of the motifs is beneficial for the formation of **2**, indicating that only a part of the hydrogen-bonded network of the reactant needs to be dismantled for cocrystallization. The breaking of O−H···O hydrogen bonds in that process is compensated by the formation of new O−H···O and O−H···N bonds in **2**. In addition, the presence of a structural motif common to **2** and the thermodynamically more stable form of citric acid (i.e., the monohydrate)[19,20] might also play a favorable role in steering the outcome of neat grinding toward the formation of **2**.

Caffeine as the Model API. Results of grinding experiments involving caffeine and citric acid are shown in Scheme 3. In contrast to theophylline, neat grinding of anhydrous caffeine with either citric acid or citric acid monohydrate provides only a solid mixture of the starting materials (Figure 5a).[29] However, neat grinding of caffeine hydrate with citric acid quantitatively provides a product (**3**) with an XRPD pattern that is different from those of the reactants (Figure 5b).

X-ray single-crystal diffraction on a single crystal grown from solution (Figure 6) established that **3** is an anhydrous 1:1 cocrystal of citric acid and caffeine. Remark-

(29) Inspection of PXRD patterns reveals that neat grinding of anhydrous caffeine (β-form) with citric acid resulted in a partial conversion to α-caffeine.

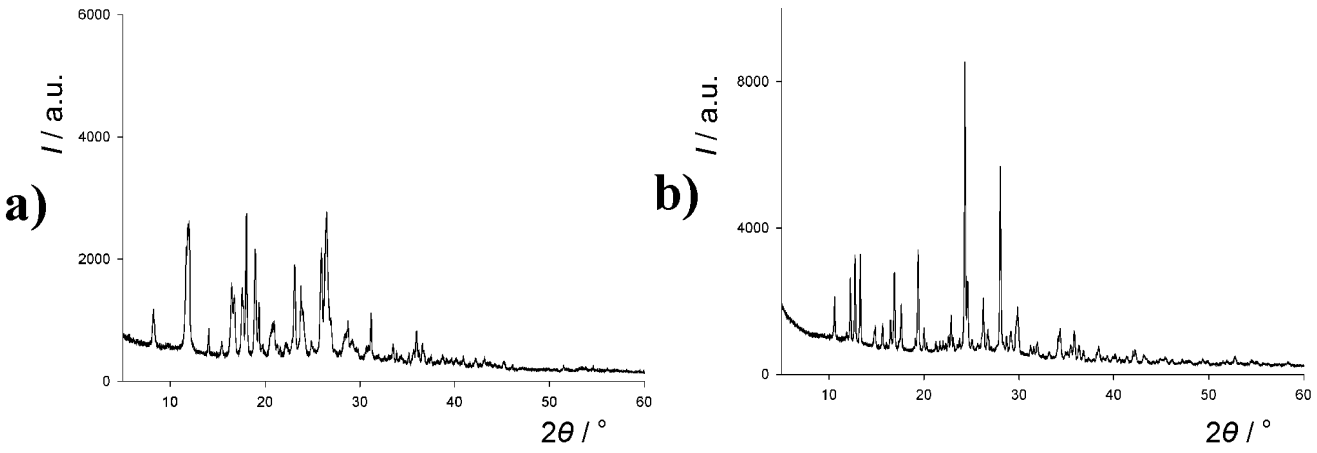
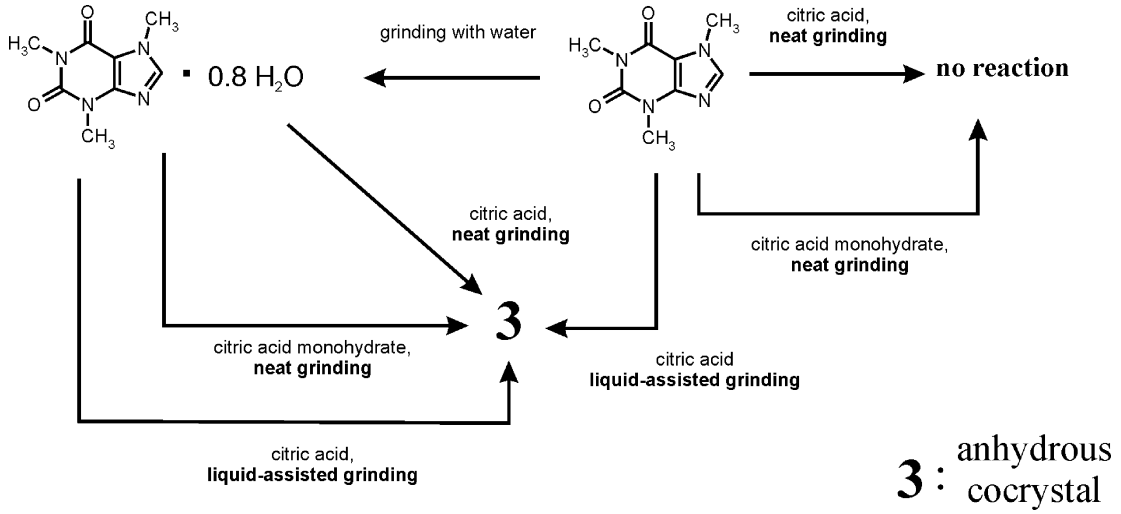


