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# Effectiveness of Dry Grinding and Wet Grinding Methods on Physicochemical Properties, Solubility, and Dissolution Rate of Nimodipine-HPMC Nanoparticles

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**ABSTRACT**

Nimodipine is a dihydropyridine calcium channel blocker that shares the general properties of nifedipine but operates mainly on cerebral blood vessels. Nimodipine is a drug belonging to the Biopharmaceutical Classification System (BCS) class II, which has low solubility and high permeability. This study aimed to investigate the differences in the yield of nanoparticles produced by the dry grinding and wet grinding methods on the physicochemical properties, solubility, and dissolution rate of nimodipine nanoparticles. Furthermore, the nanoparticles were prepared with a nimodipine:HPMC ratio of 1:0.6 using two different methods. Moreover, sample characterization was carried out using Particle Size Analyzer (PSA), Scanning Electron Microscopy (SEM), Differential Scanning Calorimetry (DSC), X-ray Diffraction (XRD), and Fourier Transform Infrared (FT-IR). In addition, the solubility test was carried out in $CO^2$-free distilled water, while the dissolution rate was carried out in phosphate buffer pH 7.2. It was found that the solubility of pure nimodipine in $CO^2$-free distilled water was 0.339 µg/mL, the physical mixture was 1.948 µg/mL, the dry grinding nanoparticles were 3.367 µg/mL, and the wet grinding nanoparticles were 19.952 µg/mL. Additionally, according to the dissolution test results, the percentage of pure nimodipine dissolution after 60 minutes was 33.947%, the physical mixture was 39.482%, the dry grinding nanoparticles were 49.798%, and the wet grinding nanoparticles were 56.484%. Based on the results of the study, it can be concluded that the nimodipine-HPMC nanoparticles significantly increased the solubility and dissolution rate of nimodipine.

**Keywords:** Nimodipine, HPMC, Nanoparticle, Solubility, Dissolution Rate

## INTRODUCTION

Nimodipine is a dihydropyridine calcium channel blocker that shares the properties of nifedipine but operates primarily on the cerebral vessels. Nimodipine is used to treat cerebrovascular disorders and is primarily intended as a first choice for the prevention and treatment of ischemic neurological deficits after aneurysmal subarachnoid hemorrhage (Sweetman, 2009). Nimodipine is a drug belonging to the Biopharmaceutical Classification System (BCS) class II, which has low solubility and high permeability. Moreover, drugs in this category typically have a limited dissolution rate due to their low bioavailability. By increasing the solubility and dissolution rate, the level of bioavailability for this class II category can be increased (Gohil, 2014).

In order to increase drug solubility, various methods can be carried out, including pH adjustment and salt formation, polymorphs, cocrystals, cosolvents, surfactants, cyclodextrins, particle size adsorption, amorphous solid dispersions, and lipid-based formulations (Williams *et al*., 2013). There are many researchers who have conducted research on nimodipine, including Alhagiesa and Ghareeb in 2021. In their research, the formation of nanoparticles was carried out using an anti-solvent technique. It was discovered that nimodipine solubility in the nanoparticles increased twenty-fourfold. In addition, according to the dissolution test, micronized nimodipine revealed an increase in dissolution rate and solubility of 5.22 times compared to nimodipine (Zu *et al*., 2014).

Nanoparticles are particles with a size of 1–1000 nm that aim to increase the solubility of active substances that are difficult to dissolve, improve poor bioavailability, modify drug delivery systems to allow drugs to reach specific areas directly, improve the absorption of a macromolecular compound, and reduce the irritating effect of active substances on the gastrointestinal tract (Mohanraj & Chen, 2006). Moreover, nanoparticles can be prepared by wet grinding or dry grinding; both methods are equally useful for particle size reduction. In addition, a polymer that serves as a drug carrier for specific targets is required to prepare nanoparticles (George *et al*., 2019).

