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Preparation and Characterization of Theophylline−Nicotinamide Cocrystal

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Abstract:

Cocrystals have been increasingly recognized as an attractive alternative for solid forms of drug products. In this work, nicotinamide (NCT) was employed as a cocrystal former with the active pharmaceutical ingredient theophylline (TP). The theophylline−nicotinamide cocrystal (hereafter TP-NCT cocrystal) was prepared by solid-state grinding and slow evaporation from ethanol, and was characterized by differential scanning calorimetry (DSC), thermogravimetric analysis (TGA), hot-stage optical microscopy (HSM), Raman spectroscopy, and powder X-ray diffraction (PXRD) techniques. Pharmaceutically relevant properties such as powder dissolution rate, solubility and dynamic vapour sorption (DVS) of the TP-NCT cocrystal were evaluated. The results show that, the TP-NCT cocrystal, obtained in a 1:1 molar ratio of theophylline and nicotinamide, possesses unique thermal, spectroscopic, and X-ray diffraction properties. In addition, the solubility and hygroscopicity of the TP-NCT cocrystal were considerably higher than those of anhydrous theophylline.

1. Introduction

Active pharmaceutical ingredients (APIs) are frequently delivered to the patient in the solid state as part of such dosage forms as tablets, capsules, etc.[1] In this context the ability to deliver the drug to the patient in a safe, efficacious and cost-effective way depends largely on the physicochemical properties of the APIs in the solid state, and accordingly one of the challenging tasks in the pharmaceutical industry is to design pharmaceutical solid materials with specific physicochemical properties.[2] In the last years, the formation of pharmaceutical cocrystals has gained an increased interest as a means of optimizing the physicochemical properties of solid dosage forms.[3] Apart from potential improvements in solubility, dissolution rate, bioavailability and physical stability, pharmaceutical cocrystals frequently enhance other essential properties of the APIs such as hygroscopicity, chemical stability, compressability and flowability.

To date, there is a considerable debate as to what actually constitutes a "cocrystal".[4−9] Generally cocrystals are defined as crystalline materials that contain two or more components that are solid at room temperature held together by noncovalent forces such as hydrogen bonding, π-stacking, van der Waals forces, etc.[10,11] Thus the main difference between cocrystals and salts is that in salts a proton is transferred from the acidic to the basic functionality of the constituent free base molecule, or vice versa if applicable, whereas in cocrystals no such transfer occurs.[12] Although salts and cocrystals may be distinguished by whether proton transfer takes place, it can be argued that rather than a distinct difference between them, there is in fact a scale which progresses from strong ionized salts, to weak salts and through to hydrogen bonding structures.[13] On the other hand, the primary difference between cocrystals and solvates/hydrates is the physical state of the isolated pure components: if one component is a liquid at room temperature, the crystals are designated as solvates/hydrates; if both components are solids at room temperature, the crystals are designated as cocrystals.[14] Although cocrystals were discovered in the 19th century, the pharmaceutical industry has only recently developed an interest in their potential applications. The utility of the cocrystal formers in pharmaceutical products is limited by their pharmacological and toxicological properties.[15−17] Nevertheless, formation of cocrystals of an API with excipient, a different drug molecule, or a solubilizing agent, provides the opportunity to design delivery systems at the molecular level and to enhance their pharmaceutical properties.[18−22]

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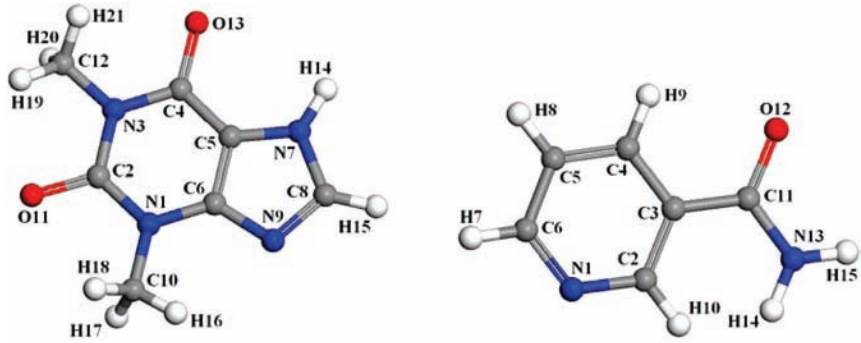
Scheme 1. **Molecular structures of (a) theophylline and (b) nicotinamide**



