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Research Article

Solubility and Scale-Up Potency of Norfloxacin-Urea Co-Crystal Prepared by Ultrasound-Assisted Slurry Co-Crystallization Method

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Abstract

Norfloxacin is an antimicrobial in treating urinary tract infections with low water solubility. This study aims to know the effect of norfloxacin-urea co-crystal formation on the solubility of norfloxacin and the potential for scale-up when prepared by ultrasound-assisted slurry co-crystallization method. Identification of the screening result of the norfloxacin-urea (1 : 1) co-crystal formation by a wet grinding method using an ethanol-acetone (1 : 1) solvent mixture was performed by powder X-ray diffractometer (PXRD). The ultrasound-assisted slurry co-crystallization method was used for co-crystal formation with five-fold the weight of norfloxacin and urea than the wet grinding method. The co-crystal product prepared by the ultrasound-assisted slurry co-crystallization method was observed for its crystal morphology and characterized by PXRD and differential scanning calorimeter (DSC). Solubility and dissolution tests in water and acetate buffer solution pH 4.0 were used to evaluate the physicochemical properties. Identification of co-crystal screening by PXRD revealed the formation of norfloxacin-urea co-crystal. The PXRD pattern of the norfloxacin-urea co-crystal product prepared by the ultrasound-assisted slurry co-crystallization method was similar to the wet grinding method. Norfloxacin-urea co-crystal has a different melting point and crystal morphology from pure norfloxacin and urea. The solubility and dissolution rate of norfloxacin-urea co-crystal was higher in water and not significantly different in acetate buffer solution pH 4.0 compared to pure norfloxacin. This study showed that the norfloxacin-urea co-crystal formation could enhance the solubility of norfloxacin in water and had the potential for scale-up when prepared using the ultrasound-assisted slurry co-crystallization method.

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INTRODUCTION

Norfloxacin is an analog of nalidixic acid, effectively treating urinary tract infections, such as gonorrhea and prostatitis[1]. This active pharmaceutical ingredient (API) has a broad antimicrobial activity to treat infections in humans and animals caused by *Escherichia coli*, *Citrobacter freundi*, *Staphylococcus aureus*, *Pseudomonas aeruginosa*, dan *Shigella*[2]. Norfloxacin is mostly given in oral solid dosage forms, such as tablets. Norfloxacin has low solubility and permeability, classified into class IV in the Biopharmaceutical Classification System (BCS)[3]. Several attempts have been made to improve the solubility of norfloxacin, among others, by forming co-crystals with nicotinic acid[3], resorcinol[4], and isonicotinamide[5].

Co-crystal are multicomponent crystals arranged stoichiometrically through weak bonds, such as hydrogen bonds between an active pharmaceutical ingredient (API) and another API or an API and a pharmaceutical excipient bound together in a crystal lattice[6,7]. The manufacture of co-crystal is an attractive strategy for the pharmaceutical industry to solve the physicochemical problems of APIs, such as solubility, stability, hygroscopicity, and mechanical properties[8,9].

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One of the limiting factors for the pharmaceutical industry in utilizing co-crystal is the difficulty in large production[10]. The manufacture of co-crystal using solution-based methods, such as solvent evaporation and cooling crystallization, although it can be done in large quantities in tanks, can be constrained by the process of crystallizing an active pharmaceutical ingredient and co-crystal former separately due to differences in the solubility of the two components. The co-crystal preparation by solid-based methods, such as dry grinding and wet grinding, produces co-crystals with less uniform size and defects[11,12]. The slurry is a solution-based method that can be used as an alternative to making large-scale co-crystals more efficiently. This method uses less solvent than solvent evaporation or cooling crystallization methods and produces uniform crystals without defects. In this method's preparation of the co-crystal, one or both pure compounds are suspended in a solvent to form a slurry[13]. The production of co-crystals using the slurry method can be assisted by ultrasonic waves to accelerate their formation, known as the ultrasound-assisted slurry co-crystallization or sonic slurry method[14,15].

