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Characterization of the Physicochemical Properties of Candesartan Cilexetil – Fumaric Acid Multicomponent Crystals by Dissolving Method

Muthia Fadhila[1*], Rina Wahyuni[1], Enggy Hagline Morika[1], Sanezea Effendy[1],
[1]*Department of Pharmaceutics, School of Pharmaceutical Science Padang (STIFARM Padang), West Sumatera, Indonesia, 25147*

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ABSTRACT: Candesartan Cilexetil (CC) is an angiotensin II receptor-blocking drug (ARB) that functions as an antihypertensive. CC is a BCS class II drug, namely low solubility, and high permeability.This study aims to improve the physicochemical properties and increase the dissolution rate of candesartan cilexetil. Formation of multicomponent crystals of candesartan cilexetil – fumaric acid by solvation method using methanol. The multicomponent formation is carried out with a ratio of 1:1 mol. Evaluation of physicochemical properties was carried out using characterization tests with X-ray Diffraction (XRD), Differential Scanning Calorimetry (DSC), Fourier Transform Infrared (FT-IR), Scanning Electron Microscopy (SEM) Analysis, and treatment of dissolution profiles using pH phosphate buffer medium. 6.5. Based on this study, the results of the X-ray Diffraction pattern showed a decrease in the intensity of the degree of crystallinity. DSC thermal analysis showed a decrease in the endothermic peak. The FTIR spectrum shows no shift in wave number. SEM microscopic analysis showed that the compound was more amorphous due to the reduced degree of crystallinity. The results of the dissolution test for candesartan cilexetil in the multicomponent form were 86.44183%, the physical mixture was 72.8493%, and pure candesartan cilexetil was 33.0433%. The formation of multicomponent crystals of candesartan cilexetil - fumaric acid can improve the physicochemical properties and increase the dissolution rate of candesartan cilexetil.

KEYWORDS: Multicomponent crystal, Candesartan Cilexetil, Fumaric Acid, Dissolution rate.

I. INTRODUCTION

A drug will produce a therapeutic effect if it is in dissolved form so that it can dissolve and penetrate the membrane. Solubility will correlate with the pharmacokinetic phase of the drug in the body, namely absorption, distribution, metabolism, and excretion. However, some drugs have low solubility. So an effort is needed to increase drug solubility to achieve a therapeutic effect [1]. Drugs with low solubility are a major problem encountered in the development of drug formulations. Currently, around 40% of new compounds developed in the pharmaceutical industry have low solubility in water [2].

Solubility is one of the physicochemical properties of drug compounds which is important in neutralizing the degree of drug absorption in the gastrointestinal tract. Drugs that are small in water (poorly soluble drugs) often show low bioavailability and the rate of dissolution is the rate-limiting step in the drug absorption process [3]. The better the dissolution of a drug, the better the rate of absorption so that the pharmacological effects of drugs can be achieved quickly [4].

Many drug substances have low solubility in water or are expressed as practically insoluble in water so therapeutic concentrations are not reached. Various attempts have been made to increase drug solubility, namely by forming salts and dispersing, multicomponent crystals [5].

One of the compounds that has low solubility in water is candesartan cilexetil. Candesartan Cilexetil (CC) is an angiotensin II receptor blocker (ARB) that functions as an antihypertensive [6]. CC is a BCS class II drug, namely low solubility and high permeability [7, 8]. Fumaric acid is easily soluble in water. Fumaric acid has the chemical formula $C_4F_4O_4$ and a molecular weight of 116.07 g/mol. White powder or colorless crystals, soluble in water and ether, melting point of 287°C [9].

Multicomponent is a technique to improve the physicochemical properties of pharmaceutical sedatives, such as solubility, dissolution rate, stability, and crystallinity. The interactions that occur to be able to form multicomponent crystals are covalent interactions between molecules or ions

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contained in crystals of pharmaceutically active substances and coformers [10].

This study was conducted to increase the dissolution rate of Candesartan Cilexetil. The multicomponent formed from candesartan cilexetil with fumaric acid will be characterized using X-ray Diffraction (XRD), Differential Scanning Calorimetry (DSC), Fourier Transform Infrared (FT-IR), Scanning Electron Microscopy (SEM) Analysis, and determination of dissolution profiles.

II. MATERIALS AND METHOD

Materials
Candesartan Cilexetil (Zhejiang, China), fumaric acid (PT. Merck), aquadest (PT. Novalindo), methanol (PT. Novalindo), Potassium Dihydrogen Phosphate (KH_2PO_4), and Sodium Hydroxide (NaOH).