Dry grinding is a simple and widely used method in pharmaceutical technology. This dry grinding method is frequently used for the size reduction of pharmaceutical materials (Tozuka *et al*., 2011). Moreover, from an economic and ecological perspective, dry grinding is also one of the most preferred methods (Tawakoli *et al*., 2007). In this dry grinding, mechanical energy is imparted, driving drug-excipient interactions via van der Waals forces or hydrogen bonds. The resulting drug-excipient composite particles often demonstrate stability, have a low tendency to agglomerate, and retain activation (Hui *et al*., 2014). Wet grinding is a method that is often used in the pharmaceutical industry to manufacture nanocrystals because it is simple, relatively fast, can reduce production costs, and can be operated intermittently (batch mode) or continuously (re-circulation mode). This method involves using frictional forces to reduce the particle size (Moschwitzer, 2013).

## MATERIALS AND METHODS

The materials used in this study were nimodipine (Lusochimica, Italy), HPMC (Merck, Germany), Sodium Dihydrogen Phosphate (Merck, Germany), Methanol pa (Novalindo, Indonesia), and distilled water (Novalindo, Indonesia).

### Preparation of Nimodipine-HPMC Nanoparticles Using the Dry Grinding Method

Weighing was carried out for each nimodipine:HPMC (1:0.6 gram). Then, 15 big balls were put into the chamber, which was already filled with 0.9-cm-diameter zirconium ball mill balls. Furthermore, the grinding process was carried out using a planetary ball mill to grind the materials into nanoparticles at a speed of 125 rpm for 60 minutes. Finally, it was stored in a desiccator.

### Preparation of Nimodipine-HPMC Nanoparticles Using the Wet Grinding Method

Weighing was carried out for each nimodipine:HPMC (1:0.6 gram). Then, 15 big balls were put into the chamber, which was already filled with 0.9-cm-diameter zirconium ball mill balls. Furthermore, the grinding process was carried out using a planetary ball mill to grind the materials into nanosuspensions at a speed of 125 rpm for 60 minutes. After that, it was dried using a freeze dryer to obtain nimodipine-HPMC nanoparticles. Finally, it was stored in a desiccator.

### Particle Size Analyzer (PSA) Analysis

In accordance with the Dynamic Light Scattering principle, PSA (Horiba SZ-100, Japan) analysis was conducted on nimodipine, HPMC, the physical mixture, dry grinding nanoparticles, and wet grinding nanoparticles. In this method, the samples were dispersed using 50 mL of distilled water as the dispersing medium. In addition, repeated sample measurements were carried out three times to obtain two sets of data with a difference of less than 20 nm.

### Scanning Electron Microscopy (SEM) Analysis

SEM (Hitachi Type S-3400N®, Japan) analysis was carried out on nimodipine, HPMC, the physical mixture, dry grinding nanoparticles, and wet grinding nanoparticles. Before the analysis was carried out, the samples were coated with a thin layer of palladium-gold. In addition, SEM worked using a voltage set at 10 kV and a current of 12 mA.

### Differential Scanning Calorimetry (DSC) Analysis

Thermal analysis was carried out on nimodipine, HPMC, the physical mixture, dry grinding nanoparticles, and wet grinding nanoparticles. The DSC was carried out using DSC equipment (Setaram DSC 131 Evo, France). Furthermore, samples of 5 mg were placed in a closed aluminum pan. The DSC device was programmed for a temperature range of 30–200°C and a heating speed of 10°C/min.

### X-ray Diffraction (XRD) Analysis

X-ray diffraction analysis was carried out on nimodipine, HPMC, the physical mixture, dry grinding nanoparticles, and wet grinding nanoparticles. The analysis of the samples was carried out at room temperature using an X-ray diffractometer (Philips X'Pert Pro-PANalytical, The

Netherlands) with a Cu, Kα filter, a current of 5 mA, and a voltage of 30 kV. In addition, samples were measured in reflection mode at 2 degrees with an angle range of 4°–40°.

**Fourier Transform Infrared (FT-IR) Spectroscopic Analysis**

FT-IR spectroscopic (Perkin Elmer L1600300 Spectrum Two, USA) analysis was carried out on nimodipine, HPMC, the physical mixture, dry grinding nanoparticles, and wet grinding nanoparticles. A small amount of samples (±3 mg) were mixed with 10 mg KBr, after which they were placed in the sample holder of the FT-IR spectroscopic instrument, and the samples were analyzed at room temperature. In addition, the spectrum was measured in the range of 400–4000 $cm^{-1}$ wavenumber.

