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Optimization of Ball Ratio in Planetary Ballmill in Nimodipine-poloxamer 188 Nanoparticle Formulation Process

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Abstract: Nimodipine is a drug that belongs to the class II biopharmaceutical classification system which has low solubility with high permeability. The ball mill ratio is a factor that affects the results of milling using a planetary ballmill. This study aims to see the optimal ball ratio in the milling process with a planetary ball mill in the physicochemical characterization of nimodipine-poloxamer 188 nanoparticles and their dissolution rate. Milling in a planetary ball mill was carried out using zirconium balls at a ratio of 20%, 25%, and 30% to the volume of the vessel respectively for 1, 2, and 3 nanoparticles. The characterization of nanoparticles includes PSA with the results showing a reduction in particle size, XRD there is a decrease in peak intensity, DSC there is a decrease in melting point, FT-IR doesn't change the wave number, SEM shows morphologically a change in shape, TLC indicates no chemical interaction, in the assay, the percentage of nimodipine and nanoparticles 1,2,3 was respectively 98.91%, 99.85%, 100.73%, 99.31%. the solubility test of nimodipine and nanoparticles 1,2,3, respectively 0.3390 g/ml, 19.8698 g/ml, 6.0673 g/ml, 8.4405 g/ml, and the dissolution test showed an increase in the 60th minute of nanoparticles 1,2 and 3 respectively 61,5841%, 52,3159%, 56,6027% compared with 23.3978% pure nimodipine. The results of the ANOVA test of solubility and dissolution rate showed that there was a significant difference between nimodipine-poloxamer 188 nanoparticles and pure nimodipine.
***Keywords**:* Nimodipin, Poloxamer-188, Nanoparticle, Planetary Ballmill.

I. Introduction

Nimodipine is a dihydropyridine calcium channel blocker which has the general properties of nifedipine, but acts primarily on cerebral vasculature. Nimodipine is used in cerebrovascular disorders, especially as the first choice for the prevention and treatment of ischemic neurologic deficits after aneurysmal subarachnoid hemorrhage [1]. Based on the Biopharmaceutical Classification System (BCS), Nimodipine is included in the class II category. Drugs in this category exhibit high absorption rates with low dissolution rates [2]. The bioavailability of drugs belonging to this category usually has a limited dissolution rate. The level of bioavailability for this class II category can be increased by increasing the solubility and dissolution rate of the drug [3].

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Poloxamer 188 is an amphiphilic block copolymer formed by the combination of ethylene oxide (hydrophilic) and propylene oxide (hydrophobic) units. Poloxamer has been widely used for nanocrystal stabilization. Poloxamer 188 is able to produce smaller particle diameters compared to other cosurfactants. This is presumably because the HLB value is quite large, namely 29, so it works more effectively on the water phase which is the outer phase of the system. Particles surrounded by poloxamer 188 become more difficult to combine with each other, so the system becomes more stable [4].
With the advancement of science and technology, there are many methods that can be used to increase solubility, one of which is nanoparticles. Nanoparticles are particles measuring 1-1000 nm which aim to overcome the solubility of poorly soluble active substances, improve poor bioavailability, modify drug delivery systems so that drugs can directly enter certain areas, increase the absorption of a macromolecular compound, and reduce the irritating effect of the active substance on the skin. digestive tract. digestibility [5]. The manufacture of nanoparticles can be broadly classified into two categories, namely bottom-up in the form of the formation of nanostructures atom by atom or molecule by molecule. In the bottom-up approach, the drug is dissolved in an organic solvent and then precipitated upon addition of an antisolvent in the presence of a stabilizer. Then a top-down approach consists of reducing the particle size from large drug particles to smaller particles using various grinding techniques such as media milling, microfluidization and high pressure homogenization [6].

Milling is the core process in powder manufacturing technology, there are various types of ball milling methods based on the movement of the grinding ball, such as vibration mill, attritor and planetary ballmill. Planetary ball mills represent high energy milling along with shaker mills, stirred mills, and vibration mills [7]. Since grinding conditions greatly affect the properties of the resulting powder, it can be controlled by changing the grinding ball, milling vessel, rotation speed, ball-to-powder ratio, ball filling ratio etc. to obtain a final product with the desired characteristics [8].

