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Solid Dispersion System Candesartan-cilexetil Mannitol Co-Grinding Method

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ABSTRACT

Research on solid dispersion systems had been done to improve physicochemical characteristics and the dissolution rate of candesartan-cilexetil a had been conducted. Candesartan cilexetil is included in BCS (Biopharmaceutical Classification System) class II, which has low solubility and high permeability which causes poor absorption of drugs in the digestive tract. Solid dispersions were prepared through the grinding method using mannitol. The formula with 3 comparisons between candesartan-cilexetil and mannitol 1:1, 1:3, and 1:5. A mixture of physics of candesartan cilexetil-mannitol was made without a solid dispersions system which was 1:1 as a comparison. Solid dispersion formed was characterized by particle size distribution analysis, Fourier transforms infrared (FT-IR), X-ray diffraction, scanning electron microscopy (SEM), differential scanning calorimetry (DSC), determination rate, and dissolution test. The result particle size distribution analysis showed grinding method there were solid dispersions mixed perfectly. The FT-IR of this analysis showed no interaction between candesartan-cilexetil mannitol in solid dispersion powder. The result of X-ray diffraction showed a decrease in crystallization degree. The DSC result showed a shift in endothermic peak candesartan-cilexetil. The manufacture of a solid dispersion system of candesartan-cilexetil mannitol can improve the physicochemical characteristics and the dissolution rate of candesartan-cilexetil compared with physical mixtures. The result in the dissolution was solid dispersion 1 = 53.1990 %, solid dispersion 2 = 54.3621 %, and solid dispersion 3 = 62.3621 %. The statistical result of dissolution efficiency using the Kruskal-Willis test with significant = 0.009(< 0.05) showed the difference among the dissolution efficiency of candesartan-cilexetil, physical mixture, and each solid dispersion.

Keywords: Candesartan-cilexetil, co-grinding, solid dispersion

Introduction

The systemic absorption of a drug product compares a series of rate processes. The process includes drug release after drug disintegration, drug aqueous environment dissolution, and cell membrane absorption into the systemic circulation for solid oral drug products. One of the factors determining the rate of pharmaceutical dissolution for poorly soluble pharmaceuticals is how quickly it dissolves in the gastrointestinal tract (Shargel et.al, 2004). As solid oral medication formulations, the process includes drug release, drug dissolution in an aqueous environment, and drug absorption across cell membranes into the systemic circulation. A well-known method for improving the solubility and rate of dissolution of poorly water-soluble substances is solid dispersion (SD) of active pharmaceutical ingredients (APIs) in hydrophilic carriers (Bertoni et al., 2020).

A group of solid products called solid dispersions includes a hydrophilic matrix and a hydrophobic drug (Mannem, et.al, 2018). The grinding process is an additional method to accelerate dissolution by decreasing the poorly water-soluble drugs particularly smaller, especially when the poorly water-soluble drug is combined with hydrophilic excipients (Nazem et al., 2022). To improve the way that poorly water-soluble drugs dissolve, various that are poorly water-soluble dissolve, a number of chemical and physical changes have been proposed (Azharshekoufeh et al., 2017). Amorphous drugs with poor water solubilities are frequently delivered using solid dispersions stabilized by one or more polymers and these formulations have gained great market success (Shi et al., 2022).

Candesartan-cilexetil is used for treating hypertension, when administered orally, it completely catalyzes the hydrolysis from candesartan-cilexetil to candesartan, an active moiety (Pansuriya et al., 2020). The Biopharmaceutical Classification System (BCS) classifies this active pharmaceutical ingredient (API) as belonging to group II due to its high lipophilicity and low water solubility (Kondoros et al., 2022). Its oral bioavailability ranges from 15 to 40 %, making GIT absorption poor (Pansuriya et al., 2020). Candesartan is a non-tetrazole monocarboxylic acid angiotensin receptor blocker, which shows how it affects glucose and insulin metabolism by acting as an agonist at the peroxisome proliferator-activated gamma receptor (PPAR) in a similar way to thiazolidine. The ARB class in general unknown

however shares this advantageous impact on insulin activity (Althanoon et al., 2022).

