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Formulation and physical evaluation of *Gnetum gnemon L.* peel extract tablets using variation concentration of Na-CMC and starch 1500

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Abstract

Gnetum gnemon L. peel extract contains flavonoid compounds, which are used to lower cholesterol levels. It needs to be formulated into tablets to maximize the potential of the *Gnetum gnemon* L. peel extract. This research aims to determine the effect of variations in Na-CMC and starch 1500 concentrations on the physical properties of granules and tablets. The method used was wet granulation, using variations in Na-CMC and starch 1500 concentrations Formula 1 (5%: 6%), Formula 2 (3%: 8%), and Formula 3 (1%: 10%). The evaluation included the physical properties of granules (flow rate, angle of repose, compressibility) and the physical properties of tablets (organoleptic, weight uniformity, hardness, friability, and disintegration time). The data obtained were then analyzed statistically. The results showed that the addition of Na-CMC binder and starch 1500 disintegrant affected the granules and tablets. Formula 1 produces granules and tablets with better physical properties compared to Formula 2 and Formula 3. This research concludes that the concentration of Na-CMC and starch 1500 affects the physical properties and Formula 1 is the best formula with a ratio of Na-CMC (5%) and starch 1500 (6%).

Keywords

Gnetum gnemon L., Peel extract tablets, Na-CMC, Starch 1500

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Introduction

Hypercholesterolemia is a condition that can increase the risk of coronary heart disease, stroke, high blood pressure, obesity and other health problems (1). Hypercholesterolemia can occur in individuals if total cholesterol levels are ≥ 200 mg/dl (2). Based on the Indonesian health survey reported by (3), The results of the prevalence of total cholesterol revealed that the age group of 55–64 had the greatest cholesterol, at 21.2%. In addition, the results also showed that 26.2% of men and 29.4% of women had high total cholesterol levels. Based on the data and the increased risk of accompanying diseases, hypercholesterolemia must be a concern to overcome.

Statins are common drugs used to treat hypercholesterolemia (4). Statins are known to have side effects such as rhabdomyolysis although with a percentage of 1-10%, statins also have interactions with the cytochrome p450 enzyme group (5). Other alternatives are needed, such as the use of plant extract as antihypercholesterolemic.

Based on previous research, *Gnetum gnemon* L. peel extract (2.275 mg/kg BW) can reduce cholesterol levels in Wistar rats (6). *Gnetum gnemon* L. peel extract contains flavonoid (7). Flavonoid compounds can reduce cholesterol synthesis by inhibiting the activity of the acyl-CoA cholesterol acyl transferase (ACAT) enzyme in HepG2 cells which plays a role in reducing cholesterol esterification in the intestines and liver and inhibiting the activity of the 3-hydroxy-3 methyl-glutaryl-CoA enzyme which causes inhibition of cholesterol synthesis (6,8). To utilize the *Gnetum gnemon* L. peel extract, it is necessary to formulate it into tablets.

Tablets are a solid dosage form with or without additional excipients that are made by compression (9). In previous research, excipients in tablets such as binders and disintegrants influenced the physical properties of granules and tablets (10). It is necessary to research the binder and disintegrant in tablet preparations. This research used Na-CMC as a binder and starch 1500 as a disintegrant. Physical evaluation was carried out to assess the quality of granules and tablets.

Method

Materials and instruments

The materials used in this study were *Gnetum gnemon* L. (Randudongkal, Pemalang Regency, Indonesia) and other pharmaceutical-grade materials such as Na-CMC, starch 1500, aerosil, lactose, magnesium stearate, ethanol 96%, and aquadest. The instruments used in this study include rotary evaporator (Boeco), waterbath (Memmert), granule flow test (PT. Bawono), tap density volumeter BKDY-100B (Biobase), oven (Memmert), single punch tablet machine (Biobase), hardness tester THT-3 (Biobase), friability tester CS-2 (Biobase), disintegration tester (Minhua pharmaceutical machinery), and other supporting tools.

Gnetum gnemon L. peel extraction

The *Gnetum gnemon* L. peel was wet sorted then washed clean and the sample was weighed. Then the sample was dried by being dried for three days. Furthermore, the dried *Gnetum gnemon* L. peel was weighed and powdered. The extraction using the maceration method, the solvent is ethanol 96% for 24 hours. The ratio of simplicia and solvent is 1:10. The process is continued using a rotary evaporator at a temperature of 50°C and concentrated using waterbath. The extract was calculated for yield, water content, and identification of flavonoid compounds.