Figure 5. X-ray powder diffraction patterns of a product of neat grinding: (a) anhydrous caffeine and citric acid and (b) caffeine hydrate and citric acid.

Scheme 3. Caffeine as the Model API[a]



[a] A summary of neat and liquid-assisted grinding experiments involving combinations of anhydrous and hydrated forms of caffeine and citric acid. Liquid-assisted grinding experiments were performed using water as the liquid phase.

ably, **3** also formed quantitatively upon grinding together both hydrated reactants, as well as upon liquid-assisted grinding of caffeine and citric acid in the presence of liquid water. The results show that using caffeine hydrate instead of anhydrous caffeine enables cocrystallization upon neat grinding with both anhydrous citric acid and citric acid monohydrate. In the crystal structure of **3**, caffeine and citric acid form centrosymmetric four-membered rings. The rings are held together via O−H···N hydrogen bonds between the carboxylic acid groups of citric acid molecules and imidazole nitrogen atoms of caffeine, as well as O−H···O hydrogen bonds between the alcohol and keto functionalities of the acid and caffeine, respectively (Figure 7a). Citric acid assumes a conformation not previously observed in the solid, with two terminal carboxylic acid groups almost parallel (angle: 17.5°).[18] The rings assemble to form hydrogen-bonded layers in the crystallographic *bc*-plane. In particular, rings are linked in the crystallographic *b* direction by way of O−H···O hydrogen bonds between molecules of citric acid,

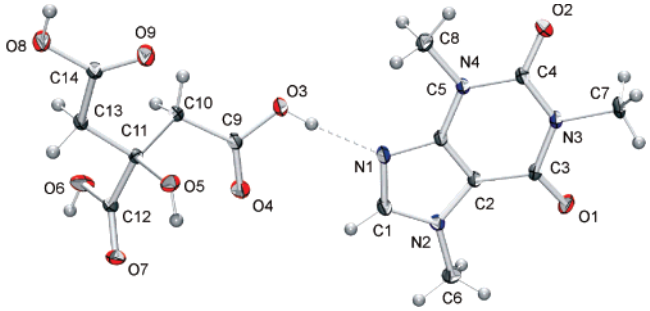


Figure 6. ORTEP representation of the asymmetric unit of **3**. Non-hydrogen atoms are shown as ellipsoids at the 50% probability level.

while the linking in the *c* direction is accomplished via O−H···O bonds involving citric acid and caffeine (Figure 7b).

Hydration Stability Experiments. Preliminary hydration stability experiments are summarized in Scheme 4. In contrast to previously studied cocrystals of theophylline and caffeine with carboxylic acids, the anhydrous cocrystal **1**

