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Formulation of Multicomponent Crystal Candesartan Cilexetil – Maleic Acid 1:1 Using Solvent Drop Grinding Method

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ABSTRACT:
Candesartan cilexetil is a compound with low solubility in water. This study aims to increase the dissolution rate of candesartan cilexetil by forming multicomponent candesartan cilexetil and 1:1 maleic acid using the solvent drop grinding method and using methanol as solvent. Evaluation of the multicomponent candesartan cilexetil was characterized by X-Ray Diffraction (XRD), Differential Scanning Calorimetry (DSC), FT-IR spectroscopy, Scanning Electron Microscopy (SEM), an assay using UV spectrophotometer and determination of the dissolution profile using a paddle – type instrument. Based on this study, the XRD test showed a decrease in the intensity of crystallinity, the DSC test decreased the melting point, the SEM test showed morphological changes in multicomponent, determination of the rate that can be 99.4211%, and the dissolution test, there was an increase of 2.6 times compared to the solubility of single candesartan cilexetil. This indicates that the salt-type multicomponent can increase the dissolution rate of candesartan cilexetil pure.

KEYWORDS: Multicomponenst Crystal, Candesartan Cilexetil, Maleic Acid, Dissolution Rate.

I. INTRODUCTION

Candesartan cilexetil is a compound antihypertensive That Works with the method that hinders receptors angiotensin, so it gets in the way change angiotensin I become angiotensin II And cause No happening vaso constriction vessels blood so that cause decline occurs pressure blood. Besides That candesartan cilexetil Also can cause a decline in pressure Which can cause the heart to pump blood, so candesartan is Also used on patients who fail heart [1]. In the system, BCS (Biopharmaceutics Classification System), compound This belongs to compound class II, Which own solubility is low And permeability high [2].

Sour Maleat is the wrong one coformer on cocrystalWhich can use because it has two acid groups carboxylates (COOH) and own good solubility in water [3]. In the study previously cocrystal Which formed with coformer sour maleate that is exemestane – sour maleate 1:1 with the slurry method which results in solubility which increases the rate of dissolution compared to the original crystal [4], atorvastatin calcium – sour maleate with results its solubility increase as big 192% through cocrystal formation [5].

Multicomponent crystal is wrong one technique of manipulating crystal in the formation of new phases and change of properties physicochemistry something drug, so that can be used to increase solubility, dissolution rate, physical and chemical stability as well compressibility. Interactions which happen For can form multicomponent these crystals are interactions between molecules and ions contained in the crystal of the active substance pharmaceutical And coformer in a manner covalent. A multicomponent crystal formed foreseen based on supramolecular synthon which formed and difference mark pKa between the second substance so that crystal formed can be determined to become salt or cocrystal. Multicomponent crystal consists of solvate, salt, and cocrystal [6].

Solvent drop grinding is one of the techniques using milling which is followed with the addition of a little solvent. The solvent used is a solvent that can dissolve a second substance. Technique solvents drop grinding own profit compared to the method other, like the ability To control the formation of the polymer [7].

This research was conducted with the purpose to increase the solubility of candesartan cilexetil so can increase the rate of its dissolution. Multicomponent Which is formed from candesartan cilexetil with sour maleate will be

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characterized using X-Ray Diffraction (XRD), Differential Scanning Calorimetric (DSC), Spectroscopy FT-IR, analysis of microscopic scanning electrons Microscopy (SEM), and Test Dissolution.

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II. METHODOLOGY

Material

The material used between others: candesartan cilexetil (Zhejiang, China), maleic acid (Merck), aqua dest (PT Novalindo), methanol (PT Novalindo), Potassium Dihydrogen Phosphate (KH 2 PO 4) (PT Novalindo), Sodium Hydroxide (NaOH) (PT Novalindo).

Making Mixture Candesartan Cilexethyl-Acid Physical Maleat 1:1

Mixture physique candesartan cilexetil – sour maleate made with comparison 1:1 mole, mixed in the mortar, And stirred for 30 minutes without the use of pressure. after the process mixing is finished save the mixture physique in a desiccator.

Manufacturing of Multicomponent Crystals Candesartan Cilexetil – Maleic Acid 1:1

Multicomponent candesartan cilexetil – maleic acid made with comparison 1:1 mol crushed with the addition of 2 mL methanol, then crushed for ± 15 minutes. After the candesartan cilexetil mixture, the acid maleate and methanol start dry up so add return 2 mL methanol, And crush return during ± 15 minutes, until the formed mass dries, input in vials and save in a desiccator. Then perform various characteristic tests on multicomponent crystal candesartan cilexetil – maleic acid formed.