Tablet formulation

The previous research explained the *Gnetum gnemon* L. peel extract of 2.275 mg/kgBW can reduce hypercholesterolemia in Rats (200 g) (6). The dose needs to be converted to a human dose (60 kg). The dose for humans is 25.48 mg. The design formula for a tablet is shown in Table 1. The tablets are divided into 3 formulas with a concentration of Na-CMC and starch 1500, it is Formula 1 (5%:6%), Formula 2 (3%:8%), and Formula 3 (1%:10%). Tablets produced 300 pieces, so the materials are shown in Table 2. In Formula 1, the extract is weighed at 7.64 g and dried by adding 2.54 g of aerosol. Then, mix the dried extract with 120.60 g of lactose and 9 g of starch 1500 until homogeneous. Add 7.5 g of Na-CMC dissolved in 28 ml of water slowly and evenly while stirring until it forms a mass. After mixing, the results are sieved using sieve no. 12 mesh and dried in an oven at 50° C for 3 hours. The dried granules are then sieved again with sieve no. 14, add 1.5 g of magnesium stearate, and 1.2 g of talc, then mix until homogeneous. After that, test the physical properties of the granules and continue with the tablet machine. The tablets are subjected to physical evaluation. This manufacturing process is similar for all formulas with the only difference being the weighing of the materials in Table 2.

Table 1. The design formula for a tablet

Materials	Function	Formula 1 (mg)	Formula 2 (mg)	Formula 3 (mg)
Gnetum gnemon L. peel extract + aerosil	Active substance	33.97	33.97	33.97
Na-CMC	Binder	25	15	5
Starch 1500	Disintegrant	30	40	50
Lactosa	Filler	402.03	402.03	402.03
Mg stearate	Lubricant	5	5	5
Talc	Glidant	4	4	4
Tablet weight		500	500	500

Table 2. The design formula for 300 tablets

Materials	Formula 1 (g)	Formula 2 (g)	Formula 3 (g)
Gnetum gnemon L. peel extract + aerosil	10.81	10.81	10.81
Na-CMC	7.5	4.5	1.5
Starch 1500	9	12	15
Lactosa	120.60	120.60	120.60
Mg stearate	1.5	1.5	1.5
Talc	1.2	1.2	1.2

Granules and tablets evaluation

Flow rate and angle of repose were tested using a flowability tester. Granules (100 grams) were weighed and placed into a closed funnel. The funnel was then slowly opened, and the granules were allowed to flow. The time required (in seconds) for all granules to pass through the funnel was recorded using a stopwatch. From these data, the flow rate of the granules was calculated. After that, the angle of repose of the granules was calculated (11).

Compressibility index tested using volumenometer. The granules were put into a glassware until reached a volume of 100 ml (Vo), and then the glassware was placed in

a volumenometer. The volume change that occurred during tapping was recorded as (Vt). The compressibility of the granules was calculated ((Vo-Vt)/Vo))x100% (11).

The organoleptic test includes an assessment of the shape, color, and smell of the tablet. This test is carried out simply by observing the tablet visually (12,13).

The weight uniformity of tablet test is carried out by weighing 20 tablets to calculate their average weight. During this test, no more than two tablets should have a weight that exceeds the limit specified in column A (5%) of the average weight. In addition, no tablet should have a weight that deviates more than the limit specified in column B (10%) of the average weight (14).

Tablet hardness was tested using a hardness test. The samples used were 6 tablets. The tablet was placed in the middle of the hardness tester and then pressed until the tablet appeared cracked (15,16).

The friability of tablet test using friability tester. 20 tablets were cleaned and weighed before the tablets were tested. Furthermore, the tablets were put into the friability tester and run for 100 rotations or 4 minutes at a speed of 25 rpm. After the testing process was complete, it was cleaned and weighed. The percentage of tablet friability was calculated (10,16).

The disintegration time of tablet test using a disintegration tester. One tablet was placed in each of the six tubes in the disintegration time tester. Furthermore, the test medium is distilled water (37–39°C). The time required for all tablets in the basket to disintegrate must be calculated.

Selection of the best formula

Selection of the best formulation based on suitability of physical property requirements and considering statistical tests using one way ANOVA (Analysis of Variance) with a confidence level of 95%.