The ball filling ratio is one of the most significant operating parameters which directly affects the smooth running of the product [9]. According to Deniz, (2012) in his research stated that the optimum ball filling ratio value is 35% [10]. Meanwhile, according to ksüzoğlu & Uçurum, (2016) stated that the optimal ball filling ratio is 30% [11].

Based on the description above, this research will optimize the ball ratio on a planetary ballmill in the formulation of Nimodipine-poloxamer 188 nanoparticles so as to produce Nimodipine nanoparticles that have good solubility.

II. Material & Methods

2.1 Material

Nimodipine, Poloxamer-188, Potassium Dihydrogen Phosphate, Sodium Hydroxide, Methanol pa, distilled water, and chloroform.

2.2 Method

2.2.1 Nimodipine Raw Material Inspection

Examination of raw materials for Nimodipine is carried out according to the methods listed in the Indonesian Pharmacopoeia Edition 5, including description, solubility, and assay.

2.2.2 Inspection of Poloxamer-188

The examination of Poloxamer-188 was carried out according to the method listed in the Handbook of Pharmaceutical excipient $6th$, including description and solubility [12].

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2.2.3 Formulation of Nanoparticle

Table 1 : Formula Design of Nimodipine-poloxamer 188 nanoparticles

Formulation	Nimodipine (g)	Poloxamer-188	Ball Ratio	Number of Balls	
				D = 0,9 cm	D = 0,5 cm
1	3	1,5	20 %	31	125
2	3	1,5	30%	38	155
3	3	1,5	40%	45	180

Nimodipine and poloxamer-188 were added to the vessel, then it was ground using a planetary ballmill with ball ratio of 20% 25% and 30% at 131 rpm for 2 hours. After grinding, the Nimodipine-Poloxamer 188 nanoparticles were characterized.

2.2.4 Characterization of Nimodipine-Poloxamer 188 Nanoparticle

1. Particle Size Analyzer (PSA).

This method uses a dispersing medium to disperse the sample. Aquades dispersion media. Sample measurements were repeated three times to obtain two data with a difference of less than 20 nm.

2. X-Ray Diffraction (XRD)

X-ray diffraction analysis of the sample powder was carried out at room temperature using an X-ray diffractometer. The measurement conditions are Cu metal target, Kα filter, 30 kV voltage, 5 mA current, the instrument is operated at a scanning speed of 4°, the measurement analysis is in the 2 4-40o range. The sample is placed in the sample holder and leveled to prevent particle orientation during sample preparation. Analyzes were performed on Nimodipine, Poloxamer 188, and nanoparticles 1, 2, and 3.

3. Differential Scanning Calorimetry (DSC)

Thermal analysis of the samples was carried out using a differential scanning calorimetry tool which was calibrated. A sample of 5 mg was placed in a closed aluminum pan. The DSC device is programmed in a temperature range of 30℃ - 200℃ with a heating rate of 10℃ per minute. This analysis was carried out on Nimodipine, Poloxamer 188, and nanoparticles 1,2, and 3.

4. Fourier Transformasi-Infra Red (FT-IR)

FT-IR analysis was carried out by means of the sample being ground into a powder with potassium bromide in a mortar until homogeneous and then transferred to a mold and the sample was then compressed in a disc under vacuum, and the sample was scanned at a wave number of 400-4000 1 to evaluate the state of the art. molecular samples of Nimodipine, Poloxamer 188, Nanoparticles 1,2 and 3 .

5. Scanning Electron Microscopy

The powder sample is placed in a sample holder made of aluminum and coated with 10 nm thickness gold. The samples were then observed at various magnifications of the SE apparatus. The voltage is set at 10 k V and the current is mA.

6. Thin Layer chromatography

Thin layer chromatography test was carried out using chloroform and methanol as mobile phase with a ratio of 9:1 and silica gel 60 F254 as stationary phase. Saturation is done by placing the filter paper into the chromatography chamber, sealing it tightly and leaving the filter paper completely wet. The test solution in the form of Nimodipine, Nimodipine-poloxamer 188 nanoparticles 1, Nimodipine-poloxamer 188 nanoparticles 2, and Nimodipine-poloxamer 188 nanoparticles 3 that have been dissolved are spotted with a distance of 1 cm from the bottom edge of the 60 F254 silica gel plate, put into the vessel must reach the bottom edge chamber, the sample that has been spotted should not be submerged in the chamber. Close the chamber and allow the mobile phase to propagate to the limit of the creepage distance. Remove the plate and dry in the air, observe the spots with ultraviolet light, then determine the Rf value.

