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Preparation of Efavirenz – PVP K-30 Solid Dispersionby Spray Drying Technique.

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ABSTRACT

A preparation of solid dispersion system ofefavirenz–polyvinylpyrrolidone(PVP) K-30 has been conducted. Solid dispersion was prepared by solvent evaporation method with ratio 2:1, 1:1 and 1:2 (w/w) and dried by spray drying technique. Characterizations of samples were performed by X-ray diffraction, thermal analysis, Scanning Electron Microscopy (SEM), and FT-IR spectroscopy. Dissolution rate testwas done in distillated water medium with 0.5 % w/v Sodium Lauryl Sulphate (SLS). Efavirenz assay was done by High Performance Liquid Chromatography (HPLC) using acetonitrile:acidacetic (80:20) as mobile phase. Powder X-ray diffractogram of solid dispersion showed an amorphous solid with amorphous halo diffractogram and a decline in the intensity of the interference peak, while intactefavirenz showed crystalline solid diffractogram. Thermal analysis indicated the changes of melting point from solid dispersion at ratio 1:1 and 1:2, where melting point of these two solid dispersion was in between of pure substances. Meanwhile, solid dispersion at ratio 2:1 had the same melting point of the pure substances. SEM analysis of solid dispersions indicated a spherical habit which efavirenz likely dispersed into the polymer. FT-IR analysis of solid dispersions indicated there was a shift of the wave number spectrum compared to pure efavirenz and PVP K-30 which indicated that hydrogen bonding was likely to be formed. Percentage Q_{120} of dissolved efavirenz was 64.61±0.20% which was lower than solid dispersions at ratio 2:1, 1:1 and 2:1, which were 66.43±0.11%, 74.44±0.09%, and 73.53±0.07%, respectively.

Keywords: Efavirenz, PVP K-30, spray drying, dissolution rate

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INTRODUCTION

Efavirenz is a Non-nucleoside Reverse Transcriptase Inhibitors (NNRTI) class of antiretroviraldrugs which specific to HIV type 1. This drug is categorized in class II (low solubility – highpermeability) according to Biopharmaceutical Classification System (BCS). Therefore, an increase in the rate of dissolution and bioavailability efavirenz needs to be done in order to achieve therapeutic effect [1, 2].Solubility and dissolution rate is one of the decisive factors in the process of absorption, particularly for oral preparations. Therefore, several methods have been done to improve the solubility and dissolution rate of efavirenzsuch ascomplex with cyclodextrins[2], solid dispersion [3, 4], using surfactant [1], co-micronization[5], and co-crystal formation [6].

Solid dispersion system is an effective method to increase the solubility of poorly water soluble drugs [7]. In manufacturing solid dispersion system, it is very important to understand the physicochemical properties of the drug and a suitable carrier in order to increase the dissolution rate of drugs and solve the solubility problems[8].Spray drying is an attractive and simply technique that recently developed to produce powders with the size up to nanometer. The advantages of drying process using spray dryer are drying time is short and the final product is relatively stable[9].

Polyvinylpyrrolidone (PVP) isan inert soluble watercarrier that can be used toincrease dissolution rate and solubility of drugs by inhibiting the growth of crystals in the transformation phase.Previous research using a rotary evaporator as dryer, suggested an increase in the dissolution rate of efavirenz using two kinds polymer: PEG 8000 and PVP K-30, with a ratio of each polymer 1: 5, 1:10, and 1:15, yet these two polymers did not show statistically significant difference [10]. Another study stated that the dissolution rate of efavirenz improved by forming a solid dispersion system of efavirenz-PEG6000 with a ratio of 1: 1 and 1: 2 [3]. Therefore, this present study was carried out to prepare solid dispersion of efavirenzwith PVP K-30 usingspray drying technique. The aims of this research are to improve the dissolution rate of efavirenz with the formation of solid dispersion system and to determine the influence of the concentration of PVP K-30 to the dissolution rate of efavirenz. Characterization of solid dispersion is done by Differential Thermal Analysis (DTA), Scanning Electron Microcopy analysis (SEM), X-ray diffraction analysis, and Fourier Transform Infrared (FTIR) Spectroscopy, and dissolutionrate study.

EXPERIMENTAL

Materials

Efavirenz (Kimia Farma, Indonesia), Poly vinyl pyrrolidone K-30 (Delta Chemical, Indonesia), Sodium Lauryl Sulfate (BratacoChemika, Indonesia), ethanol 96% (BratacoChemika, Indonesia), methanol pro analysis (Merck, Germany), acetonitrile grade HPLC (Merck, Germany), acetate acid (Merck, Germany) and distilled aqua. All materials were used as received.