The selection of a co-crystal former is a critical stage that can affect the success of co-crystal formation. Urea is a compound often used as a co-crystal former and can increase the solubility of active pharmaceutical ingredients, including agomelatine[16], bumetanide[17], catechin[18], and febuxostat[19]. The presence of two amide groups in urea has an excellent opportunity to form a co-crystal with norfloxacin, as well as the formation of norfloxacin-isonicotinamide co-crystal where hydrogen bonds occur between the amide group in isonicotinamide and the carboxylate group in norfloxacin[5].

Studies on co-crystal formation between norfloxacin and urea have yet to be reported, even though these two components can form co-crystals and increase the solubility of norfloxacin. The ultrasound-assisted slurry co-crystallization method can be an option in manufacturing norfloxacin-urea co-crystal on a large scale because it uses only a tiny amount of solvent and produces uniform crystals without defects. This study aims to determine the effect of norfloxacin-urea co-crystal formation on the solubility of norfloxacin and also to know its potential scale-up when prepared using the ultrasound-assisted slurry co-crystallization method.

MATERIALS AND METHODS

Materials

Norfloxacin was purchased from Beijing Mesochem Technology Co., Ltd (China), while urea was obtained from PT. Merck Indonesia. Sodium acetate, acetic acid, ethanol, and acetone were also purchased from PT. Merck Indonesia. The equipment used for the co-crystal preparation was a mortar grinder (Retsch RM 200) and Branson 3510-DTH ultrasonic. The types of equipment used for co-crystal characterization and evaluation consisted of a differential scanning calorimeter (Shimadzu DSC-60 plus), polarizing microscope (Olympus BX-53), powder X-ray diffractometer (Rigaku Miniflex), orbital shaker (IKA KS-260), water bath shaker (Lab Companion BS-11), Dissolution tester (ZRS6G), and ultraviolet spectrophotometer (Shimadzu UV-1800).

Methods

Screening of norfloxacin-urea co-crystal formation by wet grinding method

Screening of norfloxacin-urea co-crystal formation was carried out by the solvent-drop grinding method[20,21]. Norfloxacin and urea were weighed at 0.638 g (0.002 mol) and 0.120 g (0.002 mol), respectively, and put into a mortar grinder. After adding three drops of the ethanol-acetone (1 : 1) solvent mixture, the powder mixture was ground for ten minutes and left until all the solvent had evaporated. The grinding product was placed in a closed vial before being characterized by a powder X-ray diffractometer.

Characterization of the wet grinding product by powder X-ray diffractometer (PXRD)

The PXRD pattern was collected by irradiating approximately 500 mg of the norfloxacin-urea wet grinding product with an X-ray generated from Cu-Kα radiation at 2θ 5-45° using a Rigaku Miniflex diffractometer. Scans were performed at a speed of 10° per minute and a step-width of 0.02°. The scans were also conducted on each pure compound (norfloxacin and urea).

Preparation of norfloxacin-urea co-crystal by ultrasound-assisted slurry co-crystallization method

Norfloxacin-urea co-crystal was prepared using the ultrasound-assisted slurry co-crystallization method[14]. In the vial, 3.19 g (0.01 mol) of norfloxacin and 0.6 g (0.01 mol) of urea were dispersed in 2 mL ethanol-acetone (1 : 1) solvent mixture and

sonicated at a frequency of 42 kHz for 20 minutes using a Branson 3510-DTH ultrasonic. At the end of the sonication process, the suspension turned into a cake-like solid at the bottom of the vial. The solid was removed from the vial, and the crystal morphology was observed under a polarizing microscope. After the solid was dried, it was characterized by PXRD and differential scanning calorimeter (DSC) methods.

Crystal morphology observation by polarizing microscope

The solid resulting from the manufacture of norfloxacin-urea co-crystal by the ultrasound-assisted slurry co-crystallization method was placed on a slide and observed for crystal morphology using an Olympus BX-53 polarizing microscope. Crystal morphology was also observed in each recrystallized physical mixture of norfloxacin-urea (1 : 1), pure norfloxacin, and urea in an ethanol-acetone (1 : 1) solvent mixture. The recrystallization was carried out by placing 1-3 mg of each material on a glass object and dripping it with the solvent until dissolved and allowed to crystallize again.

