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Optimization of Povidone and Sodium Starch Glycolate Formulas in the Formulation of Solid Sow of Noni Fruit Extract (Morindacitrifolia L.)

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ABSTRACT: Noni fruit (Morindacitrifolia L.) is a traditional medicinal plant widely used for alternative and complementary medicine. Scopoletin and quercetin are some of the active compounds in noni fruit that can provide immunomodulatory effects. This study aims to determine the total flavonoid content in noni fruit extract and the optimum formula of solid sprinkle formulation of noni fruit extract (Morindacitrifolia L.) with variations in the concentration of povidone as a binder and sodium starch glycolate as a disintegrant. Evaluation of the characteristics of the sprinkle formulation includes organoleptic test, ethanol free test, moisture content, flow time, angle of repose, compressibility index, dissolution time, and content uniformity. Formula optimization is carried out using the simplex lattice design method. The optimum formula is then analyzed using one-sample t-test method. The total flavonoid content in the ethanol extract of noni fruit was 1.654 mg QE/g. The optimum formula of the sprinkle formulation was obtained at a proportion of 2.703% povidone and 2.297% sodium starch glycolate. The sprinkle formulation was in the form of light brown granules with a sweet taste and distinctive aroma, and it was ethanol-free based on qualitative testing. The physical characteristics of the optimum formula were as follows: moisture content 1.913%, flow rate 13.415g/s, angle of repose 30.303o, compressibility index 6.282, dissolution time 250.16 seconds, and content uniformity 11.905%.

KEYWORDS: Noni; sprinkle formulation; formula optimization

I. INTRODUCTION

Noni fruit (Morindacitrifolia L.) contains various metabolites that can provide pharmacological effects. The bioactive components of noni consist of polysaccharides and phytochemical compounds. The polysaccharide components exhibit immunomodulatory, anticarcinogenic, and antitumor activities, while phytochemical compounds possess antioxidant, immunomodulatory, antibacterial, antiinflammatory, antidiabetic, antitumor, anticancer, antiviral, hepatoprotective, and antidementia activities[1].

Based on the research conducted by Sogandi and Rabima (2019), the ethanol extract of noni fruit contains phytochemical compounds such as anthraquinone, alkaloid, tannin, flavonoid, steroid, saponin, and phenol[2]. One of the phytochemical compounds in noni fruit that can provide immunomodulatory effects is flavonoids (quercetin, kaempferol, and catechin). Quercetin can inhibit the release of histamine by basophils or mast cells stimulated by antigens. Quercetin and catechin reduce the expression of COX-2, decrease the secretion of nitric oxide by stimulated macrophages, reduce T-cell proliferation and IL-2 secretion by inhibiting the MAPK and phospholipase-C pathways[1]. The research conducted by Zumrotul (2015) indicates that noni fruit extract can enhance the immune response in mice at a dose of 300 mg/kg by increasing the number of T lymphocytes (CD4+)[3].

Noni fruit extract needs to be formulated into a pharmaceutical dosage form, so it will be more convenient to consume. In this study, the extract will be formulated into sprinkle formulation. Sprinkle formulation is a pellet or granule form that can be consumed along with food[4]. It can cover the bitter taste of noni fruit[5], making it more palatable. As a solid dosage form, sprinkle formulation is more stable compared to

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liquid formulations during storage. In comparison to other solid forms (capsule and tablet), sprinkle formulation is easier to consume for children and individuals experiencing dysphagia due to its smaller size[4].

Sprinkle formulation requires excipients such as sweetener, filler, lubricant, binder, and disintegrant[4]. Binder and disintegrant are components that influence the physical properties of granules[6,7]. In this study, formula optimization will be conducted for povidone and sodium starch glycolate (SSG). Povidone serves as a binder, while sodium starch glycolate (SSG) is a disintegrant[8].

Based on the description above, this research aims to determine the total flavonoid content in noni fruit extract (Morindacitrifolia L.)

as an active ingredient with potential immunomodulatory activity. The extract is then formulated into a sprinkle formulation by optimizing the components of povidone and sodium starch glycolate. Formula optimization is conducted using the simplex lattice design method[9].