Cocrystals can be prepared through evaporation[23] or cooling[24] of a heteromeric solution, cogrinding the components,[25] sublimation,[26] growth from the melt[27] or slurry.[28,29] Solution crystallization is the preferred method for cocrystal's formation, particularly to obtain single crystals for structure analysis.[30,31] However, precipitation of the individual components instead of the desired cocrystal and formation of undesired solvates/hydrates frequently take place in the solution-based approach.[32] Recently, more and more cocrystals have been constructed by the neat grinding of two (or more) components together with a mortar and pestle or in a mixer mill, which has been termed "solid-state grinding".[33,34] In addition to its 'green' nature in which it avoids excessive use of organic solvent, solid-state grinding also provides a means of obtaining nearly quantitative yields with a common particle size.[35] A significant enhancement to solid-state grinding is popularly known as solvent-drop grinding, liquid-assisted grinding or kneading,[36] whereby the cocrystallization kinetics may be notably enhanced by the addition of a few drops of solvent. Despite its simplicity, a major drawback of the grinding method is that the product solid is usually too small in particle size for single-crystal X-ray diffraction to determine the structure.[32]

Theophylline. is often used in the treatment of asthma or chronic obstructive pulmonary disease (COPD).[37] Theophylline belongs to xanthine derivates and is both weakly acidic and weakly basic, with corresponding pK_a and pK_b values of 8.6 and 11.5, respectively.[38] Theophylline is apt to hydrate, which gives formulators a challenge of avoiding the interconversion between crystalline anhydrate and monohydrate forms under common processing conditions. Theophylline is known to have good potential for cocrystal formation due to the presence of O−H and N−H sites in the molecule (Scheme 1a). Thus, formation of a hydrogen bond with guest molecules is a means of modifying the physicochemical properties of theophylline.[39]

In this study nicotinamide was employed as a cocrystal former with theophylline. Nicotinamide (Scheme 1b, pK_a = 3.4) was chosen as it is the amide of niacin, one of the vitamin B family (B3), and has been used extensively for human consumption and is largely considered to be safe.[40] Besides, nicotinamide has been reported to have six polymorphs, of which only the stable form (form 1) can be obtained from solution, and the other metastable forms are obtained by supercooling of the melt or by sublimation.[4,41]

A number of theophylline cocrystals and salts have been reported to date,[8,39] but a systematic synthesis and characterization of theophylline−nicotinamide (TP-NCT) cocrystal has not, to our knowledge, been reported. This report describes the synthesis of TP-NCT cocrystal by solid-state grinding and slow

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evaporation. The physical state of TP-NCT cocrystal was characterized by powder X-ray diffraction (PXRD), differential scanning calorimetry (DSC), thermogravimetric analysis (TGA), hot-stage optical microscopy (HSM), and Raman spectroscopy. Pharmaceutical characterizations of TP-NCT cocrystal included powder dissolution rate studies and DVS measurements.

2. Experimental Section

2.1. Materials. Theophylline and nicotinamide were purchased from Sigma-Aldrich (Milwaukee, WI, U.S.A.). The purity of these chemicals was >99%. All solvents with HPLC grade were also sourced from Sigma-Aldrich and were used without further purification.

2.2. Cocrystallization via Neat Grinding. Equal stoichiometric amounts of theophylline and nicotinamide were mixed and ground with a mortar and pestle. After various grinding times the resulting powders were analyzed by Raman spectroscopy, powder X-ray diffraction, and DSC.

2.3. Cocrystallization via Slow Evaporation. A 1:1 molar ratio mixture of theophylline (54.05 mg, 0.3 mmol) and nicotinamide (36.64 mg, 0.3 mmol) was dissolved in 40 mL of ethanol with slight warming until dissolution was practically complete. The filtered solution was then allowed to slowly evaporate in a fume hood at room temperature.

2.4. Powder X-ray Diffraction (PXRD). PXRD was conducted by a MiniFlex II benchtop X-ray diffractometer at 30 kV and 15 mA with a Ni-filtered Cu Kα radiation source (λ = 1.54 Å) (Rigaku, The Woodlands, TX, U.S.A.). The samples were scanned from 5° to 35° (2θ) at a scanning rate of 0.5° per min. The diffractograms were processed using JADE 7.0 software (Materials Data, Livermore, CA, U.S.A.).

2.5. Raman Spectroscopy. Raman spectra were collected using a RamanRXN System (Kaiser Optical Systems, Ann Arbor, MI, U.S.A.) equipped with a diode laser (784.8 nm) and a fiber optic probe. Calibration was performed using a silicon standard.