PXRD patterns analysis of norfloxacin-urea co-crystal formation prepared by the ultrasound-assisted slurry co-crystallization method

The PXRD patterns analysis resulting from the manufacture of norfloxacin-urea co-crystal by the ultrasound-assisted slurry co-crystallization method was carried out according to the conditions as described in the procedure of screening the norfloxacin-urea co-crystal formation by the wet grinding method. Identification of co-crystal formation was carried out by comparing the PXRD pattern between the ultrasound-assisted slurry co-crystallization and wet grinding methods.

Thermal analysis of norfloxacin-urea prepared by the ultrasound-assisted slurry co-crystallization method

Thermal analysis of norfloxacin-urea co-crystal was conducted by a Shimadzu DSC-60 plus differential scanning calorimeter by placing 3-5 mg of sample in a tightly closed aluminum pan and heated at 10°C/minute while nitrogen gas flowed at 20 mL/minute for purging. The heating temperature range is 30-250°C. DSC analysis was also performed on pure norfloxacin and urea. The melting point is determined from the peak point of an endothermic transition.

Solubility test

The solvents used in the solubility test were water (room temperature) and acetate buffer solution pH 4.0 (37±0.5°C). The solubility test was carried out using the shake-flask method[22]. An orbital shaker was used for the solubility test in water, while a water bath shaker (Lab Companion BS-11) was used for the solubility test in an acetate buffer solution at pH 4.0. Norfloxacin-urea co-crystal was weighed equivalent to 100 mg of norfloxacin and put into each vial containing 5 mL of water and acetate buffer solution at pH 4.0. The vial containing the co-crystal dispersion in water was shaken for 24 hours using an orbital shaker (IKA-KS 260), while the co-crystal dispersion in acetate buffer solution pH 4.0 was shaken in a water bath shaker (Lab Companion BS-11). After completing the shaking, the samples were filtered, and the filtrate was analyzed for the norfloxacin solubility by ultraviolet spectrophotometer at 275 and 278 nm, respectively, for the samples tested in water and acetate buffer solution pH 4.0. The solubility tests were also carried out on pure norfloxacin.

Dissolution test

The dissolution test was carried out on pure norfloxacin and norfloxacin-urea co-crystal using a type 2 dissolution apparatus (paddle) with a stirring speed of 50 rpm (rotation per minute) at 37±0.5°C and 750 mL of acetate buffer solution pH 4.0 as a medium[23]. The dissolution test was also carried out in a water medium under the same conditions as the acetate buffer solution pH 4.0. As much as 5 mL samples were taken at 5, 10, 15, 20, and 30 minutes from the dissolution medium and were filtered. The percentage of norfloxacin dissolved in each sample filtrate was determined by ultraviolet spectrophotometer at 275 and 278 nm for the samples tested in water and acetate buffer solution pH 4.0, respectively.

RESULTS AND DISCUSSION

Screening of norfloxacin-urea co-crystal formation by wet grinding method

Screening for co-crystal formation is one of the steps in manufacturing co-crystals that must be carried out after selecting co-crystal forming materials[24]. Wet grinding, or liquid-assisted grinding, utilizes mechanical energy to induce the two components to form a co-crystal and a small amount of solvent can accelerate the induction process[25]. The advantages of co-crystal formation speed, efficiency in solvent use, and high success rate make this method suitable for the co-crystal formation screening stage[21]. The solubility of the two substances in the chosen solvent is significant to consider in the

preparation of co-crystal[26]. Urea is soluble in ethanol[27], while norfloxacin is slightly soluble in acetone[28]. So that in the preparation of the norfloxacin-urea co-crystal, an ethanol-acetone (1 : 1) solvent mixture was used as a solvent.

Characterization of the wet grinding product by powder X-ray diffractometer

The PXRD is a technique widely used to characterize the co-crystal formation by comparing the PXRD pattern of the product and its pure components. The PXRD patterns of norfloxacin-urea (1 : 1) wet grinding product, pure norfloxacin, and urea are shown in **Figure 1**. Norfloxacin has main peaks at 9.7°, 15.8°, 20.4°, 22.5°, 24.7°, and 27.6° of 2θ angles, while urea has major peaks at 2θ 22.2°, 22.5°, 24.7°, 31.8°, and 35.6° of 2θ angles. In the PXRD pattern of norfloxacin-urea (1 : 1) wet grinding product, the main peaks of norfloxacin and urea were not visible, but new peaks appear at angles 2θ 6.3°, 12.7°, 16.9°, 19.2°, 23.1°, and 25.8° showed by black arrows. The appearance of the new peaks and the disappearance of the peaks of pure norfloxacin and urea demonstrated that the wet grinding of the two components could change their crystal lattice due to the formation of hydrogen bonds between them. Thus, the difference in the PXRD pattern between the wet grinding product and its pure components reveals the formation of co-crystal[29,30].

