

## Cocrystals of Cefixime with Nicotinamide: Improved Solubility, Dissolution, and Permeability

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### ABSTRACT

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Cefixime is a third-generation cephalosporin antibiotic with poor solubility and permeability. Formulation of active ingredients with poor solubility in water are developed using crystal modification technology. Therefore, this study aims to improve the physicochemical properties of cefixime using cocrystallization by comparing Dry Grinding (DG) and Liquid-Assisted Grinding (LAG) methods. Cocrystal of cefixime with nicotinamide was prepared in a 1:1 molar ratio and was characterized by differential scanning calorimetry (DSC), Fourier transform infrared (FTIR), scanning electron microscopy (SEM), X-ray diffraction (XRD) methods. Properties such as solubility, dissolution rate, and permeation rate were evaluated. The solubility test results obtained:  $0.420 \pm 0.016$  (cefixime);  $0.675 \pm 0.016$  (cocrystal 1:1 LAG); and  $0.632 \pm 0.016$  (cocrystal 1:1 DG). The dissolution test results obtained:  $186.55 \pm 4.18$  (cefixime);  $232.83 \pm 4.07$  (cocrystal 1:1 LAG); and  $228.82 \pm 10.07$  (cocrystal 1:1 DG). The permeability test obtained:  $153.58 \pm 31.94$  (cefixime);  $306.22 \pm 77.81$  (cocrystal 1:1 LAG); and  $211.44 \pm 22.90$  (cocrystal 1:1 DG). Cefixime can be formed into cocrystal with nicotinamide by DG and LAG methods according to the results of characterization using DSC, FTIR, SEM, and XRD. Based on the increase in solubility, dissolution, and permeability of both methods, the LAG method showed better results than the DG in forming cocrystal cefixime with nicotinamide.

**Keywords:** cocrystal, characterization, solubility, dissolution, permeability

### INTRODUCTION

Cefixime belongs to the third-generation cephalosporin, given orally for the treatment of susceptible infections such as gonorrhoea, otitis media, pharyngitis, lower respiratory tract infections, and urinary tract infections. It has poor solubility in water, slightly soluble in alcohol, practically insoluble in ethyl acetate, and very soluble in methyl alcohol (Sweetman, 2009). Furthermore, it is classified as class IV in the Biopharmaceutics Classification System (BCS) with low solubility and permeability. The solubility in water is 55.11 mg/l while its log P value is -0.4 (Wishart *et al.*, 2006). The dissolution rate of pure cefixime is very low, for 120 minutes only about 32.45 % is dissolved in phosphate buffer pH 6.8 (Arora *et al.*, 2010).

Poor solubility and low dissolution rate from a drug with poor penetration through the gastrointestinal membranes often caused low bioavailability (Savjani *et al.*, 2012; Shaikh *et al.*, 2012), which is a system to measure the level and quantity of a drug in the systemic circulation (Qiao *et al.*, 2011). These parameters can be improved to increase its bioavailability because the dosage forms for peroral use are often degraded before reaching the systemic circulation (Savjani *et al.*, 2012; Shaikh *et al.*, 2012). Crystal modification is a technique used to develop a formulation for active ingredients with poor solubility in water. It is a technology used to develop a formulation for an active ingredient with poor solubility in water. One method of crystal modification is cocrystal (Kawabata *et al.*, 2011).

To form a multi-crystalline phase, a coformer should have a specific group, such as carboxylic acids, amides, carbohydrates, alcohols, or amino acids (Bavishi & Borkhataria, 2016). Nicotinamide has been widely used as a coformer in studies about cocrystallization. Theophylline and nicotinamide can form cocrystals in a 1:1 molar ratio by using solid-state grinding and slow evaporation methods with ethanol as solvent. The outcome is improved dissolution rate and solubility of theophylline in water is increased compared to the pure type (Lu & Rohani, 2009). Aceclofenac and nicotinamide can form cocrystals by using a neat grinding method and solution crystallization method with DMSO as the solvent, proven by using FTIR, DSC, MS, and SEM (Sevukarajan *et al.*, 2011). Four compounds from the fenamic acid family consisting of flufenamic acid, niflumic acid, tolfenamic acid, and mefenamic acid formed cocrystal with nicotinamide at 1:1 and 1:2 stoichiometry ratio. This is proven by the tenacity (validity) of carboxylic acid heterosynthon formation proven by using PXRD dan DSC (Fabian *et al.*, 2011). Cocrystal will be useful in the development of drugs to produce cefixime dosage forms with better physicochemical characteristics than other dosage. Dry Grinding (DG) was compared with Liquid-Assisted Grinding (LAG) methods to form cocrystal of cefixime with nicotinamide.

