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Formation of Candesartan Cilexetil – Nicotinamide Cocrystals Using the Solvent Drop Grinding Method

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ABSTRACT: Candesartan cilexetil is a class II Biopharmaceutical Classification System (BCS). This study aims to increase the dissolution rate of candesartan cilexetil by forming cocrystals of candesartan cilexetil – nicotinamide by solvent drop grinding method with a ratio of 1:1 mol. Evaluation of physicochemical properties of cocrystals, namely characterization by X-ray diffraction, Differential Scanning Calorimetry (DSC), Fourier Transform Infra-Red (FT-IR) spectrophotometer, Scanning Electron Microscopy (SEM) analysis, assay using UV-VIS spectrophotometer and determination of dissolution profile. Based on this study, the results of the X-ray diffraction characterization test showed that there had been a decrease in the intensity of the cocrystals, the thermal analysis of DSC showed a decrease in the endothermic peak of candesartan cilexetilcocrystals from 173,435 °C to 126,275°C, the FTIR spectrum showed no chemical interaction between candesartan cilexetil and nicotinamide. SEM showed a small crystal morphology in candesartan cilecetil - nicotinamidecocrystal, the determination of the concentration of candesartan cilexetil obtained was 100.1%. The results of the dissolution test of candesartan cilexetil in cocrystal 75.604%, physical mixture 59.159%, and pure candesartan cilexetil 50.062% this indicates an increase in the dissolution rate of cocrystal compared to pure candesartan cilexetil.

KEYWORDS: Candesartan cilexetil; Cocristal; Dissolution; solvent drop Grinding

I. INTRODUCTION

Solubility is one of the important parameters for achieving the desired drug concentration in systemic circulation to achieve the required pharmacological response [1]. Low solubility is a major problem faced in the development of new drugs. A substance that has low solubility will be absorbed more slowly, causing low drug bioavailability in the body and will also affect its pharmacological effects [2]. Candesatan is a drug with low solubility which is included in the BCS (Biopharmaceutics Classification System) class II, which has low solubility. Candesartan cilexetil is practically insoluble in water and rather difficult to dissolve in methanol. Candesartan cilexetil has a pKa value of 6 [3]. Candesartan cilexetil is an angiotensin II receptor blocker (ARB) which has been widely used for the treatment of hypertension and congestive heart failure [4,5].

Solubility enhancement techniques have an important role in increasing the dissolution rate of drugs with low solubility. For this reason, various techniques that can be used to increase the solubility of poorly soluble drugs include physicochemical modification of drugs and other methods such as particle size reduction, crystal formation, salt formation, solid dispersion, use of surfactants, complexation, and so on.

A very interesting method is the formation of cocrystals. The cocrystal technique involves modifying the crystal of a solid material by changing the intermolecular interactions that govern the breaking and formation of non-covalent bonds such as hydrogen bonds, Van Der Waals interactions, π-π bonds, electrostatic interactions, and halogen bonds [6]. The formation of cocrystals can improve several properties of a substance, such as solubility, dissolution rate, bioavailability and physical stability [7].

Based on previous research, candesartan cilexetil was made into cocrystals using coformers, namely nicotinic acid, succinic acid, nicotinamide and benzoic acid, with the result of increasing the solubility of candesartan cilexetil by 1.78 times [8]. Previous research with the active substance candesartan cilexetil, which was made with cocrystals using methylparaben customer using the dissolution method resulted in increased solubility and dissolution rate of candesartan cilexetil [8].

A coformer is one of the components in a cocrystal that functions to reduce aggregation between crystal molecules. One coformer that is

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often used is nicotinamide. Nicotinamide has an active amide group with high electronegativity, which causes strong intermolecular hydrogen bonds that are necessary for cocrystal formation. Nicotinamide is widely used as a hydrophilic coformer in cocrystal formation [9]. One of the studies carried out the synthesis of furosemide cocrystals with nicotinamide as a coformer. Cocrystal synthesis was carried out using the solvent drop grinding technique. The results obtained were an increase in the solubility of furosemide-nicotinamide compared to pure furosemide [10].