Results and Discussion

Gnetum gnemon L. peel extraction

Gnetum gnemon L. fruit (9 kg) contains peel (3 kg). The weight of the *Gnetum gnemon* L. peel obtained after the drying and pollination process was 970 grams. The results of the water content test of the Gnetum gnemon peel simplicia were 9.10%. The water content of the simplicia was appropriate (<10%) (17). Maceration was using ethanol 96%. It is universal solvent that can dissolve both non-polar and polar compounds. Extraction produces 187,79 gram and the yield is 19.35%. The results of the water content test of the *Gnetum gnemon* L. peel extract was 21.65%. The water content of the extract was appropriate (5-30%) (18). The results of identifying compounds in the extract indicate the presence of flavonoid compounds. This is indicated by a change in the color of the solution to red when magnesium powder and concentrated hydrochloric acid are added to the extract (19).

Tablet formulation

Gnetum gnemon L. extract was formulated into tablets. The dosage of active substances used in each formula of this study was 25.48 mg/tablet, this dosage was used because based on the effectiveness of this dosage it can be used as an antihypercholesterolemic. The *Gnetum gnemon* L. peel extract was made into tablets using the wet granulation method. This method was chosen to improve the material's flow properties and compression ability. The granulation results are shown in Figure 1. While the tablet compression results are shown in Figure 2.

Figure 1. Gnetum gnemon L. peel extract granules

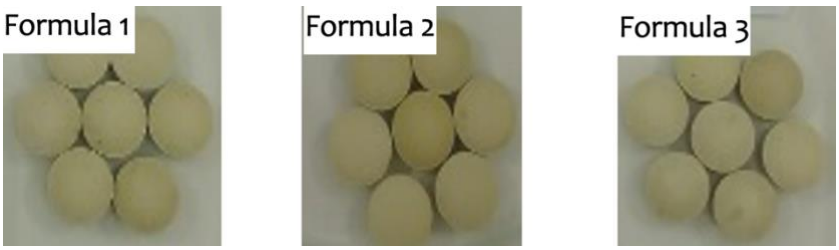

Figure 2. Gnetum gnemon L. peel extract tablets

Granules and tablets evaluation

Granule evaluation aims to determine the flow properties of the granules. Granule flow properties are determined through flow rate, angle of repose and compressibility index. It is related to the physical properties of the tablets to be produced. The results of the granules evaluation are shown in Table 3. Flow rate test measures the time required for some granules or powders to flow through a particular tool. This test is important because it is directly related to the uniformity of filling the tablet molding chamber. The results of the flow rate test affect the uniformity of weight and active ingredient content in the processed tablet, thus affecting the quality and consistency of the final tablet (20). The flow properties of granules are divided into four categories, it is free flowing, easy flowing, cohesive, and very cohesive (21). Based on these categories, all formulas are included in the easy flowing category (4-10 g/s). The angle of repose test is carried out indirectly by measuring the height of the granules and the diameter of the granules resulting from the flow properties of the granules. The angle of repose indicates the presence of friction between particles or resistance to movement between particles (22). The angle of repose is divided into four categories, it is excellent, good, passable, and very poor (21). Based on these categories, all formulas are included in the good category (20-30°). The compressibility index has been proposed as an indirect measure of bulk density, size and shape, surface area, moisture content, and materials

cohesiveness because these can influence the observed compressibility index (20,22). The compressibility index of granules is divided into six categories, it is excellent, good, fair to passable, poor, very poor and extremely poor (21). Based on these categories, all formulas are included in the excellent category. Based on the results of the granule evaluation, it was shown that the higher the Na-CMC and the lower the starch 1500 concentration would increase the flow rate, decrease the angle of repose, and also the compressibility index. Fines, cohesiveness, and particle size influence the flow properties of granules. A low percentage of fines indicates that the granules have good flow properties. The smaller the particle size, the larger the surface area so the greater the cohesion and adhesion, it will produce poor flow properties (23,24). Na-CMC and Starch 1500 have opposite functions in this formulation. Na-CMC has a mechanism to bind powder and form granules. When the concentration of Na-CMC is high and starch 1500 is low, it produces granules with a low percentage of fines and produces good granules. Overall, the flow properties of granules, formula 1 has the best flow properties.