2.6. Differential Scanning Calorimetry (DSC). DSC was conducted by use of a Mettler-Toledo DSC-822[e] differential scanning calorimeter (Mettler-Toledo, Columbus, OH, U.S.A.). Indium was used for calibration. Accurately weighed samples (5−10 mg) were placed in hermetically sealed aluminum pans and scanned from 25 to 300 °C at 3 °C/min under nitrogen purge.

2.7. Thermogravimetric Analysis (TGA). TGA was performed on a Mettler-Toledo TGA/SDTA 851[e] instrument. Approximately 2 mg sample was heated from 25 to 450 °C at 10 °C/min under nitrogen purge.

2.8. Polarized Hot-Stage Optical Microscopy (HSM). HSM analysis was carried out with a Linkam THMS 600 hot-stage (Linkam, Tadworth, UK) and an Axioskop 40 microscope with polarizer (Carl Zeiss, Oberkochen, Germany) with an attached CCD video camera (Qimaging, Surrey, BC). The crystals of theophylline and nicotinamide were heated together to 200 °C at 2 °C/min.

2.9. Powder Dissolution Rate Experiments. For powder dissolution rate studies the starting solids were first sieved using Gilson mesh sieves (Gilson, Worthington, OH, U.S.A.) to provide samples with approximate particle size ranges of 212−300 μm. A 100-mL jacketed glass crystallizer containing 50 mL of water was controlled at 25 ± 0.1 °C by a RTE-740 Digital Plus refrigerated bath (Thermo Neslab, Newington, NH, U.S.A.). The Teflon-coated magnetic stirring bar ensured proper mixing in the crystallizer. Then the sieved powders of theophylline material or TP-NCT cocrystal were added to the crystallizer, and the excess solids were kept in the solutions. At each time interval an aliquot of the slurry was withdrawn from the crystallizer and filtered through a 0.2 μm nylon filter. A 0.20 mL portion of the filtered aliquot was diluted to 100 mL with water. The concentration of the diluted portion was determined spectroscopically by measuring absorbance at 272 nm with a Cary 100 Bio UV−visible spectrophotometer with WinUV Bio software (Varian, Palo Alto, CA, U.S.A.). The extinction coefficients of theophylline and TP-NCT cocrystal were obtained through calibration experiments as 1.0323×10^4 and 1.1936×10^4 M^{-1} cm^{-1}, respectively. Calibration curve was determined in pure water. After the last aliquot was collected, the remaining solids were collected by vacuum filtration, vacuum-dried, and analyzed by DSC, TGA, and PXRD. The powder dissolution experiments were conducted by a single run for each crystal form.

2.10. Moisture Sorption and Desorption. Dynamic gravimetric vapor sorption (DVS) is a well-established method for the measurements of vapor sorption and desorption. The DVS Advantage instrument (Surface Measurement Systems, London, UK) was employed to investigate the hygroscopicity of theophylline, nicotinamide, and TP-NCT cocrystal by measuring the uptake and loss of vapor gravimetrically using a Cahn D-200 ultrasensitive recording microbalance (Thermo Fisher, Waltham, MA, U.S.A.) with a mass resolution of ±0.1 μg. The required relative humidity (RH) levels were generated by mixing dry and saturated vapor gas flows in the correct proportions using a 1179A flow controllers (MKS Instruments, Cheshire, UK). The temperature was maintained constant at 25 ± 0.1 °C. For each sample, about 100 mg was loaded onto a quartz DVS round-bottom sample pan and pre-equilibrated at 0% RH (±0.4%) in a continuous flow of dry nitrogen. The relative humidity was then increased to 90% in a 10% increment per step. The equilibration criterion dm/dt (change in mass as a function of time) was set at 0.0002%/min for all steps. After each experiment, the data were exported to Microsoft Excel using a DVS Macro.

3. Results and Discussion

3.1. Cocrystal Characterization. The PXRD diffractograms of the products of cogrinding after various grinding time t are shown in Figure 1. As the cogrinding proceeded, the intensity of the characteristic peak of theophylline at 12.7° was decreased; meanwhile the intensity of a new peak at 13.4° was increased. Furthermore, when the final ground powders were recrystallized from ethanol, the product also had a strong peak at 13.4°, which indicated that a new phase was formed during the neat grinding of theophylline and nicotinamide. The PXRD diffractograms of the mixture of theophylline and nicotinamide recrystallized from ethanol, respectively, and of the product from cocrystallization via slow evaporation from ethanol, are compared in Figure 2. The nicotinamide has a characteristic

