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Article

Effects of polyvinylpyrrolidone and poly (ethylene glycol) on preparation of ibuprofen pharmaceutical cocrystal

Xintong Yang[1], Yang Chen[1], Ning Qiao[1,2]*

[1]College of Materials Science and Engineering, North China University of Science and Technology, Tangshan, China, [2]Tangshan Key Laboratory of Functional Polymer, Tangshan, China

In this study, we investigated the effects of polymers on the pharmaceutical cocrystal formation process. Ibuprofen (IBU) was selected as the active pharmaceutical ingredient (API), nicotinamide (NIC) and saccharin (SAC) as the cocrystal coformer (CCF), ethanol/water as the solvent, polyvinylpyrrolidone (PVP) and poly (ethylene glycol) (PEG) as the representative polymers. We prepared IBU-NIC and IBU-SAC cocrystals in ethanol-water cosolvent in the absence or presence of polymers. Cocrystal screening products were characterized by FTIR, DSC, PXRD, and HPLC. The results showed that the mixture of IBU and IBU-NIC cocrystal can be prepared in ethanol-water cosolvent without polymers. The addition of PVP facilitates the formation of pure IBU-NIC cocrystal; however, no cocrystal was formed in PEG solutions. SAC could not cocrystallize with IBU in the ethanol-water solvent in the absence of polymers. Neither PVP nor PEG could facilitate the formation of the IBU-SAC cocrystal.

Keywords: Pharmaceutical cocrystal. Cocrystal preparation. Polymer. Ibuprofen. Nicotinamide. Saccharin.

INTRODUCTION

A pharmaceutical cocrystal is composed of one active pharmaceutical ingredient (API) and one coformer. As a new class of solid drugs, a pharmaceutical cocrystal can improve the physicochemical properties of poorly water-soluble drugs (Aakeröy and Salmon, 2005; Shiraki et al., 2008; Qiao et al., 2011). Ibuprofen (IBU), with the chemical name (R/S)-2-(4-isobutylphenyl) propanoic acid (Figure 1), is a non-steroidal anti-inflammatory drug (NSAID) that is widely used for its anti-inflammatory, analgesic, and antipyretic properties in treating inflammation, pain, and fever(Chow et al., 2012). However, as a class II drug under the Biopharmaceutical Classification System (BCS), IBU shows high permeability but poor aqueous solubility which limits its bioavailability. To improve the solubility of IBU, the pharmaceutical cocrystal method was applied to prepare IBU cocrystals. The most studied IBU cocrystal was made with coformer nicotinamide (NIC, Figure 1) at a molar ratio of 1:1. Researchers have successfully synthesized IBU-NIC cocrystals using the solution method (Berry et al., 2008). However, the pure IBU-NIC cocrystal product cannot be easily obtained in single kinds of pure solvent because the two cocrystal components have nonequivalent solubility in the same solvent, which may result in the crystallization of a single reactant or a mixture of individual reactant and cocrystal (Qiao et al., 2011; Chow *et al*., 2012). Several approaches have been investigated to solve this problem, such as the reaction cocrystallization (RC) approach or using cosolvents (Rager and Hilfiker, 2010; Sun et al., 2015). The RC method is more difficult to operate and the solvent species and the volume ratio need to be identified and optimized by performing many experiments.

***Correspondence:** N. Qiao. College of Materials Science and Engineering. North China University of Science and Technology. No.21 BoHaiDaDao, Caofeidian, Tangshan 063210, PR China. Phone: 86 315 8805620. E-mail: qiaoning986@163.com. ORCID: 0000-0003-3422-0821

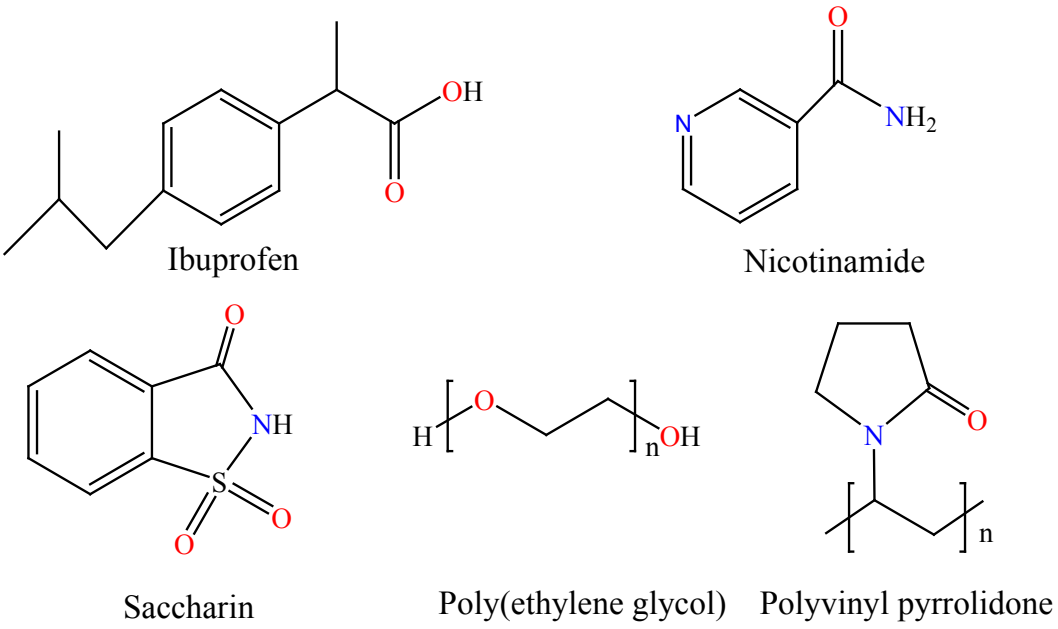


FIGURE 1 - Molecular structure of IBU, NIC, SAC, PVP, and PEG.

Surfactants or polymers can impart thermodynamic stability to cocrystals, and hence inhibit solution-mediated phase transformation (SMPT) of cocrystals. SMPT is caused by a rapid dissociation of the cocrystal to API and coformer in solution, and consequently, the precipitation of a single API solid is caused by supersaturation (Huang and Rodríguez-Hornedo, 2011; Li et al., 2013; Alhalaweh et al., 2014; Guo et al., 2016). Thus, cocrystal preparation via the solution method and cocrystal dissolution can be considered to be two directions of the complex process of API and coformer. Since polymers can impart stability to cocrystals during their dissolution by maintaining supersaturation of the cocrystal components, the polymer might have a positive role in cocrystal preparation. The addition of a proper polymer can help to obtain an equivalent concentration of two components, which is helpful for cocrystal formation with a 1:1 molecular ratio.