7. Determination of saturated solubility of Nimodipine-poloxamer 188

Solubility tests were carried out on samples of Nimodipine and nanoparticles 1, 2, and 3. which were made into a saturated solution using CO2-free distilled water. This test was carried out in a 100 mL erlenmeyer, for 24

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hours using an orbital shaker. the sample was filtered through a 1µm filter (Whatman filter paper) and then the absorbance was measured using a UV spectrophotometer at a wavelength of 238 nm.

8. Determination of Nimodipine levels in Nanoparticles

The sample is weighed equivalent to 50 mg of Nimodipine then dissolved with methanol in a 100 mL (500 ug/mL) volumetric flask, take 5 mL of the solution, put it in a 25 mL (100 g/ml) volumetric flask, take 1 ml and put it in a 10 ml volumetric flask. (10 g/ml). Measure the absorption of the solution at a wavelength of 236,20 nm. Assays were carried out on nimodipine, nanoparticles 1, 2, and 3 for 3 times.

9. Dissolution Test

Determination of the dissolution profile of Nimodipine was carried out using the paddle method. The dissolution flask was filled with 7.2 phosphate buffer medium as much as 900 mL with the temperature set at 37 ± 0.5 at a speed of 75 rpm, the Nimodipine-Poloxamer 188 nanoparticles were weighed equivalent to 50 mg. put in the paddle case and rotated. 5 mL of the dissolution solution was pipetted at 5, 15, 30, 45, and 60 minutes. In each pipetting, the solution in the flask was replaced with dissolution medium (same volume and temperature at the time of pipetting). Absorption is measured at the maximum wavelength.

III. Results & Discussion

3.1. Raw Material Inspection

On organoleptic examination, the results obtained were crystalline powder and yellow in color. The examination found nimodipine with an ultraviolet absorption spectrum obtained at a wavelength of 236.20 nm with a methanol solvent of 0.559. In the determination of nimodipine levels obtained levels of 98.9%

3.2. Formulation of Nanoparticle

(i) (ii) (iii) (iv)

Figure 1: (i) Nimodipine, (ii) Nimodipine-poloxamer 188 Nanoparticle 1, (iii) Nimodipine-poloxamer 188 Nanoparticle 2, (iv) Nimodipine-poloxamer 188 Nanoparticle3.

3.3 Characterization of Nimodipine-Poloxamer 188 Nanoparticle

1. Particle Size Analyzer (PSA)

Table 2: The results of the Nimodipine Particle Size Analyzer and Zeta Potential, Nimodipine-poloxamer 188 nanoparticles 1, Nimodipine-poloxamer 188 nanoparticles 2, and Nimodipine-poloxamer 188 nanoparticles 3.

Sample	Z-Average (nm)	Polydispersity Index	Zeta Potential
NM	1763	0,700	-32,9
NP 1	996,4	0,426	-27,0
NP 2	3894	1	-22,4
NP 3	1079	0,886	-16,5

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From the PSA results, it can be seen that the Nimodipine-poloxamer 188 nanoparticles 1 have the smallest particle size and can be said to have formed nanoparticles because they have met the requirements, where the requirements for nanoparticle size are 1-1000 nm. Nimodipine and all nanoparticles have polydispersity index values that meet the range of 0.01-0.7 but Nimodipine-poloxamer 188 nanoparticles 1 have the smallest polydispersity index values, this indicates that these nanoparticles are the most homogeneous. Pure nimodipine has a zeta potential value that is not good and all nanoparticles have a potential zeta value that meets the range, but for the nanoparticles formed it can be said that Nimodipine-poloxamer 188 nanoparticles 1 are the most stable compared to other nanoparticles because the range is closest to -30 mV. Zeta potential is a measure of the surface charge of the particles dispersed in the dispersing medium and the size of the repulsion between the particles. Nanoparticles with a zeta potential value above +/- 30 mV have higher stability so they can prevent aggregation, this is because the larger and farther the surface charge, the greater the repulsion energy and the smaller the tendency to recombine.

