INTRODUCTION

Most active pharmaceutical ingredients have either poor solubility or poor permeability, or both. The bioavailability of orally administered drugs depends strongly on the drug's solubility in aqueous medium, so the solubility behavior of drugs is one of the most challenging tasks in the design of oral dosage. In drugs with poor water solubility, low bioavailability is often observed after oral administration since in vivo dissolution of a drug can be a rate-limiting step [1,2].

Lansoprazole (LPZ) {2-[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl] methyl sulfinyl-1H-benimidazole} is a proton-pump inhibitor that acts on membrane H+/K+ -ATPase in gastric parietal cells. It is widely used to treat a variety of acid-related disorders, including peptic ulcers, both duodenal and gastric, symptoms of gastroesophageal reflux disease, erosive esophagitis, drug-induced ulcers, and hypersecretory syndromes, such as Zollinger–Ellison and Helicobacter pylori infections [3,4]. LPZ is a Class II drug under the Biopharmaceutics Classification System. These drugs are characterized by high permeability, but poor solubility. Therefore, increasing the rate of dissolution of LPZ is paramount to increase the rate of drug absorption [5,6].

One way to improve drug solubility is through cocrystallization, a method which involves the modification of a crystalline drug substance by the addition of a coformer. Cocrystallization can improve the solubility, dissolution rate, bioavailability, and stability of an active substance. The methods used for cocrystallization include the solvent and grinding methods [7].

Many ways of producing cocrystals have been reported. The most common methods are based on solution and grinding. The dilution method involves mixing the two components comprising the active ingredient of the drug and the coformer in a solvent or mixture of solvents. Dissolution includes several methods, such as evaporation, reaction crystallization, and cooling. Dilution is used in many cocrystal formations, but the process requires a considerable amount of solvent [7,8]. Grinding methods consist of mixing the stoichiometric cocrystal components and grinding them either manually, using a mortar and pestle, or mechanically, using a ball mill or a vibratory mill [8]. There are two different techniques for cocrystal formation using grinding methods, namely, dry grinding and solvent-drop grinding.

In this research, cocrystals of LPZ using nicotinamide (NCT) as the coformer were produced using the solvent evaporation and solvent-drop grinding methods. NCT is highly soluble in water, which should increase the rate of dissolution of LPZ [9,10]. Cocrystals produced in this way should have better solubility, increasing the bioavailability of LPZ. Dissolution tests were conducted on pure LPZ and the cocrystals of LPZ-NCT. The cocrystals were characterized by infrared spectroscopy, X-ray powder diffraction (XRD), and differential scanning calorimetry (DSC).

METHODS

Materials
LPZ was kindly provided by PT Clinisindo, Indonesia (Cipla, India). NCT and methanol were purchased from Brataco, Indonesia. Double-distilled water was purchased from Ikapharmindo, Indonesia.

Preparation of cocrystals of LPZ-NCT using the solvent evaporation method
LPZ and NCT at a molar ratio of 1:1 and 1:2 were dissolved in methanol by stirring. The solvent was evaporated and the residue dried at room temperature. The mixture was stored in a desiccator [11].

Preparation of cocrystals of LPZ-NCT using solvent-drop grinding method
A required amount of LPZ and NCT with a molar ratio of 1:1 and 1:2 was placed in a ball mill. Methanol was then added. The mixture was evaporated at room temperature and stored in a desiccator [11].
Preparation of a physical mixture of LPZ-NCT
A mixture of LPZ and NCT was produced with a molar ratio of 1:2. The mixture was placed in a mortar, homogenized with a spatula, and then stored in a desiccator.

Determination of LPZ content
The LPZ content was determined by weighing a specified amount of the LPZ-NCT cocrystals in a volumetric flask, dissolving it in methanol, and filling it to the desired volume with double-distilled water. The samples were then assayed using an ultraviolet-visible (UV–VIS) spectrophotometer at a wavelength of 283 nm [12].

Characterization of cocrystals
Crystal form
The crystal forms of the LPZ-NCT cocrystals and LPZ and NCT were observed through polarization microscopy. Samples were placed on a slide, covered with a cover glass, and observed at a microscope under ×400–1000.

Fourier-transform infrared (FTIR) spectroscopy
The LPZ-NCT cocrystals were analyzed using FTIR (Shimadzu 8400S, Japan) by mixing KBr in a mortar. The wavelength analyzed was 400–4000 cm⁻¹, and characteristic peaks were recorded [4].

XRD
X-ray patterns of the LPZ-NCT cocrystals were recorded using an X-ray diffractometer with Cu as the anode material, at a voltage of 40 kV and a current of 40 mA. The samples were analyzed at angles 2θ of 2–30° at scan rates of 1°/min [4].

DSC
DSC measurements were performed using a PerkinElmer type 600 setup. The samples of the LPZ-NCT cocrystals and the pure LPZ (2.5–5 mg) were hermetically sealed in aluminum pans and heated at a constant rate of 10°C/min within a temperature range of 25–250°C, with a flow rate of 20 mL/min using nitrogen gas [4].