In this study, the effects of polymers on cocrystal formation were investigated. Polyvinylpyrrolidone and poly(ethylene glycol) (molecular structures shown in Figure 1) were selected as representative polymers. IBU was selected as the API; the IBU-NIC cocrystal formation process in solution was further investigated in the presence of polymers. Saccharin (SAC, Figure 1) is widely used in pharmaceutical cocrystal research; several pharmaceutical cocrystals have been developed using SAC as the coformer (Basavoju et al., 2008; Alhalaweh et al., 2012; Lee et al., 2015; Qiu and Li, 2015). SAC and NIC have similar structures, which contain an amide group and an aromatic ring; thus, it was also selected as the coformer in this study for cocrystallization with IBU. SAC can cocrystallize with IBU through the wet grinding method (Hashib et al., 2015); however, there is no reference regarding the successful formation of the IBU-SAC cocrystal through the solution method. In this study, we prepared IBU-NIC and IBU-SAC cocrystals in ethanol-water cosolvent in the absence or presence of polymers. The cocrystal screening products were characterized by FTIR, DSC, and PXRD. The solubility of the successfully prepared pure cocrystal products was determined by HPLC and compared to pure API. The effects of polymers on the IBU cocrystal formation process have been discussed.

MATERIAL AND METHODS

Material

Ibuprofen (IBU, ≥98% purity) was obtained from Jianglai Reagent Co., Ltd. (Shanghai, China) and dried

for 12 h at 40 °C before use. Nicotinamide (NIC, ≥99% purity) and saccharin (SAC, ≥98% purity) were obtained from Aladdin Industrial Co. (Shanghai, China) and used as received. Polyvinylpyrrolidone K30 (PVP), poly (ethylene glycol) (PEG, Mn = 1 kDa and PDI = 1.07), methanol (99.9% purity), and potassium dihydrogen phosphate (KH_2PO_4, ≥98% purity) were purchased from Tianjin Guangfu Fine Chemical Research Institute (Tianjin, China) and used as received. Ethanol from Yongda Chemical Reagent Co., Ltd. (Tianjin, China) was of analytical grade and used as received. Potassium bromide (KBr, ≥99% purity) purchased from Yongda Chemical Reagent Co., Ltd. (Tianjin, China) was dried for 24 h at 50 °C and finely ground immediately before use.

Preparation of IBU cocrystals

IBU–NIC cocrystals and IBU-SAC cocrystals were prepared using the solution method. A mixture of API (IBU) and CCF (NIC or SAC) with a 1:1 molar ratio, and 40 g of ethanol-water mixture with an ethanol-to-water ratio of 3:1 (v/v) were added in a crystallizer flask of 100 mL. The crystallizer flask was immersed in a thermostatic bath and mechanically stirred at 25 °C. After stirring for about 1 h, the mixture of API and CCF dissolved completely; a transparent solution was obtained. After incubation for 24 h at 20 °C, a solid sample precipitated at the bottom of the flask, which was collected by filtration and dried under vacuum.

To assess the effect of polymer on IBU cocrystal formation, the above experiment was repeated using the same ethanol-water cosolvent with a pre-dissolved polymer of 20 mg/mL PVP, 40 mg/mL PVP, 100 mg/mL PEG, and 200 mg/mL PEG, respectively.

The samples obtained in this section were characterized by FTIR, DSC, and PXRD to identify the formed cocrystals. The solubility of the cocrystals was determined by HPLC.

Fourier transform infrared spectroscopy (FTIR)

A Bruker VERTEX 70 FTIR spectrometer (Bruker Corporation, Germany) was used in the KBr diffuse reflectance mode (sample concentration: 2 mg in 20 mg KBr) for collecting the IR spectra of the samples. The settings used to record the data were as follows: resolution = 2 cm^{-1}, data range = 4000–400 cm^{-1}, and the number of runs per spectrum = 5.

Differential scanning calorimetry (DSC)

Thermal analyses of the samples were performed on a NETZSCH DSC 200F3 (NETZSCH group, Germany), which was calibrated for temperature and cell constants using indium (mp. =156.61 °C) and zinc (mp. = 419.53) °C. The samples (5–10 mg) were crimped in non-hermetic aluminum pans (NETZSCH, JYL0040 Φ 8 × 2.1 mm). The measurements were conducted at a heating rate of 10 °C/min in the range of 20 to 260 °C under a nitrogen flow rate of 20 mL/min.

Powder X-ray diffraction (PXRD)

The PXRD patterns were recorded using a Rigaku D/max 2500 PC diffractometer (Rigaku Corporation, Japan). Data collection was performed at room temperature using monochromatic Cu/Kα radiation (λ= 1.54180 Å), 40 kV/100 mA, in the 2θ region between 3°and 40°, a step of 0.02°, and a scan rate of 10°/min.

High-performance liquid chromatography (HPLC)

The equilibrium solubility of IBU and IBU cocrystals was determined using the Agilent 1100 HPLC system. A Zorbax-Extend C18 column (5 μm, 150 × 4.6 mm) at room temperature was used. The mobile phase consisted of 70% methanol and 30% potassium dihydrogen phosphate (0.01 mol/L), and the flow rate was maintained at 1 mL/min using an isocratic method. The concentration of IBU was measured at 263nm. HPLC calibration was performed for IBU using standard solutions of 100 μg/mL, 200 μg/mL, 400 μg/mL, 600 μg/mL, and 800 μg/mL. An excess amount of sample was added to a certain volume of PBS buffer (pH 7.4). The suspension was placed in a thermostatic bath with constant stirring at 20 °C. After 24 h of dissolution, the aliquot of the solution was filtered through 0.45 μm filters and diluted for determining the concentration of IBU by HPLC.

RESULTS AND ANALYSIS

FTIR spectra for the IBU-NIC samples

The FTIR spectra for pure IBU, NIC, and the IBU-NIC cocrystal screening sample prepared in the ethanol-water cosolvent in the absence of polymers (IBU-NIC-Ethanol/Water) are shown in Figure 2.