Mannitol called sugar alcohol is widely used in pharmaceutical formulations and food products (Thakral et al., 2022). Mannitol is a powder that dissolves in water at 216 mg/mL and has a melting point of 168 °C (Martau et al., 2020). Its high solubility in water and safety as an excipient makes it an eligible candidate as a polymer for the formulation of solid dispersion with a poorly soluble drug like candesartan-cilexetil (Shittu et al., 2022). Combining hydrotropic compounds has a significant synergistic impact on improving the solubility of medicine with low water solubility, the two main components of solid dispersion are generally the hydrophobic drug and the hydrophilic carrier (Ali et al., 2022).

The aims of this study are to improve the solubility and dissolution rate of candesartan cilexetil, a weakly water-soluble medication, by applying hydrotropic and combined hydrophilic agents in solid dispersion methods.

Research Method

Material and equipment

Candesartan cilexetil (Baoji Guokang Bio-Technology Co., Ltd), Potassium Dihydrogen Phosphate (Bratachem), Sodium hydroxide (Bratachem), Liquid paraffin (Bratachem), Ethanol (Bratachem), Polysorbate 80 (Bratachem), Aqua demineralization (Bratachem), (Fourier transforms infrared (FT-IR) (PerkinElmer), X-ray diffraction (X'pert Pro PANalytical), scanning electron microscopy (SEM) (Hitachi Type S-3400N), differential scanning calorimetry (DSC) (Setaram, Type Evo-131), dissolution test (Copley Scientific Type NE4-COPD), Spectrofotometry UV-Vis (Shimadzu 1800), Planetary Ball Mill (Retsch), Optilab Microscope (OptiLab Viewer ®), pH meter (Hanna Instrumen HI-2211).

Experiments

1. Solid Dispersion Preparation

   Prepared solid dispersion formed of preparing in planetary ball mills, candesartan-cilexetil and mannitol are mixed in ratios of 1:1, 1:2, and 1:3.
2. Preparation of Physical Mixtures

   The physical mixture developed by manufacturing mannitol and candesartan-cilexethyl was combined in a mortar and stirred. The weight of each formula is determined by the composition. Mannitol and candesartan cilexetil are combined in a mortar and pestle, agitated, and then kept in a desiccator.
3. Evaluation of Candesartan cilexethyl-Mannitol Physical Mixtures and Solid Dispersion Systems
   a. Particle Size Distribution Analysis

      Determination of particle size distribution using a microscope connected to an optilab digital device and laptop. Examination of the particle size distribution was carried out by counting 1000 particles.
   b. Fourier Transforms Infrared Analysis

      Samples prepared using the disc method were put through tests, then they were evaluated at wave numbers 400–4000 cm^{-1} (Kumar *et, al*., 2015). Rotate the sample clockwise, then set the background order (> 50 scans), then insert the sample into a clean and dry sample holder. The first scan occurs immediately after the sample is injected (while the music is playing); if it hits 90, the second scan is interrupted until the sample is analyzed and the spectrum is reportedly being monitored.
   c. X-ray Diffraction Analysis

      Samples were prepared on the preparation table, where samples were gathered, packed into a press holding machine using two spoons of a spatula in order to get the necessary peak. After the sample has been properly prepared, it is introduced into the XRD instrument, and the outcomes are shown on the monitor.
   d. Differential Scanning Calorimetry

      DSC analysis was carried out by weighing a number of samples and placing them in an aluminum container, heating, and measuring from a temperature of 30-220 °C. A constant heating rate of 10 °C per minute with nitrogen gas flowing through endothermic and exothermic processes will be recorded on the monitor.
   e. Determination of Candesartan-cilexethyl Content in Solid Dispersion Formula

      Candesartan cilexethyl solution was prepared at a concentration of 10 µg/mL, absorption was measured at a wavelength range of 200-400 nm with a spectrophotometer UV-Vis. Repetition for determination of levels was carried out three times. Candesartan cilexetil has a maximum absorption wavelength of 252-256 nm.
   f. Determination of Candesartan-cilexethyl Dissolution Profile in Phosphate Buffer pH 6.5

      Determination of the candesartan-cilexethyl dissolution test based on USP (The United States Pharmacopeia) using a type II dissolution apparatus with the peddle method with 900 mL of phosphate buffer solution pH 6.5, the

temperature set to ±37 ◦C ±0.5 ◦C. Then the solid dispersion powder was put into the container and rotated at 50 RPM for 60 minutes. The dissolution solution was pipetted 5 mL at 5, 10, 15, 30, 45, and 60 minutes. Each pipette was replaced with a dissolution medium. The absorption of the solution that has been pipetted from the dissolution medium is measured at the maximum wavelength. The level of candesartan dissolved at any time can be calculated using the calibration curve.