Saturated solubility
To determine the saturated solubility of the LPZ-NCT cocrystals, approximately 50 mg of the LPZ-NCT cocrystals were weighed and added to 100 mL of double-distilled water, and the resulting slurries were stirred on a magnetic stirrer at 25±0.5°C. An aliquot of the slurry was double filtered at 0.45 µm. The diluted samples were then assayed using a UV–VIS spectrophotometer at a wavelength of 283 nm.

Dissolution study
The dissolution tests were conducted using a USP type II apparatus to determine the initial dissolution rate of the LPZ-NCT cocrystals. The LPZ-NCT cocrystals, the LPZ and NCT physical mixture, and the pure LPZ were weighed equivalent to 50 mg of LPZ. The dissolution test was performed at 37±0.5°C for 1 h using double-distilled water. Then, 5 mL aliquots were withdrawn at 5, 10, 15, 20, 25, 30, 40, 50, and 60 min and replaced with an equivalent amount of fresh medium to maintain the sink condition and analyzed using a UV–VIS spectrophotometer at a wavelength of 283 nm.

RESULTS AND DISCUSSION
Determination of drug content
Table 1 shows the yield value and LPZ content in the LPZ-NCT cocrystals. The results showed that the LPZ cocrystals produced using the solvent evaporation method with the ratios of 1:1 and 1:2 containing 75.08% and 58.98% LPZ, respectively. The cocrystals of LPZ produced using the solvent-drop grinding method with molar ratios of 1:1 and 1:2 containing 71.16% and 55.47% LPZ, respectively. Some loss of LPZ in cocrystals may occur during the process.

Characterization of cocrystals
Crystal form
Macroscopically, the cocrystals produced using the solvent evaporation method were in the form of a greenish-brown crystalline powder. The cocrystals produced using the solvent-drop grinding method were brown crystalline powder. The powder produced using the solvent-drop grinding method was finer than that of cocrystals produced using the solvent evaporation method.

Microscopically, there were different crystalline forms of cocrystals, as shown in Fig. 1. The cocrystals produced using the solvent evaporation method had a crystalline form like a diamond. The cocrystals produced using the solvent-drop grinding method, however, had an irregular crystalline form. The cocrystals produced using the solvent evaporation method had a more crystalline form than that of cocrystals produced using the solvent-drop grinding method. The differences in crystal form were due to

| Method          | Molar ratio LPZ-NCT | Yield value LPZ (%w/w) | LPZ content in cocrystals (%w/w) |
|-----------------|---------------------|------------------------|----------------------------------|
| Solvent         | 1:1                 | 99.9±0.71              | 75.08±0.53                       |
| evaporation     | 1:2                 | 98.0±1.69              | 58.98±1.02                       |
| Solvent-drop    | 1:1                 | 94.6±1.57              | 71.16±1.18                       |
| grinding        | 1:2                 | 96.8±0.85              | 55.47±0.49                       |

| a | b | c | d | e | f |
|---|---|---|---|---|---|
| SE 1:1 | SE 1:2 | PM 1B | SDG 1:1 | SDG 1:2 | LNZ |

Fig. 1: Microscopic crystalline forms of the lansoprazole (LPZ)-nicotinamide (NCT) cocrystals produced using (a) solvent evaporation (SE) method with a molar ratio of 1:1, (b) SE with a molar ratio of 1:2, (c) physical mixture of LPZ-NCT, (d) solvent-drop grinding (SDG) method with a molar ratio of 1:1, (e) SDG with a molar ratio of 1:2, and (f) the pure LPZ.

Fig. 2: Possible hydrogen bonding between lansoprazole and nicotinamide.
the manufacturing method, in which the solvent-drop grinding and milling processes are carried out at a constant speed using a vibrating mill. This leads to the production of a crystalline form which is smaller than the crystals produced using the solvent evaporation method [13].

**FTIR**

Interactions between the substances occur through hydrogen bonding between LPZ and NCT. A hypothetical possibility of hydrogen bonding of the cocrystals of LPZ is shown in Fig. 2.

The FTIR spectra of cocrystals produced using all of the methods, for LPZ, NCT, and physical mixtures between LPZ-NCT, are presented in Fig. 3. The characteristic absorption of cocrystals shows peaks at 1398.44 to 1402.30 cm\(^{-1}\) denoting hydrogen bonds between S=O of LPZ and atom H from the amide group of NCT. The FTIR spectra show shifting peaks between the atom four of LPZ and atom H from the amide group of NCT at 1402.30 to 1398.44 cm\(^{-1}\). In addition, there are new wavelengths between 1697.41 and 1681.98 cm\(^{-1}\).

Based on the observed wavelengths of the FTIR spectrum of cocrystals of LPZ, it can be concluded that the manufacture of cocrystals of LPZ and NCT resulted from hydrogen bonding between LPZ and NCT.