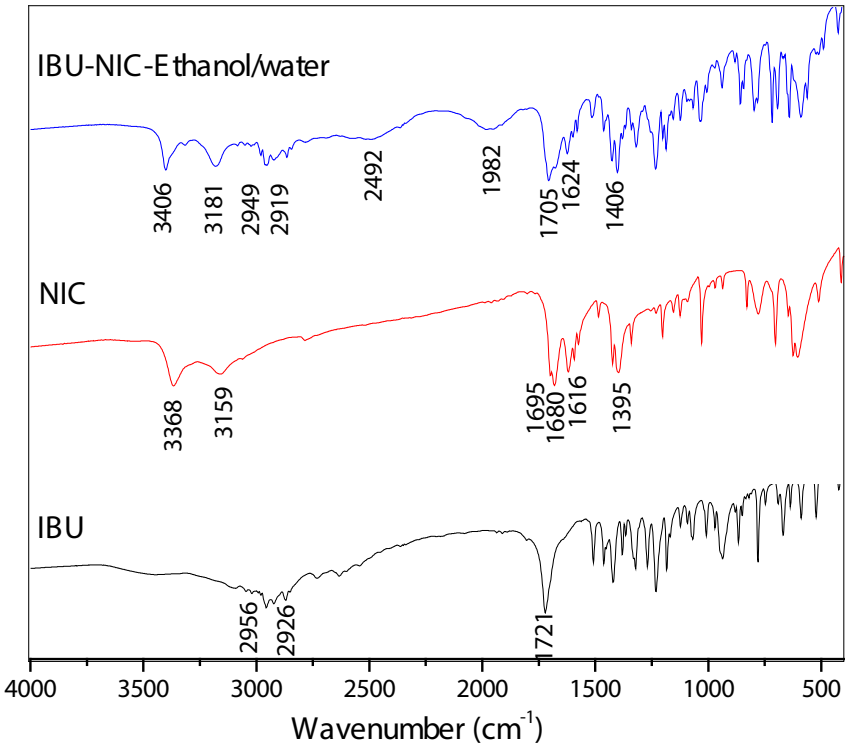


FIGURE 2 - IR spectra for IBU, NIC, and IBU-NIC-Ethanol/water samples.

The IR spectrum for IBU showed peaks at 2956 cm^{-1} and2926 cm^{-1}, which corresponded to the stretch of the hydroxyl group (O-H); the peak at 1721 cm^{-1}corresponded to the stretch of the carbonyl group (C =O). NIC showed characteristic peaks of 3368 cm^{-1} and 3159 cm^{-1}, corresponding to the stretch of the amino group (NH_2), a peak of 1616 cm^{-1} for the bend of the amino group (NH_2), double peaks of 1695 $cm^{-1}$and 1680 cm^{-1} for the carbonyl group (C =O), and a peak of 1395 cm^{-1} for the bend of (C-N) in the amide group.

The IR spectrum of IBU-NIC-Ethanol/water was different from those of IBU and NIC, suggesting that both molecules were present in a new phase. The stretching frequencies of the hydroxyl group O-H and the carbonyl group C =O of IBU were red-shifted to 2949, 2919, and 1705cm^{-1}, respectively. This suggested that the carboxyl group of IBU formed a strong hydrogen bond in the cocrystal screening product. The characteristic peaks of NIC were blue-shifted to 3406, 3181, and 1624 cm^{-1}, corresponding to the amino group (NH_2); the peaks for the carbonyl group (C =O) shifted to 1705 cm^{-1}, and the peak for the C-N group shifted to 1406 cm^{-1}. IR analysis was performed to preliminarily identify the formation of IBU-NIC cocrystals prepared in the ethanol-water cosolvent in the absence of polymers.

The IR spectra of the IBU-NIC cocrystal screening samples prepared in the ethanol-water cosolvent in the presence of polymers are shown in Figure 3.

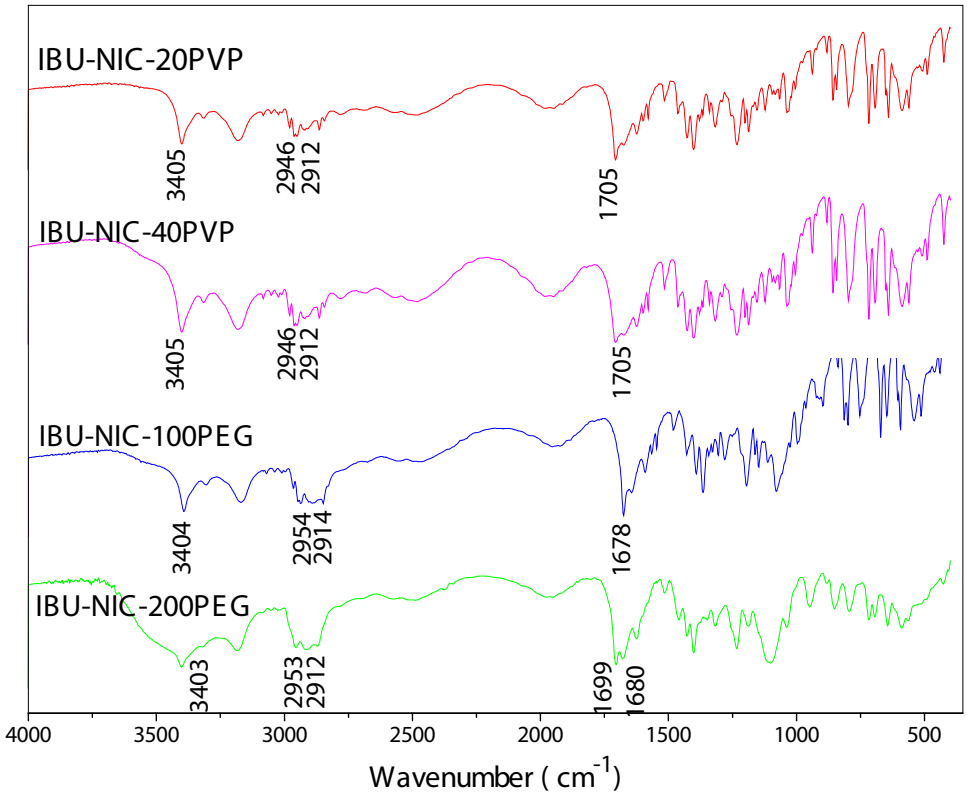


FIGURE 3 - IR spectra of IBU-NIC cocrystal screening products prepared in polymer solutions.