Result and Discussion

The study of the particle size distribution can be seen in Figure 1 that the candesartan cilexetil powder has a size spread starting from the range of 0 – 200 µm, physics mixture candesartan cilexetil-mannitol powder has a larger particle size than the single candesartan cilexetil powder, this is due to the mannitol having a larger size compared to pure candesartan cilexetil powder. Pure candesartan cilexetil has a uniformly small particle size when compared to solid dispersions, this is because candesartan cilexetil and mannitol in the manufacture of molecularly homogeneous solid dispersion powders then undergo merging and form smaller particle sizes after going through the milling process compared to the manumaftureof physical mixtures which are only mixed with a spatula.

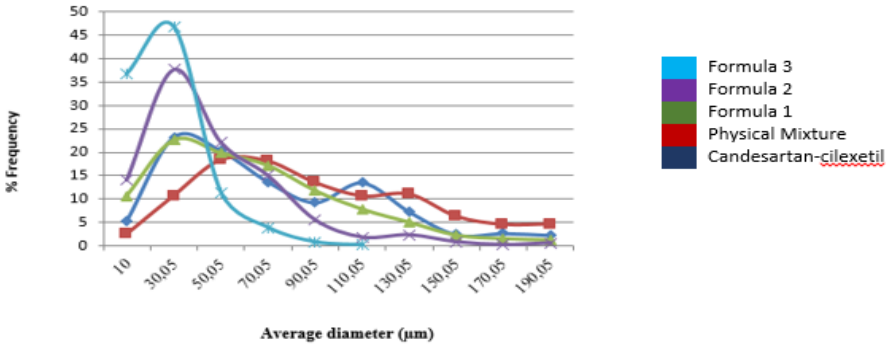

Figure 1. The frequency distribution curve for particle size physical mixtures and solid dispersion

The result of the X-ray diffraction (Figure 2) analysis showed that the milling process resulted in a reduction and uniformity of the particle size of the active substance particles into mannitol chains so that it would produce a crystalline lattice that was different from the lattice. Initially and followed by a decrease in the degree of crystallinity caused by changes in the surface of the crystal that undergoes grinding. The solid dispersion of candesartan cilexetil-mannitol gives a diffused diffraction pattern, a very significant decrease in the intensity of the crystalline peaks of candesartan cilexetil compared to the crystalline peaks formed in the physical mixture, which means that there is a decrease in the crystal form and leads to amorphous formation. The decrease in the degree of crystallinity causes the solubility of candesartan cilexetil to be high.

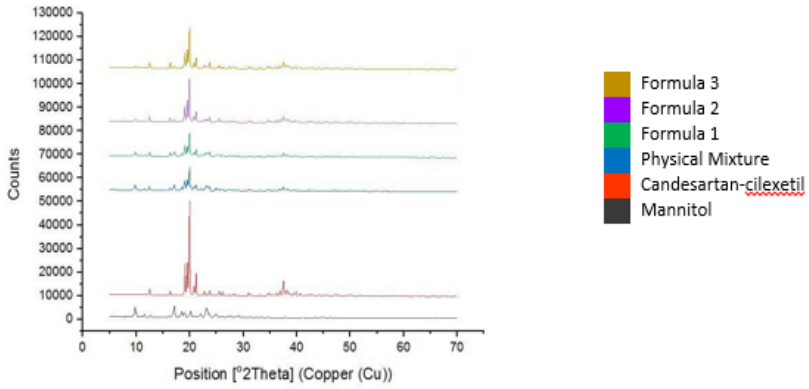

Figure 2. X-ray diffractogram of Candesartan-cilexetill, Mannitol, Physics Mixture, Solid Dispersion F1, F2, F3