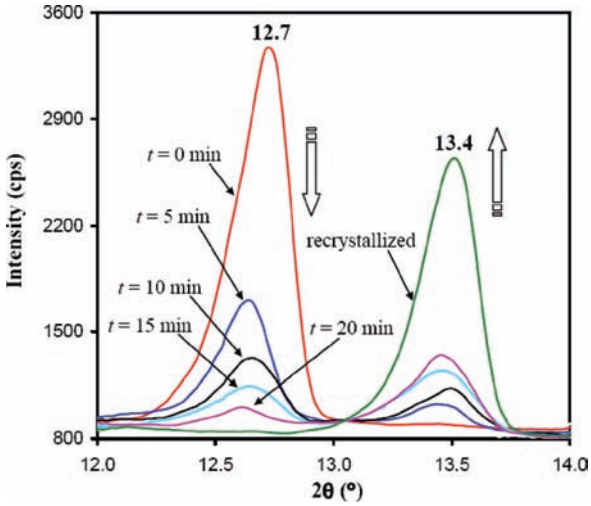

Figure 1. **Variation in intensities of the peaks 12.7° and 13.4° as cogrinding of theophylline and nicotinamide proceeded.**

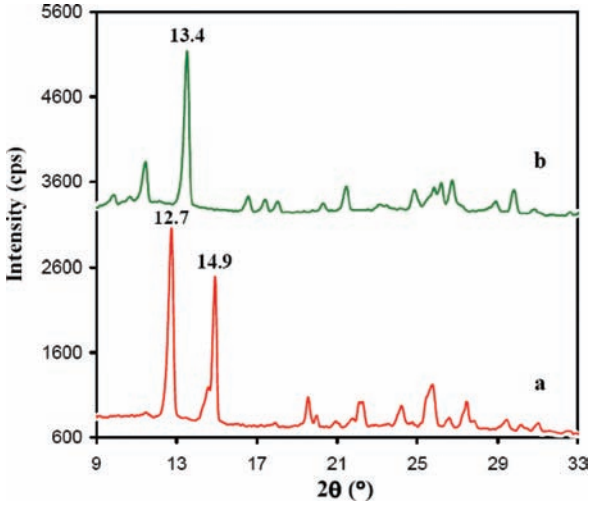

Figure 2. **Powder X-ray diffraction patterns for (a) the mixture of recrystallized theophylline and recrystallized nicotinamide; (b) product of cocrystallization via slow evaporation.**

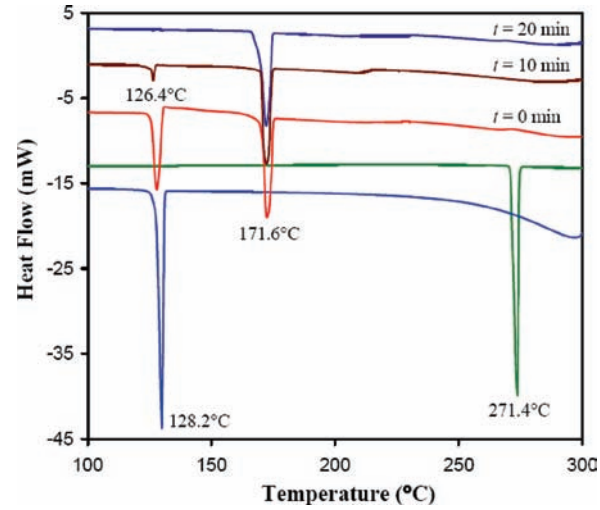

Figure 3. **DSC analyses of the resulting powders after various grinding time.**

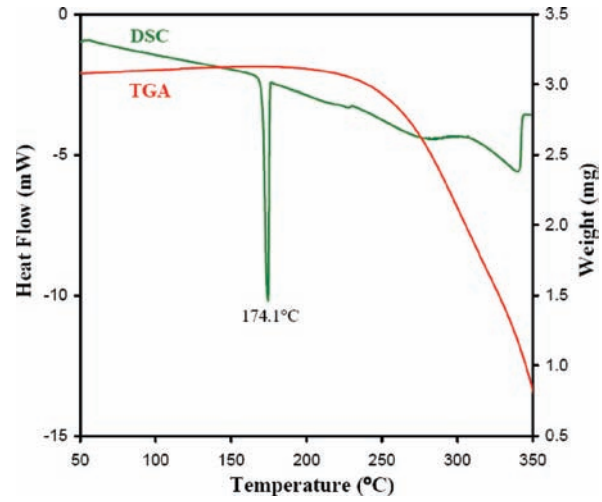

Figure 4. **DSC and TGA curves of the cocrystallization product from slow evaporation.**

diffraction peak at 14.9°, which does not appear in the PXRD diffractogram of the product of cocrystallization via slow evaporation.

