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Methods of Dry and Wet Grinding for Nimodipine-HPMC Nanoparticles: Impact on Physical and Chemical Characteristics, Solubility, and Rate of Dissolution

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ABSTRACT

Although it primarily affects the blood arteries in the brain, the dihydropyridine calcium channel blocker nimodipine has many of the same basic characteristics as nifedipine. Nimodipine has a low solubility and a high permeability, making it a medication belonging to class II of the Biopharmaceutical Classification System (BCS). The purpose of this research was to compare the physicochemical characteristics, solubility, and dissolving rate of nimodipine nanoparticles made using the dry and wet grinding techniques, as well as any changes in the yield between the two. In addition, the nanoparticles were made utilizing two separate procedures with a nimodipine:HPMC ratio of 1:0.6. Additionally, X-ray diffraction (XRD), Fourier transform infrared (FT-IR), scanning electron microscopy (SEM), differential scanning calorimetry (DSC), and particle size analyzers (PSAs) were used for sample characterisation. Furthermore, phosphate buffer pH 7.2 was used for the dissolving rate test, and CO2-free distilled water was used for the solubility test. The following values were determined for the solubility of nimodipine: 0.339 µg/mL for pure nimodipine in CO2-free distilled water, 1.948 µg/mL for the physical mixture, 3.367 µg/mL for dry grinding nanoparticles, and 19.952 µg/mL for wet grinding nanoparticles. The findings of the dissolving tests also showed that after 60 minutes, the physical combination dissolved 33.942 percent, the dry grinding nanoparticles 49.79 percent, and the wet grinding nanoparticles 56.484 percent of the nimodipine. Researchers found that adding nimodipine-HPMC nanoparticles to the drug made it far more soluble and enhanced its rate of dissolution.

Nicodipine, High-Performance Microcapsule, Solubility, and Rate of Dissolution

INTRODUCTION

Similar to nifedipine, nimodipine is a calcium channel blocker that acts mainly on the arteries in the brain. Treatment of cerebrovascular diseases, including ischemic neurological impairments after aneurysmal subarachnoid hemorrhage, is the primary goal of nimodipine (Sweetman, 2009). Nimodipine has a low solubility and a high permeability, making it a medication belonging to class II of the Biopharmaceutical Classification System (BCS). Because of their poor bioavailability, medications in this class also tend to have a slow rate of dissolution. One way to improve the bioavailability of this class II drug is to make it more soluble and dissolve it faster (Gohil, 2014). Methods such as adjusting the pH and forming salts, using polymorphs, cocrystals, cosolvents, surfactants, cyclodextrins, amorphous solid dispersions, particle size adsorption, and lipid-based formulations are among those that may be used to enhance the solubility of drugs (Williams et al., 2013). Alhagiesa and Ghareeb were among the several researchers that studied nimodipine in 2021. An anti-solvent approach was used to create nanoparticles in their study. It was found that the solubility of nimodipine in the nanoparticles was twenty-four times higher. Furthermore, the dissolution test showed that micronized nimodipine was 5.22 times more soluble and had a faster rate of dissolution than nimodipine alone (Zu et al., 2014).

Nanoparticles, which are particles with a size ranging from 1 to 1000 nm, are designed to enhance the bioavailability of drugs, modify drug delivery systems to target specific areas, improve macromolecular compound absorption, and decrease the gastrointestinal tract irritation caused by active substances (Mohanraj & Chen, 2006). In addition, wet grinding and dry grinding are two equally effective ways for reducing particle size while preparing nanoparticles. Nanoparticle preparation also requires a polymer that can transport drugs to precise sites (George et al., 2019). In the field of pharmaceutical technology, dry grinding is a common and easy approach. Tozuka et al. (2011) noted that medicinal products are often ground using this dry grinding process. According to Tawakoli et al. (2007), dry grinding is also favored from an ecological and economic standpoint. The medication and excipient engage via hydrogen bonds or van der Waals forces driven by mechanical energy provided during this dry grinding process. According to Hui et al. (2014), the composite particles made of drug and excipients are generally stable, don't clump easily, and keep their activation. The pharmaceutical sector often employs the wet grinding process for nanocrystal manufacturing due to its simplicity, speed, ability to lower production costs, and continuous or intermittent operation (batch mode or re-

circulation mode). In this technique, the particle size is decreased by use of frictional forces (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 desiccators.