Table 3. Granules and tablets evaluation

Evaluation		Formula 1	Formula 2	Formula 3
Granules	Flow rate	6.78±0.07 g/s	6.54±0.11 g/s	6.13±0.05 g/s
	Angle of repose	27.10±0.31°	28.38±0.34°	29.31±0.16°
	Compressibility	3.00±1.00%	6.00±1.00%	10.00±1.00%
Tablets	Organoleptic	Shape: Flat Round Colour: Light Green Smell: Extract	Shape: Flat Round Colour: Light Green Smell: Extract	Shape: Flat Round Colour: Light Green Smell: Extract
	Weight uniformity	No two tablets deviated by 5% and no single tablet deviated by 10%	No two tablets deviated by 5% and no single tablet deviated by 10%	No two tablets deviated by 5% and no single tablet deviated by 10%
	Hardness	5.74±0.43 kg	3.03±0.42 kg	1.31±0.27 kg
	Friability	0.43±0.01%	5.7±0.11%	8.78±0.64%
	Disintegration time	8.48 ±0.28 minutes	4.02±0.38 minutes	1.08±0.11 minutes

Tablet evaluation aims to determine the quality of tablets produced through organoleptic tests, weight uniformity, hardness, friability, and disintegration time. The organoleptic test aims to observe visually. It is shape, colour, and smell to determine the characteristics of the tablet. The results show that all formulas have the same organoleptic test. The weight uniformity test aims to determine deviations in tablet weight and ensure uniformity of active substance. Tablets with an average weight of 500 mg, should not be more than two tablets that deviate more than 5% from the average weight and no one tablet should deviate more than 10% from the average weight (14). All formulas meet weight uniformity requirements. Tablet hardness test aims to evaluate the physical resistance of tablets to mechanical stress, such as shocks and pressure during shipping or packaging, which can cause cracking or crushing to the tablet. The requirement for tablet hardness is 4-8 kg (25). Formula 1 is appropriate for these requirements. The tablet friability test is a parameter that describes the strength of the tablet surface in resisting various treatments that cause abrasion on the tablet

surface. The greater the percentage of friability, the greater the mass of the tablets lost and affects the level of active substances. The tablet friability test requirement is <1% (26). Formula 1 is appropriate for these requirements. The disintegration time test aims to determine the time it takes for a tablet to disintegrate into small particles when in contact with a liquid medium. The tablet disintegration time requirement is <15 minutes (26). Based on the results of the tablet evaluation, it was shown that the higher the Na-CMC and the lower the starch 1500 concentration would decrease friability, increase hardness, and also disintegration time. Na-CMC as a binder and starch 1500 as a disintegrant have opposite functions in this formulation. The higher the concentration of the binder, the greater the attractive force between the powder particles so that the particles will be arranged more tightly (27). Starch 1500 as a disintegrant has a swelling mechanism which causes the particles to expand, and then the tablet is crushed (28). Overall, formula 1 has the best tablet evaluation.

Selection of the best formula

The selection of the best formula in the preparation of *Gnetum gnemon* L. peel extract tablets is based on the evaluation of physical properties (granules and tablets) and statistical analysis. The results of the consideration of the best formula are shown in Table 4. Flow rate test of granules all formulas do not have appropriate requirements but are still classified as easy to flow. Formula 2 and 3, the hardness and friability of the tablets do not appropriate the requirements. Formula 1 is the best with a combination of Na-CMC and starch 1500 is 5%:6%.

Table 4. Granules and tablets evaluation

Evaluation	Formula 1	Formula 2	Formula 3	Properties
Flow rate	-*	-*	-*	all formulas are not appropriate for the requirements (>10g/s) but it is included in the easy flowing category (4-10 g/s)
Angle of repose	√*	√*	√*	all formulas are included in the good category (20-30°). Formula 1 is the best angle of repose.
Compressibility index	√*	√*	√*	all formulas are included in the excellent category. Formula 1 is the best compressibility index
Organoleptic	√	√	√	all formulas have the same characteristics
Weight uniformity	√	√	√	all formulas are not appropriate to the requirements.
Hardness	√*	-*	-*	only formula 1 is appropriate the requirements (4-8 kg)
Friability	√*	-*	-*	only formula 1 is appropriate the requirements (<1%)
Disintegration time	√*	√*	√*	all formulas are appropriate the requirements (<15 minutes)

(√) : Appropriate the requirements; (-) : Does not appropriate the requirements; (*) : Significant for each formula

Conclusion

The combination of Na CMC as binder and starch 1500 as disintegrant affects the physical properties *Gnetum gnemon* L. peel extract granules and tablets. The best combination of Na CMC and starch 1500 is 5%:6%.

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