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Optimization of Planetary Ball Mill Size on Physicochemical Properties and Dissolution Rate of Nimodipine- PVP K-30

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A B S T R A C T

Nimodipine is a compound that is insoluble in water and is included in the biopharmaceutical classification system (BCS) class II. This study looks at the characterization of nimodipine-PVP K-30 with the wet grinding method using a planetary ball mill at 200 rpm with large and small ball sizes. Nimodipine was made into 3 formulas, namely a physical mixture (1:0.6), formula 1 with 24 large balls (1:0.6), and formula 2 with 143 small balls (1:0.6). Evaluation of physicochemical properties includes size distribution, surface morphology, functional group analysis, crystallinity properties, thermal properties, assay, and dissolution profile. The dissolution results of nimodipine, CF, F1, and F2 at 60 minutes were 33.63%, 39.48%, 74.00%, and 53.99% respectively. The evaluation results showed that in general nimodipine-PVP K-30 could improve the physicochemical properties and increase the dissolution rate of nimodipine.

Keywords: Nimodipine, PVP K-30, Wet Milling, Planetary ball mill

Introduction

Nimodipine is a dihydropyridine calcium channel blocker with selectivity for cerebral vessels and significant therapeutic indications. Nimodipine is used for the prevention and treatment of ischemia, neurological disorders, and other cerebrovascular disorders, such as stroke which is indicated to have a biological rhythm (Sweetman, 2009). Nimodipine is a drug belonging to the class II Biopharmaceutical Classification System (BCS) class with low solubility and high permeability. The bioavailability of drugs belonging to this category generally has a limited dissolution rate. The level of bioavailability for this class II category can be increased by increasing the solubility and dissolution rate (Gohil, 2014).

An important physicochemical property of a substance is solubility, for a drug to enter the circulation system and produce a therapeutic effect, the drug must first be in a dissolved form. Relatively insoluble compounds often show imperfect or erratic absorption in the gastrointestinal tract which can affect drug bioavailability (Ansel, 2008). Solubility is one of the important parameters for achieving the desired drug concentration in the systemic circulation to produce a pharmacological response (Savjani et al., 2012). Particle size reduction was carried out using the wet milling method. This method is widely used in the pharmaceutical industry because the equipment used can be made simply, and can use non-organic solvents so it is cheaper and environmentally friendly (Moschwitzer 2012).

Nimodipine has been studied by many researchers including research conducted by (Muralichand & Bhikshapathi, 2018) showing that nimodipine solid dispersion formulation using solvent evaporation technique is a very effective strategy to increase the bioavailability of nimodipine with poor solubility. Another study conducted by (Zu *et al.*, 2014) that the micronized nimodipine dissolution test showed an increase in dissolution and solubility rates with the recrystallization process.

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Based on the description above, the researcher is interested in researching the characterization of the nimodipine-PVP K-30 formulation with a planetary ball mill to produce good solubility and report using Particle Size Distribution Analysis, Scanning Electron Microscopy (SEM), Fourier Transform Infrared (FT-IR), Diffraction X-Ray (XRD), Differential Scanning Calorimetry (DSC), assay, and dissolution rate.

Methods

Materials

Nimodipine (Lusochimica, Italy), PVP K-30 (Merck), Potassium Dihydrogen Phosphate (Merck), Sodium Hydroxide (Merck), Methanol pa (Novalindo), and aqua dest (Novalindo).

Preparation of Nimodipine-PVP K-30

In this study, nimodipine was prepared using a wet mill method using a planetary ball mill with a milling time of 90 minutes.

Table 1. Nimodipine-PVP K-30 Formula Design

Formula	Nimodipine (g)	PVP K-30(g)	Number of balls
CF	1	0.6	
F1	1	0.6	24 big balls
F2	1	0.6	143 small balls

Particle Size Distribution Analysis

Analysis of Particle Size Distribution Microscopes must first be calibrated with a stage micrometer before use. Then some powders are dispersed in liquid paraffin and dripped on a glass object. Then put it under the microscope, observe the particle size of the powder and count the number of particles as many as 1000 particles. Analyzes were performed on nimodipine, PVP K-30, CF, F1, and F2.

Scanning Electron Microscopy (SEM) Analysis

The powder sample was placed in an aluminum sample holder and coated with palladium with a thickness of 10 mm. The samples were then observed at various magnifications. The voltage is set at 20 kV mA current (Whalley & Langway, 1980). This analysis will show the particle shape morphology of nimodipine, PVP K-30, CF, F1, and F2.

Fourier Transformation Infra-Red (FT-IR) Analysis

FT-IR analysis was carried out by grinding the sample until it was powdered with potassium bromide in a mortar until it was homogeneous then transferred to a mold the sample was then compressed into a disc under vacuum, and the sample was scanned at a wave number of 400-4000 cm^{-1} to evaluate functional groups. From samples of nimodipine, PVP K-30, CF, F1, and F2 (Liu *et al*., 2010).