II. EXPERIMENTATION

2.1. Materials and Equipments

a. The materials used are noni fruit, 96% ethanol (Anugrah Jaya Chemical), methanol (Smart Lab), glacial acetic acid (Smart Lab), sulfuric acid (Smart Lab), iron(III) chloride (Merck), ammonia (Merck), toluene (Smart Lab), hydrochloric acid (Smart Lab), Mayer's reagent, Dragendorff's reagent, chloroform (Smart Lab), magnesium powder (Merck), amyl alcohol (Merck), Whatman filter paper, distilled water (Anugrah Jaya Chemical), ethyl acetate (Smart Lab), n-hexane (Smart Lab), silica gel TLC plates F254 (Supelco), quercetin, ethanol p.a. (Smart Lab), aluminum chloride (Smart Lab), sodium acetate (Loba Chemie), povidone K30 (JH Nanhang Life Sciences), sodium starch glycolate (Sigachi), mannitol (Shijiazhuang Huaxu Pharmaceutical), aspartame (Changzhou Guanghui Biotechnology), magnesium stearate, lactose (Alpavit), and food-grade 96% ethanol (Indo Acidatama).

b. The equipments used are water bath (MEMMERT WNB14), rotary evaporator (Heidolph), scales (CAMRY, Lion Star, OHAUS PX224/E), oven (MEMMERT UF55), grinder (FOMAC FGD-Z500), vortex (Heidolph), fume hood (Nadiso), UV lamp (CAMAG), sieves with mesh sizes 12 and 14, stopwatch, hotplate (Cimarec), flow tester, moisture analyzer (OHAUS MB95), UV-Vis spectrophotometer (Cary 60), micropipette (Socorex), mortar and pestle.

2.2. Methods

2.2.1. Extract Preparation

The plant determination was carried out at the Jatinangor Herbarium, Plant Taxonomy Laboratory, Department of Biology, Faculty of Mathematics and Natural Sciences, Universitas Padjadjaran. The noni fruits were obtained from Karangrahayu, Bekasi Regency, West Java. The drying process was carried out by natural air drying for five days[10]. The dried noni fruits were then ground into powder. Loss on drying test was conducted using a moisture analyzer. Loss on drying value should be equal to or less than 10%[5].One kilogram of powdered crude drug was soaked in 3 liters of 96% ethanol solvent. The maceration process was repeated three times, each time using 1 liter of 96% ethanol solvent. Maceration was carried out for 48 hours with occasional stirring. The macerate was filtered using filter paper to obtain a liquid extract. The liquid extract was concentrated using a rotary evaporator at 40°C[10], then further concentrated using a water bath at 50°C and an oven at 45°C. The moisture content of the extract was determined using a moisture analyzer. Moisture content should be equal or less than 10%[5]. The extract yield was then calculated using the following formula[11].

$$\%\text{Yield} = \frac{\text{Extract weight obtained}}{\text{The weight of dried noni fruits}} \times 100\%$$

2.2.2. Ethanol-Free Test

The test was carried out by reacting 0.5 grams extract with 1 mL glacial acetic acid and 1 mL concentrated sulfuric acid in a test tube. The sample was homogenized and heated, with the tube's mouth covered with cotton. If no ester aroma was detected in the sample, the extract was ethanol-free[2].

2.2.3. Phytochemical Test

The phytochemical tests carried out included phenol test, anthraquinone test, alkaloid test, flavonoid test, tannin test, saponin test, triterpenoid test, and steroid test[2, 12, 13].