Characterization Multicomponent Crystal
X-ray Diffraction analysis

Use XRD (Philips X'Pert Pro-PAN, London) Where the sample is done on diffraction X-ray, with the use of metal target Cu, Kαfilter, voltage 40 Kv, current 35 mA radiated radiation within the crystal region of the sample, which is measured with a vertical goniometer. Patterns will be obtained using wide stages of 0.020° with detector resolution at angle diffraction between 3° and 80° in the temperature room [8].

Analysis Differential Scanning Calorimeter (DSC)

Differential Scanning Calorimetry (DSC) analysis: this analysis uses DSC (SETARAM Type EVO-131; France), carried out by weighing a sample of 5 mg And heating on pan aluminum at a temperature of 25 - 200 °C at a speed warm-up of around 10 °C/min [9].

Fourier Transform Infrared analysis

Analysis This using FT-IR (Perkin Elmer FT-IR, USA). And dry, then do an analysis sample Which has been prepared with method KBr disc, and analyzed at intermediate wavenumbers 4000 - 600 cm -1. The sample is crushed until become powder with KBr and then moved to the print die the sample is then pressed inside something disc on condition empty air [9].

Scanning Electron Microscopy

Using SEM (Hitachi S-3400N, Japan) where the powder samples were placed on a place sample made of aluminum And coated with a gold thickness of 10 nm. The sample is then observed with various enlargement tools SEM. Voltage arranged on 20 kV And current 12 mA [8].

Determination of Dissolution Profile

Test dissolution was done using tool II (paddle type) with speed stirring at 50 rpm. The medium used is solution buffer phosphate pH 6.5 as much as 900 mL with temperature arranged at 37°C ± 0.5°C After temperature is reached, put some samples i.e. the equivalent of 50 mg of candesartan cilexetil in receptacle dissolution. Solution dissolution pipettes 5 mL on minute to 5, 10, 15, 30, 45 And 60. At the moment pipette is replaced with a dissolution medium (volume and temperature). same at the time of pipetting). Uptake solution Which has a pipette from medium dissolution is measured on long wave maximum. The rate candesartan the cilexetil dissolved every time can be counted with the use of curve calibration [10].

III. RESULTS AND DISCUSSION

Analysis diffraction ray X is used to characterize material crystal, which will provide information about parameter structural like crystallinity, strain, crystal orientation, and crystal defects [11]. On testing diffraction X-ray, compound candesartan cilexetil denotes a solid crystalline as the diffractogram shows peak interference Which is typical And sharp on corners 2θ: 9.8491°, 17.1811°, 20.2491° And 23.2976°. On the diffractogram sour maleat show peak Which typical And sharp in corner 2θ: 9.8491°, 17.1811°, 20.2491° And 23.2976°. On diffractogram mixture

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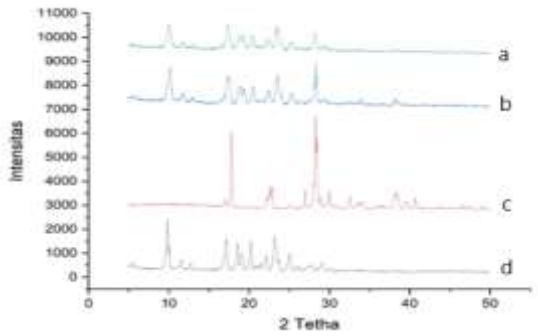
physically shows a distinctive peak and is sharp at an angle of 2θ: 9.8491°, 17.1811°, 20.2491° And 23.2976°. The multicomponent diffractogram shows peaks Which typical And sharp on corner 2θ: 9.8491°, 17.1811°, 20.2491° And 23.2976° (Fig 1).

From the results obtained can it is concluded that the combined diffractogram between candesartan cilexetil, physical mixture, and multicomponent already show a difference significant in decline intensity on corner 2θ, And identify the formation of an amorphous. The amorphous form will dissolve faster Because the intensity decrease so the energy needed For off smaller compared to the crystal shape.



Picture 1. Overlays XRD candesartan cilexetil (d), maleic acid (c), mixture physique candesartan cilexetil - maleic acid (b), and multicomponent candesartan cilexetil - maleic acid (a).

Differential Scanning Calorimetry (DSC) test, where DSC is one of the methods to determine crystal properties. DSC is used to evaluate changes in thermodynamic properties that occur when crystals are given heat energy, for example during recrystallization, melting, and solid-phase transformation. The DSC thermogram shows endothermic or exothermic peaks [12, 13]. On research that has been done, thermogram candesartan cilexetil showed a peak endothermic Which sharp on temperature 173.435°C Which shows incident smelting with enthalpy as big 29,634 J/g, temporary thermogram sour maleate is at an endothermic peak of 144.305°C with enthalpy as big 828,967 J/g, on mixture physique show peak endothermic on temperature 135.442°C with an enthalpy of 67.725 J/g and at multicomponent show peak endothermic on temperature 143.605°C with an enthalpy of 26.91 J/g (Figure 2).