Preparation of solid dispersion

Efavirenz and PVP K-30 was mixed with a ratio of 2:1, 1:1, 1:2 (w/w). Efavirenzwas dissolved in ethanol 96%, while PVP K-30 was dissolved in distilled water. The solution was homogenized using a magnetic stirrer. Once homogeneous, the mixture was dried using a Mini spray dryer B-290with condition as followed: inlet temperature 120°C, outlet temperature 80°C. The spray dried powder was kept in a tightly sealed container in desiccator.

Scanning Electron Microscope (SEM) analysis

Sample powder was placed on the sample holder aluminum and coated with gold. The sample was observed at various magnifications SEM tool with the voltage was set at 20kV and the current was 12mA. SEM analysis was conducted for pure efavirenz, PVP K-30, solid dispersion ofefavirenz-PVP K-30.

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Differential Thermal Analysis (DTA)

Thermal analysis of samples was carried out by using a differential thermal analyzer calibrated with Indium temperature. A small amount of sample (5-7 mg) was placed on an aluminum pan. DTA temperature was programmed in a range from 30°C to 250°C with a heating rate 10°C per minute. Analysis was performed for efavirenz, PVP K-30, solid dispersion of efavirenz-PVP K-30.

Powder X-Ray Diffraction (PXRD) analysis

Analysis of the X-ray powder diffraction wasdone using a diffractometer. Sample was placed on pan analytical and leveled to prevent particle orientation during sample preparation. Measurement was done at conditions as follows: the target metals Cu, filter Kα, 45kV voltage, 40mA current, the analysis carried out in the range of 2 theta 10° - 40° at room temperature. Analyses was performed for efavirenz, PVP K-30, solid dispersion of efavirenz-PVP K-30.

Spectroscopy FT-Infra-red analysis

Samples were analyzed using an infrared spectrophotometer by dispersing samples on KBr plate and were compressed at high pressure (hydraulic press). Absorption spectra were recorded with (Fourier Transform Infrared) at wavenumber 4000-500cm^{-1}. Analyses was performed for efavirenz, PVP K-30, solid dispersion of efavirenz-PVP K-30

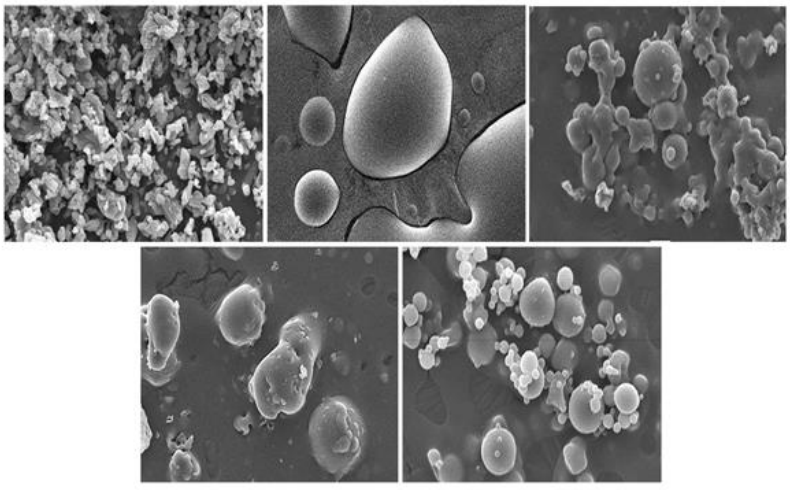
Dissolution rate study

Dissolution test was carried out using a paddle-type dissolution testat speed 50 rpm in 900 mL CO_2-free distilled water with 0.5% w / v sodium lauryl sulfate (SLS) medium at 37±0.5°C. The solution was pipetted for 5 mL and was assessed at 5, 15, 30, 45, 60, 80, 100, and 120 minute. The percentage of drug dissolved was done using HPLC with acetonitrile and 1% acetic acid (80:20) as mobile phase and condition as follow. The measurements was done triplicate.

RESULTS AND DISCUSSION

SEM Analysis

Morphology of Efavirenz, PVP K-30 and solid dispersion can be seen in Figure 1. Intactefavirenz showed a polyhedral rod-shaped crystal habit, while PVP K-30 was irregular round shape on its surface. The solid dispersion showed a spherical habit that indicated efavirenz was dispersed into PVP K-30 and formed aggregates.