2.2.4. Determination of Flavonoid Content

A quercetin standard solution was prepared by dissolving 5 mg quercetin in 50 mL

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ethanol p.a., resulting in a 100 ppm quercetin solution. The maximum wavelength was determined using the UV-Vis spectrophotometer in the range of 400-800 nm. The operating time was determined by measuring the solution's absorbance every 5 minutes for 1 hour. The Quercetin standard curve was prepared using 5 different concentrations: 20, 40, 60, 80, and 100 ppm. Each concentration was pipetted 0.5 mL, then added to 1.5 mL of ethanol p.a., 0.1 mL of 10% $AlCl_3$, 0.1 mL of 1M sodium acetate, and 2.8 mL of distilled water. The samples were incubated for 30 minutes at room temperature. The absorbance of each concentration was measured at the maximum wavelength using a UV-Vis spectrophotometer[5, 14]. The determination of the total flavonoid content in the extract is carried out by dissolving the extract in 70% ethanol to obtain a concentration of 50,000 ppm. The flavonoid content was then determined using the quercetin standard curve and calculated using the following formula[14].

$$C = \frac{Cf \times V}{M} \times Fp$$

İnformation:
C = Total flavonoid content (µg/g)
Cf = Flavonoid content in the sample solution (µg/mL)
V = Volume of the sample solution (mL)
Fp = Dilution factor
M = Sample weight (grams)

2.2.5. Thin Layer Chromatography

Thin-layer chromatography was conducted with the following parameters: mobile phase, a mixture of n-hexane and ethyl acetate in a ratio of 1:4[15]; stationary phase (TLC plate), silica gel 60 F254; test solution, 40% extract solution in methanol P; detection with UV_{366}[5]. The test solution was spotted on a pre-activated TLC plate using an oven at 110°C for 30 minutes[16]. The TLC plate was placed in a chamber containing the pre-saturated mobile phase. Detection of TLC results was performed under UV_{366} light, and the Rf value was calculated.

2.2.6. Formulation of Sprinkle Formulation

The optimization of the sprinkle formulation was conducted using the simplex lattice design method in the Design Expert application version 13[9]. The concentrations of povidone ranged from 1-3% and sodium starch glycolate ranged from 2-4%[8]. The formulation was carried out using the wet granulation method. Povidone, sodium starch glycolate, mannitol, aspartame, and lactose were placed in a mortar and ground until homogenous. Noni fruit extract was added to the mortar and ground until homogenous. After that, food-grade 96% ethanol was added to form a mass that could be molded. The mixture was sieved with a mesh size of 12 to form granules. The granules were dried at 40°C for 3 hours. The dried granules were sieved with a mesh size of 14[17]. Magnesium stearate was added as a lubricant[18]. Each formula is made in the amount of 90 grams, with three replications. The sprinkle formulations were packaged in sachets. Each sachet weighed 6 grams of granules and contained 1 gram of extract.

Table 1. Sprinkle formulation formula.

Material	Function	Formula I	Formula II	Formula III	Formula IV	Formula V
Noni fruit extract	Active ingredient	16.67%	16.67%	16.67%	16.67%	16.67%
Povidone	Binder	1%	1.5%	2%	2.5%	3%
Sodium starch glycolate	Disintegrant	4%	3.5%	3%	2.5%	2%
Mannitol	Sweetener	20%	20%	20%	20%	20%
Aspartame	Sweetener	3%	3%	3%	3%	3%
Mg stearate	Lubricant	0.5%	0.5%	0.5%	0.5%	0.5%
Lactose	Filler	54.83%	54.83%	54.83%	54.83%	54.83%
Ethanol	Wetting agent	10%	10%	10%	10%	10%

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2.2.7. Evaluation of Sprinkle Formulation

Evaluation of the sprinkle formulation includes both qualitative and quantitative tests. Qualitative evaluation involves organoleptic test and ethanol-free test. Quantitative evaluation includes moisture content, flow time, angle of repose, bulk density, tapped density, compressibility index, dissolution time, and content uniformity test.

a. Organoleptic test was conducted by observing the physical appearance of the sprinkle formulation, including shape, color, taste, and odor[19].
b. Ethanol-Free Test was conducted by reacting 0.5 grams sample with 1 mL glacial acetic acid and 1 mL concentrated sulfuric acid in a tube test. The sample is homogenized and heated, with the tube's mouth covered with cotton. If no ester aroma was detected in the sample, the sample was ethanol-free[2].
c. The moisture content of the sprinkle formulation was analyzed using a moisture analyzer. One gram of the sprinkle formulation is placed into the moisture analyzer at 105°C[19]. The moisture content requirement for the granules is 1-5%[20].
d. The flow time test was conducted by placing 50 grams sprinkle formulation into a flow tester funnel with the bottom of the funnel closed. The bottom of the funnel was then opened. The time required for the sample to flow was measured. The flow rate of the sample was then calculated[19]. The flow time of the granules is considered good if 10 grams of granules can flow in less than 1 second[21].