DSC analyses for the resulting powders after various grinding time are shown in Figure 3. As the cogrinding of theophylline and nicotinamide proceeded, the endothermal peak at about 126.4 °C decreased and finally disappeared. A melting endotherm at 171.6 °C, which differs from the melting points of either theophylline (271.4 °C) or nicotinamide (128.2 °C), occurred all the time. This also indicated that a new phase was formed between theophylline and nicotinamide during the solid-state grinding. The DSC and TGA of the cocrystallization product from slow evaporation are presented in Figure 4. The new molecular complex has a melting point at 174.1 °C and a heat of fusion of 37.1 kJ/mol. The difference in the melting points of the products from cogrinding and slow evaporation is due to different purity of samples.

The cocrystallization of theophylline and nicotinamide was also observed under polarized HSM, and the results are presented in Figure 5. The results show that the nicotinamide was first melted and a new crystal nucleated and epitaxially grew at higher temperatures. When the temperature was further increased, the TP-NCT crystal melted, which is consistent with the results of DSC analysis (Figure 3, $t = 0$ min).

As the X-ray single crystal structure is not yet available for the new solid form produced by the cocrystallization of theophylline and nicotinamide, Raman spectroscopic data were utilized to evaluate whether the complex is of a cocrystal or in the ionization state. Theophylline contains two carbonyl groups and a secondary amine. Its anhydrous crystal exhibits Raman bands at 1664 cm^{-1}, 1706 cm^{-1} (carbonyl groups), and 3123 cm^{-1} (secondary amine). When a salt is formed with amine bases, the carbonyl bands are shifted to lower frequencies by 30 to 40 cm^{-1}.[42] In addition, the N−H stretching bands corresponding to the amine base are not observed in a salt; instead, the corresponding ammonium signals of the amine base are present. In theophylline cocrystals, the theophylline N−H and carbonyls are shifted due to hydrogen bonding, but the magnitude of the shift is relatively small.[43] The Raman spectra

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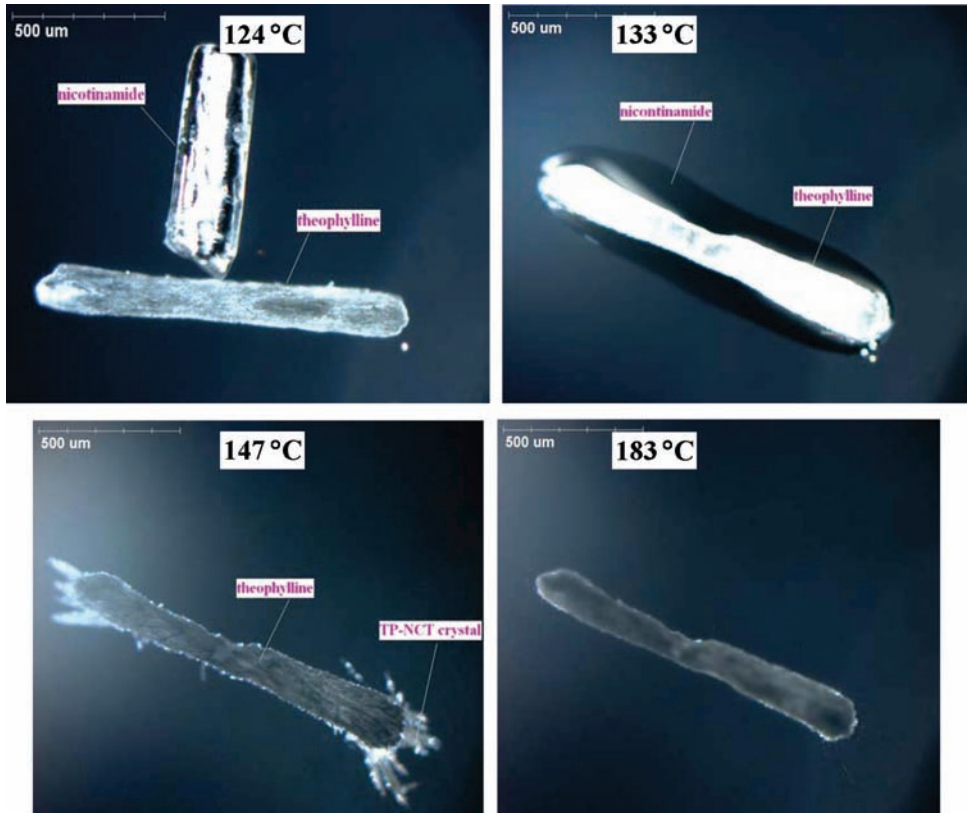

Figure 5. **Crystallization and melting behaviors of TP-NCT crystals observed under HSM.**

in the regions of 1640−1740 cm^{-1} and 3000−3300 cm^{-1} for nicotinamide, theophylline, and TP-NCT crystal are presented in Figure 6. The assignments for their most characteristic vibrational bands are listed in Tables 1 and 2.