Solvent drop grinding is a modification of the grinding technique where two materials can be ground by adding a small amount of solvent as a catalyst. The solvent used is a solvent that can dissolve both substances [11]. The solvent drop grinding technique is an easy, cheap and environmentally friendly method. Solvent drop grinding can be used to prepare pure cocrystal phases in a short time [12].

Based on the background above, researchers are interested in making candesartan cilexetil and nicotinamidecocrystals using the solvent drop grinding method. Then the cocrystals formed will be characterized using Differential Scanning Calorimetry (DSC), X-Ray Diffraction (XRD), Fourier Transform-Infrared Spectroscopy (FT-IR), Scanning Electron Microscopy (SEM), assay, and dissolution test.

II. EXPERIMENTATION

Materials used

Candesartan cilexetil (Zhejiang Huahai), Nicotinamide (Cetil Centrum), methanol (Merck), distilled water (PT Novalindo, Indonesia), Potassium Dihydrogen Phosphate (KH2PO4)(Merck), Sodium Hydroxide (NaOH)(Merck).

Formation of Candesartan cilexetil – NicotinamideCocrystals using the Solvent Drop Grinding Method

Candesartan cilexetil - nicotinamidecocrystals were prepared in a 1:1 mole ratio. Candesartan cilexetil and nicotinamide crystals were crushed by adding 1 mL of methanol and crushing for ± 15 minutes. After the mixture of candesartan, nicotinamide, and methanol begins to dry, add 1 mL of methanol again, grind for ± 15 minutes until a dry mass forms, and store in a desiccator. Then, carry out various characteristic tests on the candesartan cilexetil—nicotinamidecocrystals formed.

Making Physical Mixtures

The physical mixture of candesartan cilexetil – nicotinamide was made by weighing and mixing candesartan cilexetil and nicotinamide in a ratio of 1:1 (3.0533 g : 0.6106 g), then mixing and stirring without using pressure for 30 minutes. After the mixing process is complete, store the physical mixture in a desiccator.

Characteristics of Candesartan cilexetil, Nicotinamide, Physical Mixture and Cocrystals of Candesartan cilexetil - Nicotinamide

X-Ray Diffraction (XRD)

Analysis using an X-ray diffractometer (Philips X'pert Pro-PAN). Analysis was carried out on X-ray diffraction on the sample, using a metal target Cu, Kαfilter, voltage 40 Kv, current 30 mA radiation spread in the crystal region of the sample, which was measured with a vertical goniometer. Patterns were obtained using a step width of 0.04° with a detector resolution at a diffraction angle between 10° and 80° at room temperature [13].

Differential Scanning Calorimeter (DSC)

Analysis using a Differential Scanning Calorimeter DSC (Setaram Type EVO: 131, France). Thermal analysis was observed using Differential Scanning Calorimetry (DSC) by weighing 5 mg of the sample and heating it in an aluminum pan at 30-300°C with a heating speed of around 20°C/minute [15].

FT-IR (Fourier Transform-Infrared) Spectrophotometer

Analysis used an FT-IR (Fourier Transform-Infrared) Spectrophotometer (Perkin Elmer, USA). The test was carried out on samples prepared using the KBr disk method and analyzed at wave numbers between 400-4000 cm-1 with an FT-IR spectrophotometer. The samples were ground to powder with KBr, then transferred to a die mold, and the samples were then pressed into a disc in vacuum conditions [15].

Scanning Electron Microscopy (SEM)

Using SEM (Hitachi S-3400N, Japan), the powder sample was placed in an aluminum sample holder coated with gold at a thickness of 10 nm. The samples were then observed at various magnifications of the SEM tool. The voltage was set at 20 kV, and the current was 12 mA [13].

Dissolution Profile

The dissolution test was carried out using apparatus II (paddle type) with 900 mL of pH 6.5

International Journal of Pharmaceutical Research and Applications
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phosphate buffer solution and the temperature set to 37ºC ± 0.5ºC. After reaching the temperature, put a sample amount equivalent to 50 mg of candesartan into the dissolution container. The dissolution solution was pipetted in 5 mL at 5, 10, 15, 30, 45 and 60 minutes. When pipetting, it was replaced with a dissolution medium (same volume and temperature at the time of pipetting). The absorbance of the pipetted solution from the dissolution medium was measured at a maximum wavelength of 258.20 nm. The concentration of candesartan dissolved at any time can be calculated using a calibration curve [13].