SEM analysis of particle form showed the characteristics of candesartan cilexetil, mannitol, physical mixture, and solid dispersion (Figure 3). In the SEM results, candesartan cilexetil appears as a crystalline solid with an irregular form like a needle with a clean surface. The mannitol looks like hollow

lumps with an irregular surface texture. From the results of SEM analysis of the physical mixture of candesartan cilexetil and mannitol, it can be seen that the morphology of pure candesartan cilexetil and mannitol or still resembles the pure form, is because there has been no interaction between candesartan cilexetil and mannitol. In formula 1, the morphology of pure candesartan cilexetil and mannitol crystals is still visible, but the mannitol crystals have undergone a change in surface form, where the surface of the mannitol has a large cavity, in this co-grinding solid dispersion the surface looks covered by pure candesartan cilexetil crystals which have an irregular shape like a needle. Formula 2 shows that the crystals of candesartan cilexetil and mannitol begin to be difficult to distinguish, where the mannitol seems to spread over the candesartan cilexetil to form an aggregate with an irregular and uneven form. Formula 3 shows a hollow surface, the pure form of candesartan cilexetil and mannitol can no longer be distinguished, the uneven surface is thought to have occurred due to the interaction between the active substance and mannitol. The occurred of differences in the shape of the particle sizes of the physical mixture and solid dispersion is due to the different ways of making these two powder, where the physical mixture powder is made by mixing the two powders alone while the solid dispersion system is made by grinding it using a planetary ball mill.

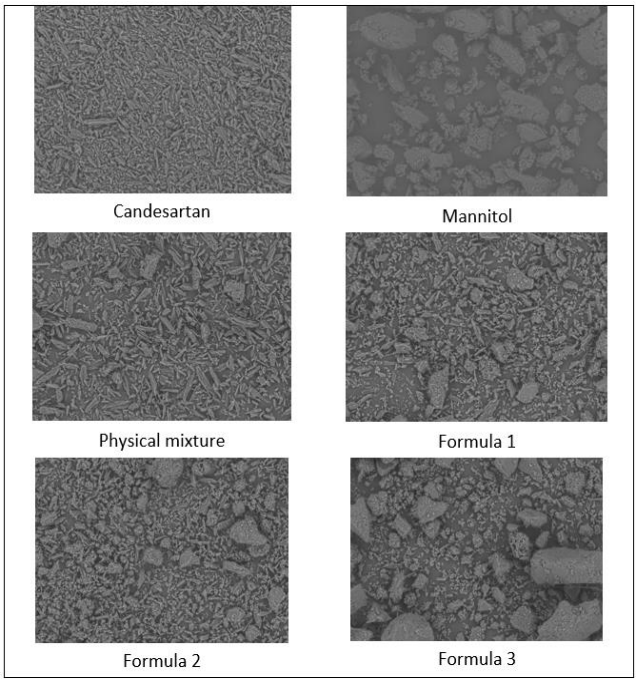

Figure 3. The figure of Candesartan-cilexetil, Mannitol, Physics Mixture, Solid Dispersion F1, F2, F3

Differential Scanning Calorimetry is an analytical instrument that is very useful in the characterization of solid-state interactions between two or more drug materials. Analysis was performed to compare the temperature of the sample with an inert reference material during a programmed temperature change. The temperature of the sample and reference will be the same if there is no change, but when a thermal event occurs such as melting, decomposition, or a change in the crystal structure of the sample, the temperature of the sample can be below the reference temperature (endothermic) or above the reference temperature (exothermic). The thermogram explains that there is a reduction in intensity and a shift in the melting point in solid dispersion powders, this indicates that the degree of crystallinity has decreased. The candesartan cilexetil DSC thermogram shows a sharp endothermic peak at a temperature of 169.916 ◦C and an enthalpy of 69.206 J/g. In the physical mixture, there are two slightly widened endothermic peaks which are suspected to be mannitol, namely at a temperature of 179.989 ◦C and an enthalpy of 26.643 J/g. The melting point of the candesartan, cilexetil, and mannitol solid dispersion powder for each formulation shifts as a result of a physical interaction. An endothermic peak was seen in Powder Solid Dispersion Formula 1 at a temperature of 166.031 ◦C and an enthalpy of 10.097 J/g, although this peak was not the melting point of the raw material and had actually decreased from the melting point of a single cilexetil candesartan. In addition, the endothermic peak in formula 2 for powder solid dispersion changed to 169.779◦C and 4.085 J/g enthalpy. The endothermic peak in solid dispersion formula 3 is observed at 170.594 ◦C and 1.474 J/g enthalpy (Figure 4).