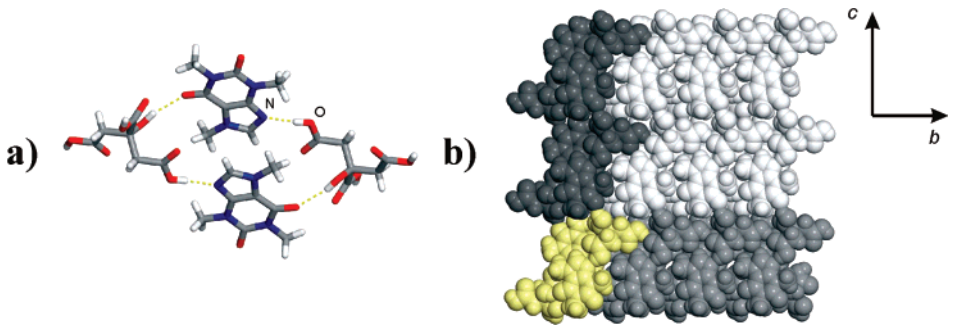


Figure 7. Representations of (a) the hydrogen-bonded ring and (b) the arrangement of the rings into layers in the cocrystal of caffeine with citric acid. For clarity, a single ring has been colored yellow and stacks of rings in crystallographic *b* and *c* directions are colored gray and black, respectively.

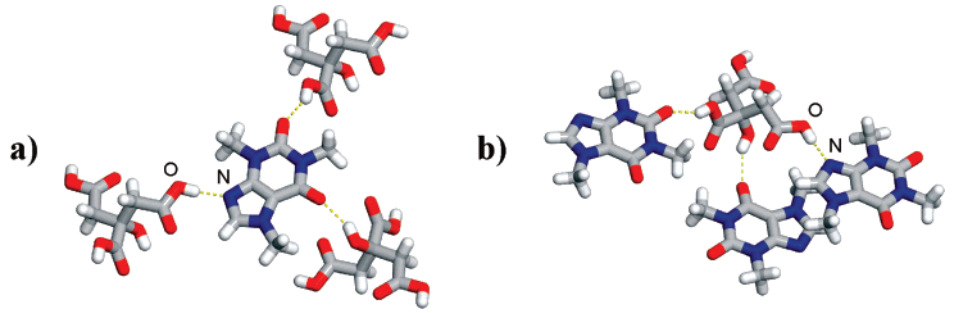
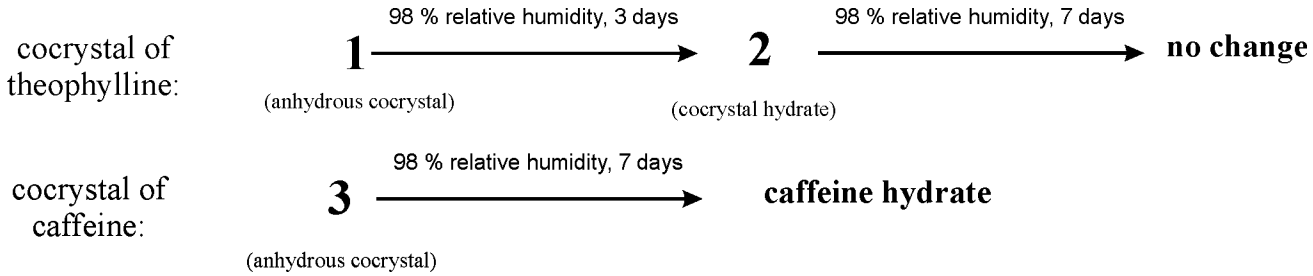


Figure 8. Two fragments of the structure of **3**, demonstrating (a) linking of a caffeine molecule with nearest-neighbor citric acid molecules and (b) linking of a citric acid molecule with nearest-neighbor caffeine molecules.

Scheme 4. A Summary of Hydration Stability Experiments Performed on **1**, **2**, and **3** over a Period of up to Seven Days



undergoes a transformation to the cocrystal hydrate upon exposure to high relative humidity levels, as evidenced by changes to the XRPD pattern of the sample. In contrast, the cocrystal **3** does not form a cocrystal hydrate, but decomposes to form caffeine hydrate upon exposure to 98% relative humidity conditions.[10,30]

The cocrystal hydrate **2** appears to be stable for at least one week upon exposure to four different relative humidity levels (0%, 43%, 75%, and 98%), demonstrating the potential of cocrystal hydrates to obtain pharmaceutical solids with improved hydration stability with respect to the parent API, as well as the parent cocrystal **1**.