Tools
X-ray Diffraction (Philips X'Pert Pro-PANalytical, The Netherlands), Differential Scanning Calorimetry (Setaram DSC 131 Evo, France), Fourier Transform Infrared (Perkin Elmer L1600300 Spectrum Two, USA), Scanning Electron Microscopy (Hitachi Type S- 3400N®, Japan), UV – VIS spectrophotometer (Shimadzu ED23 1800®, Japan), pH meter (Mettler Toledo), and dissolution test kit (Copley Scientific NE4-COPD, UK).

Manufacturing of Multicomponent Crystals
Candesartan Cilexetil: Fumaric acid prepared with 1:1 mol, candesartan cilexetil as the active substance 1.5266 g and fumaric acid as a coformer 0.2901 g dissolved in elemeyer, then 200 mL methanol was added. In the mixing process, let it form a clear solution for ± 10 minutes assisted by a sonicator, then leave it at room temperature for ± 10 days until the solution evaporates, until a dry mass is formed and weigh the powder to determine the total weight, put it in a vial, then store in a desiccator. Then carry out various characteristic tests on the multicomponent candesartan cilexetil - fumaric acid formed.

X-ray Diffraction analysis
Analysis using Cu target metal, Kαfilter, 40 Kv voltage, 30 mA radiation current spread in the sample crystal region, as measured by a vertical goniometer. The patterns will be obtained using 0.04° step widths with detector resolution at diffraction angles between 10° and 80° at room temperature.

Differential Scanning Calorimetry analysis
The sample was weighed 5 mg and heated in an aluminum pan at a temperature of 30 - 300 °C with a heating rate of about 20 °C/minute.

Fourier Transform Infrared analysis
Samples were prepared using the KBr disc method and analyzed at wave numbers between 400–4000 cm^{-1}. The sample was crushed to a powder state with KBr, then transferred to a die and the sample was then compressed onto a disc under vacuum.

Scanning Electron Microscopy
The powder sample was placed in a sample holder made of aluminum and coated with 10 nm thick gold. The samples were then observed at various magnifications by the SEM tool. The voltage is set at 20 kV and the current is 12 mA.

Determination of Dissolution Profile
The dissolution test was carried out using apparatus II (paddle type) with a stirring speed of 50 rpm. The medium used was 900 mL of phosphate buffer pH 6.5 with the temperature set at 37°C ± 0.5°C. After the temperature was reached, a number of samples were added, equivalent to 50 mg of candesartan cilexetil, into the dissolution vessel. The dissolution solution was pipetted 5 mL at 5, 10, 15, 30, 45, and 60 minutes. During pipetting, it was replaced with a dissolution medium (same volume and temperature at the time of pipetting). The absorption of the solution that has been pipetted from the dissolution medium is measured at the maximum wavelength. The level of candesartan cilexetil dissolved at any time can be calculated using the calibration curve.

III. RESULTS AND DISCUSSION

In X-ray diffraction testing, it is used to characterize solid interactions between two solid components, whether a new crystalline phase is formed or not. If a new crystalline phase is formed as a result of the interaction between the two components, it will be observed in a real way from the X-ray diffractogram [11]. From the X-ray diffraction results, it can be seen that the pure candesartan cilexetil diffractogram shows a distinctive and sharp interference peak at an angle of 2θ: 10.0311°, namely 1530.1411 at 17.3631°, namely 1104.287, at 20.4831°, namely 769.9292 at 24.0191° which is 559.5879. On the fumaric acid diffractogram it shows a distinctive and sharp peak at an angle of 2θ: 22.9986° namely 1494.119, at 28.8616° namely 1123.771, at 38.7286° namely 1439.597 (Figure 1).

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From the overall results of X-ray diffraction, the combination of candesartan cilexetil – fumaric acid with the dissolution method has shown a significant difference in the decrease in the intensity of crystallinity at an angle of 2θ, and identified that an amorphous form was formed. The amorphous form will dissolve faster because the intensity of crystallinity decreases so that the energy needed to escape is smaller than the crystalline form.

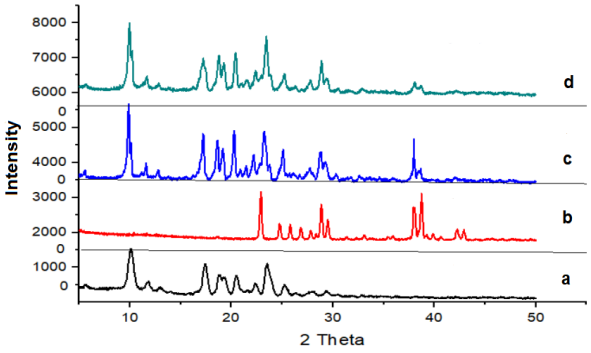

Figure 1: X-ray diffractogram overlay of candesartan cilexetil (a), fumaric acid (b), physical mixture (c), and multicomponent (d).

