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Research Article

Nanoparticle of Telmisartan and Polyvinylpyrrolidone K-30: Characterization and Dissolution Study

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Abstract

Background: Telmisartan (TEL) is an orally active nonpeptide angiotensin II antagonist drug. The drug acts on a subtype of AT1 receptors, which serves to cope with high blood pressure (hypertension). TEL is a class II Biopharmaceutical Classification System (BCS), which is a drug that has low solubility in water and high permeability. **Objectives:** This study aims to determine the effect of the formation of TEL-PVP K-30 nanoparticles through the solvent drop grinding method on the characteristics of physicochemical properties and the rate of dissolution of TEL. **Methods:** Nanoparticles are made in 2 formulas, namely formula 1: 1 and formula 1: 2. **Results:** Characterization of the Particle Size Analyzer (PSA) was performed with the results of the formula 1:1 24nm, and the formula 1:2 35nm. X-ray Diffraction (XRD) analysis resulted from a decrease in the intensity of crystallinity degrees. Fourier Transform Infrared (FT-IR) Spectroscopy occurs wave number shift. Differential Scanning Calorimetry (DSC) decreases in melting point. The dissolution rate was carried out using a pH 7.5 phosphate tart medium. **Conclusion:** The result of the dissolution rate has increased by 3.3 times for formula 1:1 and 2.9 times for formula 1:2.

Keywords: Telmisartan; polyvinylpyrrolidone K-30; nanoparticles; and solvent drop grinding.

INTRODUCTION

TEL is an Angiotensin II Receptor Blocker (ARB) class drug that is used for the prevention and treatment of hypertension. TEL belongs to class II based on the Biopharmaceutical Classification System (BCS) because it has low solubility in water and high permeability [1]. One of the main problems of TEL is its low solubility in water which causes a slow rate of dissolution so that its therapeutic effect will be reduced [2].

Several studies have been conducted to improve the solubility and dissolution of TEL, among them the formation of solid dispersions of TEL-PVP K-30, PEG 4000, β-cyclodextrin [3]; the formation of inclusion complexes with β-cyclodextrin [4]; amorphous formation with PVP K-30 [5]; cocrystal formation of TEL-oxalic acid [1]; the formation of nanoparticles [6]. Nanoparticles are particles measuring 1-100 nanometers [7]. Nanoparticles aim to overcome the solubility of active substances that are difficult to dissolve, improve poor bioavailability, modify the drug delivery system so that the drug can go directly to a specific area, increase the stability of the active substance from environmental degradation (enzymatic decomposition, oxidation, hydrolysis), improve the absorption of a macromolecular compound, and reduce the irritating effect of the active substance on the GI tract [8].

The formation of nanoparticles can be carried out using polymers, one of which is the polyvinylpyrrolidone polymer K-30. Polyvinylpyrrolidone is also known by the names povidone, kollidone, plasdone, and polyvidone. Polyvinylpyrrolidone is a white or yellowish-white powder, odorless or weakly smelling, tasteless, and hygroscopic. Polyvinylpyrrolidone is easily soluble in water, ethanol, methanol, and chloroform, practically insoluble in ether, hydrocarbons, and mineral oils [9]. Many methods can be used for the formation of nanoparticles, one of which is solvent drop grinding. Solvent drop grinding is one of the techniques by grinding followed by the addition of a small amount of solvent. The solvent used is a solvent that can dissolve both substances that are useful as catalysts. The solvent drop grinding method has advantages over other methods, such as the ability to control the formation of polymorphs, better crystallization, as well as increase the selectivity of the cocrystallization [10].

The formation of TEL-PVP K-30 nanoparticles was carried out with various characterizations. The characterization of the nanoparticle was evaluated by Particle Size Analyzer (PSA), X-ray Diffraction (XRD) analysis, Fourier Transform Infrared (FT-IR) Spectroscopy, and Differential Scanning Calorimetry (DSC). The dissolution rate was carried out in phosphate buffer pH 7.5.

MATERIAL AND METHODS

Tools

The tools used in this study were planetary ball mills (Retsch Type PM 100, Germany), Particle Size Analyzer (Horiba SZ-100, Japan), X-ray Diffraction (Philips X'Pert Pro-PANalytical, The Netherland), Fourier Transform Infrared (Perkin Elmer L1600300 Spectrum Two, USA), Differential Scanning Calorimetry (Equivalent DSC 131 Evo, France), UV-Vis

Spectrophotometer (Shimadzu ED23 1800®, Japan), and Dissolution Test Equipment (Cop Scientificley NE4-COPD, UK).