III. RESULTS AND DISCUSSION

In this study, candesartan cilexetil was used as the raw material (active substance), which is one of the drugs used to treat hypertension. Candesartan cilexetil is an angiotensin II receptor blocker (ARB) widely used to treat hypertension and congestive heart failure [4,5].

Candesartan cilexetil is a compound that is practically insoluble in water, but candesartan cilexetil has medicinal activity. Based on these problems, the researchers tried to form a candesartan cilexetil-nicotinamidecocrystal using the solvent drop grinding method with a 1:1 mole ratio between the active substance and the coformer used. The aim of forming candesartan cilexetil - nicotinamidecocrystals is expected to increase the dissolution percent of candesartan cilexetil to increase the absorption rate and bioavailability of candesartan cilexetil.

The candesartan cilexetil compound shows a crystalline solid because the diffractogram shows a characteristic and sharp interference peak at the corners. It can be seen that the diffractogram formed at a predetermined angle of 2θ has varying peaks. The physical mixture of candesartan cilexetil - nicotinamide 1:1, when compared at the same 2θ angle, shows a lower interference peak when compared to candesartan cilexetil. This data can be seen in Figure 1. Based on the data above, the combined diffractogram between candesartan cilexetil, nicotinamide, and the mixture of physical and cocrystals already show differences in the degree of crystallinity. Where the decrease in intensity indicates a reduction in the crystalline properties of candesartan cilexetil in the cocrystal formula towards salt properties, where the salt form will dissolve more quickly, the intensity decreases so that the energy required to release is smaller than the crystalline form.

Thermal analysis uses a Differential Scanning Calorimeter (DSC) tool. The DSC thermogram of candesartan cilexetil shows a single and sharp endothermic peak at a temperature of 173,435 °C, which is the melting point and enthalpy of 29,634 (J/g). The nicotinamidethermogram shows an endothermic peak at 131,332°C with an enthalpy of 136,693 J/g. The physical mixture thermogram has two peaks, which indicate an endothermic peak at a temperature of 127.032°C and an enthalpy of 11.577 (J/g). In the cocrystalthermogram, one peak shows an endothermic peak at a temperature of 126.275°C and an enthalpy of 18.714 (J/g). In the thermogram of the combination of candesartan cilexetil, nicotinamide, the physical mixture and the cocrystal formula above, it can be seen that there is a shift in the melting point to a lower temperature. The melting point has a close relationship with solubility, the higher the melting point, the smaller the solubility; conversely, if the melting point is lower, the solubility will be greater. This analysis shows that the cocrystal formula's melting point decreases, which increases the solubility of the candesartan cilexetil – nicotinamide 1:1 cocrystalformula .

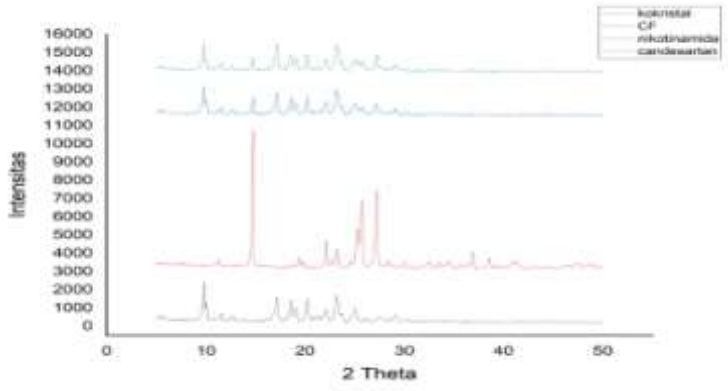

Figure 1.Combined X-ray diffractogram of candesartan cilexetil, nicotinamide, physical mixture, and cocrystal.