$$\text{Flow rate (grams/second)} = \frac{\text{weight of granules (grams)}}{\text{flow time (seconds)}}$$

e. The angle of repose was determined by placing 50 grams of the sprinkle formulation into a flow tester funnel with the bottom of the funnel closed. The bottom of the funnel was then opened. The height and diameter of the sample stack were measured to determine the angle of repose[19]. Granules that flow easily have an angle of repose less than 40°[22].

$$\text{Tan } \theta = \frac{2 \text{ .stack height (cm)}}{\text{averagediameter (cm)}}$$

f. Compressibility index was determined based on the values of bulk density and tapped density. Bulk density was determined by measuring the volume of 25 grams sprinkle formulation in a measuring glass. The volume to determine the tapped density was measured after tapping the measuring glass for 500 times. Afterward, the bulk density and tapped density was calculated[19].Granules with good flow properties have a compressibility index of ≤ 15[23]. The value of the compressibility index was calculated using the following formula[21].

$$\text{Carr İndex} = \frac{(\text{tapped density} - \text{bulk density})}{\text{tapped density}}$$

g. Dissolution time was determined by dissolving 5 grams of sprinkle formulation in 50 mL water with continuous stirring. The time required for the sample to dissolve is measured using a stopwatch. The dissolution time requirement is less than 5 minutes[17].
h. Content uniformity was determined by establishing the total flavonoid content of 10 sachets sprinkle formulation. Each sachet of sprinkle formulation was taken 1.5 grams and dissolved in 10 mL 70% ethanol to obtain a concentration equivalent to 50,000 ppm of the extract. A sample solution was taken in the amount of 0.5 mL, then added with 1.5 mL of ethanol p.a., 0.1 mL of 10% $AlCl_3$, 0.1 mL of 1M sodium acetate, and 2.8 mL of distilled water. The sample solution was incubated for 30 minutes at room temperature. After that, the absorbance of the sample was measured at the maximum wavelength using a UV-Vis spectrophotometer[5,14]. The uniformity test meets the criteria if the acceptance value of 10 dosage units is ≤ 15%[24].

Acceptance value = $|M - \underline{X}| + ks$
Information:
M = reference value
$\underline{X}$ = content uniformity data mean
k = acceptance constant
s = standard deviation

2.2.8. Data Analysis

The results of the evaluation, including moisture content, flow time, angle of repose, compressibility index, dissolution time, and content uniformity, were analyzed using the Design Expert version 13 with the simplex lattice design method. This analysis led to the determination of the optimum formula considering variations in povidone and sodium starch glycolate. The optimum formula was determined based on desirability values. The confirmation test of the

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optimum formula was analyzed using one-sample t-test[9].

III. RESULT AND DISCUSSION

3.1. Yield of Dried Noni Fruit and Extract

The noni fruit used is ripe and characterized by its greenish-white to white color. Ripe noni fruit has a higher rutin and catechin content compared to unripe fruit[25]. Dried noni fruit has a brown color, bitter taste, and distinctive odor. A total of 15.1 kg of fresh fruit produces 2.81 kg of dried fruit with 6,573% loss on drying value. The dried noni fruit was extracted using the maceration method. The noni fruit extract has a dark brown color, bitter taste, and distinctive aroma. The yield of ethanol extract obtained was 21,5% with 3,523% moisture content.

3.2. Ethanol-Free Test

The noni fruit extract tested ethanol-free or no ethanol content based on the qualitative analysis. The ethanol-free test used ethanol as a positive control and extract as the sample. The positive control produced a distinctive ester aroma, while the sample emitted the smell of glacial acetic acid. Glacial acetic acid did not react with the sample, so no ester aroma was detected. Esterification reaction between alcohol and glacial acetic acid produced ethyl acetate (ester) while sulfuric acid acted as catalyst.