2. X-Ray Diffraction (XRD)

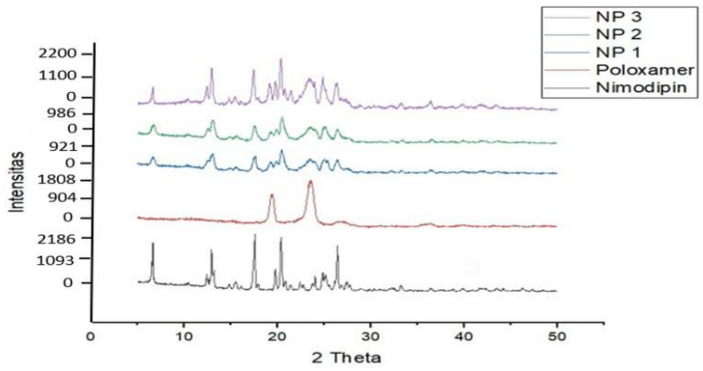

Figure 2: X-ray diffractogram of Nimodipine, Poloxamer 188, Nimodipine-Poloxamer 188 1, Nimodipine-Poloxamer 188 2, and Nimodipine-Poloxamer 188 nanoparticles 3.

Based on the analysis of the diaphthogram peaks above on the sample, it can be concluded that there is a decrease in intensity at angle 2θ on pure Nimodipine to nanoparticles, this indicates that the nanoparticles formed are more amorphous. However, the data from the diaphtogram shows that Nimodipine-poloxamer 188 1 nanoparticles have the smallest peak intensity value from the others, which indicates that these nanoparticles have the smallest particle size as well.

3. Differential Scanning Calorimetry (DSC)

Table 3: Thermogram analysis data of pure Nimodipine, Poloxamer 188, Nimodipine-Poloxamer 188 Nanoparticles 1, Nimodipine-Poloxamer 188 Nanoparticles 2, and Nimodipine-Poloxamer 188 Nanoparticles 3.

Sample	Enthalpy (J/g)	Temperatur (^{0}C)	Peak max (^{0}C/s)	Peak height	Onset (^{0}C/s)	Offset (^{0}C/s)
NM	94,205	123,71 & 137,53	128,732 /648	-11,916	125,89 /629,145	131,403 /663,757
PX	142,904	42,73 & 65,65	54,164 /208,4	-14,733	49,843 /182,832	56,782 /222,546
NP 1	38,002	36,84 & 57,9	48,041 /174	-2,571	42,041 /141,967	53,236/ 202,612
NP 2	39,759	36,42 & 56,26	47,404 /170,4	-3,103	41,923 /141,021	53,033/ 200,554
NP 3	64,666	37,41 & 62,00	53,741 /207	-4,571	46,472 /167,283	56,523/ 221.964

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From the results of the DSC thermogram, it can be seen that there is a decrease in the enthalpy value and the endothermic peak point of pure nimodipine and nanoparticles due to the small particle size and the active substance Nimodipine has mixed with the poloxamer so that there is an interaction between the two compounds resulting in a shift in the peak of the thermogram. DSC thermogram results on pure Nimodipine, Nimodipine-poloxamer 188 1 nanoparticles, Nimodipine-poloxamer 188 2 nanoparticles, and Nimodipine-poloxamer 188 3 nanoparticles indicate that Nimodipine-poloxamer 188 1 nanoparticles have the lowest enthalpy value.