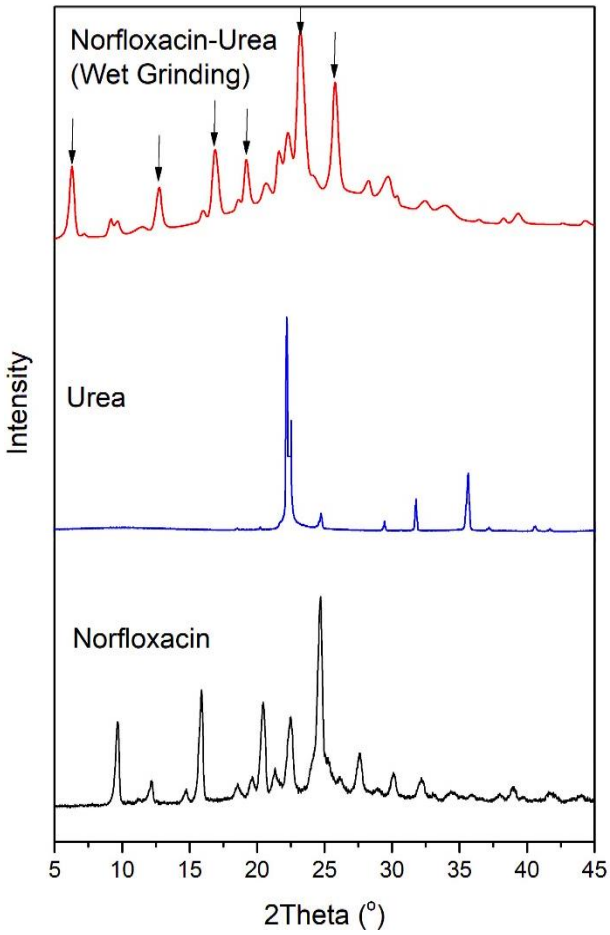

Figure 1. Powder X-ray diffraction patterns of norfloxacin-urea wet grinding product, pure norfloxacin, and urea.

Preparation of norfloxacin-urea co-crystal by ultrasound-assisted slurry co-crystallization method

The ultrasound-assisted slurry co-crystallization method was used to obtain more sufficient amounts of co-crystal for solubility and dissolution tests[21]. In this method, the weight of norfloxacin and urea was increased five-fold compared to the wet grinding method to produce more co-crystals in each manufacturing process. Early identification of the co-crystal product is needed to ensure the success of co-crystal formation by this method. The simple identification is by comparing the co-crystal morphology of the ultrasound-assisted slurry co-crystallization product with the recrystallization result of the physical mixture of the two pure compounds and each pure component. **Figure 2** shows that the ultrasound-assisted slurry co-crystallization product has the same crystal morphology as the recrystallization product of the norfloxacin-urea physical

mixture and different crystal morphology from the recrystallization product of pure norfloxacin and urea. This indicates that ultrasound-assisted slurry co-crystallization can also be used for norfloxacin-urea co-crystal preparation. The presence of ultrasonic vibrations and a small amount of solvent can induce the formation of co-crystal nuclei and then be followed by crystal growth[31]. However, characterization by PXRD and DSC methods was needed to ensure the formation of norfloxacin-urea co-crystal.