**Solubility Test**

In the solubility test, nimodipine, the physical mixture, dry grinding nanoparticles, and wet grinding nanoparticles were made into a saturated solution using 100 mL of $CO^2$-free distilled water. A sample equivalent to 10 mg of pure nimodipine was dissolved in a 100-mL Erlenmeyer and then shaken with an orbital shaker for 24 h at room temperature. After that, the sample was filtered through a 0.45 µm filter (Whatman filter paper), and the concentration of nimodipine was determined from the absorbance measurement at 238 nm using an ultraviolet-visible light (UV-Vis) spectro-photometer (Shimadzu ED23 1800®, Japan).

**Dissolution Rate Profile Study**

The dissolution rate study of nimodipine, the physical mixture, dry grinding nanoparticles, and wet grinding nanoparticles was carried out using the paddle method (Copley Scientific NE4-COPD, UK) at 37 ± 0.5°C at a speed of 100 rpm for 60 min with a medium of phosphate buffer pH 7.2. Moreover, five mL of each dissolution medium was pipetted at 5, 10, 15, 30, 45, and 60 min. In addition, the absorbance of the solution that had been pipetted from the dissolution medium was measured using a UV-Vis spectrophotometer (at 238.40 nm) to determine the amount of nimodipine dissolved.

## RESULTS AND DISCUSSION

In order to measure the particle size distribution, a particle size analyzer (PSA) (Malvern Mastersizer 3000, UK) was used with the aim of determining the particle size of nimodipine, the physical mixture, dry grinding nanoparticles, and wet grinding nanoparticles. According to the results of the measurements, the particle size of nimodipine obtained was 1763 nm, a physical mixture was 4942 nm, dry grinding nanoparticles were 3462 nm, and wet grinding nanoparticles were 822.6 nm. These results showed that wet grinding nanoparticles had the smallest particle size and could be considered to have formed nanoparticles because they met the requirement for nanoparticle size, which is 1-1000 nm (Mudshinge *et al*., 2011; Maheshwara *et al*., 2014), while other nanoparticles had sizes that were larger than the specified range. Different grinding methods could result in different particle sizes being formed, and both the wet grinding method and the dry grinding method formed good nanoparticles, which were wet grinding nanoparticles. In addition, nanocrystal research for oral administration has been carried out by Li *et al*. (2015), in which the particle size was 833.3 nm.

The polydispersity index is a parameter that describes the particle size distribution of the nanoparticle system. Based on the results, the polydispersity index for nimodipine was 0.700, the physical mixture was 1, dry grinding nanoparticles were 1, and wet grinding nanoparticles were 0.523. The aforementioned results showed that nimodipine and the dry grinding nanoparticles had a polydispersity index value that met the requirement range of 0.01-0.7. Moreover, the wet grinding nanoparticles had the smallest polydispersity index value, indicating that these nanoparticles are the most homogeneous. It is because the smaller the polydispersity index value, the narrower the particle size distribution, which means it is more homogeneous (Ohenoja *et al*., 2014). The results of the analysis of nimodipine, HPMC, the physical mixture, dry grinding nanoparticles, and wet grinding nanoparticles by SEM (Figure 1).

The aim of the Scanning Electron Microscopy (SEM) test was to compare the surface shapes of nimodipine and HPMC before and after grinding with a planetary ball mill. In the SEM results at 1000x magnification, nimodipine appeared as a crystalline solid with a rod shape that looked like large chunks with a rough surface texture. Moreover, HPMC at 1000x magnification appeared like large, irregular lumps. Meanwhile, in the physical mixture at 1000x magnification, it appeared as one large irregular lump.