## MATERIALS AND METHODS

Cefixime and nicotinamide were acquired from PT. Dexa Medica, Palembang, Indonesia. Meanwhile, dialysis membrane, ethanol, potassium dihydrogen phosphate, and sodium hydroxide were purchased from Sigma-Aldrich.

### Cocrystal Preparation

#### Cocrystallization via Dry Grinding (Cocrystal 1:1 DG)

About 1.258 of Cocrystal was made by mixing 1:1 molar ratio of cefixime (1.014 mg) and nicotinamide (244 mg) in mortar for  $\pm 15$  min.

#### Cocrystallization via Liquid-Assisted Grinding (Cocrystal 1:1 LAG)

Cocrystal was made by mixing 1:1 molar ratio of cefixime (1.014 mg) and nicotinamide (244 mg) in mortar for  $\pm 15$  min. Furthermore, ethanol was added and the cocrystal was dried at room temperature for at least 1 day.

### Cocrystal Characterization

#### Differential Scanning Calorimetry (DSC)

Thermal analysis of cefixime, nicotinamide, cocrystal 1:1 LAG, and cocrystal 1:1 DG were conducted by differential scanning calorimeter (Shimadzu, DSC-60 Plus, Japan). Accurately weighed 5-10 mg of the samples were placed in aluminum pans and scanned from 25 to 300 °C. The temperature rate adjusted to 10 °C/min under nitrogen purge with flow rate at 30 ml/min.

#### Fourier Transform Infrared (FTIR)

Spectra of cefixime, nicotinamide, cocrystal 1:1 LAG, and cocrystal 1:1 were conducted by Fourier transform infrared (Thermo Fisher Scientific, Nicolet iS10, USA). Each spectrum was derived from 32 single average scans collected in the range of 650-4,000  $\text{cm}^{-1}$  at the spectral resolution of 4  $\text{cm}^{-1}$ .

#### X-Ray Diffraction (XRD)

Crystal structure of cefixime, nicotinamide, cocrystal 1:1 LAG, and cocrystal 1:1 DG were conducted by X-ray diffraction (Bruker, D2 Phaser, USA), and the samples were scanned from 0° to 50° (2 $\theta$ ).

#### Scanning Electron Microscopy (SEM)

Morphology of cefixime, nicotinamide, cocrystal 1:1 LAG, and cocrystal 1:1 DG were analyzed by scanning electron microscopy (JEOL, JSM-6510LA, Japan). Samples were mounted in holder and SEM photographs were scanned with an electron beam of acceleration potential of 15 kV.

### Cocrystal Properties

#### Solubility Test

Solubility test was carried out by weighing samples equivalent to 10 mg pure cefixime then putting each one in the flacon which contained 10 ml of distilled water. The test was conducted by using a shaking thermostatic water bath (Julabo, USA) for 2 hours, and each sample was tested three times. The absorbance was measured by UV-Vis spectrophotometer (Thermo Fisher Scientific, Genesys 10S, USA) at a wavelength of 288 nm then the concentration of the saturated solution was calculated.

#### Dissolution Test

The dissolution test was performed by using the basket method dissolution tester (Vanguard DC 6, USA). Samples were weighed equivalent to 200 mg pure cefixime then put into a capsule shell. Furthermore, they were put into the dissolution baskets, that was placed in a dissolution flask filled with 900 ml media, phosphate buffer pH 7.2.