The Differential Scanning Calorimeter (DSC) test is a method for determining crystal properties such as heat capacity and enthalpy of a sample. DSC can measure the amount of heat absorbed or released during the transition [12]. On the candesartan cilexetil thermogram, it shows a sharp endothermic peak at 173.435 °C indicating a melting event with an enthalpy of 29.634 J/g, while the fumaric acid thermogram is at an endothermic peak of 295.519 °C with an enthalpy of 827.918 J/g, on the physical mixture it shows a peak endothermic at a temperature of 176.483 °C with an enthalpy of 23.16 J/g, and the multicomponent showed an endothermic peak at a temperature of 161.324 °C with an enthalpy of 13.889 J/g. (Figure 2).

From the results of the DSC thermogram, it can be seen that there is a decrease in the melting point and enthalpy of the multicomponent. The melting point has a close relationship with solubility, the higher the melting point, the lower the solubility.

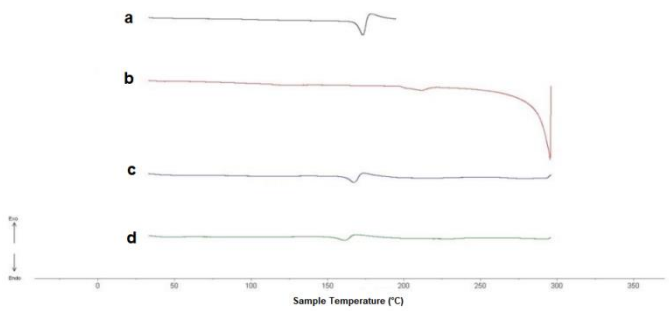

Figure 2: DSC thermogram of candesartan cilexetil (a), fumaric acid (b), physical mixture (c), and candesartan cilexetil-fumaric acid multicomponent (d).

FT-IR (Fourier Transformation Infra–Red) spectroscopy analysis was performed to identify functional groups in a compound by comparing it with the spectra of standard compounds, especially in the fingerprint region (wave number 1500-500 cm-1). The energy of infrared radiation is related to the energy required for the vibration of a bond to occur. Thus, the amount of energy absorbed by the compound will affect the molecular conditions of the compound [13]. The results of the characterization of the FT-IR spectrum of pure candesartan cilexetil showed the presence of the NH functional group, the OH functional group, the C=O functional group, and the N=N functional group. In the FT-IR spectrum of fumaric acid, you can see the presence of the OH functional group and the C=O functional group (Figure 3). The physical and multicomponent mixtures have infrared spectral peak characteristics that are almost the same as those found in candesartan cilexetil and fumaric acid. Thus, it can be concluded that there was no significant chemical interaction between candesartan cilexetil and fumaric acid after the formation of a physical and multicomponent mixture.

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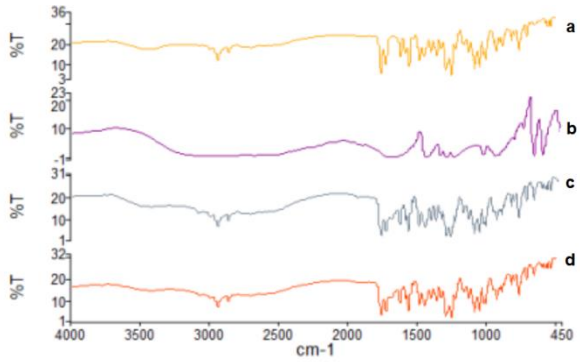
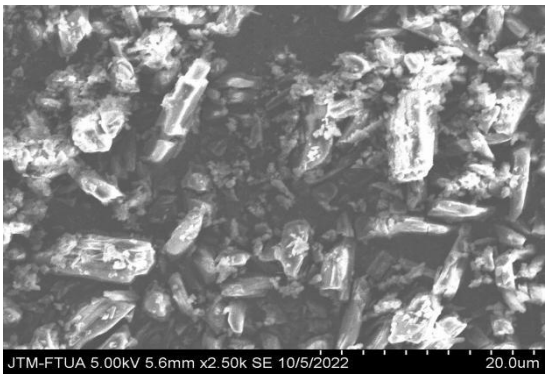


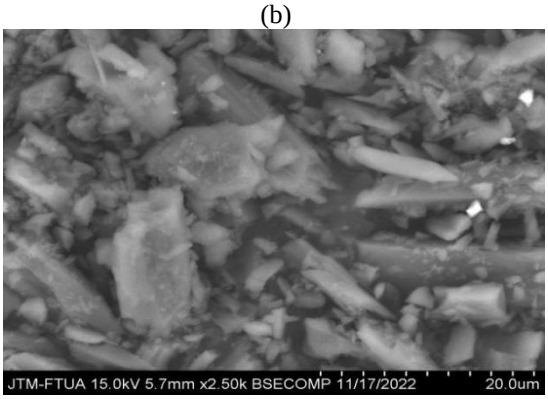
Figure 3: FT-IR overlay of candesartan cilexetil (a), fumaric acid (b), physical mixture (c), and multicomponent (d).