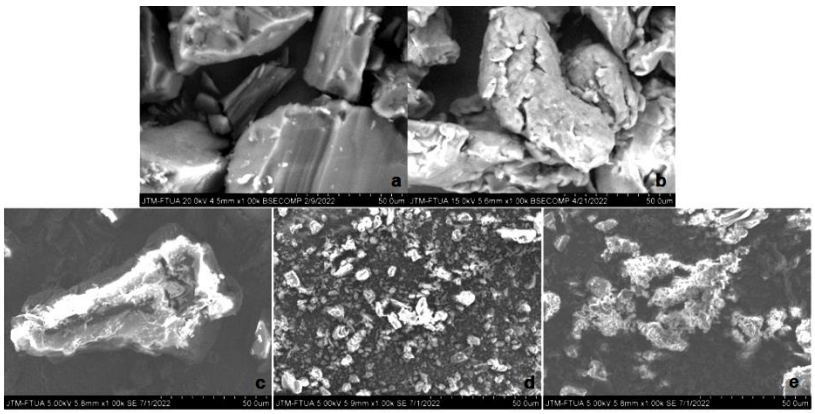

Figure 1: Scanning electron microscopy images with same magnification 1000x (a) nimodipine, (b) HPMC, (c) physical mixture, (d) dry grinding nanoparticles, (e) wet grinding nanoparticles

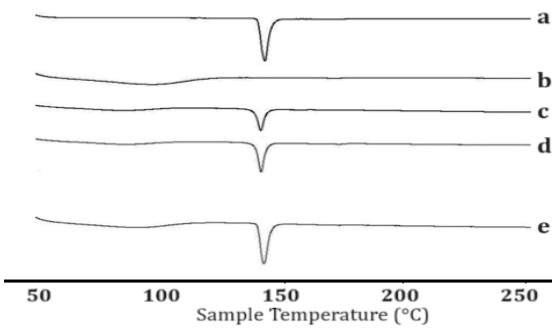


Figure 2: Differential scanning calorimetry analysis of (a) nimodipine, (b) HPMC, (c) dry grinding nanoparticles, (d) wet grinding nanoparticles, (e) physical mixture

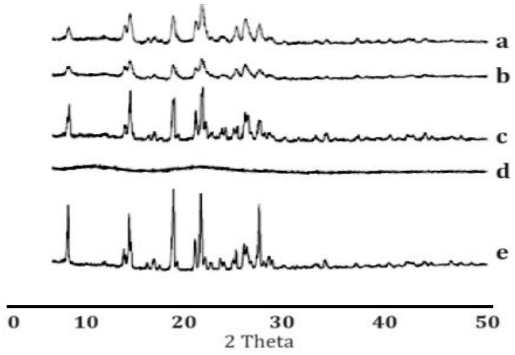


Figure 3: Overlay X-ray diffraction analysis (a) nimodipine, (b) HPMC, (c) physical mixture, (d) dry grinding nanoparticles, (e) wet grinding nanoparticles