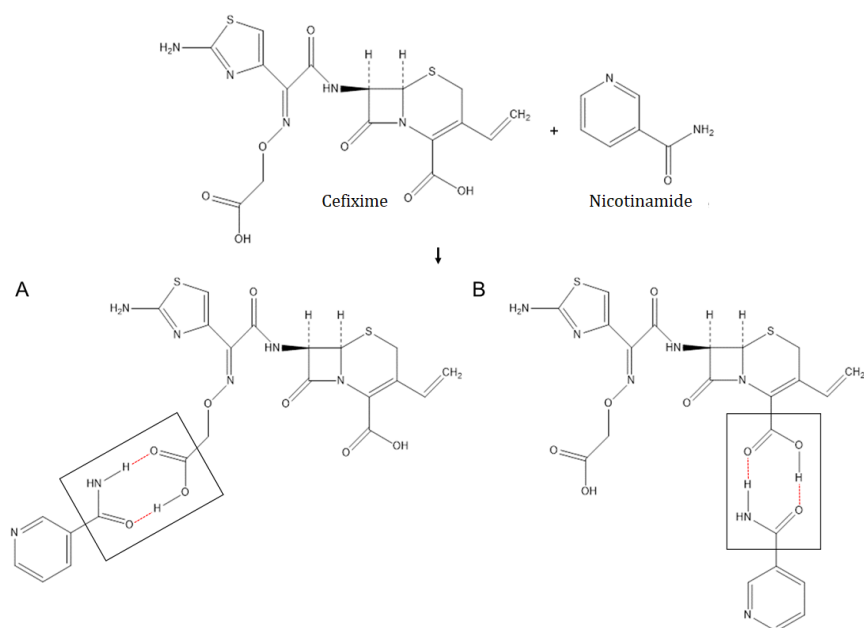


Figure 1. Perspective view of an intermolecular hydrogen bond between cefixime and nicotinamide. A hydrogen bond was formed between the amide moiety of nicotinamide and the carboxylic moiety of cefixime that bonded to hydroxylamine (A). A hydrogen bond was formed between the amide moiety of nicotinamide and the carboxylic moiety of cefixime that bonded to the nitrobenzene ring (B).

The temperature was adjusted to  $37 \pm 0.5$  °C and the rotation speed was at 100 r/min. The test was carried out for 45 min, and each sample was tested three times. The absorbance was measured by UV-Vis spectrophotometer (Thermo Fisher Scientific, Genesys 10S, USA) at a wavelength of 288 nm then the concentration of dissolved samples was calculated.

#### Permeability Test

Permeation test was conducted by modified Franz cell method using dialysis membrane. Samples were weighed equivalent to 50 mg pure cefixime then put into donor compartments suspended by 2 ml of water. In addition, receptor compartments were filled with 125 ml phosphate buffer pH 7.2 with rotation speed at 100 r/min and flow rate at 75 r/min for 23 hours. The absorbance was measured by UV-Vis spectrophotometer (Thermo Fisher Scientific, Genesys 10S, USA) at the wavelength of 288 nm and then the concentration of diffused samples was calculated.

## RESULTS AND DISCUSSION

Many methods such as dry and liquid-assisted grinding can be used in cocrystallization. Dry grinding is used by mixing the cocrystal components together using a mortar and pestle, as well as ball or vibratory mill. In liquid assisted milling, a small amount of liquid is added to the mixture during grinding (Frisic & Jones, 2009;

Korotkova & Kratochvíl, 2014). The presence of solvent as a liquid phase can increase the rate of cocrystal formation due to increased molecular diffusion (Alatas & Uekusa, 2013). The choice of solvent used in the solvent-drop grinding method is very important, and should be able to dissolve at least a small part of the substance. Ethanol is used as a liquid phase because it can dissolve cefixime and nicotinamide.

Cocrystallization was formed by the supermolecular synthon which is formed by hydrogen bonds. These intermolecular bonds occur between hydrogen and other electronegative atoms such as nitrogen (N), oxygen (O), and phosphorus (P) (Kumar & Nanda, 2017). The strength of this bond is weaker than covalent but stronger than other non-covalent bonds (dipole, ionic and other bonds) (Williams *et al.*, 2013). Cefixime and nicotinamide were able to form hydrogen bonds through the heterosynthon supermolecular interaction between carboxylic moiety (-COOH) of cefixime with the amide moiety (-CONH<sub>2</sub>) of nicotinamide (Figure 1). The selection of nicotinamide as a cofomer was based on a synthon approach. The synthon-based approach is a simple method for predicting cocrystal formation, and it suggests that certain functional groups are present in the API and cofomers will play an important role in cocrystal formation (Alatas & Uekusa, 2013; Thakuria *et al.*, 2013).

### Cocrystal Characterization DSC Analysis

DSC overlay curve of 4 samples, and the result confirmed that cefixime and nicotinamide were able to form cocrystal (Figure 2). This was proved by the decrease of the melting point from 200.92 °C to 178.96 °C. The melting point of cocrystals were in between the constituent components (cefixime and nicotinamide). The result showed similarity with research conducted by Schultheiss & Newman (2009), where a compound's melting point can be changed through the formation of cocrystal. The melting point of cocrystal was between that of the active ingredient and the coformer or lower than both. A high melting point is produced when cefixime is bonded to each other due to the dipole-dipole forces. The intermolecular forces of attraction will make the compound have a high melting point. The decrease in the melting point of cocrystals is caused by the interaction between different molecules, namely the carboxylic moiety in cefixime and the amide in nicotinamide through hydrogen bonds. There was a correlation between the melting point of a compound with solubility where a high value showed low solubility (Qiao *et al.*, 2011). The result of cocrystal DSC showed that its melting point is lower than pure cefixime, and the decrease of melting point can be predicted by the increase of solubility. The result can be confirmed in the solubility test which has been carried out. According to Mbah *et al.* (2011), the permeability of a drug can be increased by using eutectic system. The decrease of a compound's melting point can increase its permeability.