X-Ray Diffraction (XRD)Analysis

X-ray diffraction analysis of sample powders was carried out at room temperature using an X-ray diffractometer. with measurement conditions as follows: target metal Cu, filter Kαvoltage 30 kV, current 5 mA, instrument operated in scan speed 4°, measurement analysis in the range 2 Θ 4- 40° The sample is placed on the sample holder (glass) and flattened to prevent particle orientation during sample preparation (Okonogi & Puttipipatkhachorn, 2006). Analysis was performed on nimodipine, PVP K-3, CF, F1, and F2.

Differential Scanning Calorimetry (DSC) Analysis

Thermal analysis of the samples was carried out using a temperature-calibrated differential scanning calorimetry device. A sample of 5 mg was placed in a closed aluminum pan. The DSC device is programmed at a temperature range of 30℃-200℃ with a heating speed of 10℃ per minute. This analysis was performed on nimodipine, PVP K-30, CF, F1, and F2.

Dissolution Test

This analysis was performed on nimodipine, CF, F1, and F2 using a USP type II dissolution apparatus. Using 900 ml of pH 7.2 phosphate buffer medium at a temperature of 37 ℃ ± 0.5 ℃ at a speed of 100 rpm. The dissolution solution was pipetted as much as 5 ml at 5, 10, 15, 30, 45, and 60 minutes. The absorption of the solution that had been pipetted from the dissolution medium was measured at the maximum wavelength. The level of dissolved nimodipine at each time can be calculated using the calibration curve equation using linear regression. The test was carried out in three repetitions (Ministry of Health of the Republic of Indonesia, 2014).

Results and Discussion

Grinding is one method that can be used to reduce particle size. The planetary ball mill works using friction between the powder and the grinding ball. In this study, the active substance nimodipine was used. Nimodipine is a dihydropyridine calcium channel blocker, (Biopharmaceutical Classification System) class 2 with low solubility and high permeability. Thus affecting the speed of drug absorption in the body (Sweetman, 2009). This study aims to see the effect of ball size on the nimodipine-PVP K-30 formulation with a planetary ball mill.

Particle size distribution analysis was carried out by counting 1000 particles to see if the substance particles were distributed and if there was a decrease in particle size. The average particle size diameter of formula 1 is 52.4 µm and formula 2 is 28.6 µm, from the average particle size it can be seen that the particle size of formula 2 is smaller than that of formula 1, this is influenced by the size and number of balls, the smaller and the more balls used, the smaller the particle size of the powder.

The Scanning Electron Microscopy (SEM) test aims to see the surface shape of nimodipine, PKP K-30, CF, formula 1, and formula 2. In the SEM results at 1000x, magnification Nimodipine shows the morphology of a crystalline solid with a shape like large chunks with a rough surface texture, which can be seen in Figure 1.

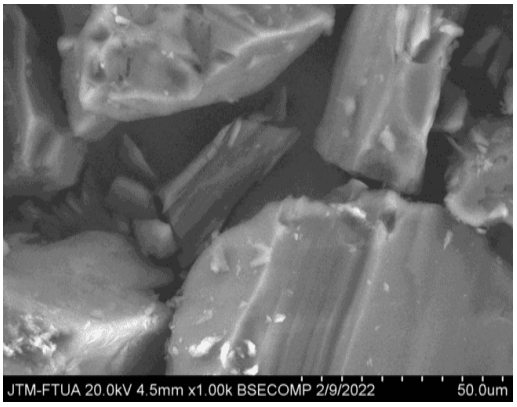

Figure 1. Morphology of nimodipine

While in PVP K-30 (figure 2) at 1000x magnification, the morphology is spherical in shape with larger particle sizes, while in CF (figure 3) at 1000x magnification, the morphology can still distinguish the active substance from the polymer.