Figures 1: Morphology of (a) intact efavirenz, (b) PVP K-30, (c) Solid dispersion at ratio 2:1, (d) Solid dispersion at ratio 1:1 (e) Solid dispersion at ratio 1:2

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Powder X-ray diffraction (PXRD) analysis

The XRD diffractogram of the samples can be seen in Figure 2. Specific interference peaksof pure efavirenzat 2θ were 14.24; 15.26; 19.28; 21.28; and 22.05. It can be seen that diffractogram of efavirenzshowed the crystalline solids, whereas the solid dispersion showed halo amorphous diffractogramthat showed a decline in the intensity of the interference peak. A decrease in the intensity of the interference peaks indicate changes in the degree of crystallinity[11].

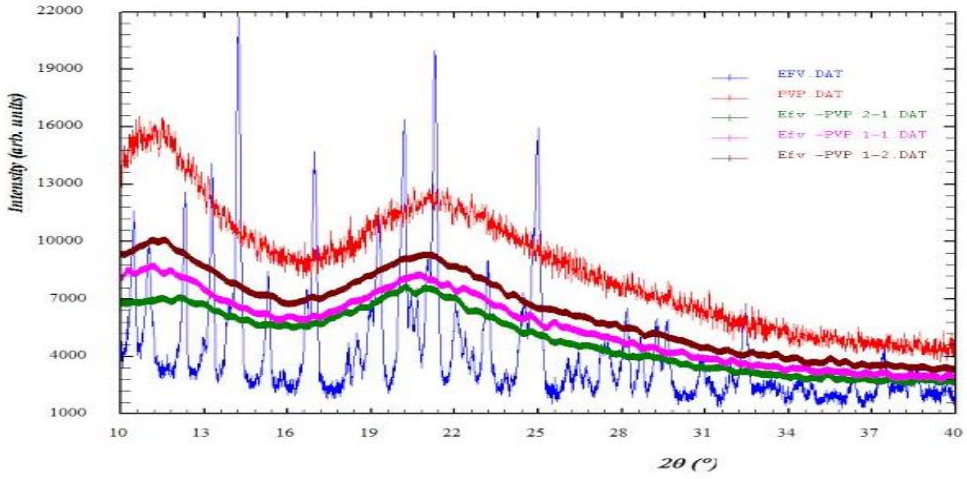

Figure 2: Diffractogram of Efavirenz and solid dispersion at different ratio

Thermal analysis

Thermal analysis was conducted using Differential Thermal Analyzer in order to evaluate the changes in thermodynamic once the materials get heat energy which is describe by the endotherm profile[12].Melting point of intactefavirenzwas 138.9°C, whilethe water loss temperature ofPVP K-30 was 149°C,asshown in Figure 3. The curve of intactefavirenz had a sharp endothermic peak which indicated its crystallinity. Thesolid dispersion at ratio 2:1 had also two peaks at 137.3°C and 179.2°C which represented efavirenz and PVP K-30. On the other hand, melting point of solid dispersion at ratio 1:1 and 1:2 were 142.2°C and 149.4°C, respectively, which was in between of pure materials. This indicated that interaction had occurred between efavirenz and PVP K-30 at these ratio, where this interaction caused a decrease in endothermic peak intensity. This result was in accordance with the XRD analysis which solid dispersion was amorphous phase.