This strengthens the X-ray diffraction results due to the interaction between candesartan-cilexethyl and mannitol (Figure 2). In general, the results of the DSC thermogram of solid dispersion powders for each formula show a shift in the mannitol melting point. These results support the statement that solid dispersion properties follow the carrier's properties, namely mannitol. The DSC results also strengthen SEM data that solid dispersion of the morphological form of pure candesartan-cilexethyl is not particularly obvious.

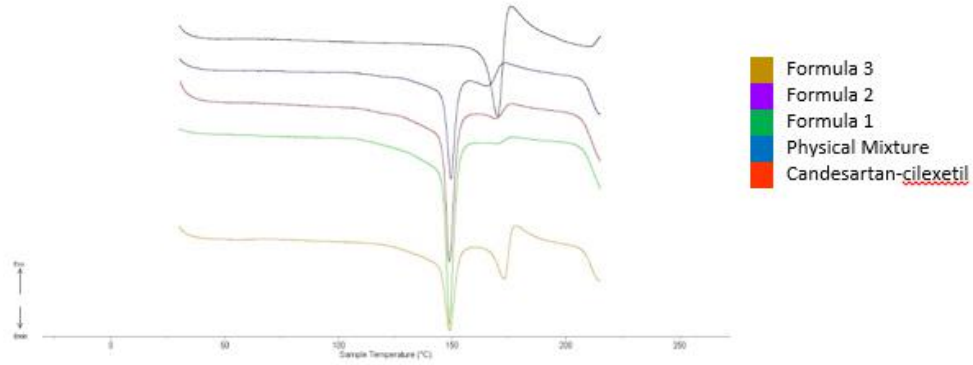

Figure 4. Thermogram of Candesartan-cilexetil, Mannitol, Physics Mixture, Solid Dispersion F1, F2, F3

The study was continued with FT-IR spectroscopy analysis which aimed at qualitative analysis including analysis of functional groups and identifying mixed compounds. The energy at the peak of the visible spectrum corresponds to the vibrational frequency of some of the sample molecules. Measurements in the middle infrared spectrum are at a length of 2.5-5.0 µm or wave number of 4000-400 cm^{-1}. The O-H functional group is present in the main peaks of pure candesartan cilexetil at wave numbers 3750-3000 cm^{-1}, the CH3 functional group is present at wave numbers 3000-2700 cm^{-1}, the CC functional group is present at wave numbers 2400-2100 cm^{-1}, the functional group C=O is present at wave numbers 1900-1650 cm^{-1}, and the functional group C=C-H is present at wave numbers 1000-650 cm^{-1}. Pure candesartan cilexetil contains the functional groups O-H at wave number 3670.45 cm-1, CH3 at wave numbers 2855.86 cm^{-1} and 2940.74 cm^{-1}, C-C at wave number 2153.59 cm^{-1}, C=O at wave number 1720.43 cm-1, C=C at wave number 1550.73 cm-1, C-H at wave number 1355.49 cm^{-1} and C=C-H at wave number 910.87 cm^{-1}. The FT-IR spectrum of mannitol, shows a wide peak at wave number 3737.46 cm^{-1} which indicates the presence of O-H functional groups in complex molecules such as cellulose, saccharides and other molecules that have very strong absorbing groups (Figure 5).

The results of the physical mixture's characterization indicated the presence of candesartan cilexetil functional groups at a number of wave numbers: CH3 at 2854.44 cm^{-1} and 2941.00 cm-1, CC at 2150.07 cm-1, C=O at 1735.33 cm^{-1}, C=C at 1551.06 cm^{-1}, C-H at 1355.74 cm^{-1} and 1450.34 cm^{-1}, and C=C-H at 989.16 cm^{-1}. There is also a peak indicating the presence of a functional group from mannitol at wave number 3671.85 cm-1. The appearance of peaks indicating the presence of functional groups belonging to candesartan and mannitol indicates that there is no interaction between candesartan cilexetil and mannitol. In the results of the characterization of solid dispersion powder formulas 1, 2, and 3 there were also peaks indicating the presence of the candesartan cilexetil functional group, namely at wave numbers 3680.23; 3366.66; 3680.67; 3527.70; 3723.59; 3524.91 cm^{-1} which indicates the OH functional group, at wave number 2860.67; 2940.79; 2934.81; 2735.12; 2899.58 cm^{-1} which indicates the presence of the CH3 functional group, at wave number 1735.57; 1739.09; 1743.79 cm^{-1} which indicates the presence of the C=O functional group, at wave number 1551.98; 1552.20; 1552.10 cm^{-1} which indicates the presence of the C=C functional group, at wave number 1356.97; 1446.32; 1355.56; 1438.37; 1352.94; 1433.60 cm^{-1} which indicates the presence of the C-H functional group, at wave number 896.76; 794.89; 751.58 cm-1 which indicates the presence of the C=C-H functional group. In the solid dispersion formulas 1 and 3, there is a functional group C≡C at wave number 2151.68; 2245.53 cm^{-1}. The loss of some of the candesartan cilexetil peaks indicates an interaction between candesartan cilexetil and mannitol in the preparation of a solid dispersion between candesartan and mannitol (Figure 5).