4. Fourier Transformasi-Infra Red (FT-IR)

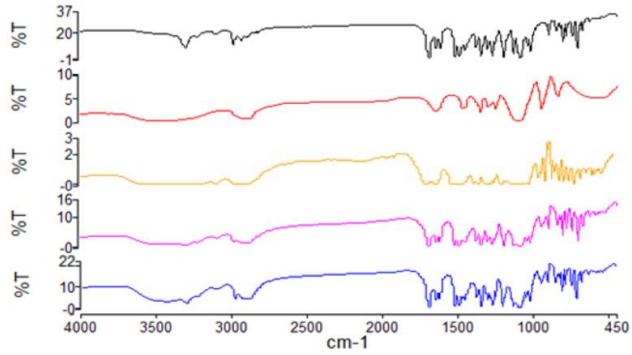
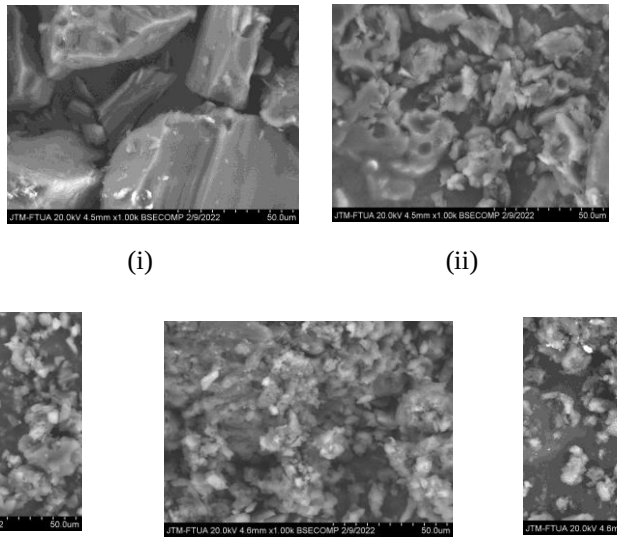


Figure 3: Pure Nimodipine FT-IR Spectrum Overlay, Poloxamer-188, Nimodipine-Poloxamer 188 Nanoparticles 1, 2 and 3.

Fourier transform infrared (FT-IR) analysis was conducted to identify functional groups in a compound and to determine the structure of a compound by comparing its fingerprint area. The results of the FT-IR spectrum of pure Nimodipine, Poloxamer-188, Nimodipine-poloxamer 188 nanoparticles 1, Nimodipine-poloxamer 188 nanoparticles 2, Nimodipine-poloxamer 188 nanoparticles 3 did not have missing or added functional groups but there was a wave shift, this indicates no structural changes after forming nanoparticles.

5. Scanning Electron Microscopy



(i) (ii)

(iii) (iv) (v)

Figure 4: (i) Nimodipin, (ii) Poloxamer-188, (iii) Nimodipine-poloxamer 188 Nanoparticle 1, (iv) Nimodipine-poloxamer 188 Nanoparticle 2, (v) Nimodipine-poloxamer 188 Nanoparticle 3.

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The Scanning Electron Microscopy (SEM) test aims to see the surface shape of Nimodipine and poloxamer before and after milling with a Planetary Ballmill. In the SEM results, all samples showed almost the same except for nimodipine which was seen as a crystalline solid with a rod shape like a large lump with a rough surface texture. for Nimodipine-poloxamer 188 nanoparticles 2 and 3 showed almost the same results as Nimodipine-poloxamer 188 nanoparticles 1, namely the presence of small particles but there were also some particles that had undergone agglomeration so that larger particles were seen.

6. Thin Layer chromatography

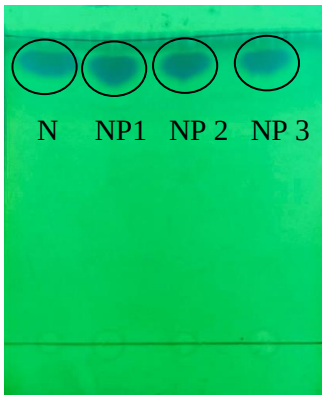

Figure 5: TLC pattern result of Nimodipine, Nimodipine-Poloxamer 188 nanoparticles 1, Nimodipine-Poloxamer 188 nanoparticles 2, Nimodipine-Poloxamer 188 Nanoparticles 3 with Chloroform: Methanol (9;1) as mobile phase.

After being tested, the results obtained in the form of one spot formed with an Rf value for Nimodipine 0.8, Nimodipine-poloxamer 188 nanoparticles 1 was 0.78, Nimodipine-poloxamer 188 nanoparticles 2 was 0.8, and Nimodipine-poloxamer 188 nanoparticles 3 was 0.8. This indicates that there is no chemical interaction or decomposition of Nimodipine and Poloxamer 188 after grinding with different ball ratio variations because only one stain is formed and the Rf results obtained are not much different.