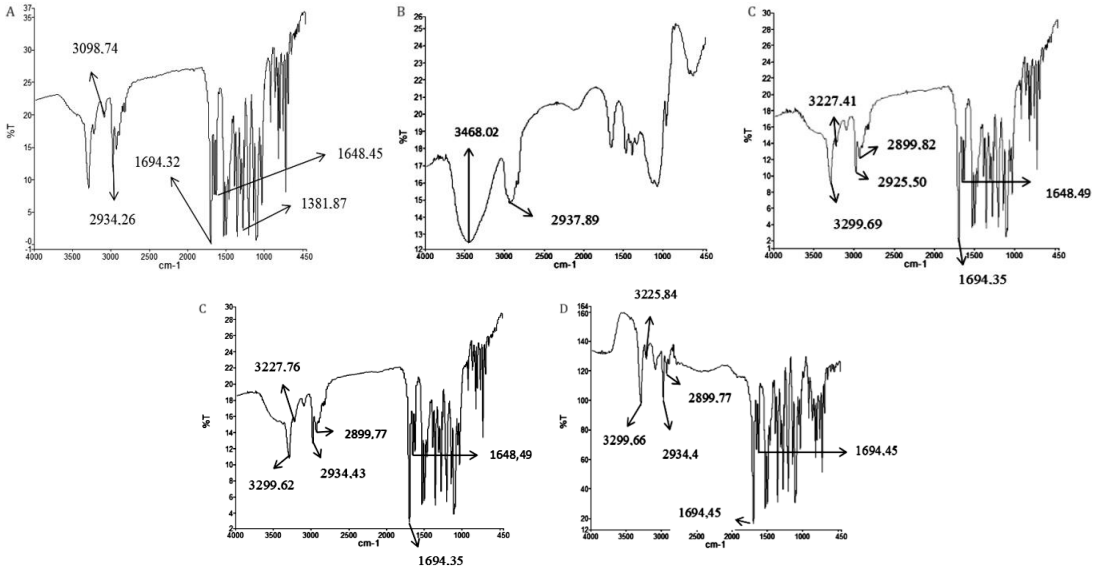


Figure 4: Fourier transform infrared spectroscopic analysis of (a) nimodipine, (b) HPMC, (c) physical mixture, (d) dry grinding nanoparticles, (e) wet grinding nanoparticles.

nanoparticles at 1000x magnification showed that the particle size was small and evenly distributed. Meanwhile, in the SEM results for wet grinding nanoparticles, the size was small, but some formed aggregates or clumps and were distributed evenly. In addition, based on the research conducted by Papadimitriou *et al*. (2009) on nanoparticles that were tested using the SEM test, the photographs showed that most of the drug-loaded nanoparticles had a regular spherical shape.

Differential scanning calorimetry (DSC) analysis is a method for investigating temperature variations and phase transition energies and exploring the lattice morphology of drugs in mixed systems. The DSC analysis was carried out to detect interactions between drugs and excipients (Teng *et al*., 2019).

The nimodipine thermogram results showed a sharp endothermic peak at a temperature of 128.732 °C, which is a melting event of nimodipine with an enthalpy of 94.2015 (J/g). The HPMC thermogram showed an endothermic peak of 81.64 °C with an enthalpy of 140.306 (J/g). The dry grinding nanoparticle thermogram showed an endothermic peak of 126.975 °C with an enthalpy of 43.323 (J/g). The wet grinding nanoparticle thermogram showed an endothermic peak of 127.155 °C with an enthalpy of 57.195 (J/g). The physical mixture thermogram showed an endothermic peak of 128.319 °C with an enthalpy of 87.728 (J/g) (Figure 2). The melting point of the physical mixture was detected to be the same as that of pure nimodipine (Fu *et al*., 2013). Moreover, the results of the DSC thermogram showed that there was a decrease in the enthalpy value and endothermic peak of pure nimodipine and nanoparticles due to the small particle size, and the active substance nimodipine has been mixed with HPMC so that an interaction occurred between the two compounds, resulting in a shift in the thermogram peak (Teng *et al*., 2019). Furthermore, the DSC thermogram results on pure nimodipine, the physical mixture, dry grinding nanoparticles, and wet grinding nanoparticles showed that dry grinding nanoparticles had the lowest enthalpy value. Based on the DSC thermogram data above, the endothermic peak was not much different from the study of Zhao *et al*. (2014), which was 126°C, and Ghareeb and Neamah (2017), which was 126.73°C. According to research conducted, the melting point of nimodipine could experience a slight shift due to grinding in a lower direction (Novita *et al*., 2014).

X-ray diffraction was used to determine whether a compound was in crystalline or amorphous form in the presence of diffraction peaks. The appearance of diffraction peaks indicated that the compound was in the form of crystals, while amorphous material formed a diffraction hump (Bunaciu *et al*., 2015). The results of X-ray diffraction analysis of pure nimodipine compound showed sharp and clear peaks at an angle of 2θ, which was at an angle of 17.5776, with a yield of nimodipine 2126.179 units, HPMC 410.8513 units, the physical mixture 1237.971 units, dry grinding nanoparticles 981.8932 units, and wet grinding nanoparticles 611.1561 units (Figure 3). Based on the analysis of the diffractogram peaks above in the sample, it can be concluded that there was a decrease in intensity at the 2-theta angle from pure nimodipine to nanoparticles, indicating that the formed nanoparticles were more amorphous, so the dissolution rate has increased (Windriyati *et al*., 2020). The results of the diffractogram data showed that the wet grinding nanoparticles had the smallest peak intensity value compared to the others.