As shown in Figure 6 and Table 1, during the formation of TP-NCT crystal the N7−H and C=O bands of theophylline are shifted to higher or lower frequencies by 8 to 23 cm^{-1}, which suggests that the molecular complex of theophylline and nicotinamide is a cocrystal.[8,46] On the other hand, if the amide carbonyl group of nicotinamide is involved in an intermolecular hydrogen bond, that peak is expected to shift to lower frequencies.[20,47] As shown in Table 2, the Raman spectrum for pure nicotinamide in the starting material has bands at 1677 cm^{-1} and 1092 cm^{-1}, corresponding to C=O stretching and NH_2 rocking, respectively. During the cocrystallization of nicotinamide with theophylline, these bands in the cocrystal were shifted to 1674 cm^{-1} and 1106 cm^{-1}, respectively. The decrease in the C=O stretching frequency of nicotinamide from 1677 cm^{-1} to 1674 cm^{-1} indicates that the amide carbonyl group is participating in a relatively weak hydrogen bonding. The increase in the NH_2 rock frequency from 1092 cm^{-1} to 1106 cm^{-1} suggests that amide amine group is involved in a strong hydrogen bonding. Moreover, a new band at 3214 cm^{-1}, which does not occur in either theophylline or nicotinamide (Figure 6b), appears in the TP-NCT cocrystal. The band at 3214 cm^{-1} in the TP -NCT cocrystal can be assigned to the N−H stretching in the strong hydrogen bonding between H15 in nicotinamide and N9 in theophylline (Figure 7). The exact heterosynthons and/or homosynthons in the TP-NCT cocrystal can be obtained through X-ray single crystal structural analysis which is currently underway in our laboratory.

3.2. Cocrystal Properties. *3.2.1. Powder Dissolution Rate.* Powder dissolution rate profiles for theophylline and TP-NCT cocrystal in water at 25 °C are shown in Figure 8. The peak concentration (0.056 M) for powdered theophylline was obtained after approx 8 min, whereas the maximum concentration (0.061 M) for TP-NCT powders appeared at about 7 min. At the same dissolution time, the concentration of TP-NCT in water was consistently higher than that of theophylline. For example, at 20 min the concentrations of theophylline and TP-NCT were about 0.034 and 0.052 M, respectively. The DSC, TGA, and PXRD analyses of the solid filtrates obtained from both powder dissolution experiments demonstrate both residues are anhydrous theophylline instead of its hydrate or cocrystal, which indicates that in water the TP-NCT cocrystal is unstable and will dissociate. As for the dissolution of TP-NCT in water, the complexation between theophylline and nicotinamide may cause the increase in theophylline solubility in solution. During the powder dissolution of pure theophylline in water, the concentration of theophylline first goes up and then comes down. This can be attributed to the recrystallization of theophylline. On the other hand, as to the system of theophylline and citric acid, Karki et al.[48] have found that theophylline and citric acid readily form a cocrystal hydrate (as long as water is present in the reaction mixture, either as lattice-bound hydrate water or in

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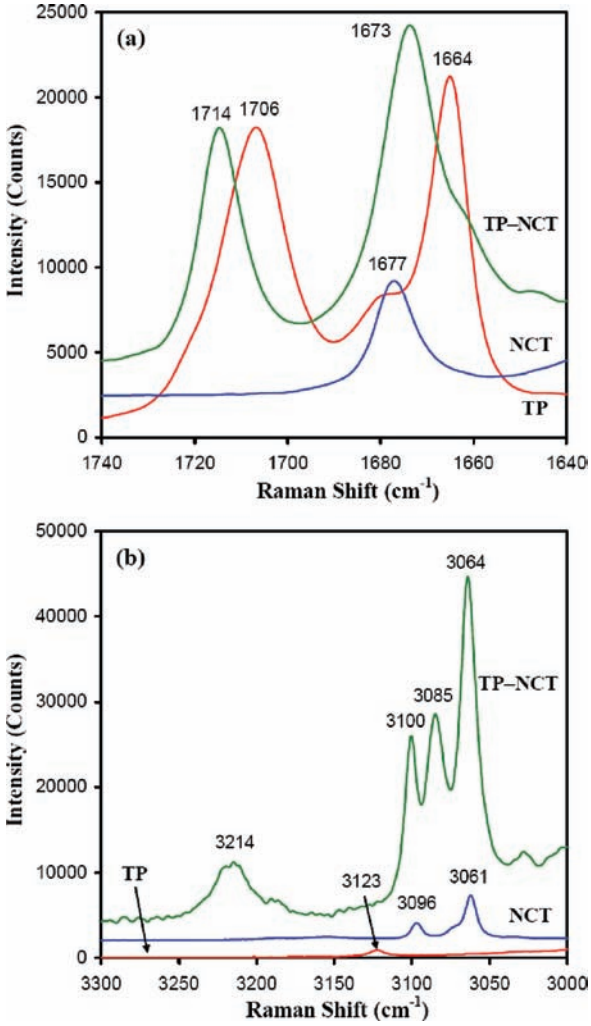