International Journal of Pharmaceutical Research and Applications
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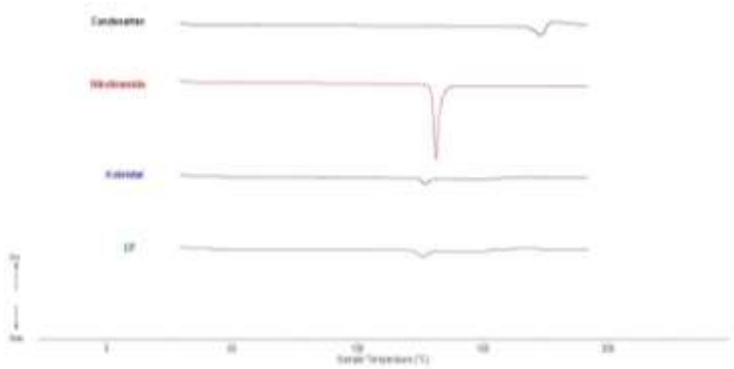

Figure 2. DSC thermogram of candesartan cilexetil powder, nicotinamide, physical mixture, and candesartan cilexetil – nicotinamidecocrystals

Infrared spectroscopy analysis is carried out to identify functional groups in a compound. Each absorption band at a certain wave number describes the presence of a specific functional group. The analysis results are in the form of a chromatogram signal relating the percentage of transmittance to the wavelength of the wave [15].

The results of the characterization of the infrared spectrum above candesartan cilexetil powder show that there is a C-O ester functional group at a wave number of 1282.01 cm-1, a C=O functional group at a wave number of 1872.28 cm-1, an aromatic C-H functional group at a wave number of 2993.64 cm-1 and the N-H functional group at the wave number 3412.08 cm-1. The FT-IR spectrum of nicotinamide powder shows a peak at the wave number in the aromatic C-H functional group at a wave number of 2785.04 cm-1, the C=C and C-O functional groups in the functional group have no wave numbers, the C=O functional group at a wave number of 1906 .65, NH functional group at wave number 3366.85. In the FT-IR spectrum, the physical mixture and cocrystal formula have infrared spectrum peak characteristics that are almost the same as the infrared spectrum found in candesartan. From the FT-IR analysis data, it can be concluded that there was no significant chemical interaction between candesartan and after cocrystal formation due to the similarity of the functional group areas.

The surface morphology of a sample can be seen using Scanning Electron Microscopy (SEM). The morphology of a sample can be seen from its surface shape. Based on particle shape analysis using Scanning Electron Microscopy (SEM) with various magnifications, it shows the characteristics of candesartan cilexetil, nicotinamide, physical mixture, and cocrystals. In the SEM results with a magnification of 2500 times, candesartan cilexetil is seen as a crystalline solid with the shape of tiny needles. Meanwhile, the morphological form of nicotinamide at 2500 times magnification looks like a rod shape. At a physical mixture with a magnification of 2500 times, the surface morphology of pure candesartan cilexetil can still be seen. With a magnification of 2500 times, the cocrystal does not show the surface morphology of candesartan cilexetil in the form of tiny needles, but it has been combined with nicotinamide.

The difference in particle shape of the physical mixture and cocrystals is because the physical mix is made only by simple mixing without any special treatment that could damage the shape of each ingredient, and there has been no interaction with nicotinamide. Meanwhile, cocrystal powder is made using the solvent drop grinding method, the morphological form of candesartan cilexetil is no longer visible because the crystalline phase of candesartan cilexetil has been dispersed on the surface of the outer phase of nicotinamide.

This shows that the cocrystalline powder produces a more amorphous compound. The change in the shape of the cocrystal indicates that a physical reaction has occurred between candesartan cilexetil and nicotinamide.