The samples prepared in the 20 mg/mL PVP pre-dissolved solution (IBU-NIC-20PVP) and the 40 mg/mL pre-dissolved PVP solution (IBU-NIC-40PVP) had a similar IR spectrum, with characteristic peaks at 2946 cm^{-1} and 2912 cm^{-1} for the hydroxyl group (O-H) of IBU, a characteristic peak at 1705cm^{-1} for the carbonyl group (C=O) of IBU; peaks at 3405 $cm^{-1}$and 1705cm^{-1} corresponding to the amino group (NH_2) and the carbonyl group (C=O) of NIC. The IR spectra of the sample IBU-NIC-20PVP and IBU-NIC-40PVP showed characteristic peaks similar to those of IBU-NIC-Ethanol/water, which indicated the possibility of cocrystal formation in the presence of PVP, but the concentration of PVP did not affect the IR spectra of the samples.

The IR spectra of the sample prepared in the 100 mg/mL PEG pre-dissolved solution (IBU-NIC-100PEG) and the sample prepared in the 200 mg/mL PEG (IBU-NIC-200PEG) solution showed peaks around 2954/2953 cm^{-1}, which were the characteristic peaks of pure IBU. The IR spectra of IBU-NIC-100PEG and IBU-NIC-200PEG also showed the characteristic peak of pure NIC at1678, 1699, and 1680 cm^{-1}. This suggested the presence of the starting materials of IBU and NIC in the samples of IBU-NIC-100PEG and IBU-NIC-200PEG; thus, the possibility of pure IBU-NIC cocrystal formation in PEG solution was eliminated.

FTIR spectra of the IBU-SAC samples

The IR spectra of the IBU, SAC, and IBU-SAC cocrystal samples prepared in the ethanol-water cosolvent in the absence of the polymer (IBU-SAC-Ethanol/water) are shown in Figure 4.

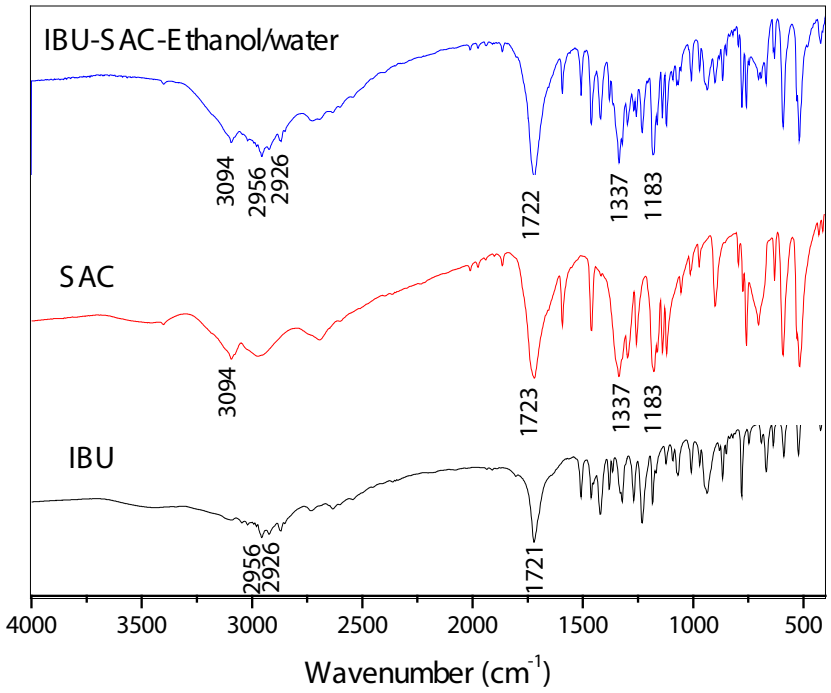


FIGURE 4 - IR spectra for IBU, SAC, and IBU-SAC-Ethanol/Water samples.

The IR spectrum of IBU was described in a previous section. The IR spectrum of SAC had characteristic peaks at 3094 $cm^{-1}$and 1723 cm^{-1} corresponding to the stretch of N-H and C =O of the secondary amide group. Additionally, SAC had characteristic peaks at 1337 $cm^{-1}$and 1183 cm^{-1} corresponding to the asymmetric and symmetric stretch of the SO_2 group.

The IR spectrum of IBU-SAC-Ethanol/water showed peaks at 3094, 2956, 2926, 1722, 1337, and 1183 cm^{-1}, which contained the characteristic peaks of IBU and SAC. This indicated that the molecules of the two starting materials present in the sample of IBU-SAC-Ethanol/water did not change. IBU-SAC-Ethanol/water is a physical mixture of IBU and SAC. No new products were formed.

The IR spectra of the IBU-SAC cocrystal screening samples prepared in the ethanol-water cosolvent with pre-dissolved polymers are shown in Figure 5. The IR spectrum of all samples showed characteristic peaks around 2956, 2926, and 1721 cm^{-1} for pure IBU and peaks around 3094, 1337, and 1183 cm^{-1} for pure SAC. This suggested that all samples were physical mixtures of IBU and SAC; thus, the possibility of pure IBU-SAC cocrystal formation in the PVP or PEG solution was eliminated.