Figure 6. **Raman spectra in the regions of (a) 1640−1740 cm^{-1} and (b) 3000−3300 cm^{-1}.**

Table 1. **Assignment for the most characteristic vibrational bands of theophylline in starting material and TP-NCT[44]**

TP (cm^{-1})	TP-NCT (cm^{-1})	band assignment[a]
555	563	pyrimidine breathing
667	678	α (pyrimidine)
928	918	α (imidazole)
948	955	α (imidazole)
969	985	ρ (CH_3)
1052	1058	ν (N1−CH_3)
1084	1106	ν (N3−CH_3)
1247	1250	β (N7−H)
1425	1419	β (C8−H)
1610	1615	ν (C5−C6)
1664	1673	ν (C=O)
1706	1714	ν (C=O)
3123	3100	ν (N7−H)

[a] ν = stretching; β = in-plane deformation; α = in-plane ring deformation; ρ = CH_3 rocking.

liquid-assisted grinding), while caffeine and citric acid can only form an anhydrous cocrystal, even when water is present. They proposed that the preference of theophylline−citric acid to form cocrystal hydrate was because of the similarity between the crystal structures of the cocrystal hydrate and the reactant hydrates. On the basis of this theory, it is not surprising that the solid residues in the powder dissolution experiments were not hydrates, as the transformation from anhydrate to hydrate did not take place.[49]

Table 2. **Assignment for the most characteristic vibrational bands of nicotinamide (NCT) in starting material and TP-NCT[45]**

NCT (cm^{-1})	TP-NCT (cm^{-1})	band assignment[a]
788	788	δ (ring)
834	820	γ (C−H)
1042	1042	ν (ring)
1092	1106	$NH_{2\ rock}$
1123	1123	δ (C−H)
1160	1152	ν (ring)
1677	1673	ν (C=O)
3061	3064	ν (C−H)
3096	3085	ν (C−H)

[a] ν = stretching; δ = in-plane bending; γ = out-of-plane bending.

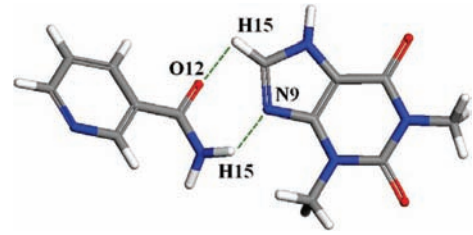

Figure 7. **Perspective view of an intermolecular hydrogen bond between theophylline and nicotinamide.**

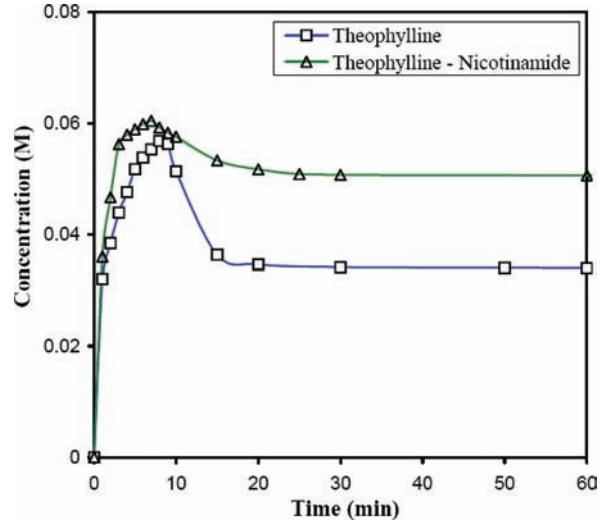

Figure 8. **Powder dissolution rate profiles for theophylline and TP-NCT cocrystal, respectively.**