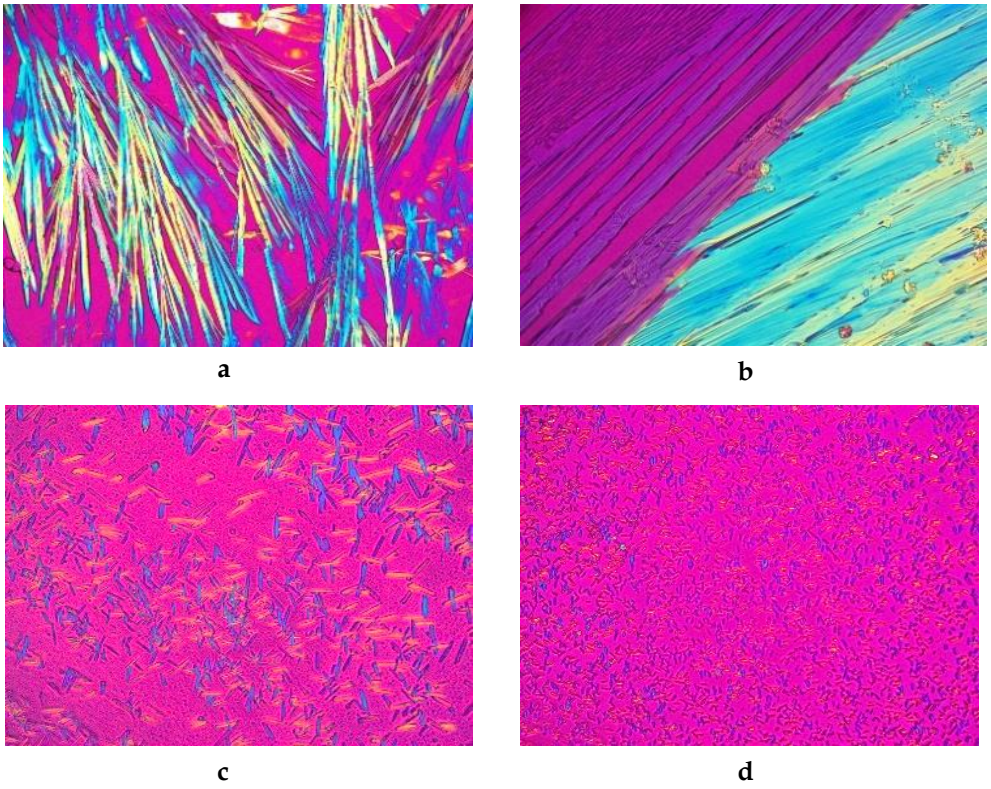

Figure 2. Crystal morphology of (**a**) norfloxacin, (**b**) urea, (**c**) physical mixture norfloxacin-urea (1 : 1) after recrystallized from ethanol-acetone (1 : 1) solvent, mixture, and (**d**) norfloxacin-urea co-crystal prepared by ultrasound-assisted slurry co-crystallization observed by polarizing microscope at a magnification of 200x.

PXRD patterns analysis of norfloxacin-urea co-crystal formation prepared by the ultrasound-assisted slurry co-crystallization method

The powder X-ray diffractometer can be used to characterize the different crystal structures or polymorphs of two or more materials by comparing the PXRD patterns of these materials[32,33]. Therefore, this technique can also be applied to identify the successful co-crystal formation of some methods by comparing the PXRD patterns. **Figure 3** shows a co-crystal product prepared by the ultrasound-assisted slurry co-crystallization method having a PXRD pattern similar to the PXRD pattern of co-crystal prepared by the wet grinding method. As in the PXRD pattern prepared by the wet grinding, the main peaks of norfloxacin and urea were also not visible in the ultrasound-assisted slurry co-crystallization product, and new peaks appeared at the same 2θ angle as the wet grinding product.

Thermal analysis of norfloxacin-urea co-crystal

The DSC thermogram in **Figure 4** showed the only endothermic transition at 187.3°C, corresponding to the norfloxacin-urea co-crystal melting point. An endothermic transition due to the melting of norfloxacin occurs at 215.2°C, a characteristic of norfloxacin Form A[34], while urea melted at 130.0°C. The DSC thermogram of a co-crystal is characterized by its melting point between or below the individual pure components. The results of this characterization using PXRD and DSC confirmed that the ultrasound-assisted slurry co-crystallization method could be used to manufacture norfloxacin-urea co-crystal in larger quantities than the wet grinding method, so it has the potential to be further developed on large scale.