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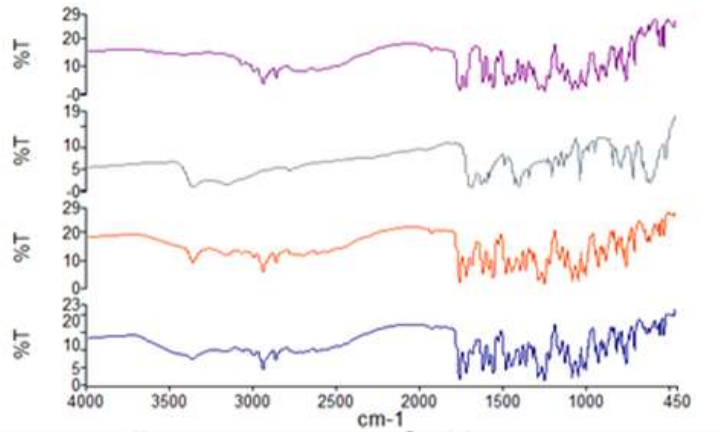
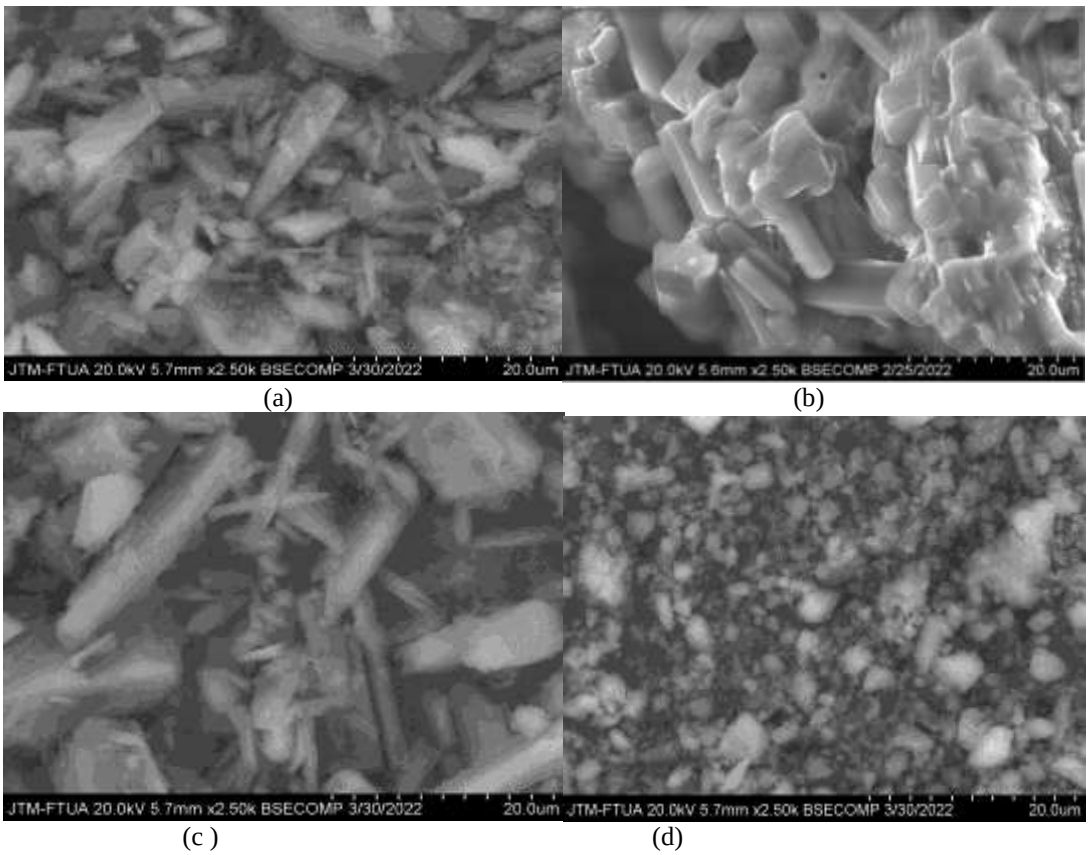


Figure 3. FT-IR Spectrum of Candesartan cilexetil, Nicotinamide, Physical Mixture, and Cocrystal



(a) (b)

(c) (d)

Figure 4.Morphology of scanning electron microscopy (a) candesartan cilexetil; (b) Nikotinamide ; (c) Physical Mixture ; (d) cocrystal.