Scanning Electron Microscopy (SEM) analysis is used to determine the surface morphology of a sample microscopically and provides information about the surface texture of the sample. Based on the SEM results, it can show the characteristics of candesartan cilexetil, a physical mixture, and multicomponents at the same magnification of 2500 times. Candesartan cilexetil appears as a crystalline solid with a rod shape. The morphology of fumaric acid is also seen in the form of large blocks with uneven surfaces. The physical mixture of candesartan cilexetil – fumaric acid is like a crystal block. In the multicomponent candesartan cilexetil with fumaric acid prepared by the dissolution method, there are crystal blocks with smaller particle sizes (Figure 4). This shows that the interaction between candesartan cilexetil and fumaric acid can affect the crystal morphology of each substance. The occurrence of differences in the shape of the physical and multicomponent mixed particles is due to the different ways of preparing the two samples.

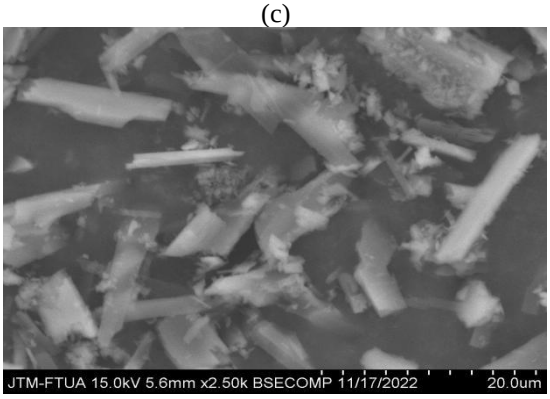


(a)

(b)



(c)



(d)

Figure 4: SEM photos of candesartan cilexetil (a),fumaric acid (b),physical mixture (c)multicomponent candesartan cilexetil-fumaric acid (d).

In determining the dissolution profile of candesartan cilexetil, the physical and multicomponent mixtures showed that the physical and multicomponent mixtures increased the dissolution rate compared to pure candesartan cilexetil. In the dissolution test it can be seen that the percent dissolution in the 60th minute of piperine was 33.0433%, the physical mixture was 72.84933% and the multicomponent was 86.44183% (Figure 5). From the results obtained, it can be seen that the multicomponent candesartan cilexetil – fumaric acid has a good dissolution rate

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using the dissolution method. Factors that affect the dissolution rate such as particle size. In addition, factors that cause an increase in the dissolution rate are the relationship between drug solubility and melting point. If the melting point is low, it will have a weak lattice energy thereby increasing the solubility and dissolution rate.

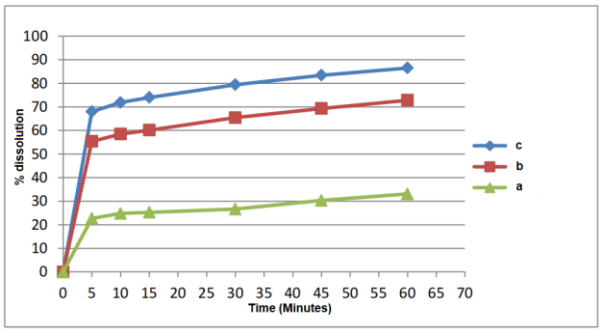

Figure 5: Curve of % dissolved substance in phosphate buffer pH 6.5 at a wavelength of 258.00 nm. Candesartan cilexetil (a), physical mixture (b) multicomponent candesartan cilexetil-fumaric acid (c).

IV. CONCLUSION

Based on research that has been done with the formation of multicomponent candesartan cilexetil – fumaric acid using the dissolution method, it can be concluded that multicomponent candesartan cilexetil can be formed using fumaric acid as a coformer, the manufacture of multicomponent candesartan cilexetil – fumaric acid with the dissolution method can have a significant effect, by increasing the rate of dissolution of candesartan cilexetil as indicated by percent dissolution of candesartan cilexetil 33.0433%, physical mixture 72.84933% and multicomponent 86.44183% at 60 minutes.

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