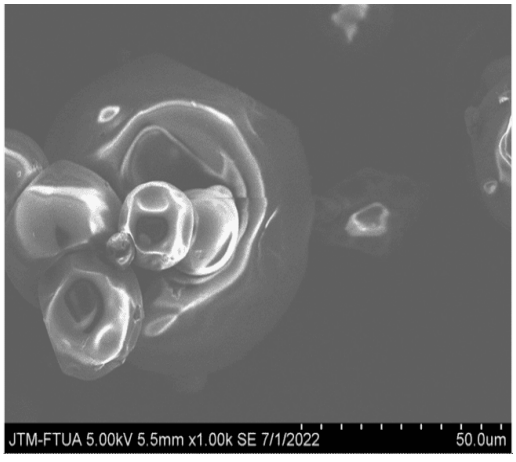

Figure 2. Morphology of PVP K-30

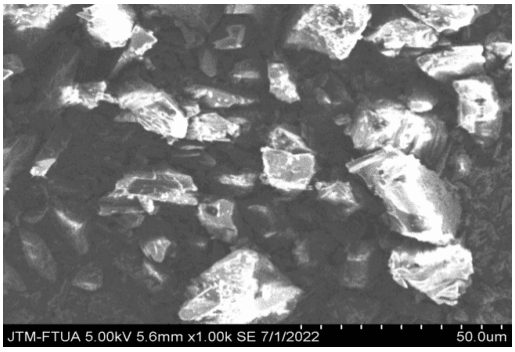

Figure 3. Morphology of the physical mixture

Whereas formulas 1 and 2 at 1000x magnification (figure 4) have a more irregular shape. This has confirmed that nimodipine and PVP K-30 crystals have been distributed in the formula so that the morphology of nimodipine and PVP K-30 cannot be distinguished.

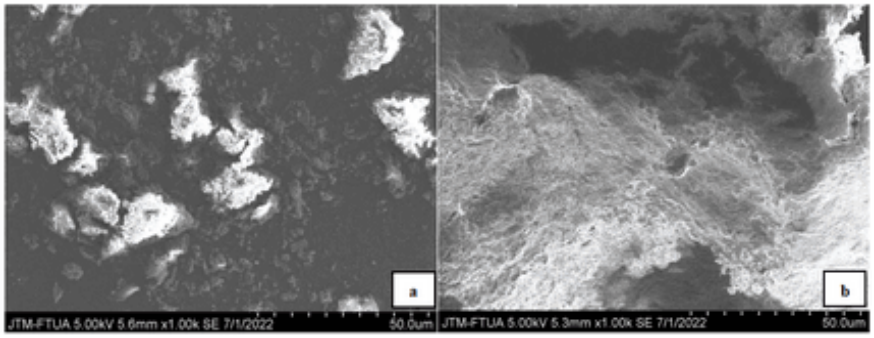

Figure 4. Morphology of formulas 1 (a) and 2 (b)

Fourier Transform Infra-Red (FT-IR) analysis was performed to identify functional groups in a compound and to determine the structure of a compound by comparing its fingerprint regions. The results of FT-IR analysis in formula 2 show that there is an N-H functional group at wave number 3300.69 cm^{-1}, a C-H functional group at wave number 2934.85 cm^{-1}, C=O functional group at wave number 694.39 cm^{-1}, the functional group –CH3 at wave number 823.54 cm^{-1}, functional group C=C at wave number 1660.75cm^{-1}, C-N functional group at wave number 1309.24cm^{-1}. From the FT-IR analysis, it can be concluded that the results of F2 experienced a shift in functional groups as can be seen in Figure 5.

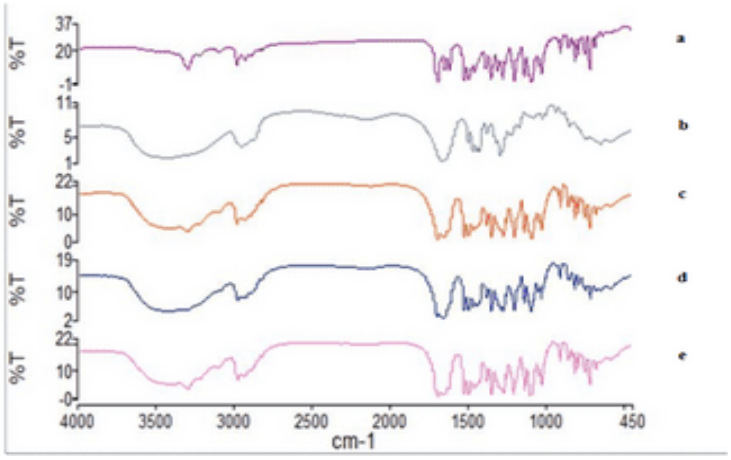

Figure 5. FT-IR spectra of nimodipine (a), PVP K-30 (b), CF (c), F1 (d), and F2 (e)

Analysis of the X-ray diffraction pattern diffractogram was carried out to determine changes in the properties of the drug compounds from nimodipine, PVP K-30, CF, F1, and F2. Formula 1 results show sharp and clear peaks at 2Θ, namely at 12.87160 with a height of 778.9327 counts at 17.57760 with a height of 536.2191 counts, and at 20.39860 with a height of 804.4775 counts and at 26.39160 with a high 502.7595 counts. Formula 2 results show sharp and clear peaks at 2Θ, namely at 12.87160 with a height of 728.8753 counts at 17.57760 with a height of 552.6243 counts, and at 20.39860 with a height

of 656.4116 counts and 26.39160 with a The height of 459.2922 counts can be seen in Figure 6. Based on the peak diffractogram analysis above, it can be concluded that there is a decrease in intensity at an angle of 2Θ for nimodipine, this indicates that the formula formed is more amorphous.