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 desiccators.

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 wave number.

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 CO2-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

Nimodopine, the physical mixture, dry grinding nanoparticles, and wet grinding nanoparticles were all subjected to a particle size analyzer (PSA) test (Malvern Mastersizer 3000, UK) in order to quantify the distribution of particle sizes. Wet grinding nanoparticles had a size of 822.6 nm, dry grinding nanoparticles of 3462 nm, a physical mixture of 4942 nm, and nimodipine of 1763 nm, as shown by the measurements. According to these findings, out of all the nanoparticles tested, those that underwent wet grinding had the smallest particle size, falling within the range of 1-1000 nm (Mudshinge et al., 2011; Maheshwara et al., 2014). In contrast, the other nanoparticles exhibited sizes that exceeded this range. Both the wet and dry grinding processes produced high-quality nanoparticles, called wet grinding nanoparticles, and various grinding techniques may produce particles of varying sizes. Li et al. (2015) also conducted nanocrystal study with 833.3 nm particle size for oral delivery. Parameterizing the distribution of nanoparticle sizes is the polydispersity index. Wet grinding nanoparticles had a value of 0.523, physical mixture was 1, and nimodipine had a polydispersity index of 0.700, according to the data. The polydispersity index values of nimodipine and the dry grinding nanoparticles were within the specified range of 0.01-0.7, as shown in the previous findings. Furthermore, the most homogenous nanoparticles were those produced by wet grinding, as their polydispersity index value was the lowest. The reason for this is because a lower value for the polydispersity index indicates a more homogenous distribution of particle sizes (Ohenoja et al., 2014). Nimodipine, high-performance magnetic resonance spectroscopy (SEM) findings for the physical mixture, dry grinding nanoparticles, and wet grinding nanoparticles (Figure 1).

This scanning electron microscopy (SEM) experiment compared the pre- and post-grinding surface morphologies of nimodipine with high-performance microcrystalline cellulose (HPC) using a planetary ball mill. At a magnification of 1000x, the scanning electron micrograph (SEM) revealed nimodipine to be a crystalline solid resembling a rod, with a surface that was both rough and big in size. At a magnification of 1000x, HPMC also looked like big, lumpy things. It seemed like one big mass when seen with a 1000x magnification in the physical mixture.

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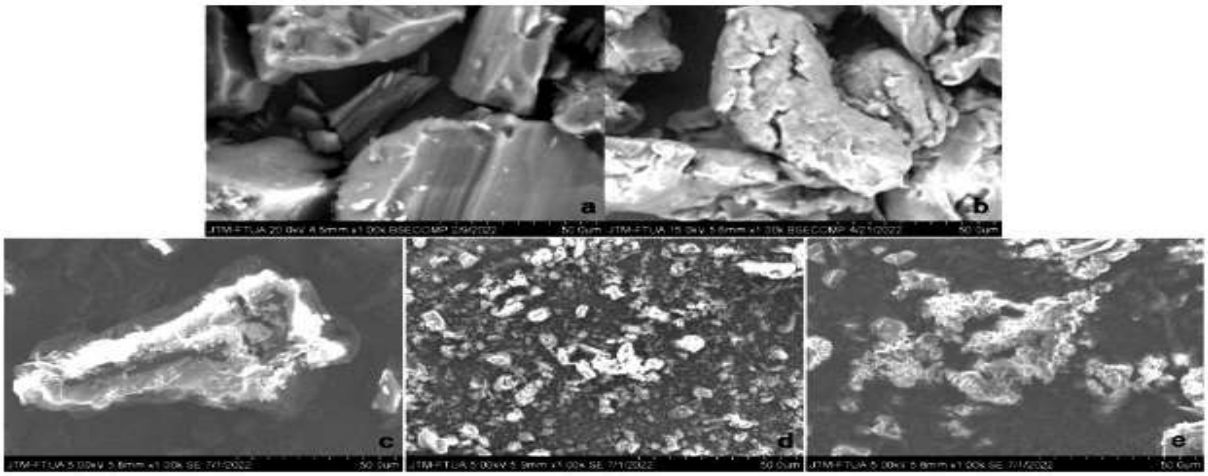