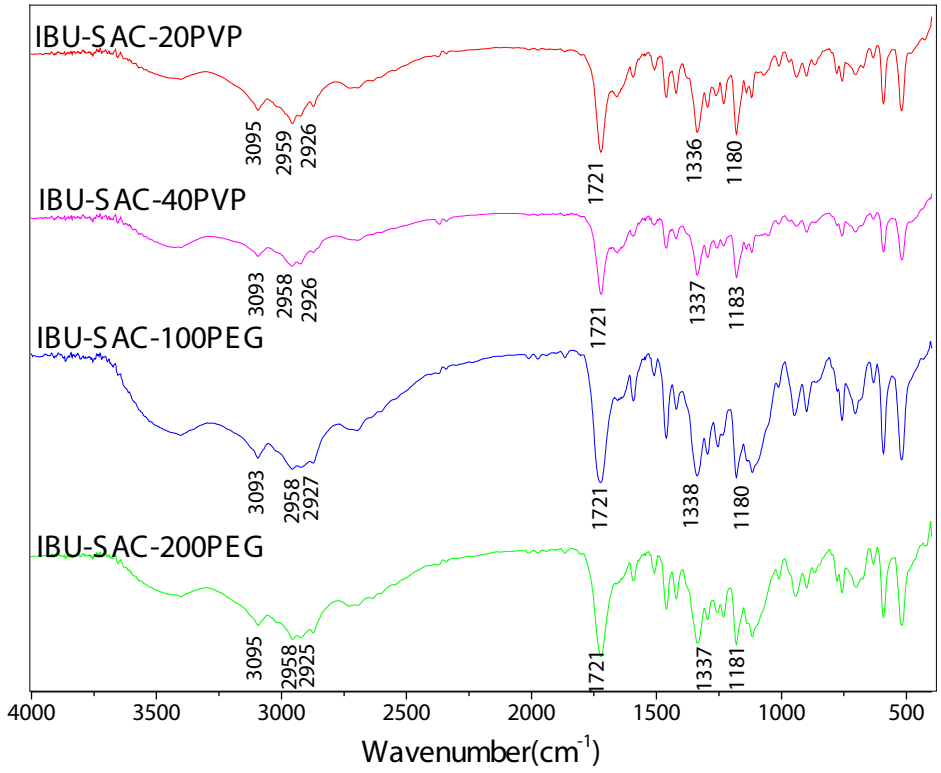


FIGURE 5 - IR spectra of IBU-SAC cocrystal screening products prepared in polymer solutions.

To summarize the FTIR analysis results: (i) the formation of IBU-NIC cocrystals prepared in the ethanol-water cosolvent in the absence of a polymer and with pre-dissolved PVP was preliminarily identified by the IR characteristic peaks. A PVP concentration of 20 and 40 mg/mL used in this study had no effects on cocrystal formation; (ii) The addition of PEG led to the unsuccessful formation of IBU-NIC cocrystal; (iii) IBU and SAC could not form cocrystals either in the pure ethanol-water cosolvent or in the pre-dissolved polymer (PVP or PEG) solutions.

The FTIR technique is a convenient method to eliminate the possibility of cocrystal formation, while it can be used to only preliminarily identify the formation of cocrystals. Cocrystal formation identified by FTIR required further confirmation by other characteristic methods.

DSC analysis

DSC characterization was performed to further identify the formation of the IBU cocrystals. The DSC curves for the IBU cocrystal screening samples prepared in this study are presented in Figure 6.

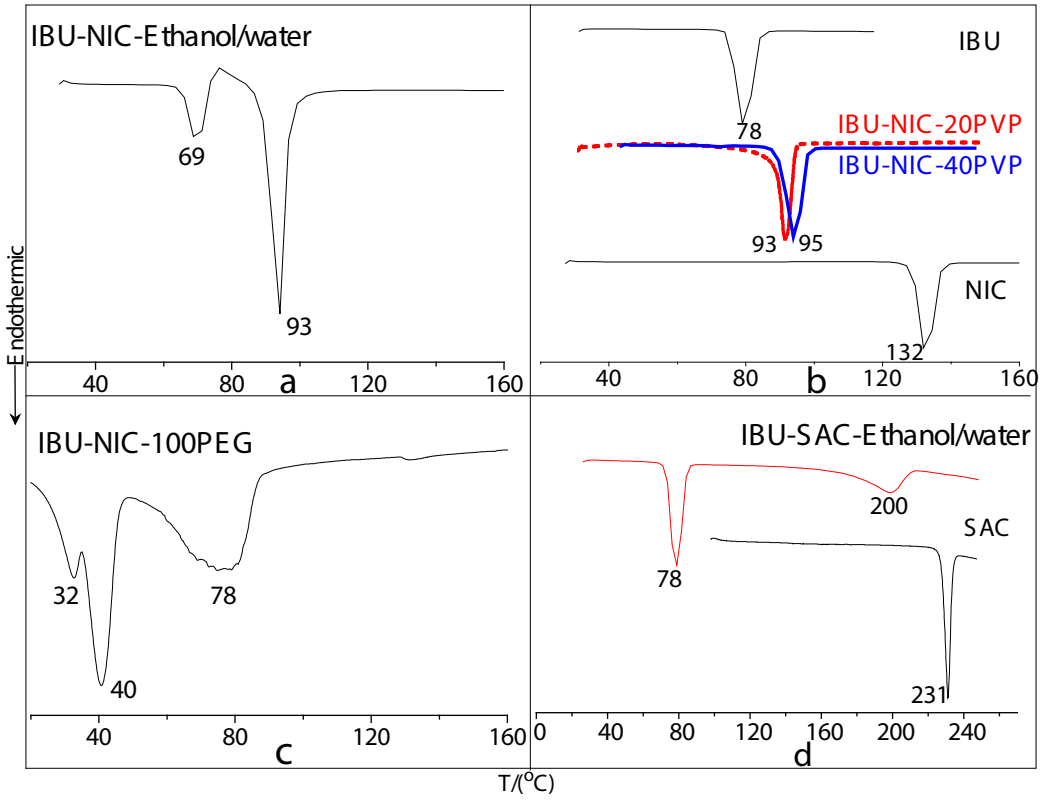


FIGURE 6 - DSC curves for IBU cocrystal samples (a: IBU-NIC-Ethanol/water; b: IBU, NIC, IBU-NIC-20PVP, and IBU-NIC-40PVP; c: IBU-NIC-100PEG; d: IBU-SAC-Ethanol/water, SAC) T/°C.

Among all IBU cocrystal screening samples, only those samples prepared in PVP solutions showed a single endothermic transition which indicated a pure component of the sample. The samples of IBU-NIC-20PVP and IBU-NIC-40PVP had similar thermal behavior. A comparison of the thermal behavior of samples IBU-NIC-20PVP and IBU-NIC-40PVP related to IBU and NIC is shown in Figure 6b. Pure IBU and NIC showed a single endothermic transition, attributed to melting at 78 °C and 132 °C, respectively, which was similar to the findings of other studies (Berry et al., 2008; Chow *et al.*, 2012). The DSC curve for IBU-NIC-20PVP and IBU-NIC-40PVP showed a single endothermic transition attributed to the melting transition around 93~95 °C, which was between that of the individual components. This suggested the formation of a new compound, which was similar to the reported thermal behavior of IBU–NIC cocrystals (Berry et al., 2008; Chow et al., 2012).