In determining the dissolution profile of candesartan cilexetil, the physical and cocrystal mixture was carried out using a type 2 dissolution apparatus with phosphate buffer medium pH 6.5. Determination of the maximum absorption wavelength of candesartan cilexetil in phosphate buffer medium pH 6.5 obtained a wavelength of 258.20 nm with an absorbance of 0.315. The calibration curve for candesartan cilexetil phosphate buffer pH 6.5 obtained a regression equation of the line y = 0.01055x – 0.03945 with a regression coefficient 0.99983.

Determining the dissolution profile of the cocrystal and the physical mixture of candesartan cilexetil and nicotinamide showed an increase in the dissolution rate of all formulas. The increase in

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the dissolution rate is due to the addition of nicotinamide and the effect of the cocrystal in each formula. The cocrystal method has a better increase in the dissolution rate compared to the physical mixture.

Percent dissolved of the physical mixture and Thecocrystals at 60 minutes on average are as follows: Physical mixture: 59.159%, and cocrystals 75.604%. So, the difference in the ratio of cocrystal preparation dramatically influences the increase in the dissolution rate of candesartan cilexetil. The solvent drop grinding method can cause candesartan cilexetil to change shape to become amorphous and trapped in the nicotinamide cavity. Compared to the physical mixture, the cocrystal for the dissolution profile has a better dissolution rate. This may be due to the ratio between the physical mixture and the cocrystal used being the same (1:1), but the manufacturing method is different.

Another factor that causes an increase in the dissolution rate is the relationship between drug solubility and melting point. A solid with a lower melting point will have a weak lattice energy, thereby increasing the solubility and dissolution rate of a substance .

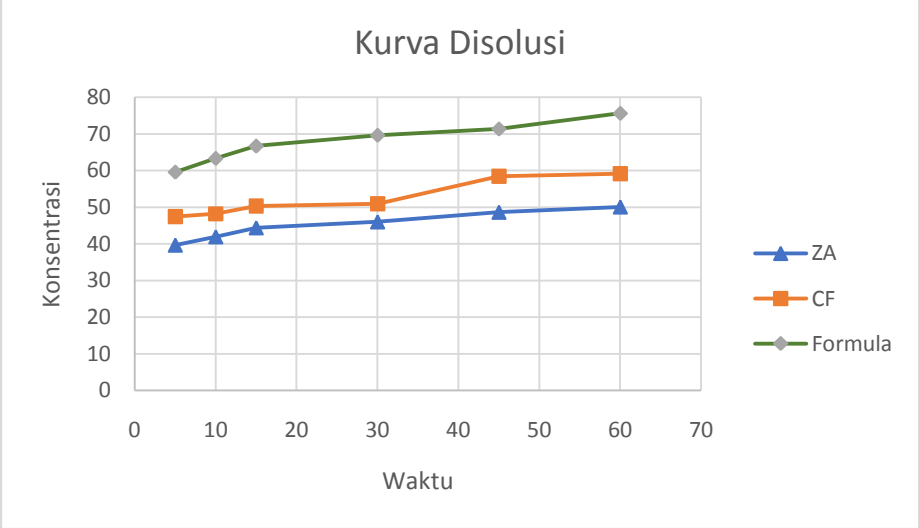

Figure 5. Dissolution profile curves of active substances (ZA), physical mixtures (CF), and cocrystals in phosphate buffer medium pH 6.5

IV. CONCLUSION

Based on research that has been carried out with the formation of candesartan cilexetil - nicotinamidecocrystals using the solvent drop grinding method, it can be concluded that:

There are differences in physicochemical characterization after the formation of candesartan cilexetil-nicotinamidecocrystals. This can be seen in the physicochemical evaluation of candesartan cilexetil, the physical mixture, and the cocrystal formula, which include X-ray diffraction analysis of a decrease in intensity, differential scanning calorimetry (DSC) decrease in melting point and decrease in enthalpy, and scanning electron microscope (SEM) morphological changes. In general, it is found that the cocrystal formula can improve the physicochemical properties of the cocrystal.

The formation of candesartan cilexetil—nicotinamidecocrystals influences the dissolution rate, which shows an increase in the percent dissolved by 1.5 times compared to pure candesartan cilexetil.

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