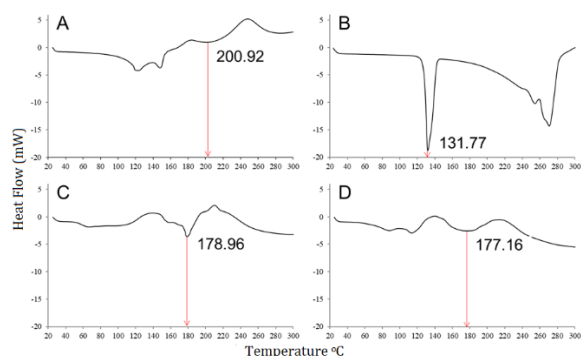


Figure 2. Curve of DSC for cefixime sample with a melting point at 200.92 °C (A), nicotinamide with its melting point at 131.77 °C (B), cocrystal 1:1 LAG with its melting point at 178.96 °C (C), and cocrystal 1:1 DG with its melting point at 177.16 °C (D).

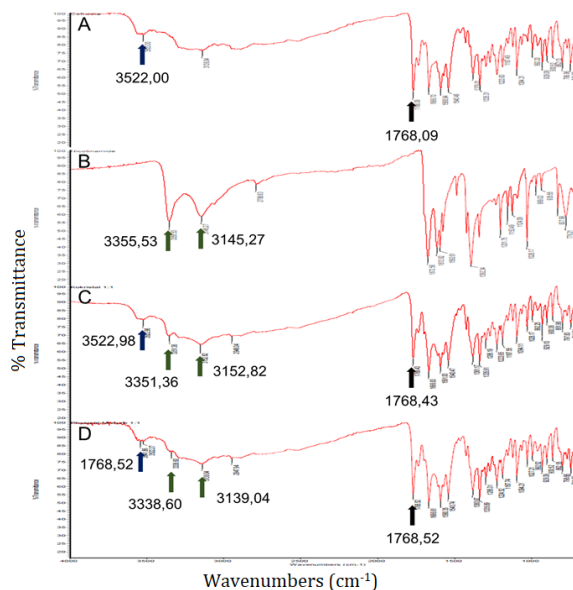


Figure 3 Spectra FTIR for cefixime (A), nicotinamide (B), cocrystal 1:1 LAG (C), and cocrystal 1:1 DG (D). Arrows showed the shifting of the peak for group C=O stretching from 1768.09 to 1768.43 (cocrystal 1:1 LAG) and 1768.52 (cocrystal 1:1 DG).

### FTIR Analysis

The interaction between carboxyl acids in cefixime and amides in nicotinamide can be analyzed using FTIR in the form of a spectrum that represents each functional group in the compound. The interaction is indicated by a change in the intensity of the specific spectrum of each functional group that plays a role in hydrogen (Kumar & Nanda, 2017). Specific functional groups of cefixime appeared at the wavelength of 3,139.04 (O-H stretching); 1,768.09 (C=O stretching); 1,223.60 (C-O stretching); 929.08 (O-H out-of-plane). Furthermore, specific functional groups of nicotinamide appeared at the wavelength of 3,351.75 and 3,151.14 (N-H stretching); 1,672.56 (C=O stretching); 1,613.92 (N-H bending); 700.34 (N-H out-of-plane), while cocrystal 1:1 LAG appeared at the wavelength of 1,768.43 (C=O stretching); 1,223.95 (C-O stretching); 929.10 (O-H out-of-plane). Specific functional groups of cocrystal 1:1 DG appeared at the wavelength of 1,768.52 (C=O stretching); 1,224.52 (C-O stretching); 929.39 (O-H out-of-plane), as seen in Figure 3. Cocrystals 1:1 (LAG and DG) showed different spectra compared to cefixime from the change of peak intensity for O-H and C=O groups of cefixime. For cocrystal 1:1 there was a shift in the

functional group C=O stretching from 1,768.09 to 1,768.43 (LAG) and 1,768.52 (DG); C-O stretching from 1,223.60 to 1,223.95 (LAG) and 1,224.52 (DG). This spectral shift occurs due to intermolecular interactions between cefixime and nicotinamide through hydrogen bonds.