Discussion

That all studied cocrystals and the hydrate of the theophylline cocrystal exhibit a 1:1 ratio of the cocrystal former to model API is somewhat surprising, having in mind that citric acid has four potential hydrogen bond donor sites. Comparison of the crystal structures reveals that the 1:1 stoichiometry is achieved in a different way in the cocrystal of caffeine than in the cocrystal hydrate involving theophylline. In the cocrystal with caffeine, each citric acid molecule forms three hydrogen bonds to three different caffeine molecules. However, caffeine unexpectedly acts as a 3-fold hydrogen bond acceptor via imidazole nitrogen atom and two keto functionalities, in that way forming hydrogen bonds with three different citric acid molecules (Figure 8).[31]

In the theophylline cocrystal hydrate, each molecule of theophylline participates in four hydrogen bonds: one to a citric acid molecule, one to a water molecule, and two to neighboring theophylline molecules. Citric acid acts as a

(30) Exposure of **3** to 98% relative humidity conditions results in the formation of a sticky solid. Inspection of the solid using XRPD reveals the presence of only solid caffeine hydrate, suggesting that citric acid is contained in the liquid phase.

(31) For the only previous example where caffeine acts as a 3-fold hydrogen bond acceptor toward OH donors, see: Martin, R.; Lilley, T. H.; Bailey, N. A.; Falshaw, C. P.; Haslam, E.; Magnolato, D.; Begley, M. J. Polyphenol-Caffeine Complexation. *Chem. Commun.* **1986**, 105−106. CCDC reference code: DIJWAU.

4-fold hydrogen bond donor, but forms only one hydrogen bond to theophylline. Consequently, unlike in case of the cocrystal of citric acid with caffeine, the 1:1 stoichiometric ratio of the model API to the pharmaceutical cocrystal former is a consequence of the predominance of hydrogen bonds between like molecules.

Concluding Remarks

We have demonstrated two strategies of screening for hydrates of two-component pharmaceutical cocrystals: (1) neat grinding using a hydrated form of a reactant and (2) liquid-assisted grinding using water as the liquid phase. Our results demonstrate that the use of hydrated rather than anhydrous reactants during cocrystallization via neat grinding can result in different outcomes, i.e., that a hydrated reactant can either enable the formation of an anhydrous cocrystal (as in the case of caffeine) or steer the reaction toward the formation of a cocrystal hydrate (as in case of theophylline).[32] The ability to form an anhydrous cocrystal by using hydrated reactants is particularly important for those APIs that are difficult to obtain in anhydrous form but readily form hydrates or for those instances where the hydrated form is preferred (e.g., because of cost). On the other hand, we also demonstrate that pharmaceutical cocrystal hydrates can offer improved hydration stability relative to the corresponding APIs and anhydrous cocrystals. Specifically, whereas theophylline undergoes a reversible transformation to theophylline hydrate on exposure to a relative humidity level higher than 60%, the cocrystal hydrate **2** exhibits stability in a range of relative humidities from 0% to 98%.[33] We rationalize the facile formation of the cocrystal hydrate involving theophylline by considering similarities between the solid-state structures of the reactants and the product. The results of liquid-assisted grinding experiments involving water as the liquid phase are independent of the form of reactant used in the experiment (i.e., hydrated or anhydrous form), suggesting that liquid-assisted grinding is more suitable as a method of screening for cocrystal hydrate formation than neat grinding. It would also seem to be a powerful method of screening for API hydrate formation. We believe that the study of grinding reactions involving hydrated reactants, as well as screening for cocrystal hydrates using liquid-assisted grinding, will help to assess the stability of pharmaceutical cocrystals toward hydration. We are currently pursuing the structural characterization of the anhydrous cocrystal of theophylline and citric acid from powder X-ray diffraction data, as well as further neat and liquid-assisted grinding experiments involving model APIs and pharmaceutical cocrystal formers that exist in hydrated and anhydrous forms (e.g., *meso*-tartaric acid).

Acknowledgment. We thank Dr. Neil Feeder and Dr. Pete Marshall for useful and fruitful discussions. We acknowledge the Pfizer Institute for Pharmaceutical Materials for funding. Dr. John E. Davies is gratefully acknowledged for providing single-crystal X-ray diffraction data.

Supporting Information Available: Powder X-ray diffraction patterns for all relevant materials, along with crystallographic information for **2** and **3** in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

MP0700054

(32) The formation of cocrystal hydrates by crystallization from solution has previously been observed; see: Zaitu, S.; Miwa, Y.; Taga, T. A 2:1 Molecular Complex of Theophylline and 5-Fluorouracil as the Monohydrate. *Acta Crystallogr.* **1995**, *C51*, 1857−1859. CCDC reference code: ZAYLOA

(33) 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.