7. Determination of saturated solubility of Nimodipine-poloxamer 188

The purpose of the solubility test is to see the effect of particle size on solubility. The solubility of pure Nimodipine in water was 0.3390 g/mL, Nimodipine-poloxamer 188 nanoparticles 1 was 19.8698 g/mL, Nimodipine-poloxamer 188 nanoparticles 2 was 6.0673 g/mL, and Nimodipine-poloxamer 188 nanoparticles 3 was 8,4405 of g/mL. From the results obtained, it can be seen that the solubility of Nimodipine-poloxamer 188 1 nanoparticles increased 58 times higher than pure Nimodipine, while Nimodipine-poloxamer 188 2 increased 17 times higher, and Nimodipine-poloxamer 188 nanoparticles increased 24 times higher. These results are directly proportional to the particle size, where the smaller the particle size, the more surface area of the particle to interact with the solvent so that the better the solubility. The results of analysis solubility of Nimodipine, Nimodipine-poloxamer 188 nanoparticles 1 , Nimodipine-poloxamer 188 nanoparticles 2 , and Nimodipine-poloxamer 188 nanoparticles 3 were processed statistically using one way ANOVA in the SPSS 20 program. Homogeneity test results using Levene Statistics were obtained that the calculated F value = 3.317 with sig = 0.078 (> 0.05), which means that the data is homogeneously distributed, so the ANOVA test can be performed. The ANOVA test results showed that the value of sig = 0.000 (<0.05), which means H0 was rejected, this indicates that the solubility of Nimodipine, Nimodipine-poloxamer 188 nanoparticles 1, Nimodipine-poloxamer 188 nanoparticles 2, Nimodipine-poloxamer 188 nanoparticles 3 gives meaningful influence. From the results above, it can be said that the solubility is influenced by particle size, where the smaller the particle size, the better the solubility compared to the larger particle size.

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8. Determination of Nimodipine levels in Nanoparticles

In the determination of pure nimodipine levels, the levels of 98.91% were obtained, Nimodipine-poloxamer 188 nanoparticles 1 was 99.85%, Nimodipine-poloxamer 188 nanoparticles 2 was 100.73%, and Nimodipine-poloxamer 188 3 was nanoparticles 99.31%, where these results are consistent with with the range of requirements for nimodipine levels listed in the literature, namely nimodipine levels of not less than 98.5% and not more than 101.5% (Ministry of Health of the Republic of Indonesia, 2014).

9. Dissolution Test

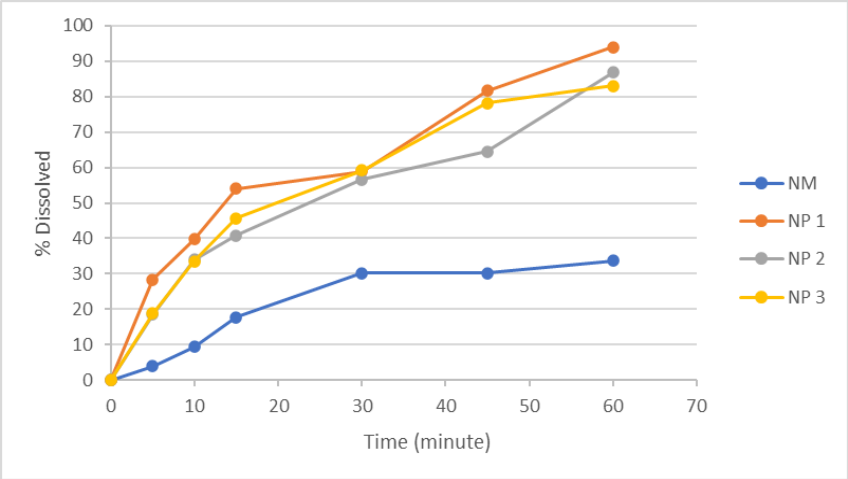

Figure 6 : Dissolution profile curves of pure nimodipine, Nimodipine-poloxamer 188 nanoparticles 1, Nimodipine-poloxamer 188 nanoparticles 2, and Nimodipine-poloxamer 188 nanoparticles 3 in phosphate buffer pH 7.2