The DSC curve of the sample IBU-NIC-Ethanol/water (Figure 6a) had two thermal events: a major endothermic peak around 93 °C, which was due to the melting of the IBU-NIC cocrystal, and another endothermic peak around 69 °C resulting from the melting of the IBU residue. The two endothermic peaks for the sample of IBU-NIC-Ethanol/water indicated that this sample was a mixture of IBU and IBU-NIC cocrystals, the shifting of the melting point peaks from that of pure IBU and IBU-NIC cocrystal could be explained by the presence of the second components in the mixture.

The IBU-NIC samples prepared in PEG solutions with 100 or 200 mg/mL had similar DSC curves, and both showed more than one peak. An example of a DSC curve of IBU-NIC-100PEG is shown in Figure 6c.The peaks appeared around 32 and 40 °C and could be attributed to the melting of the PEG residue; a peak appeared around 78 °C with a broad melting range from 60 to 100 °C, which was due to the melting of the IBU and NIC mixture. The results of the DSC test demonstrated that no IBU-NIC cocrystal formed in the PEG solutions, which was preliminarily identified by the FTIR test.

For the IBU-SAC cocrystal screening samples, the FTIR results eliminated the possibility of cocrystal formation in all solvents. The results of the DSC test further demonstrated that the IBU-SAC samples were a mixture of IBU and SAC, rather than IBU-NIC cocrystals. A typical DSC curve for the IBU-SAC-Ethanol/water sample is shown in Figure 6d. The curve has two endothermic peaks around 78 °C and 200 °C resulting from the melting of IBU and SAC (Basavoju et al., 2008). The shifting of the SAC melting point from that of pure SAC could be explained by the mixture state.

PXRD analysis

The FTIR results showed that IBU-NIC cocrystals can be prepared in the ethanol-water cosolvent in the absence of polymer and the presence of PVP. The results of the DSC test further demonstrated that pure IBU-NIC cocrystals can only be formed in PVP solutions. The PXRD technique was used to identify the crystal structure of the IBU-NIC cocrystal prepared in PVP solutions. The PXRD patterns of IBU, NIC, IBU-NIC-Ethanol/water, IBU-NIC-20PVP, and IBU-NIC-40PVP are shown in Figure 7.

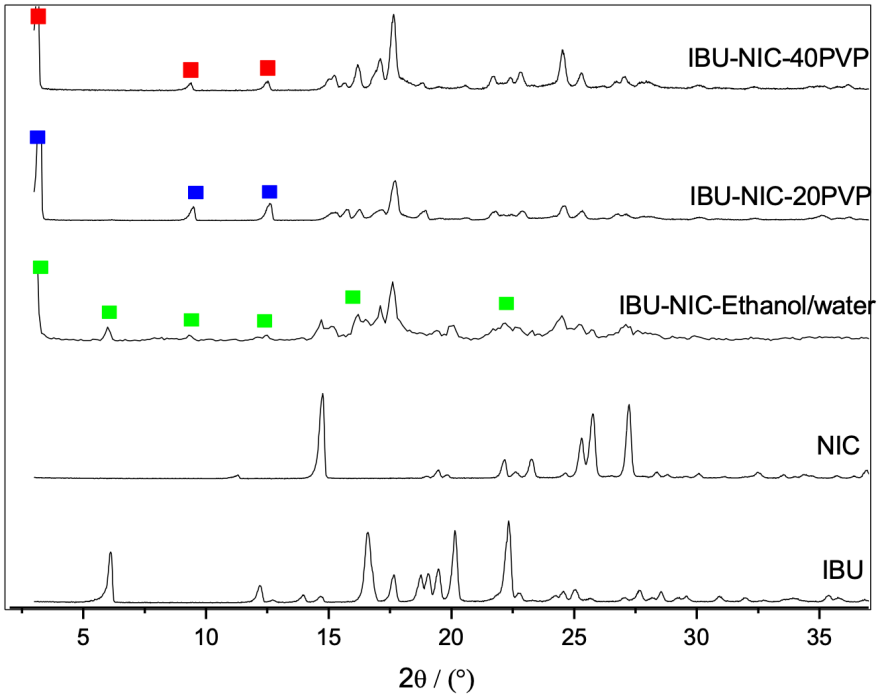


FIGURE 7 - PXRD patterns of IBU, NIC, IBU-NIC-Ethanol/water, IBU-NIC-20PVP, and IBU-NIC-40PVP.

Pure IBU showed characteristic peaks at 2θ 6.1°, 12.1°, 16.6°, 17.6°, 18.7°, 19°, 19.5°, 20.1°, and 22.2°. NIC showed characteristic peaks at 2θ 11.3°, 14.7°, 19.4°, 22.1°, 22.5°, 23.2°, 25.2°, 25.7°, and 27.2°. The samples of IBU-NIC-20 PVP and IBU-NIC-40 PVP had similar PXRD patterns, which were different from those of IBU and NIC. The characteristic peaks of IBU-NIC-20 PVP and IBU-NIC-40 PVP around 2θ 3.1°, 9.3°, and 12.7° showed the formation of a new phase, which was similar to that of IBU-NIC cocrystal as reported in another study (Berry et al., 2008). The IBU-NIC-Ethanol/water sample showed characteristic peaks of IBU-NIC cocrystals at 2θ 3.1°, 9.3°, and 12.7°. Additionally, the sample also had some IBU characteristic peaks around 6.1°, 16.6°, and 22.2°. The PXRD results indicated that the IBU-NIC-Ethanol/water sample was not pure IBU-NIC cocrystals; these results were similar to those of the DSC test.

HPLC analysis

The above-mentioned characterization results showed the formation of pure IBU-NIC cocrystals in the ethanol-water cosolvent with pre-dissolved PVP solutions. The equilibrium solubility of IBU-NIC cocrystals prepared in PVP solutions was determined by performing HPLC, and then, it was compared to the solubility of pure IBU. The HPLC calibration for IBU measurement was performed, and a standard curve was obtained with a linear range from 100 to 800 μg/mL and regression equation $Y = 145.46X + 408.87$, $R^2 = 0.9999$ (Figure 8).