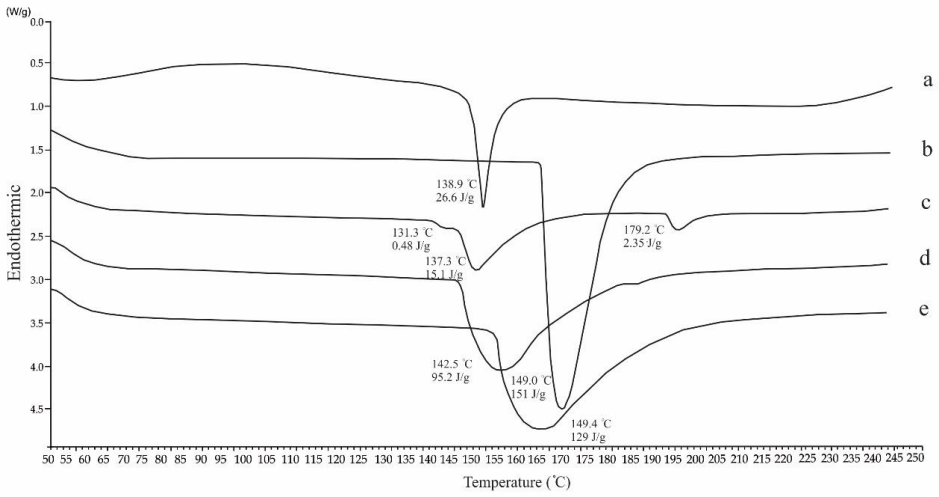

Figure 3: Thermogram DTA (a) intact efavirenz, (b) PVP K-30, (c) Solid dispersion at ratio 2:1, (d) Solid dispersion at ratio 1:1 (e) Solid dispersion at ratio 1:2

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Spectrophotometry Infra-red (IR)

Infrared spectroscopy is often used to investigate the interaction between the drugs with the polymer in the sample.Efavirenz which has N-H bond showed its absorbance at wave length number 3314.82 cm^{-1} as can be seen in Figure 4. The N-H bond usually depict at wave length number 3060-3500 cm^{-1}. N-H bond of efavirenzis at wavenumber 3314.82 cm^{-1}.After the formation of solid dispersions contained bond N-H peak indicates the shift. N-H bond of solid dispersion 1: 1 and 1: 2 showed a shift towards wavenumber 3404.13 cm^{-1} and 3419.99 cm^{-1}.

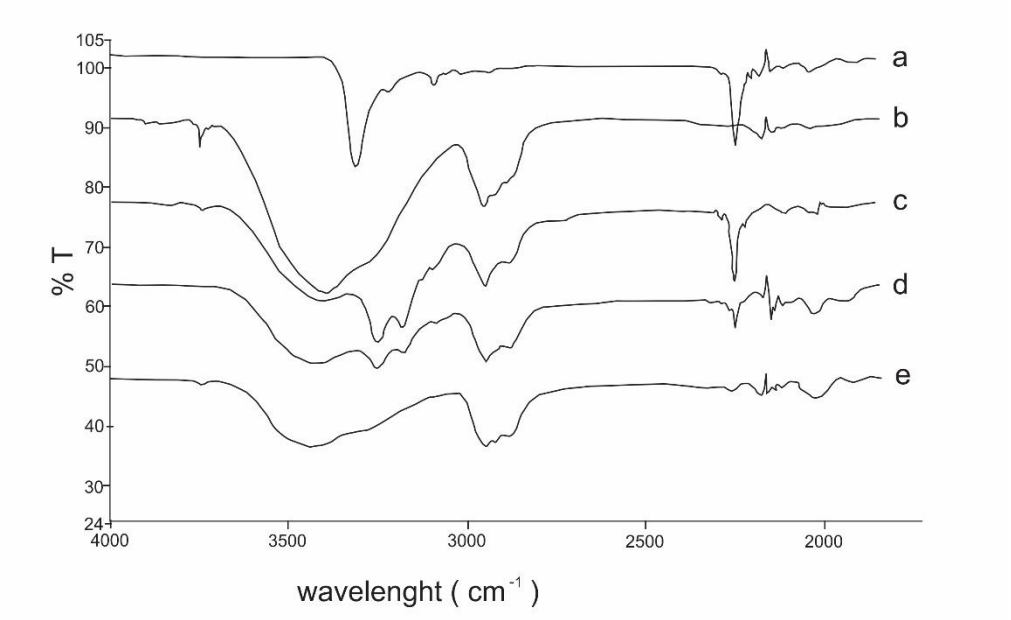

Figure 4: FT-IR spectrum of (a) pure efavirenz, (b) PVP K-30, (c) Solid dispersion at ratio 2:1, (d) Solid dispersion at ratio 1:1 (e) Solid dispersion at ratio 1:2

A shift wave numbers allegedly due to the hydrogen bonds between the two components. Hydrogen bonding occurs due to the carbonyl group of the amide binds to efavirenz in PVP K-30 or a carbonyl group of PVP K-30 binds to the amine group on efavirenz [13]. The results of FT-IR analysis supports the results of previous analysis, that the solid dispersion shift the absorption band was occurred that showed a change in the crystal structure of the drug in the solid dispersion.