3.2.2. DVS Studies. Dynamic vapour sorption and desorption isotherms for nicotinamide, theophylline, and their cocrystals are shown in Figures 9, 10, and 11. At all levels of relative humidity (RH), the percentages of sorbed water of TP-NCT cocrystal were consistently higher than those of theophylline or nicotinamide. For example, at 90% RH, the sorbed water by TP-NCT, NCT, and TP were about 0.24%, 0.20%, and 0.023%, respectively. These results indicate that the hygroscopicity of theophylline is remarkably increased when the cocrystal of TP-NCT is formed. Besides, the sorption−desorption

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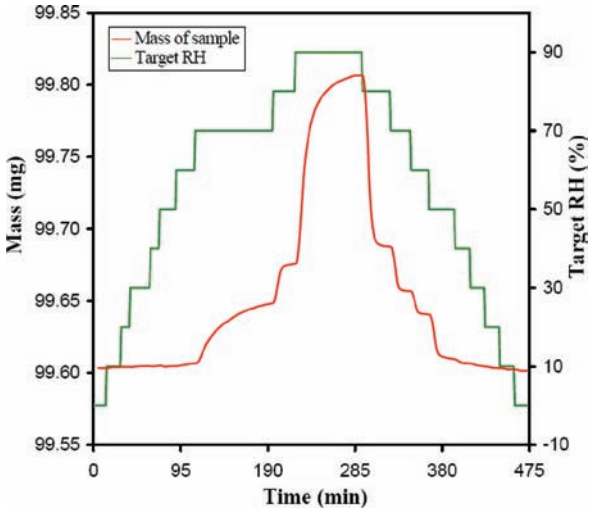

Figure 9. **Moisture sorption and desorption profiles for nicotinamide at 25 °C.**

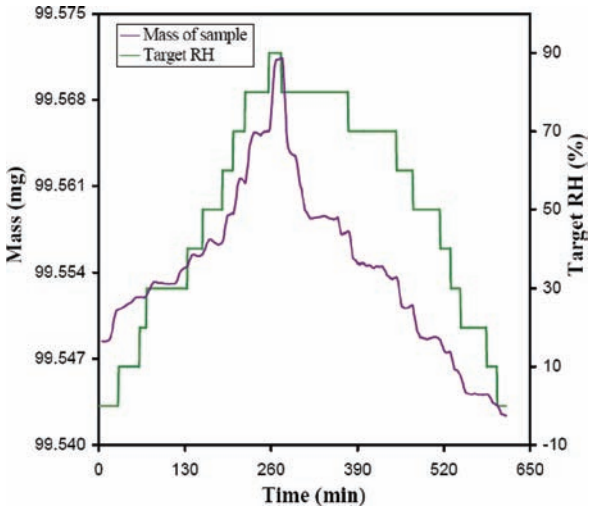

Figure 10. **Moisture sorption and desorption profiles for theophylline at 25 °C.**

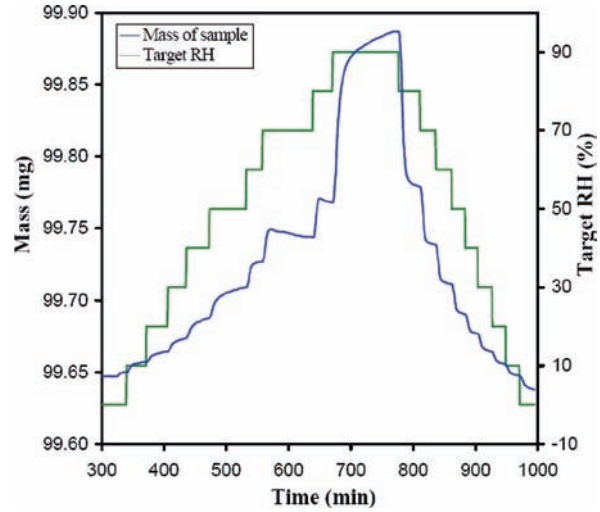

Figure 11. **Moisture sorption and desorption profiles for TP-NCT cocrystals at 25 °C.**

curves suggest that there is no solid-state transformation or dissociation of the cocrystal under the experimental conditions (Figure 11).

4. Conclusions

This study demonstrates that theophylline and nicotinamide can form a cocrystal in a 1:1 molar ratio during the solid-state grinding or slow evaporation from ethanol. Compared with anhydrous theophylline, the TP-NCT cocrystal is more soluble and has a higher hygroscopicity. When the TP-NCT cocrystal is dissolved in water, the increased concentration of theophylline can be attributed to the complexation between theophylline and nicotinamide. The growth of single crystal and in-depth structure analysis of TP-NCT cocrystal are presently being investigated in our laboratory.

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