3.3. Phytochemical Test

The ethanol extract of noni fruit contains phenolic compounds, anthraquinones, steroids, saponins, tannins, alkaloids, and flavonoids. The phytochemical profile of the ethanol extract of noni fruit in this study is consistent with the research by Sogandi&Rabima (2019)[2]. The identification of secondary metabolites in the extract involves chemical reactions between compounds in the extract and specific reagents.

Table 2. Phytochemical test results of noni fruit extracts.

Phytochemical Test	Standart Test	Extract
Phenol	Blackish-blue to deep black	+
Anthraquinone	Red	+
Steroid	Green or blue	+
Triterpenoid	Purple or red	-
Saponin	There is foam 1-10 cm	+
Tannin	Greenish-black	+
Alkaloid	White and/or red precipitate	+
Flavonoid	Red, orange, or yellow	+

3.4. Determination of Flavonoid Content

The determination of total flavonoid content using quercetin as a reference standard. Quercetin is a flavonol compound that has a keto group at the C-4 atom and hydroxyl groups at the C-3 or C-5 atoms. The keto and hydroxyl groups in flavonoids and flavonols can react with $AlCl_3$ reagent, forming colored complex compounds[14].The determination of total flavonoid content was carried out at a maximum wavelength of 435 nm with an operating time of 30 minutes. The quercetin standard curve has an R^2 value of 0.9984 with the linear equation y = 0.0089x - 0.0033. The result of total flavonoid content in noni fruit extract is 1,654 mgQE/g or 0.165%.

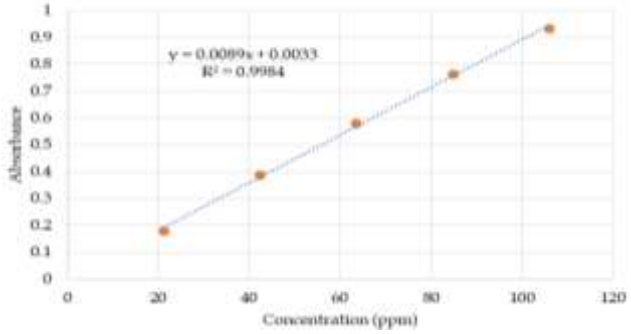

Figure 1. Quercetin calibration curve.

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Table 3. Result of total flavonoid content in noni fruit extract.

Concentration	Replication	Absorbance	Total flavonoid content
50650 ppm	1	0.7302 ± 0.004	1.654 ± 0.036 mgQE/g
	2	0.7583 ± 0.024	
	3	0.7580 ± 0.008	

3.5. Thin Layer Chromatography (TLC)

Scopoletin is a derivative compound of coumarin that fluoresces blue when exposed to UV light at 366 nm. Coumarin compounds have conjugated double bonds and chromophore groups that can interact with UV light. The chromophore group in scopoletin is capable of absorbing UV light, resulting in a fluorescent spot[15].Based on the results of thin-layer chromatography, the blue fluorescent spot has an Rf value of 0.700. The identification of scopoletin in the noni fruit extract is consistent with the previous research, Rf value 0.710[15]. Therefore, the noni fruit extract positively contains scopoletin.

Figure 2. TLC result of 366 UV lamp.

3.6. Formula Optimization of Sprinkle Formulation

Each formula was evaluated qualitatively and quantitatively. The evaluation results are presented in Tables 4 and 5.

Table 4. Results of Qualitative Evaluations.

Formula	Organoleptic Test	Ethanol-Free Test
I	Granules, light brown color, sweet taste, distinctive odor	-
II	Granules, light brown color, sweet taste, distinctive odor	-
III	Granules, light brown color, sweet taste, distinctive odor	-
IV	Granules, light brown color, sweet taste, distinctive odor	-
V	Granules, light brown color, sweet taste, distinctive odor	-

Table 5. Results of Quantitative Evaluations.