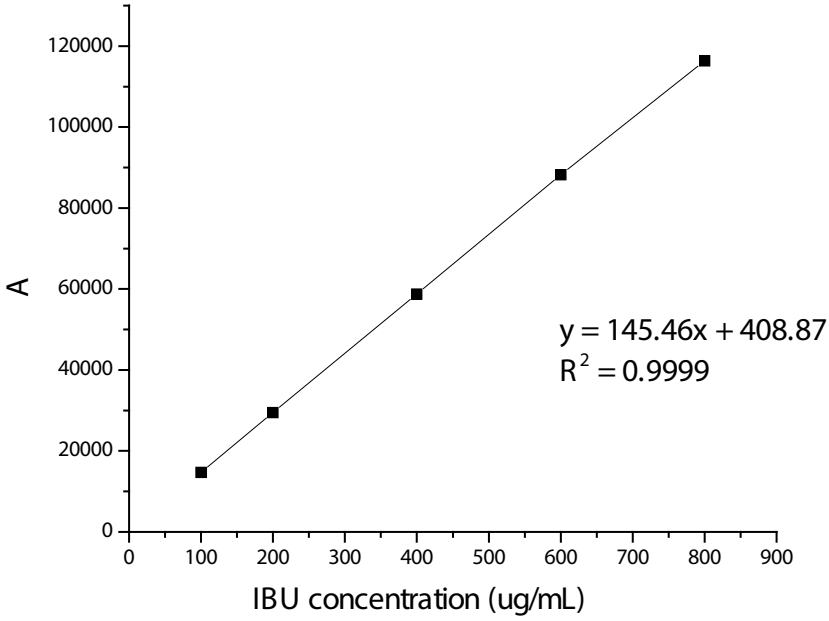


FIGURE 8 - HPLC calibration curve for the measurement of IBU.

The equilibrium solubility of the tested samples in a PBS buffer (pH 7.4) was determined by HPLC and calculated based on the above-mentioned equation. The results showed that pure IBU had an equilibrium solubility of 1.57×10^{-3} mmol/mL, while IBU-NIC-20PVP and IBU-NIC-40PVP had equilibrium solubilities of 2.30×10^{-3} mmol/mL and 2.37×10^{-3} mmol/mL, respectively, which were about 1.5 times higher than that of pure IBU.

DISCUSSION

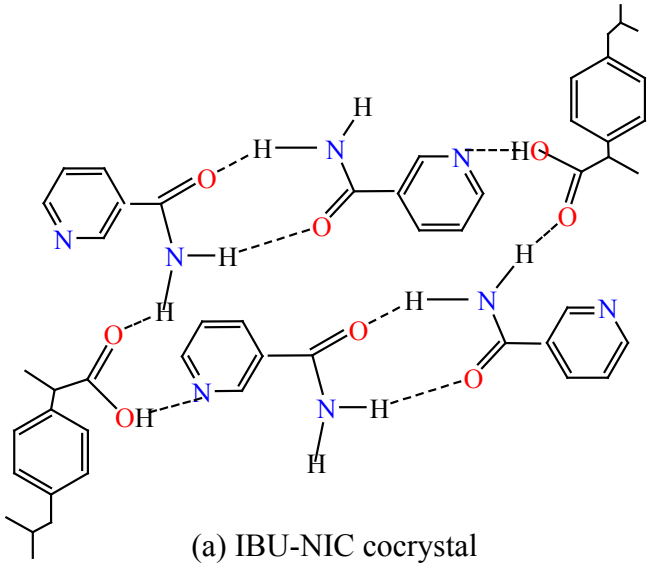
Through an overall analysis of characterizations, the results of IBU cocrystal screening in five solvents with and without polymers are summarized in Table 1. NIC and SAC were selected as cocrystal coformers. First, the possibility of cocrystal formation was assessed by analyzing the molecular structure of these cocrystal component candidates. IBU has a carboxylic acid group, which can serve as a hydrogen bond (H-bond) donor and acceptor. NIC has an amide group, which can provide one H-bond acceptor and two H-bond donors. Additionally, the N atom in the pyridine ring of NIC can act as an H-bond acceptor. Most pharmaceutical cocrystals are constructed from intermolecular interactions of H-bonds (Bis et al., 2007; Miroshnyk et al., 2009).The molecular properties of IBU and NIC provide the structural possibility for the formation of IBU-NIC cocrystals. In this study, the IBU-NIC cocrystals were successfully prepared in the control group of ethanol-water cosolvent in the absence of polymers. A possible IBU-NIC cocrystal molecule constructed through H-bond is shown in Figure 9a, as proposed in other studies (Berry *et al*., 2008). The NIC dimmer synthon was first assembled through the formation of the H-bond between the amide groups of two NIC molecules. Then, IBU was linked to

the NIC dimmer through the H-bond of (O–H··· N) formed between the hydroxyl group of carboxylic acid and the pyridine ring of the first NIC molecule and the H-bond of (N–H···O) formed between the carbonyl group of carboxylic acid and the amide of the second NIC molecule. The H-bond connections of IBU to NIC led to a herringbone ladder for IBU, which helped to form a long-range order of IBU-NIC cocrystals. Although IBU-NIC cocrystals can be formed in ethanol/water cosolvent, the product is a mixture of API and cocrystals, as shown in the DSC thermogram in Figure 6a. This could be due to the nonequivalent dissolving of IBU and NIC (Chow et al., 2012). NIC is more soluble than IBU. Cocrystal formation through the solution method is sensitive to the composition of the solution. During crystallization, the solubility of cocrystal components in the solution might change with external conditions. The single-component crystal, IBU, could precipitate because supersaturation occurred to the relative less soluble reactant (Qiao et al., 2011).

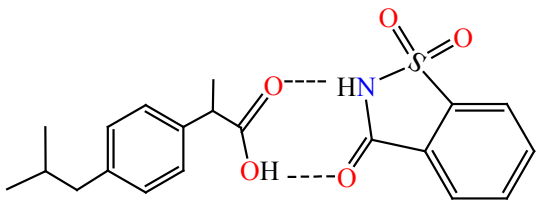
TABLE I - Summary of the results of IBU cocrystal screening in different solvents

Solvent	CCF	
	NIC	SAC
Ethanol/water	+/- [a]	- [c]
Ethanol/water -20PVP	+ [b]	-
Ethanol/water -40PVP	+	-
Ethanol/water -100PEG	-	-
Ethanol/water -200PEG	-	-

a: symbol "+/-" represent mixture of cocrystal and starting material
b: symbol "+" represent cocrystal formed
c: symbol " - " represent no cocrystal formed



(a) IBU-NIC cocrystal



(b) IBU-SAC cocrystal

FIGURE 9 - Molecular structure design of IBU cocrystals.