**X-ray diffraction (XRD)**

Fig. 4 shows a diffractogram of LPZ cocrystals, prepared through the solvent evaporation method, with molar ratios of 1:1 and 1:2. The results represent an increase in intensity compared with pure LPZ, indicating changes or additions to the form and structure of the crystal grid on cocrystals. The diffractograms of the cocrystals from solvent-drop grinding methods showed a decrease in intensity compared with diffractograms of pure LPZ. This is because the solvent-drop grinding method causes particle size reduction by milling at high speed. Diffractogram intensity has also increased, indicating the formation of crystals in cocrystals of LPZ [4].

**DSC**

Thermograms of the LPZ-NCT cocrystals are shown in Fig. 5. The LPZ-NCT cocrystals have a lower melting point than pure LPZ. This finding
The thermogram results indicate that pure LPZ has a melting point of 170.52°C. Cocrystals produced using the solvent-drop grinding method with a molar ratio of 1:2 showed a decreased melting point compared with pure LPZ, at a temperature of 123.27°C. Cocrystals from the solvent evaporation method with a molar ratio of 1:2 showed a decrease of melting point to 124.38°C, and the physical mixture of LPZ-NCT has a melting point of 129.51°C.

Characterization using DSC showed that fusion energy is needed to melt a sample of cocrystal. The thermogram showed an increase in fusion energy over pure LPZ. The energy required to melt the cocrystal was greater than that required to melt pure LPZ [10,13].

**Solubility**

Cocrystals of LPZ exhibited increased solubility compared with LPZ, as shown in Fig. 6. The solubility of cocrystals produced using the solvent evaporation method with a molar ratio of 1:1 was increased by 1.1-fold, and that for a molar ratio of 1:2 was increased by 1.37-fold compared with pure LPZ. Similarly, the solubility of cocrystals produced using the solvent-drop grinding method at a molar ratio of 1:1 was increased by 1.7-fold, and that for a molar ratio of 1:2 was increased by 2.28-fold, whereas the physical mixture between LPZ and NCT with a molar ratio of 1:2 was increased by 1.25-fold compared with pure LPZ.

Cocrystals produced using the solvent-drop grinding method with a molar ratio of 1:2 had the highest increase in solubility. The increase in solubility of cocrystals is due to several mechanisms. The grinding process is carried out at high speed, resulting in the reduction of the crystalline form of LPZ. NCT is also highly soluble in water, contributing to the increased solubility of LPZ [14].

From the results of the saturated solubility tests, it appears that cocrystals produced using all methods and the physical mixture of LPZ-NCT showed an increase in solubility when compared with pure LPZ.

**Dissolution study**

Fig. 7 shows the dissolution profiles of the LPZ-NCT cocrystals, which revealed that the percentage of dissolved LPZ from the LPZ-NCT cocrystals produced using the solvent-drop grinding method with a molar ratio of 1:2 was increased by 8.4-fold when compared with pure LPZ. The solubility of cocrystals from the same method with a molar ratio of 1:1 increased in 5 min the amount of dissolved drug by 6.58-fold. Cocrystals produced using the solvent evaporation method with a molar ratio of 1:1 increased by 6.33-fold in 5 min and for a molar ratio
of 1:2, 7.4-fold. On the other hand, the physical mixture of LPZ-NCT with a molar ratio of 1:2 was increased by 3.87-fold compared with pure LPZ.

The increase in the cumulative amount of LPZ dissolved was apparent in 60 min. The percentage of cocrystals produced using the solvent-drop grinding method with a molar ratio of 1:2 showed the greatest improvement, in which the 60 min increase was 1.44-fold, and a molar ratio of 1:1 was increased by 1.44-fold. Cocrystals produced using the solvent evaporation method with a molar ratio of 1:1 increased by 1.07-fold, and that for a molar ratio of 1:2 was increased by 1.32-fold. The physical mixture between LPZ and NCT with a molar ratio of 1:2 was increased by 1.26-fold when compared with pure LPZ.

Based on the results of the dissolution test, it appears that the cocrystals of LPZ using NCT as a coformer increase the dissolution of LPZ in water due to the hydrogen bonds in the cocrystals of LPZ. These hydrogen bonds can improve the dissolution of the cocrystals [15]. The increasing dissolution of cocrystals caused by the grinding process is carried out at high speed in the solvent-drop grinding method. NCT is highly soluble in water, contributing to the increased dissolution rate of LPZ.

CONCLUSION

The formation of the cocrystals of LPZ using NCT as coformer with a molar ratio of 1:1 and 1:2 using the solvent evaporation and solvent-drop grinding methods was confirmed by the presence of hydrogen bonding in the infrared spectrum, the addition of a crystal grid on X-ray diffraction, and a decline in the melting point in the thermal analysis. Moreover, the LPZ-NCT cocystal produced using the solvent-drop grinding method with a molar ratio of 1:2 showed the greatest increase in solubility in water. The LPZ-NCT cocrystals produced using the solvent-drop grinding method had the highest dissolution rate within 5 min, and it was an increase of 8.4-fold compared with pure LPZ.

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CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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