Formula	Moisture Content (%)	Flow Rate (g/s)	Angle of Repose (°)	Compressibility Index	Dissolution Time (s)	Content Uniformity (%)
I	2.667 ± 0.158	10.418 ± 1.046	28.734 ± 0.341	9.320 ± 1.243	122.910 ± 2.867	11.272 ± 1.221
II	2.077 ± 0.143	12.607 ± 1.312	29.410 ± 0.724	8.925 ± 2.592	183.020 ± 4.394	11.612 ± 2.238
III	1.863 ± 0.156	12.487 ± 0.869	30.223 ± 0.705	6.944 ± 0.285	210.397 ± 3.541	12.158 ± 1.604
IV	2.037 ± 0.332	13.982 ± 0.662	30.095 ± 1.233	6.722 ± 1.512	240.613 ± 1.846	10.204 ± 2.547
V	1.730 ± 0.238	13.962 ± 0.858	31.691 ± 0.354	5.424 ± 0.149	259.947 ± 2.100	11.583 ± 0.635

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The optimum formula was determined based on quantitative analysis data. The evaluation data used for formula optimization are the results of evaluations that show significant differences between formulas. The presence of significant differences is determined by ANOVA statistical analysis. If there is a significant difference, the p-value < 0.05. Based on the results of statistical analysis, the evaluation data that show significant differences are flow rate, angle of repose, compressibility index, and dissolution time. Therefore, confirmation tests are only conducted on these four evaluation parameters.

Table 6. The equation of SLD for each response.

Response	Equation of SLD
Flow rate	Y = 14.38A + 11B
Angle of repose	Y = 31.35 + 28.71B
Compressibility Index	Y = 5.47A + 9.47B
Dissolution time	Y = 269.71A + 137.04 B

Y = response; A = povidone concentration; B = SSG concentration

Based on the optimization results, the composition of povidone and sodium starch glycolate that resulted in the optimum formula is 2.703% and 2.297%. The obtained desirability value is 0.833. The maximum desirability value is one. The closer the value is to one, the better the desirability. The criteria for evaluation results specified for analysis using the simplex lattice design method are as follows:

Table 7. Results of Qualitative Evaluations.

Name	Goal	Lower Limit	Upper Limit	Importance
Flow rate (g/s)	maximize	10	15	3
Angle of repose (^{o})	is in range	25	35	3
Compressibility Index	minimize	5	15	3
Dissolution time (s)	is in range	60	250	3

3.7. Confirmation Test of Sprinkle Formulation

The response predicted from the Simplex Lattice Design is then compared with the experimental results. The statistical analysis used is the one sample t-test. The one sample t-test is employed to test the significance of the difference in means between each experimental value obtained and the theoretical values predicted from the Simplex Lattice Design.

Table 8. Results of confirmation test using one-sample t-test.

Response	Prediction	Experiment	P-value	Result
Flow rate (g/s)	13.881	13.415 ± 0.918	0.472	not significant
Angle of repose (°)	30.958	30.303 ± 0.350	0.083	not significant
Compressibility index	6.062	6.282 ± 0.988	0.737	not significant
Dissolution time (s)	250.000	250.16 ± 1.700	0.886	not significant

Table 8 shows that the responses of flow rate, angle of repose, compressibility index, and dissolution time exhibit results that are not significantly different between the predictions from the Design Expert software and the experimental results. The significance values of each response are greater than 0.05. The lack of significant difference between the Simplex Lattice Design predictions and the experimental results can be concluded that the software is valid for optimizing the noni fruit extract sprinkle formulation.

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IV. CONCLUSION

Based on the results of the study, the total flavonoid content in the ethanol extract of noni fruit is 1.654 mg QE/g. The optimum formula of the sow formulation was obtained at the proportion of 2.703% povidone and 2.297% sodium starch glycolate. The sprinkle formulation is in the form of light brown granules with a sweet taste and distinctive aroma, and is ethanol-free based on qualitative tests. The physical characteristics of the optimum formula are as follows: moisture content 1.913%, flow velocity 13.415 g/s, angle of repose 30.303o, compressibility index 6.282, dissolving time 250.16 seconds, and weight uniformity 11.905%.

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