Figure 1: Scanning electron microscopy images with same magnification 1000x (a) nimodipine, (b) HPMC, (c) physical mixture, (d) dry grinding nanoparticles, (e) wet grinding nanoparticles

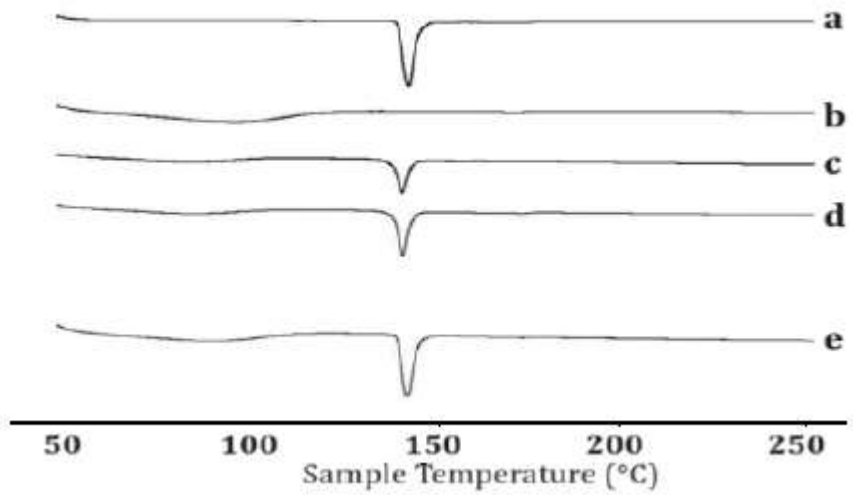

Figure 2: Differential scanning calorimetry analysis of (a) nimodipine, (b) HPMC, (c) dry grinding nanoparticles, (d) wet grinding nanoparticles, (e) physical mixture

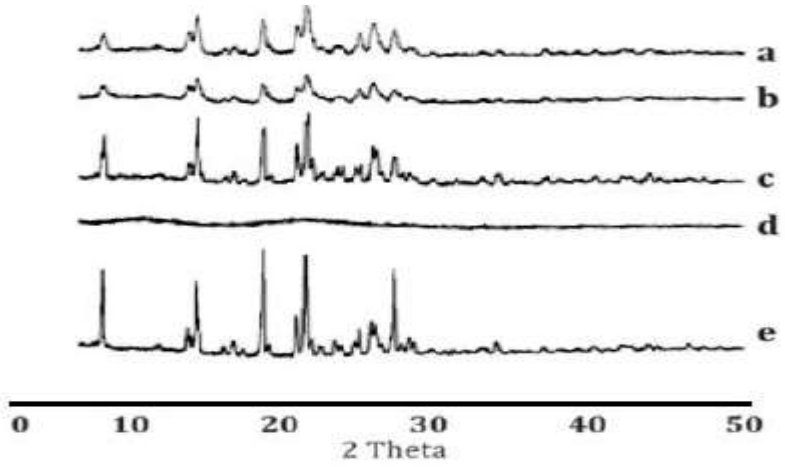

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Figure 3: Overlay X-ray diffraction analysis (a) nimodipine, (b) HPMC, (c) physical mixture, (d) dry grinding nanoparticles, (e) wet grinding nanoparticles