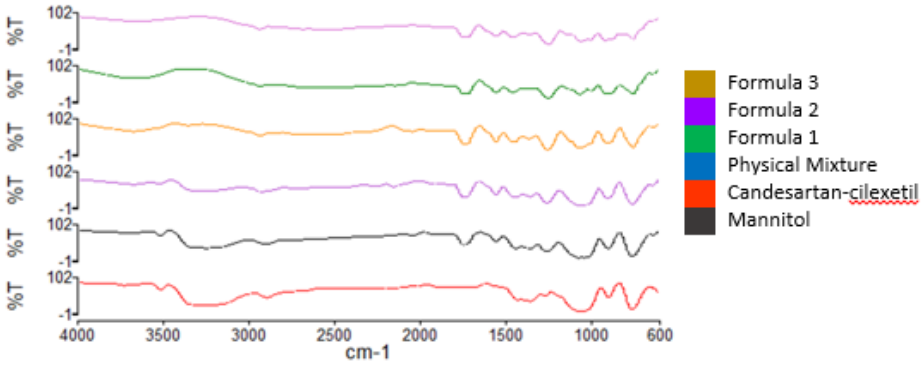

Figure 5. The spectrum of Candesartan-cilexetil, Mannitol, Physics Mixture, Solid Dispersion F1, F2, F3

After examining the particle size distribution, X-ray diffraction, FT-IR, SEM, and DSC, the assays in solid dispersion and physical mixtures were carried out. Determination of the maximum absorption wavelength of candesartan-cilexetil in ethanol solvent obtained the maximum wavelength of candesartan-cilexetil of 254.80 nm with an abruption of 0.492. According to the Japanese Pharmacopoeia Committee, 2011, the maximum wavelength of candesartan-cilexetil is 252-256 nm. Based on these results, calibration curves were obtained, and the regression equation's outcomes are y = 0.04979 x – 0.00426 and r = 0.9999 (Figure 6). The results of the assay showed that the pure candesartan-cilexethyl content was 100.7418 %, the physical mixture was 100.8757 %, the solid dispersion number one was 101.9426 %, the solid dispersion number two was 101.0765 %, and the solid dispersion number three was 101.2774 %. According to the assay results obtained in line with USP (The United States Pharmacopeial Convention, 2016) criteria, the sample's candesartan cilexethyl content is between 90 % and 110 %.

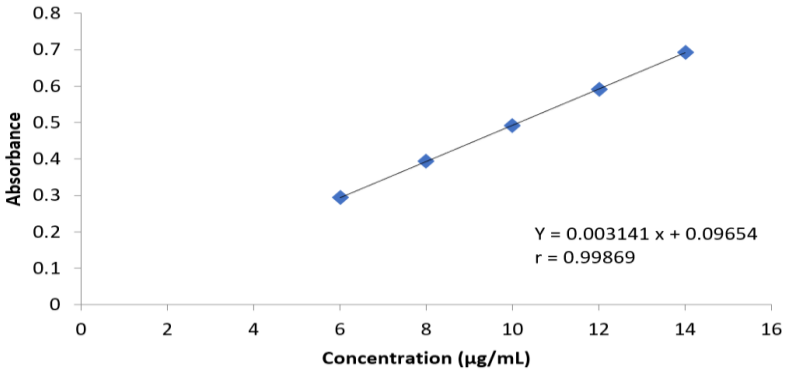

Figure 6. Calibration curve of candesartan-cilexetil in ethanol 96 %

Dissolution profiles of pure candesartan cilexethyl, physical mixtures, and solid dispersion powders were carried out using phosphate buffer medium pH 6.5 (The United States Pharmacopeial Convention, 2016). Determination of the maximum wavelength of candesartan-cilexethyl in phosphate buffer medium pH 6.5 using a UV-Vis spectrophotometer. At a maximum absorption of 0.536, a maximum absorption wavelength of 257.00 nm is obtained. From the measurement results, we get a regression equation y = 0.003141 x + 0.09654 with a value of r = 0.99869.