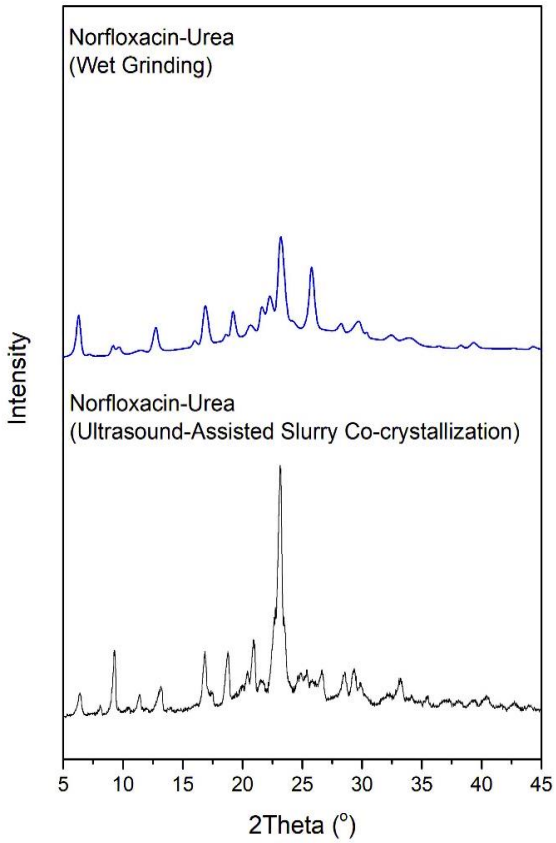

Figure 3. Powder X-ray diffraction patterns of norfloxacin-urea prepared by ultrasound assisted slurry co-crystallization and wet grinding methods.

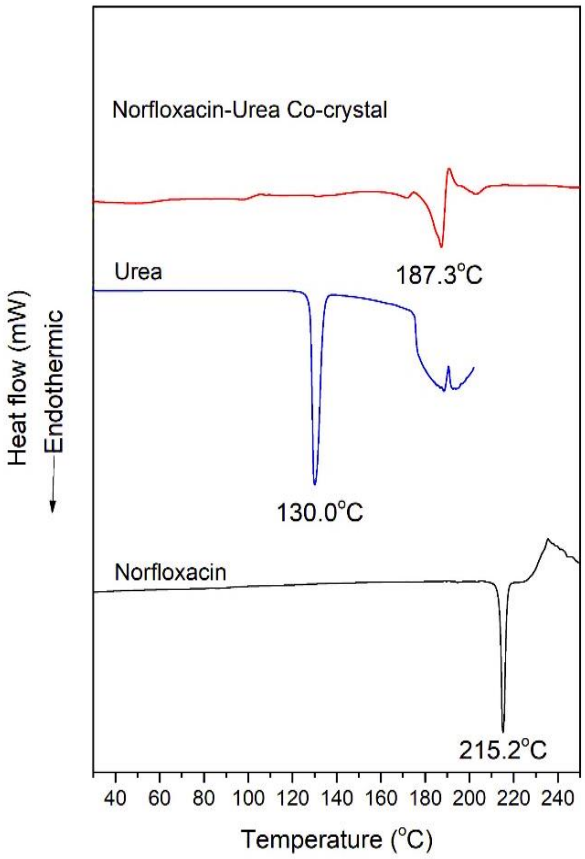

Figure 4. Differential scanning calorimetry thermograms of norfloxacin-urea co-crystal, pure norfloxacin, and urea.

Solubility test

Table I shows that the norfloxacin-urea co-crystal formation can increase the solubility of norfloxacin in water by as much as 1.9-folds compared to pure norfloxacin. The increase in solubility in the water is caused by the norfloxacin and urea molecules rearrangement to form hydrogen bonds or, in other words, due to changes in the crystal packing. The mechanism for increasing the drug solubility in the co-crystal is caused by the dissociation or re-breaking of weak hydrogen bonds between the drug and co-crystal former in an aqueous medium in a quick time (minutes or hours) so drug molecules become more easily wetted and dissolve[35]. Unlike in a water medium, the increasing solubility of norfloxacin in acetate buffer solution pH 4.0 was insignificant (1.1-folds) after the formation of norfloxacin-urea co-crystal. Norfloxacin is amphoteric, so its solubility depends on pH[3]. The solubility of norfloxacin in acetate buffer solution pH 4.0 was much higher than in water due to the protonation of the N atom in the piperazine ring[36]. Thus, the solubility of norfloxacin in the acetate buffer solution pH 4.0 was more due to ionization in an acidic environment than due to the hydrogen bonds formation, so there was no significant difference between the solubility of norfloxacin-urea co-crystal and pure norfloxacin in this medium.