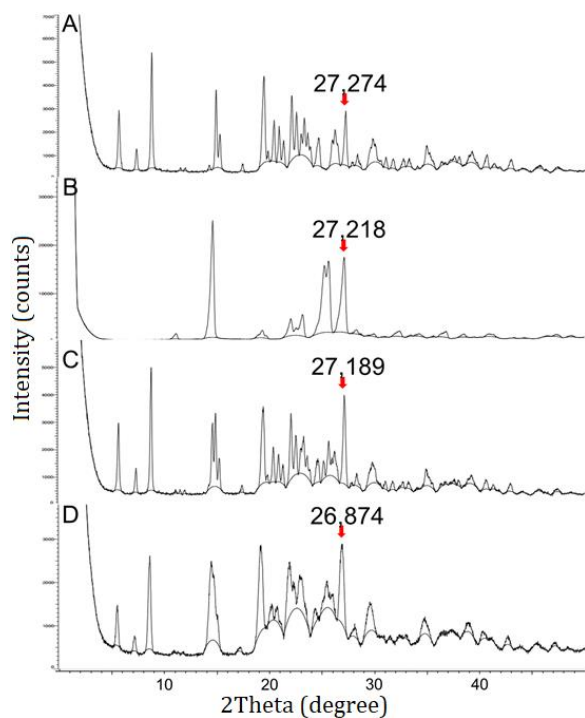


Figure 4. The XRD pattern for cefixime (A), nicotinamide (B), cocystal 1:1 LAG (C), and cocystal 1:1 DG (D). Arrows showed the peak of cefixime at  $2\theta$  27.274° and the peak of nicotinamide at  $2\theta$  27.218° were merged into a sole peak  $2\theta$  27.189° for cocystal 1:1 LAG and  $2\theta$  26.874° for cocystal 1:1 DG.

#### XRD Analysis

The crystallinity of the compound can be determined using PXRD to distinguish these compounds in crystalline or amorphous form by the presence of diffraction peaks. The appearance of a diffraction peak indicates that the compound is crystalline, while amorphous will form a diffraction hump (Bunaciu *et al.*, 2015). Furthermore, the diffraction peak represents each crystal lattice in a compound. The result of the XRD test showed the specific pattern of cefixime at  $2\theta$  5.751°; 8.859°; 14.969°; 19.512°; 22.152°; and 27.274°. Pattern of XRD nicotinamide is at  $2\theta$  14.744°; 25.349°; 25.721°; and 27.218°, while XRD cocystal 1:1 LAG is at  $2\theta$  5.772°; 8.879°; 14.690°; 14.986°; 19.508°; 22.135°; 25.233°; 25.176°; and 27.189°. The

pattern of XRD cocystal 1:1 DG is at  $2\theta$  5.577°; 8.677°; 14.507°; 14.758°; 19.210°; 21.929°; 25.089°; 25.495°; and 26.874° (Figure 4). The pattern of XRD cocystal 1:1 (LAG and DG) showed a different pattern for both cefixime and nicotinamide, with peaks at  $2\theta$  27.274° and  $2\theta$  27.218°. The two were merged into a sole peak at  $2\theta$  27.189° for cocystal 1:1 LAG and  $2\theta$  26.874° for cocystal 1:1 DG. This was illustrated with red dotted arrows indicating the interaction between cefixime and nicotinamide. Cocystal 1:1 LAG showed a clearer and sharper peak than cocystal 1:1 DG. The LAG method is described as solvent catalysis, where a small amount of solvent is useful as a lubricant in molecular diffusion. Meanwhile, the addition of a small amount of solvent can accelerate the cocrystallization (Brittain, 2012).

#### SEM Analysis

Cocrystallization of cefixime and nicotinamide was also observed under SEM. The cocystals show a more compact structure and form aggregations due to the interaction of hydrogen bonds between cefixime and nicotinamide (Sopyan *et al.*, 2017). The 1:1 cocystals (LAG and DG) exhibited an irregular shape but differed from the two components (Figure 5).