From the results thermogram DSC can see that happening decline point melting And enthalpy on the multicomponent. A melting point has a close relationship with solubility, the taller the point melts, the lower the solubility.

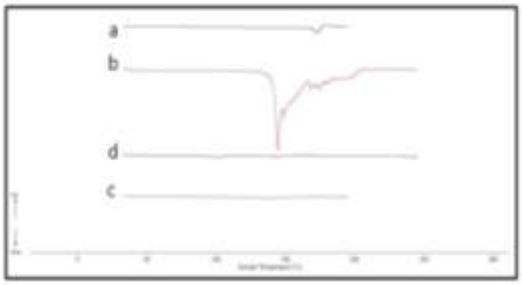
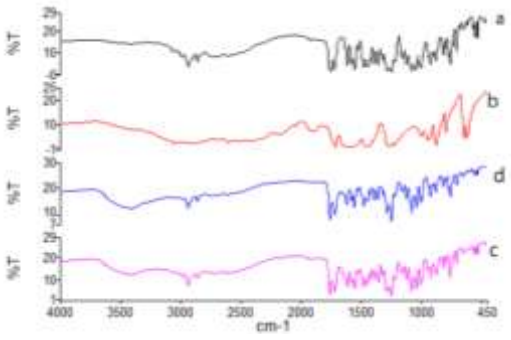


Figure 2: Thermogram DSC candesartan cilexetil (a), maleic acid (b), mixture physique candesartan cilexetil - sour maleat (c), And multicomponent candesartan cilexetil - maleic acid (d).

Analysis spectroscopy FT-IR done to identify group function on something compound. Every bond in a compound absorbs infrared light red. Bonds can experience stretching (stretch) or bonding (shrinkage). Area print finger (number wave 4000-600 cm -1) Also can be used For identifying samples by comparing the absorption spectra sample with the absorption spectrum of the compound comparison [14]. Results characterization on the FT-IR spectra of powders pure cilexetil candesartan, visible group function NH, C=O, And N=N. On the spectrum FT-IR sour maleate, seen exists group function C=O, And OH (Picture 3). From the analysis, FT-IR can be taken to conclusion that No happen interaction chemistry Which significant between candesartan cilexetil And sour maleate after the formation of multi-component, due to the similarity of functional groups in number wave 4000-600 cm^{-1}.



Picture 3 . FT-IR candesartancilexetil (a), maleic acid (b), mixture physique candesartan

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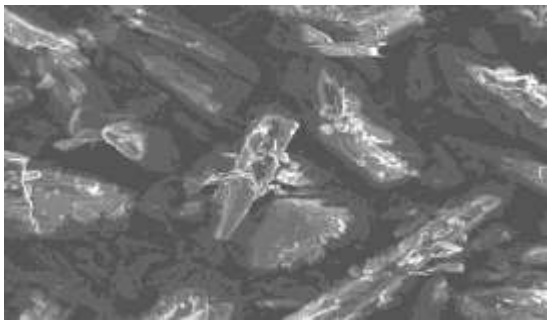
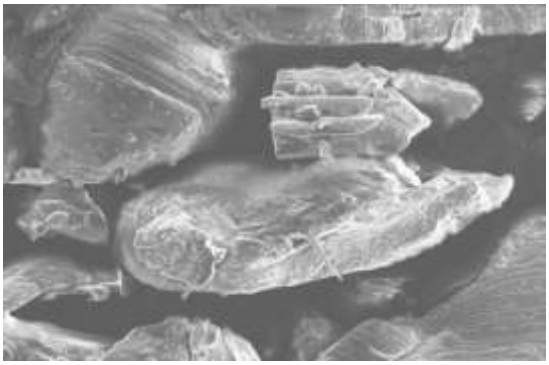
cilexetil – meleic acid (c), and multicomponent candesartan cilexetil–maleic acid.

Analysis using SEM was used to observe and characterize samples based on their surface morphology, structure, and chemical composition [15]. This tool is a tool That can give information on topography And monograph and the shape of the surface of the sample with results from a three-dimensional image high resolution [16]. Analysis this is used to know the morphology material between before And after the formation of multi-component. From the results SEM on 1000x magnification, candesartan cilexetil is seen from a solids crystal with a form stem. The sour maleate looks like habit crystals with a flat surface. On mixture physique, The morphology of candesartan cilexetil can be seen as pure and maleic acid Still can be distinguished. On multicomponent candesartan cilexetil with sour maleate Which is made with method solvents drop grinding I, candesartan cilexetil and maleic acid cannot be distinguished Again matter This showed different crystal shapes from candesartan cilexetil nor sour maleate (Figure 4).