The effects of polymers on the IBU cocrystal formation process were investigated. PVP and PEG were selected as the representative polymers. PVP is a water/ethanol-soluble polymer made from the monomer N-vinylpyrrolidone, which is widely used in the food and pharmacy industry as additives or excipients (Higuchi and Kuramoto, 1954; Mooter et al., 2001; D'Souza, Schowen, Topp, 2004; Karavas et al., 2006; Qiu et al., 2016). In this study, the samples of IBU-NIC-20PVP and IBU-NIC-40PVP prepared in PVP solutions were pure IBU-NIC cocrystals. This could be explained by the following: PVP has both hydrophilic and hydrophobic groups, and the amphiphilic properties of PVP make it a good solubility-enhancement agent for drugs that are poorly soluble in water. Therefore, the solubility of IBU could be maintained at a level equivalent to that of NIC, which helped in the formation of IBU-NIC cocrystals. The N-C =O group in the pyrrole ring of PVP interacted with IBU and NIC, which inhibited the precipitation of single cocrystal components; this was found in other studies also (Molyneux, Frank, 1961; Guo et al., 2016). Additionally, the H-bond was formed between PVP and IBU (or NIC), but the steric hindrance due to the presence of multiple pyrrole rings on the long polymer chain made

the H-bond between PVP and the cocrystal components weaker than the H-bond between API and CCF. Hence, the H-bond between PVP and the cocrystal components did not affect the cocrystal formation through the H-bond formed between the two components. Thus, pure IBU-NIC cocrystal was obtained in the PVP solution, and the concentrations of PVP additives did not affect the results. The equilibrium solubility of the pure IBU-NIC cocrystal sample prepared in PVP solutions was determined by HPLC. The results showed that the equilibrium solubility of the IBU−NIC cocrystal was about 1.5 times greater than that of pure IBU. The results of our study showed that the equilibrium solubility of cocrystal was similar to that of pure API. The solubility advantage of the cocrystal could be offset by long-term dissolution due to solution-mediated phase transformation (SMPT). SMPT was also reported in other studies (McNamara et al., 2006; Shiraki et al., 2008; Greco and Bogner, 2012; Li et al., 2013; Qiao et al., 2013).

The effects of PEG on the formation of the IBU cocrystals were also investigated. PEG is a polyether compound with many applications in pharmaceutical research (Zalipsky, 1995; Damian, 2000; Higuchi and Lach, 2010). The results of the IBU-NIC cocrystal screening in PEG were different from those of PVP solutions; IBU-NIC cocrystals were not obtained in PEG solutions in this study. The samples of IBU-NIC-100PEG and IBU-NIC-200PEG prepared in PEG solutions were found to be mixtures of the starting materials. This could be explained by the interaction between PEG and the cocrystal components. PEG is a water-soluble polymer and has a hydroxyl group that can form H-bond with solvents, API, and NIC. PEG is a linear polymer, which does not have side chains or side groups. The chain of PEG is more flexible, and it can be easily folded to reduce steric hindrance. The H-bond between API and NIC could be greatly affected by the intervention of PEG in the system; the IBU-NIC cocrystal formation was consequently affected. From another perspective, PEG had limited inhibition ability to prevent single crystal precipitation which was similar to the findings of previous studies (Hendriksen et al., 1998; Guo *et al.*, 2016). Based on the above reasons, the mixtures of IBU and NIC, instead of the IBU-NIC cocrystals, were obtained in the PEG solutions.

The SAC molecule, which has an amide group and a ring structure, was also selected as a coformer in this study to cocrystallize with IBU. The predicted molecular structure of the IBU-SAC cocrystal is presented in Figure 9b, in which IBU and SAC were assembled through a ring motif $R_2^2(8)$ H-bond formed between the carboxylic acid group and the amide group of SAC. According to empirical studies, this kind of ring motif (O-H···N) is common and robust (Vishweshwar et al., 2006). We did not obtain IBU-SAC cocrystals in the ethanol-water cosolvent. Although a short-range organization of IBU-SAC molecules can be obtained in this system, a long-range orderly organization of IBU-SAC is difficult to achieve because a connection between IBU and SAC is lacking, just like the connection between IBU and the pyridine ring in NIC. The H-bond connections between IBU and NIC led to a herringbone ladder for the IBU, which developed a robust and long chain structure. In this study, the addition of polymers, either PEG or PVP, did not contribute to the formation of the IBU-SAC cocrystals. This suggested that for compounds structurally unable to form cocrystals, the addition of polymers to the system cannot change the results. The structural properties of API and CCF determine cocrystal formation.

Polymers are complicated macromolecules; their properties vary with the monomer species, polarity, molecular weight, and distribution. The properties of pharmaceutical cocrystals also vary considerably with different APIs or CCFs. Thus, the effects of polymers on the formation of pharmaceutical cocrystals cannot be adequately determined based on limited experiments. Further studies are necessary to supplement and validate the conclusions. Related studies are ongoing in our laboratory.

CONCLUSION

The effects of polymers on the formation of IBU cocrystals were investigated through IBU cocrystal screening in five solvents with and without polymers. In this study, NIC and SAC were selected as the CCF, ethanol-water as the solvent, and PVP and PEG as the representative polymers. We found that the mixture of IBU and IBU-NIC cocrystals can be prepared in the

ethanol-water cosolvent without polymers. The addition of PVP facilitates the synthesis of pure IBU-NIC cocrystals, mainly because of equivalent solubility for the two cocrystal components generated by PVP; no cocrystals were formed in the PEG solutions because the flexibility of the PEG chain might have affected the H-bond connections between cocrystal components. SAC could not cocrystallize with IBU in the ethanol-water solvent in the absence of a polymer; the addition of neither PVP nor PEG helped in the formation of IBU-SAC cocrystals, which indicated that the structural properties of API and CCF determined the formation of the cocrystals.

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