Materials

Materials used in this study Telmisartan raw materials (Ltd. Dr. Reddy's Laboratories, CTO Unit-II, India), Polyvinyl pyrrolidone (PVP K-30) (Ltd. JH Nanhang Life Sciences CO., China), Potassium Dihydrogen phosphorate (Bratachem, Indonesia), NaOH (PT. Novalindo, Indonesia), methanol (PT. Novalindo, Indonesia), and distilled water (PT. Novalindo, Indonesia).

Manufacture of TEL-PVP K-30 Nanoparticles

TEL and PVP K-30 are mixed in a ratio of 1:1 and 1:2 grams. This mixture is then ground using a ball milling tool with a grinding time of 4 hours at a speed of 120 rpm using 42 small balls and 42 large balls.

Particle Size Analyzer (PSA)

Particle size distribution analysis uses a particle size analyzer, which works on the principle of Dynam Light Scattered. This method uses a dispersing medium to disperse the sample. The dispersing medium used aqua dest. The measurement of the sample was carried out three times until two data were obtained that had a difference of less than 20 nm. The analysis was performed on 1:1 and 1:2 nanoparticles.

X-ray diffraction (XRD) analysis

Analyses were carried out on TEL, PVP K-30, and nanoparticles. X-ray diffraction analyses of the samples were performed at room temperature using an X-ray diffractometer with Cu, Kα filter, current 30 mA, and voltage 40 kV. Samples were measured in reflection mode at 2 thetas with an angle range of 5°–50°.

Fourier transform infrared (FT-IR) spectroscopic analysis

FT-IR spectroscopic analysis was performed on TEL, PVP K-30, and nanoparticles. A small amount of sample (3 mg) was mixed with 10 mg KBr after which it was placed in the sample holder of the FT-IR spectroscopic instrument and the samples were analyzed at room temperature. The spectrum was measured in the range of 450-4000 cm^{-1} wavenumber.

Differential scanning calorimetry (DSC) analysis

Thermal analysis on TEL, PVP K-30, and nanoparticles were carried out using a DSC apparatus. Samples of 3 mg were placed in a closed aluminum pan. The DSC device is programmed in a temperature range of 50–300°C, heating speed of 10°C/min.

Dissolution rate profile study

The dissolution rate study of TEL and nanoparticles used the paddle method at 37 ± 0.5°C at a speed of 75 rpm for 60 min with mediums phosphate buffer pH 7.5. Five mL of each dissolution medium was pipetted at 5, 10, 15, 30, 45, and 60 min. The absorbance of the solution that had been pipetted from the dissolution medium was measured using a UV-Vis spectrophotometer (at 297 nm) to determine the amount of TEL dissolved.

RESULT AND DISCUSSION

Particle size distribution analysis uses a particle size analyzer (PSA), which works on the principle of Dynam Light Scattered. This method uses a dispersing medium to disperse the sample. The dispersing medium used aqua dest. The measurement of the sample was carried out three repetitions until two data were obtained that had a difference of less than 20 nm [11]. The results of the particle size analyzer formula 1:1 i.e. 0.024 µm while formula 2 is 0.035 µm. Formulas 1:1 and 1:2 already qualify as nanoparticle powders. From the results of particle size distribution, it can be concluded that the influence of the use of PVP K-30 on the formation of TEL nanoparticles will affect the particle size. Therefore, the particle size is by expectations, if the smaller the particle size, the surface area of the particle is greater so that the solubility increases [12].

X-ray diffraction (XRD) analysis is a method for characterizing solids' interaction between two solid components (solid-state interaction) and knowing whether a new crystalline phase is formed or not [13]. The results of the TEL diffractogram show a typical and sharp peak of interference at an angle of 2θ: 6.8526 which is 4691.281. The PVP diffractogram K-30 shows a characteristic and sharp peak at an angle of 2θ : 6.8526 i.e. 456.5733. On the diffractogram the 1:1 nanoparticle shows a characteristic and sharp peak at an angle of 2θ : 6.8526 which is 966.1834. On the diffractogram the 1:2 nanoparticle shows a characteristic and sharp peak at an angle of 2θ : 6.8526 which is 967.7257. Based on the analysis data, shows the existence of chemical interactions due to a reduction in intensity, which means that each formula is increasingly amorphous in nanoparticles 1: 1 and 1: 2 which can be seen in figure 1. The intensity is influenced by the crystal size and crystallinity, the reduction in intensity indicates a reduction in particle size [14].