Table I. Solubility of norfloxacin-urea co-crystal compared to pure norfloxacin (n=3)

Medium	Solubility (mg/mL)	
	Norfloxacin	Norfloxacin-urea co-crystal
Water	0.226 ± 0.007	0.430 ± 0.024
Acetate buffer solution pH 4.0	10.953 ± 0.701	12.085 ± 1.296

Dissolution test

Figure 5 shows the dissolution profiles of norfloxacin-urea co-crystal and pure norfloxacin in water and acetate buffer solution pH 4.0. The dissolution profile in the water medium showed that the percentage of dissolved norfloxacin from norfloxacin-urea co-crystal had reached more than 85% within 30 minutes, while that of pure norfloxacin only reached 56%. In contrast to the dissolution rate in water, the percentage of dissolved norfloxacin from both norfloxacin-urea co-crystals and pure norfloxacin reached more than 85% in acetate buffer solution pH 4.0. The difference in the dissolution rate profiles is related to the difference in the solubility of norfloxacin-urea and pure norfloxacin in a water medium and the similarity of their solubility in the acetate buffer solution pH 4.0.

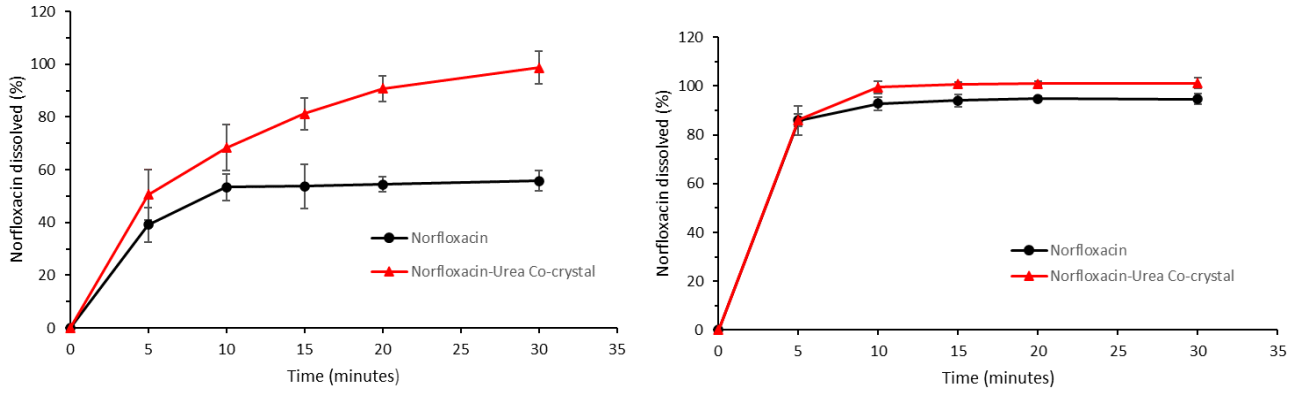

Figure 5. Dissolution profiles of norfloxacin-urea co-crystal and pure norfloxacin in the (**a**) water and (**b**) acetate buffer solution pH 4.0.

CONCLUSION

Norfloxacin-urea co-crystal was also successfully prepared by the ultrasound-assisted slurry co-crystallization method. The norfloxacin-urea co-crystal formation can enhance the solubility of norfloxacin in water and has the potential for scale-up when prepared by the ultrasound-assisted slurry co-crystallization method.

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AUTHORS' CONTRIBUTION

FA: initiated research, analyzed DSC, PXRD, and crystal morphology results, wrote manuscripts, **DS**: conducted co-crystal preparation, solubility test, and dissolution rate, **NAA**: provided advice on writing and analysis of solubility results. All authors have read and approved the publication of the manuscript.

DATA AVAILABILITY

None.

CONFLICT OF INTEREST

The authors declare there is no conflict of interest in this paper.

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