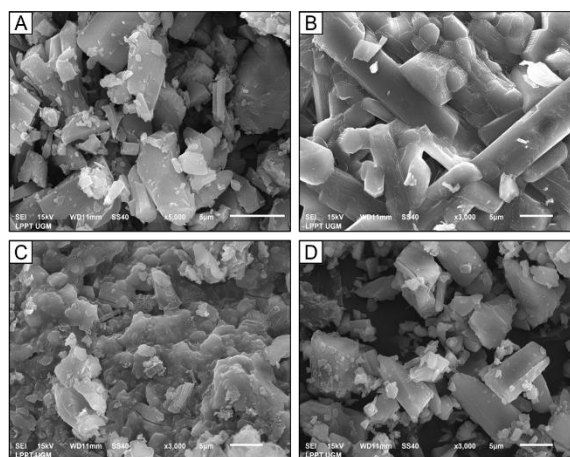


Figure 5. Photomicrograph of cefixime (A), nicotinamide (B), cocystal 1:1 LAG (C), and cocystal 1:1 DG (D) with magnification 10,000x.

#### Cocrystal Properties

##### Solubility

Solubility of cefixime, cocystal 1:1 LAG, and cocystal 1:1 DG in water are obtained at 0.420 mg/ml, 0.675 mg/ml, 0.632 mg/ml respectively. Cocystal 1:1 LAG and DG increased 1.58 and 1.48



times compared to pure cefixime (Table I). The increasing solubility of cefixime in cocrystal is consistent with the research conducted by Izutsu *et al* (2016), where coformer of cocrystal can lower the intrinsic melting point, relatively increasing the solubility of cocrystal. Increased solubility of cocrystals was affected by that of nicotinamide which is soluble in water. The solubility of cefixime is directly proportional to the therapeutic effects and the dissolution. It was concluded that the solubility of cefixime could be modified through the cocrystallization process.

Table I. Solubility test of samples in phosphate buffer pH 7.2

Sample	Solubility (mg/ml)
Cefixime	0.420 ± 0.016
Cocrystal 1:1 (LAG)	0.675 ± 0.016
Cocrystal 1:1 (DG)	0.632 ± 0.016

#### Dissolution Rate

The dissolution rate of cocrystal 1:1 LAG increased 1.25 times compared to pure cefixime with dissolved percentage of 104.73 %. Meanwhile, the rate of cocrystal 1:1 DG increased 1.18 times compared to pure cefixime with dissolved percentage of 99.58 % as shown in Figure 6. The dissolution rate of cocrystals increased with the increasing solubility of cocrystals. In several cases, the increasing dissolution of cocrystal appears in a short time under 30 min. (Karagianni *et al.*, 2018). The dissolution of cefixime in cocrystal 1:1 (LAG and DG) increased dramatically in the 6<sup>th</sup> minute. Cocrystal 1:1 LAG and DG dissolved 100 % at the 20<sup>th</sup> and 30<sup>th</sup> minute. It was concluded that the dissolution of cefixime could be modified through the cocrystallization process. These are supported by the results of the solubility test that has been carried out. Therefore, increasing the dissolution rate of cefixime will affect its permeability.

#### Permeation Rate

The permeation rate of cocrystal 1:1 LAG increased 1.99 times more than pure cefixime with the diffusion percentage of 76.55 %. Meanwhile, cocrystal 1:1 DG increased 1.37 times more than pure cefixime with the diffusion percentage of 52.86 % as shown in Figure 6. According to Izutsu *et al* (2016), the bonding of the drug with the coformer can increase the permeability by stabilizing the saturated solution and crossing the membrane by diffusion or through a transporter. Cocrystals 1:1 LAG and DG showed a significant

increase compared to cefixime from the three tests conducted. It was concluded that the permeability of cefixime could be modified through the cocrystallization process. The increase in physicochemical properties predicts that the bioavailability of cefixime will increase. The increased bioavailability makes it possible to achieve a rapid therapeutic effect (Tomaszewska *et al.*, 2013).

#### CONCLUSION

Cefixime can be formed into cocrystal with nicotinamide according to the results of characterization using DSC, FTIR, SEM, and XRD accompanied by the increasing solubility, dissolution, and permeability. The solubility of cocrystal 1:1 LAG and DG increased 1.58 (0.675 mg/ml) and 1.48 times (0.632 mg/ml) compared to pure cefixime (0.420 mg/ml). The dissolution rate increased 1.25 (104.73 %) and 1.18 times (99.58 %) compared to pure cefixime (83.84 %). Meanwhile, the permeability increased 1.99 (76.55 %) and 1.37 times (52.86 %) compared to pure cefixime (38.40 %). Cocrystallization using the LAG method showed better results compared to the DG method. Stability and bioavailability studies are required to exploit the advantages of the cocrystallization process commercially.

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