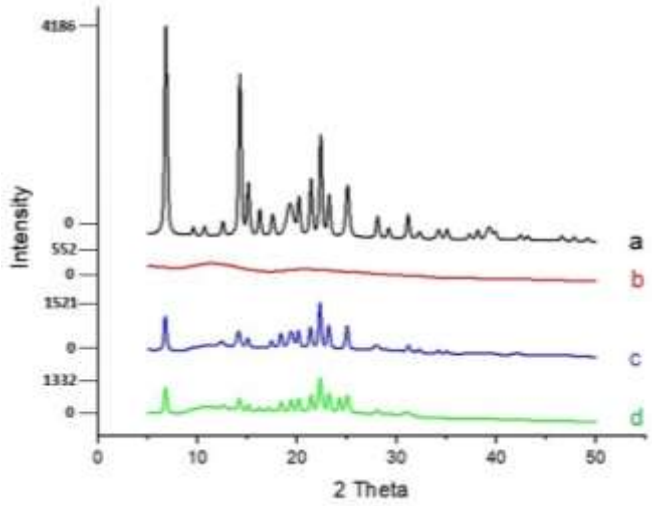

Figure 1: X-ray diffraction analysis of (a) telmisartan, (b) polyvinylpyrrolidone K-30, (c) 1:1 nanoparticle (d) 1:2 nanoparticle

Fourier transform infrared (FT-IR) spectroscopic analysis is performed to identify functional groups in a compound. Each uptake at a certain wave number describes the existence of a specific functional group. The results of the analysis are in the form of a signal chromatogram of the relationship of IR intensity to wave number [15]. In the infrared spectrum, TEL powder is seen in figure 2 there is an O-H function group at wave number 3401.15cm^{-1}, function group C=H at wave number 3058.22cm^{-1}, and function group C=O At wave number 1383.16 cm^{-1}, function group C-N at wave number 1696.84 cm^{-1}. The results of ft-IR analysis on PVP K-30 showed the existence of an O-H function group at wave number 3434.83 cm^{-1}, and function group C = H at wave number 1374.07 cm^{-1}. The results of FT-IR analysis on nanoparticles in formula 1: 1 show the existence of an O-H function functional group at wave number 3413.10 cm^{-1}, function group C = H at wave number 3058.84cm^{-1}, function group C = O at wave number 1381.60 cm^{-1}, and function group C-N at wave number 1659.82 cm^{-1}. The results of FT-IR analysis of formula 1:2 nanoparticles show the presence of an O-H function group at wave number 3433.81 cm^{-1}, function group C=H at wave number 3060.96 cm^{-1}, function group C=O

at wave number 1380.83 cm^{-1} and function group C-N at wave number 1660.90 cm^{-1}. This FT-IR analysis can be concluded in both nanoparticle formulas showing the presence of a functional group that resembles TEL, except that there is a shift in the wave number. This shows the interaction between TEL and PVP K-30 which means that there is a formation of nanoparticles between TEL and PVP K-30 which are made by the solvent drop grinding method.

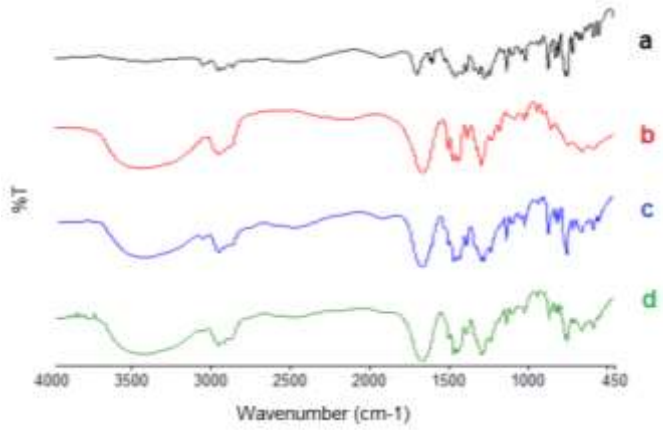

Figure 2: Fourier transform infrared spectroscopic analysis of (a) telmisartan, (b) polyvinylpyrrolidone K-30, (c) 1:1 nanoparticle (d) 1:2 nanoparticle

The Differential Scanning Calorimeter (DSC) test, is used to determine the heat and enthalpy capacity of a sample. DSC can measure the amount of heat absorbed or released during such a transition [16]. In the research that has been carried out, the TEL thermogram shows a sharp endothermic peak at a temperature of 271.916°C which is a melting event from TEL with an enthalpy of 97.281 J / g, the thermogram can be seen in figure 3. PVP K-30 showed an endothermic peak at a temperature of 102.48°C with an enthalpy of 241.005 J/g, and a nanoparticle thermogram of 1:1 saw an endothermic peak at a temperature of 88.775°C with an enthalpy of 145.024 J/g and a nanoparticle of 1:2 seen an endothermic peak at a temperature of 101.297°C with an enthalpy of 300.584 J/g.