In determining the dissolution profile of pure nimodipine powder, Nimodipine-poloxamer 188 nanoparticles 1, Nimodipine-poloxamer 188 nanoparticles 2 and Nimodipine-poloxamer 188 nanoparticles 3 showed that the powder increased the dissolution rate. The percentage of pure nimodipine dissolution at the 60th minute was 33,7462%, the percentage of dissolution of Nimodipine-poloxamer 188 nanoparticles 1 was 93.9949%, the percentage of dissolution of Nimodipine-poloxamer 188 nanoparticles 2 was 86.7714% and the percentage of dissolution of Nimodipine-poloxamer 188 nanoparticles 3 was in the 60th minute is 83.9795%. The increase in the dissolution rate is influenced 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 Nimodipine-poloxamer 188 1 nanoparticles have the highest percentage of dissolution this is due to the influence of the ball used, where the use of too many balls will produce poor results due to limited ball movement in a filled vessel so that collisions occur. that occurs between the ball and the particle is reduced and causes the powder to not grind properly so that it affects the particle size and solubility.

The results of the analysis of the dissolution efficiency of Nimodipine, Nimodipine-poloxamer 188 nanoparticles 1, Nimodipine-poloxamer 188 nanoparticles 2, Nimodipine-poloxamer 188 nanoparticles 3, were statistically processed using one-way ANOVA test in the SPSS 20 program. dissolved. The results of the homogeneity of variance test using Levene Statistics, showed that the calculated F value = 1.196 with Sig = 0.371 (> 0.05), which means that the data is homogeneously distributed, because the data obtained are homogeneously distributed, then the ANOVA test is carried out. The results of the ANOVA test calculation

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show that the value of Sig = 0.000 (<0.005) which means that H0 is rejected. This shows that the average dissolution efficiency of Nimodipine, Nimodipine-poloxamer 188 1 nanoparticles, 188 2 nimodipine-poloxamer nanoparticles, 188 3 nimodipine-poloxamer nanoparticles have a significant effect. While the results of further tests carried out using Duncan's test showed that the average dissolution efficiency was divided into 3 subsets. Where pure nimodipine is located in subset 1, Nimodipine-poloxamer 188 1 nanoparticles are located in subset 3, Nimodipine-poloxamer 188 2 nanoparticles and Nimodipine-poloxamer 188 3 nanoparticles are located in subset 2 . This means that Nimodipine-poloxamer 188 1 nanoparticles, Nimodipine-poloxamer 188 2 nanoparticles, Nimodipine-poloxamer 188 3 nanoparticles affect the dissolution rate of pure nimodipine.

IV. Conclusion

The grinding ball ratio in the milling process with a planetary ball mill has an influence on physical characteristics, but not with the chemical characteristics of Nimodipine-poloxamer 188 nanoparticles. It can be seen in the results of particle size distribution analysis using PSA and SEM results indicate a reduction or reduction in particle size which is influenced by milling ball ratio. In XRD there is a decrease in peak intensity due to milling. In DSC, the melting point decreases. While in FT-IR, no new functional groups were found but a shift in wave number occurred, and the TLC results obtained the same RF value between nimodipine and the three nanoparticles, namely 0.8, this indicates no chemical interaction. The grinding ball ratio affects the solubility and dissolution rate of Nimodipine-poloxamer 188 nanoparticles, it is shown in the solubility of Nimodipine-poloxamer 188 1 nanoparticles increased 58 times higher than pure Nimodipine, while Nimodipine-poloxamer 188 2 nanoparticles increased 17 times higher, and Nimodipine nanoparticles -poloxamer 188 increased 24 times higher, while the average dissolution efficiency for pure Nimodipine 23.3978%, Nimodipine-poloxamer 188 nanoparticles 1 was 61,5841%, Nimodipine-poloxamer 188 2 was 52.3159% nanoparticles, and Nimodipine-poloxamer nanoparticles 188 3 was 56,6027%. From the results of the dissolution efficiency, it can be seen that there is an increase in the dissolution rate. The ball ratio of 20% is the optimum ball ratio in the milling process with a planetary ball mill, this is indicated by the good characterization results for nimodipine-poloxamer 188 1 nanoparticles, where in nanoparticle 1 uses a 20% ball ratio.

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