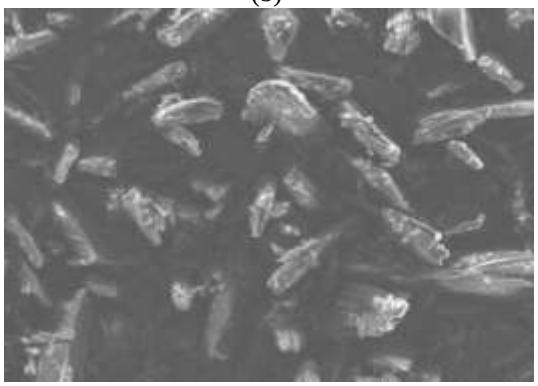
This also shows that interaction occurred between candesartan cilexetil with sour maleate which can influence the morphology crystal of each respective substance. Happening difference form physical and multicomponent mixed particles is caused because the method of manufacture of the two powders This difference, where is the powder mixture physique made with the mix of the second powder just whereas the multicomponent is made with the method of solvent drop grinding.



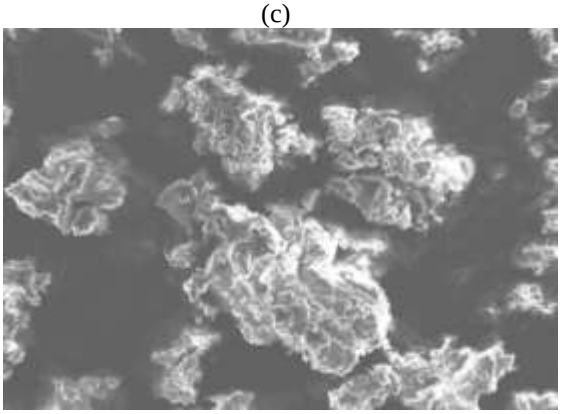
(a)



(b)



(c)



(d)

Picture 4. SEM photos of candesartan cilexetil (a),maleic acid (b),physical mixture(c), multicomponent candesartan cilexetil-maleic acid (d).

On determination profile dissolution from candesartan cilexetil, mixture physique, And multicomponent shows that on physical and multicomponent mixtures occur enhancement rate dissolution compared to with candesartan cilexetil pure. Enhancement rate dissolution is the because of the influence of addition coformer. In the dissolution test, it can be seen that the percent dissolution on minute 60th candesartan cilexetil 33.0484 %, mixture physique 56.8188 %, And

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multicomponent 92.4155 % (Figure 5). From that result obtained seen that candesartan multicomponent cilexetil - sour maleate has a good dissolution rate method solvents drop grinding. Results This caused Because on multicomponent was treated while in the mixture physique was used as a comparison done without treatment. Besides that, there are several factors too which influence the size of particles [17].

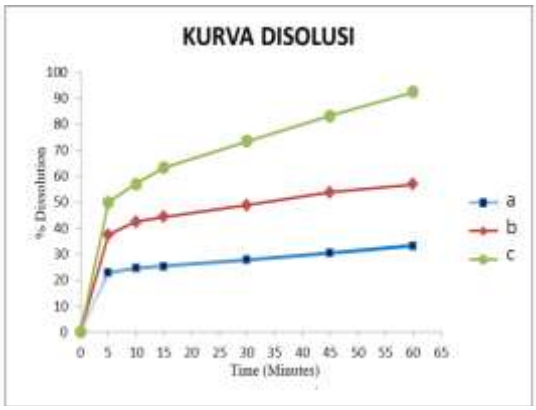

Figure 5.Curve of % dissolved substance inphosphate buffer pH 6.5 at a wavelength of 258.00 nm. Candesartan cilexetil (a), physical mixture (b) multicomponent candesartan cilexetil-maleic acid (c).

IV. CONCLUSION

Based on the study Which has been done by shaping multicomponent candesartan cilexetil – sour maleate 1:1 using the method of solvents drop grinding can be taken conclusion that the formation of multicomponent candesartan cilexetil – sour maleate 1:1 with method solvents drop grinding can repair characteristic physicochemistry candesartan cilexetil. Making multicomponent candesartan cilexetil – maleic acid 1:1 by method solvent drop grinding can improve dissolution rate of the cilexetil candesartan showed by percent dissolved candesartan cilexetil 33.0484%, mixture physique 56.8188% And multicomponent 92.4155% at 60 minutes, with an average dissolution efficiency of candesartan cilexetil 27.1102%, mixture physique 46.7830% and multicomponent 70.1660%.

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