Differential Scanning Calorimetry (DSC) analysis in this study obtained the conclusions of the results of formula 1: 1 and formula 1: 2 there was a decrease in melting point and enthalpy value compared to the values of TEL and PVP K-30, this result supports the results of XRD analysis which showed the formation of amorphous shapes or changes in the crystal lattice [14].

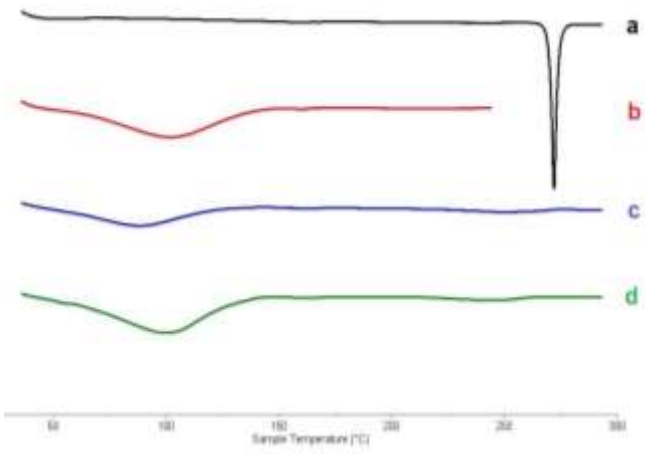

Figure 3: Differential scanning calorimetry analysis of (a) telmisartan, (b) polyvinylpyrrolidone K-30, (c) 1:1 nanoparticle (d) 1:2 nanoparticle

In determining the dissolution profile of TEL and nanoparticles, it was shown that in the dissolution profile of the nanoparticles there was an increase in the dissolution rate. The increase in the rate of dissolution was due to the influence of the addition of the K-30 PVP polymer. In the dissolution test, it was seen that the percentage of dissolution in the 60th minute of TEL was 23.0202%, nanoparticles 1:1 72.8463%, and nanoparticles 1:2 69.0846%. The dissolution results showed TEL had the slowest dissolution when compared to formula 1 and formula 2, this could indicate that the formation of TEL-PVP K-30 nanoparticles could increase the rate of TEL dissolution (Figure 4).

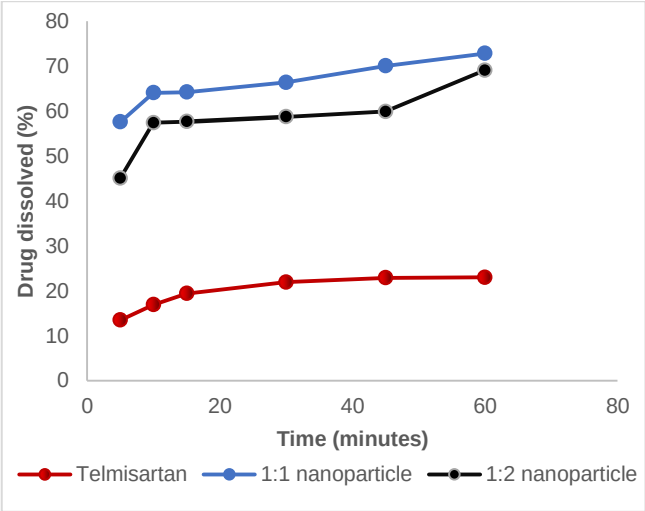

Figure 4: Dissolution rate profile of telmisartan, 1:1 nanoparticle, and 1:2 nanoparticle in mediums phosphate buffer pH 7.5 (n = 3)

CONCLUSIONS

In this study, the formation of TEL-PVP K-30 nanoparticles by solvent drop grinding method can improve the physicochemical properties of TEL, which can be seen from the results of the characterization of PSA, XRD, FT-IR, and DSC. The formation of TEL-PVP K-30 nanoparticles can increase the rate of TEL dissolution.

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