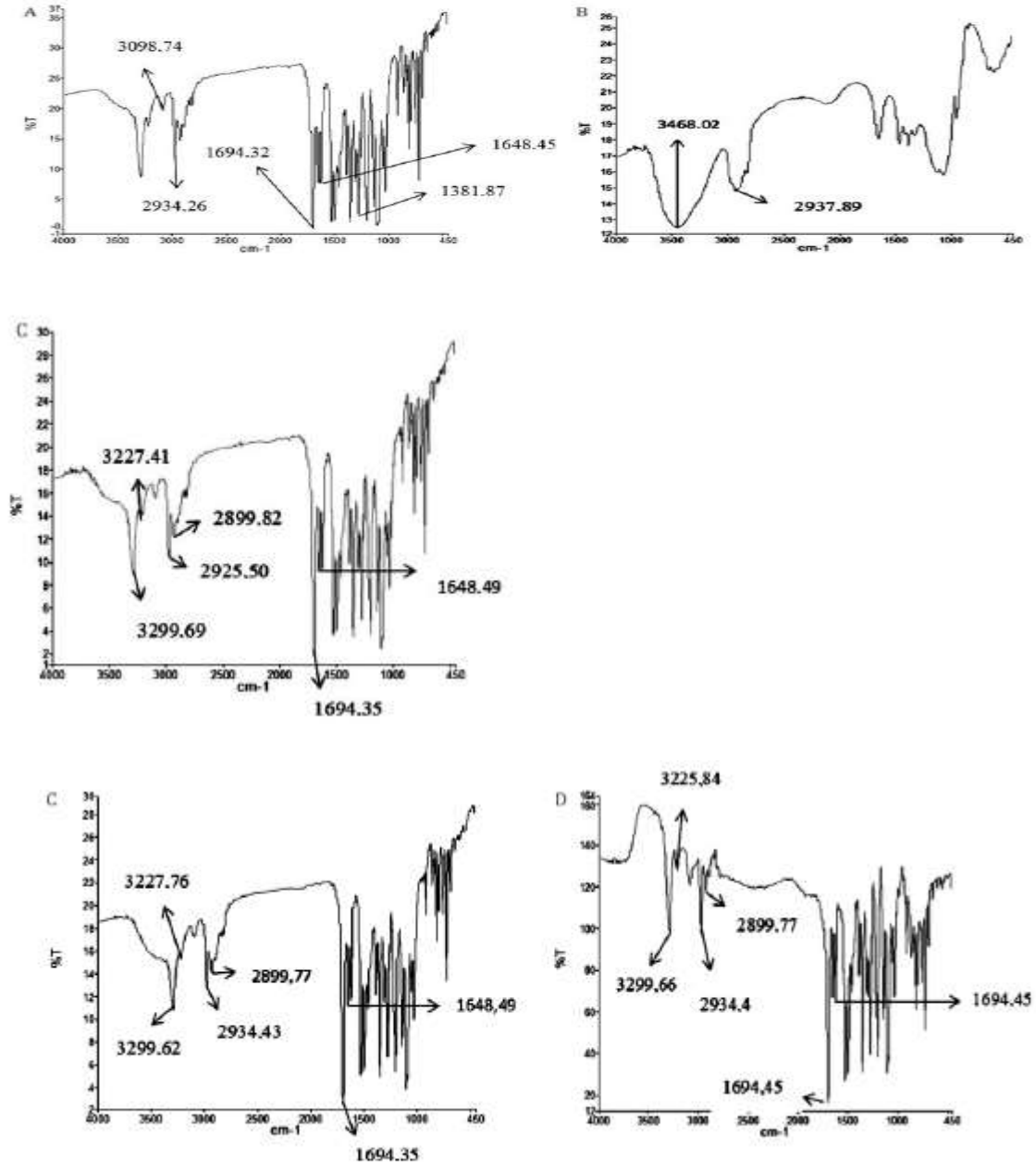

Figure 4: Fourier transform infrared spectroscopic analysis of (a) nimodipine, (b) HPMC, (c) physical mixture, (d) dry grinding nanoparticles, (e) wet grinding nanoparticles.