Dissolution rate study and efficiency dissolution

The dissolution study ofintactefavirenz and solid dispersions was conducted in900 mL CO_2-free distilled water with 0.5% w/v sodium lauryl sulfate (SLS)at 37 ± 0.5°C using paddle method at 50 rpm speed for 120 minutes [14]. The dissolution profile can be seen in Figure 5.Dissolution percentage intactefavirenz at the 60th minute was 40.28±0.14%, while the solid dispersion samples 2: 1, 1: 1, 1: 2 were 63.13±0.60%, 63.12±0.58%, and 65.99±0.53% respectively. This increase likely occur due to solubilization effect of PVP K-30 in water.The addition of hydrophilic polymer, efavirenz will be dispersed in the hydrophilic chains of polymer. At the 120th minute percentage of dissolution efavirenzwas 64.61±0.20%, while the samples of solid dispersion 2: 1, 1: 1 and 1: 2 were66.43±0.11%, 74.44±0.09%, and 73.53±0.07%, respectively. Moreover, the efficiency dissolution of solid dispersion with a ratio 2:1, 1:1 and 1:2 was 59.44±0.12%, 59.12±0.10%, and 63.14±0.07%, respectively. Dissolution efficiency of solid dispersions was higher than intact efavirenz which was 42.16±0.20%.

Improving in dissolution rate of solid dispersions results was likely influenced by particle size reduction from drying process. Small particles with high surface energy and a very weak bond lattice causes a change from crystalline phase into the amorphous phase which is more soluble in water.This results were confirmed by SEM analysis results showing efavirenz dispersed into the polymer PVP K-30 where the solubility and dissolution rate increases, and eventually increase the absorption of drugs [10, 15, 16].

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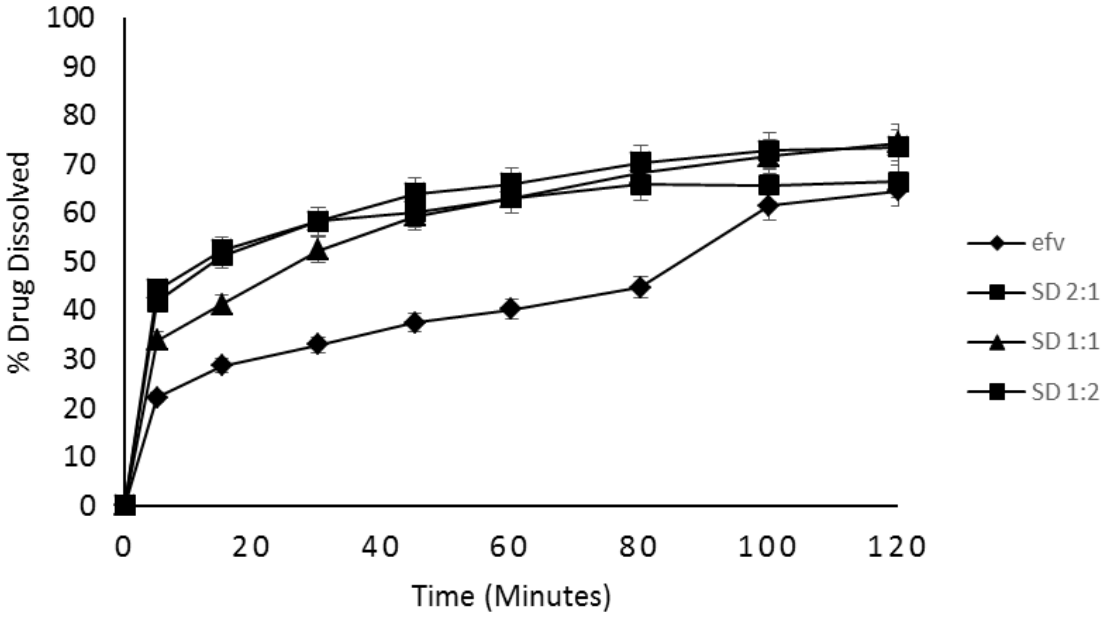

Figure 5: The dissolution profile of intact efavirenz and solid dispersion of efavirenz-PVP K-30 at different ratios.

CONCLUSIONS

Solid dispersion of efavirenz and PVP K-30 with different ratios has been manufactured and showed a significant change in crystallinity, which the solid dispersion showed amorphous phase while intact efavirenz was crystalline. The ratio of efavirenz and PVP K-30 influence thermal analysis and dissolution rate. The percentage Q_{120} of solid dispersions increased significantly compared to intact efavirenz.

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