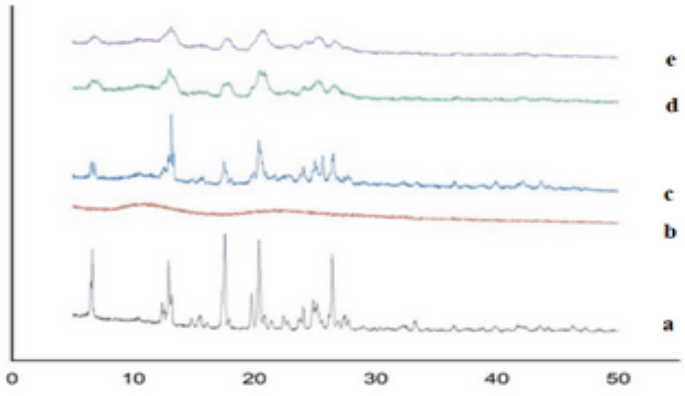

Figure 6. X-ray diffractograms of nimodipine (a), PVP K-30 (b), CF (c), F1 (d), and F2 (e)

Differential scanning calorimetry (DSC) analysis is a method to characterize the thermodynamic properties that occur when a sample is given heat energy and can measure the amount of heat absorbed or released during the transition. Nimodipine obtained enthalpy results of 94.205 (J/g). The DSC thermogram results for nimodipine, PVP K-30, CF, F1, and solid F2 are shown in Figure 7. The results show that the physical mixture has the lowest enthalpy value. Based on the results of the DSC thermogram, nimodipine has a melting point of 128.732 °C. The melting points of FI and F2 experienced a lower shift, namely 96.827 °C and 96.667°C.

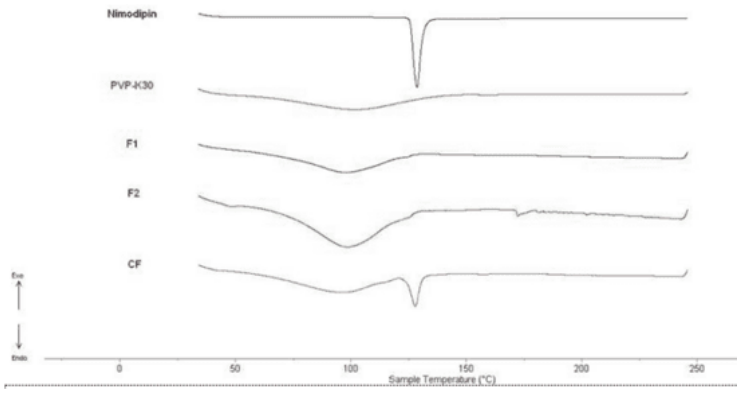

Figure 7. Thermogram Overlay nimodipin, PVP K-30, CF, F1, and F2.

Determination of the dissolution profile of nimodipine, CF, F1, and F2 was carried out using a phosphate buffer pH 7.2 medium. In determining the dissolution profile of nimodipine powder, CF, F1, and F2 showed that the dissolution rate increased in the powder. The percentage of dissolution of nimodipine muni in the 60th minute was 33.6396%, CF was 39.4840%, F1 was 74.00003%, and F2 was 53.9937%. The increase in the dissolution rate is affected by grinding which causes the particle size to be small so that it can increase the solubility of a drug. From these data, it can be seen that formula 1 has the highest percentage of dissolution.

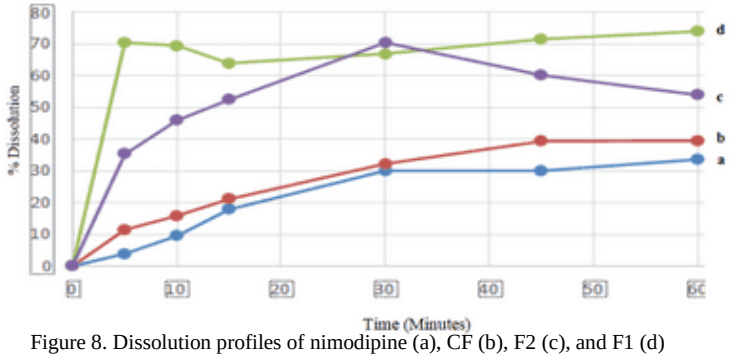

Figure 8. Dissolution profiles of nimodipine (a), CF (b), F2 (c), and F1 (d)

Conclusion

Based on research that has been done on the characterization of the nimodipine-PVP K-30 formulation with a planetary ball mill, it can be concluded that there is a change in the dissolution rate in the nimodipine grinding process because the grinding time and ball size affect the dissolution rate.

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