The next step in the dissolution test was to determine the dissolution profile of a single candesartan-cilexethyl powder, a physical mixture, and a solid dispersion of candesartan cilexethyl-mannitol in phosphate buffer dissolution medium pH 6.5. The dissolution profile was determined using a type 2 apparatus (paddle) by incorporating the equivalent of 32 mg of candesartan-cilexethyl into a cylindrical container containing 900 mL of phosphate buffer dissolution medium pH 6.5 at 37 °C ±0.5 °C with a speed of 50 rpm. 5 mL of the dissolution was pipetted at 5,10, 15, 30, 45, and 60 minutes when 5 mL of dissolution solution was taken, the solution was replaced with 5 mL of the same dissolution solution. Then the maximum absorption measurement was carried out at a wavelength of 257 nm. After measurements, the result obtained from the determination of the dissolution profile is shown in Figure 8.

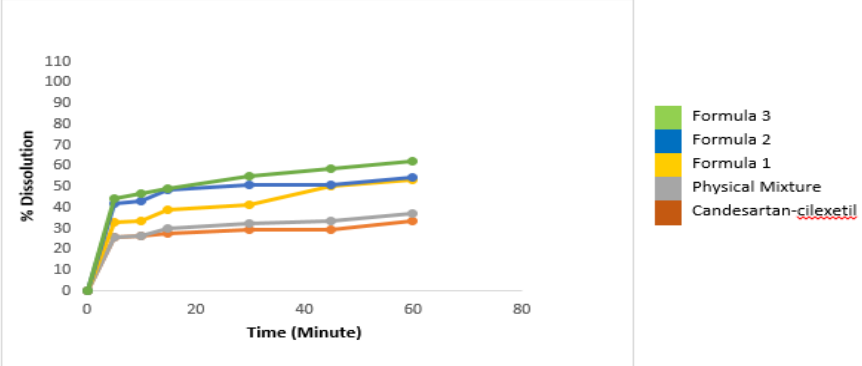

Figure 8. Candesartan Cilexetil dissolution profile curve, Physical Mixture, and Solid Dispersion F 1, F 2, F 3 in Phosphate Buffer pH 6.5

The increase in the percentage solubility of candesartan-cilexethyl in the dissolution medium was caused by the addition of hydrophilic mannitol, but the milling process still affected the rate of dissolution of candesartan-cilexethyl because it changed the crystal form of candesartan-cilexethyl to become more amorphous, reducing aggregation, thereby increasing the limitation and ability to disperse. Although it was reported in the literature that the percent dissolution obtained should not be less than 75 % in the 45th minute, based on the results of the largest dissolution percent obtained, it was only around 58 % in the 45th minute (Japanese Pharmacopoeia Committee, 2011).

Conclusion

Based on the research that has been done it can be concluded that the addition of mannitol can change the physicochemical characteristics of candesartan-cilexetil, this shows that the solid dispersion with the co-grinding method can affect changes in characterization. The dissolution rate of candesartan-cilexetil can be increased by modifying the characteristics of solid dispersions formed using the co-grinding process. The dissolution test was carried out on pure candesartan cilexetil powder, physical mixture, solid dispersion formula 1, solid dispersion formula 2, and solid dispersion formula 3 in the time interval of 5, 10, 15, 30, 45, and 60 minutes. The test results showed that The solid dispersion produced using the co-milling method can increase the dissolution rate of candesartan cilexetil. At 60 minutes the percentage obtained was candesartan cilexetil: 33.55957498 %, CF: 36.87261223 %, F 1: 53.199 %, F 2: 54.3621 %, and F 3: 62.3621 %. Of the three solid dispersion formulas, Formula 3 has the highest dissolution percentage, which is 62.36210602% in the 60th minute.

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