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 thermo gram showed

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an endothermic peak of 81.64 °C with an enthalpy of 140.306 (J/g). The dry grinding nanoparticle thermo gram showed an endothermic peak of 126.975 °C with an enthalpy of 43.323 (J/g). The wet grinding nanoparticle thermo gram showed an endothermic peak of 127.155 °C with an enthalpy of 57.195 (J/g). The physical mixture thermo gram 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 thermo gram 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).

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

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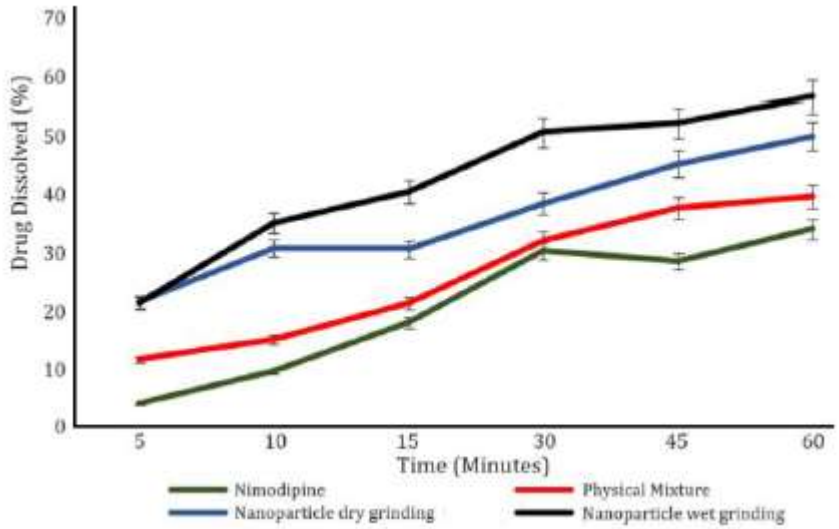

Figure 5: Dissolution rate profile of nimodipine, physical mixture, dry grinding Nanoparticles, and wet grinding Nanoparticles in phosphate buffer pH 7.2 (n = 3)

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

Increasing the dissolving rate by a wet grinding process with a planetary ball mill is a very successful way. Furthermore, the physical properties identified by the Particle Size Analyzer (PSA), Scanning Electron Microscopy (SEM), Differential Scanning Calorimetry (DSC), and X-Ray Diffraction (XRD) tests were impacted by the dry grinding technique and the wet grinding method using a planetary ball mill. Furthermore, nimodipine's solubility and dissolving rate were impacted by the grinding procedure.

REFERENCES

Abdullah, A., Mutmainnah, M., & Wikantyasning, E. R. (2022). Cocrystals of Cefixime with Nicotinamide: Improved Solubility, Dissolution, and Permeability. Indonesian Journal of Pharmacy.

Alhagiesa, A. W., & Ghareeb, M. M. (2021). The Formulation and Characterization of Nimodipine Nanoparticles for the Enhancement of solubility and dissolution rate. Iraqi Journal of Pharmaceutical Sciences (P-ISSN 1683-3597 E-ISSN 2521-3512), 30(2), 143-152.

Bunaciu, A. A., UdriŞTioiu, E. G., & Aboul-Enein, H. Y. (2015). X-ray diffraction: instrumentation and applications. Critical reviews in analytical chemistry, 45(4), 289-299.

Fu, Q., Sun, J., Zhang, D., Li, M., Wang, Y., Ling, G., ... & He, Z. (2013). Nimodipine nanocrystals for oral bioavailability improvement: preparation, characterization and pharmacokinetic studies. Colloids and Surfaces B: Biointerfaces, 109, 161-166.

George, A., Shah, P. A., & Shrivastav, P. S. (2019). Natural biodegradable polymers based nano-formulations for drug delivery: A review. International journal of pharmaceutics, 561, 244-264.

Ghareeb, M. M., & Neamah, A. J. (2017). Formulation and characterization of nimodipine nanoemulsion as ampoule for oral route. International Journal of Pharmaceutical Sciences and Research, 8(2), 591.