Moreover, Fourier transform infrared (FT-IR) analysis was carried out to identify functional groups in a compound and to determine the structure of a compound by comparing its fingerprint regions. Based on the FT-IR analysis that can be seen in Figure 4, the results of the FT-IR spectra of pure nimodipine, HPMC, the physical mixture, dry grinding nanoparticles, and wet grinding nanoparticles showed that there were no functional groups that were lost or added. Furthermore, the results showed a shift in functional groups, which was due to the formation of hydrogen bonds between nimodipine and HPMC. Functional groups could shift to different wavelengths with reduced intensity after the formation of hydrogen bonds (Alhagiesa & Ghareeb, 2021; Abdullah *et al*., 2022).

The solubility test was carried out on pure nimodipine, the physical mixture, dry grinding nanoparticles, and wet grinding nanoparticles (Table I). The purpose of the solubility test was to determine the effect of particle size on solubility. Moreover, the solubility of pure nimodipine in water was 0.3390 µg/mL, the physical mixture was 1.9484 µg/mL, the dry grinding nanoparticles were 3.3668 µg/mL and the wet grinding nanoparticles were 19.9523 µg/mL. The results of the solubility test showed that the solubility of the physical mixture increased 6 times higher than pure

nimodipine, while dry grinding nanoparticles increased 10 times higher and wet grinding nanoparticles increased 59 times higher. These results were directly proportional to the particle size, implying that the smaller the particle size, the greater the surface area of the particles to interact with the solvent, leading to increased solubility.

Table I. Solubility of nimodipine, physical mixture, dry grinding nanoparticles, and wet grinding nanoparticles (n = 3)

| Compound | Solubility ±SD (mg100/mL) | Enhancement (times) |
|---|---|---|
| *nimodipine* | 0.339±0.206 | - |
| *physical mixture* | 1.948±0.573 | 6 |
| *dry grinding nanoparticles* | 3.367±0.465 | 10 |
| *wet grinding nanoparticles* | 19.952±1.27 | 59 |

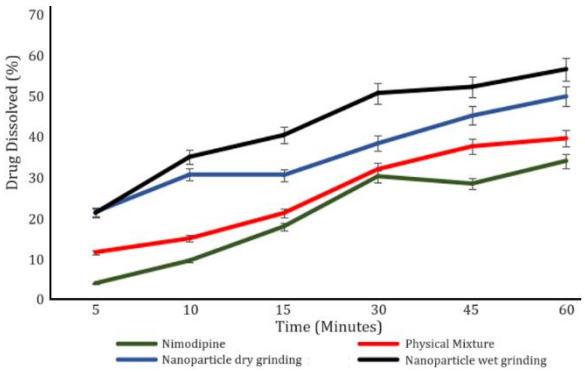


Figure 5: Dissolution rate profile of nimodipine, physical mixture, dry grinding Nanoparticles, and wet grinding Nanoparticles in phosphate buffer pH 7.2 (n = 3)

The dissolution profiles of pure nimodipine, the physical mixture, dry grinding nanoparticles, and wet grinding nanoparticles were determined using a phosphate buffer medium at pH 7.2. It was discovered through comparing the dissolution profiles of pure nimodipine powder, the physical mixture, dry grinding nanoparticles, and wet grinding nanoparticles that the dissolution rate of the powder increased (figure 5). Moreover, the percentage of dissolution of pure nimodipine after 60 minutes was 33,947%, the percentage of dissolution of the physical mixture was 39,482%, the percentage of dissolution of dry grinding nanoparticles was 49,798%, and the percentage of dissolution of wet grinding nanoparticles was 56,484%. The increase in the dissolution rate was affected by grinding and the method, which caused the particle size to be smaller so that it could increase the solubility of a drug. In addition, these results showed that the wet grinding nanoparticles had the highest percentage.

## CONCLUSION

The wet grinding method is very effective for increasing the solubility of the dissolution rate using a grinding process with a planetary ball mill. Moreover, the dry grinding method and the wet grinding method with a planetary ball mill affected the physical characteristics observed in the Particle Size Analyzer (PSA), Scanning Electron Microscopy (SEM), Differential Scanning Calorimetry (DSC), and X-Ray Diffraction (XRD) tests. In addition, the grinding method affected the solubility and dissolution rate of nimodipine.

## ACKNOWLEDGMENT

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