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Physical and Chemical Characterization of Granules from 70 % Ethanol Extract of Ganitri Leaves (*Eleocarpus serratus* L.) using Wet Granulation Method as An Anti-Osteoporosis

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Abstract

Elaeocarpus serratus L. leaves have been used as an antiosteoporosis treatment and it contains active compounds such as quercetin, rutin, and myricetin. The pre-formulation study was done by making granules from 70 % ethanol extract of this plant through the wet granulation method. These granules were determined by physical characteristics including organoleptic, flow properties, real and incompressible specific gravity, moisture, particle size distribution, and chemical characteristics including flavonoid content. The organoleptic result showed that all formulas had a strong characteristic odor and a slightly bitter taste. Formula A had a dark brown color, while formulas B and C were whitish brown. Based on the results of the flow properties test, all formulas had good flow properties because they had gone through the granulation process. The compressibility index, Hausner ratio, and % moisture content displayed that all formulas met the requirements and had almost the same value. In the assay process, the average % w/w content of formula A was 0.68 ± 0.017 %, formula B was 0.66 ± 0.044 %, and formula C was 0.16 ± 0.006 %. The most optimum formula was formula C with whitish brown color, slightly bitter taste, and strong odor, 10.90 ± 0.000 g/s of flow rate, 25.41 ± 0.000 ° of angle, 4.36 ± 0.214 % of moisture content, 13.80 % compressibility index, 1.1601 of Hausner ratio, 1772.04 µm of particle average distribution, and 0.66 ± 0.044 % w/w of percent routine flavonoid content.

Keywords: *Elaeocarpus serratus* L., Physical and chemical characterization, Wet granulation, Osteoporosis

Introduction

Osteoporosis is a bone disorder characterized by low bone density, damage to bone architecture, and weak bone strength which predispose to fractures [1]. The prevalence of osteoporosis is known to be increasing, so serious efforts need to be made to overcome the occurrence of osteoporosis [2]. Pharmacological actions that can be given to overcome these conditions are therapy by bisphosphonate, calcitonin, denosumab, estrogen, and strontium ranelate [3]. However, some of these pharmacological therapies provide uncomfortable side effects that can even harm the patient, such as bisphosphonates cause disturbances in the GIT and estrogens increase the risk of breast cancer and heart disease [1], so replaced by using herbal therapy which has fewer side effects.

Elaeocarpus serratus L., known as ganitri in Java [4] or Rudraksha in India [5] used as an anti-osteoporosis therapy and increased Alkaline Phosphatase (ALP) enzyme [6]. This enzyme plays a role in catalyzing monophosphate esters in the plasma membrane into phosphatidyl-glycolipid anchors in the process of bone formation [7]. The leaves of this plant contain flavonoids, namely quercetin, rutin, and myricetin which have an anti-osteoporosis effect by increasing osteoblast and decreasing osteoclast activity [8]. Osteoblasts play a role in the process of bone mineralization and are also associated with matrix-making [9]. Based on research by Hyun *et al.* (2014), rutin was used as an osteoblast stimulant by increasing cell proliferation, ALP enzyme, Ca^{2+}, and collagen to 95, 150, 112.3, and 126.6 %, respectively, when given 25 g/mL routinely [8].

Thus, it is necessary to develop more attractive and diverse drug dosage forms such as pills, tablets, and capsules. Raw materials were extracted by maceration method using 70 % ethanol which was then carried out by a drying process. The use of 70 % ethanol is more polar than 96 % ethanol [10] so it is easier to attract routine compounds including flavonoid glycosides which are more polar [11]. In addition, ethanol is a universal solvent that can filter both polar and non-polar compounds with a wide polarity [12]. Then extract was dried with the addition of a drying agent and evaporation was carried out to remove the solvent contained in the extract [13].

The preparation development used dry extract has properties that easily attract moisture [14] and it affects the characteristics of the extract such as poor flow properties. Therefore, it is necessary to develop the granule form of the dry extract. Granules form has advantages such as mixture more homogeneous, improving the compression characteristics of the active ingredients, reducing dust, and compacting the material [15]. Then granule form can be made in capsules or tablets [16]. The preparation of granules was carried out using the wet granulation method which right choice for the development of preparations derived from plant extracts because the use of a binder in this method causes the powder particles to have high adhesion to form a regular mixture and form a cohesive network. In this granulation process, the flowability of the powder particles will be better [17]. In this manufacture, a binder in the form of PVP-K30 is used because it can produce granules that have good flow properties, minimum angle of repose, minimum % fines, and good compatibility [18].

Granules derived from extracts of natural ingredients will be developed into medicinal preparations, so that data related to their physical and chemical characteristics must be known. These data include organoleptic data, flow properties, particle size distribution, specific gravity and compressibility index, moisture, and content of active ingredients. The characteristic test must meet the specified requirements [19]. This research aims to determine the optimal formula for granule formulation of Eleocarpus serratus extract using the wet granulation method as an anti-osteoporosis.

Materials and methods

Materials

The materials used in this study were *Elaeocarpus serratus* L., aquadest, Namaste ethanol 70 % (pro analysis), Ethanol 96 %, Cabot cab-o-sil® fumed silica, Plasdone K-30 (PVP K-30), sodium 1M acetate and 10 % aluminium chloride P. The equipment used in this research are analytical balance, rotary evaporator, Buchner funnel, stopwatch, oven, sieve, moisture analyzer, UV-spectrophotometry, grinding tools, and glassware.

Preparation of leaf extract of *Elaeocarpus serratus* L.

The leaves of the ganitri were obtained from the Baung Forest, Purwodadi, and then were dried in the air. A total of 3 - 4 kg of this plant was macerated with ± 40 L of 70 % ethanol until all the powder was completely submerged for 1 day. Then it was filtered using a Buchner funnel to obtain the filtrate and then macerated again on the remaining residue until a constant % brix value was obtained (3 times maceration). In the second maceration and so on, the addition of solvent is as much as half of the amount of the first solvent. All the filtrate obtained was mixed with a drying agent, namely Cab-O-Sil as much as 5 % of the weight of dissolved solids. Furthermore, evaporation is carried out using a rotary evaporator to obtain a dry extract.

Granule making

The wet granulation method was carried out by pouring the dry extract into a mortar with the PVP K-30 binder which has made mucilage into a mass of granules with strong grinding until a mass of granules is obtained that is easy to clench and when broken no mass falls out. After obtaining a good granule mass, then sieved with a 1.8 mm sieve. Then the granules were dried using an oven at a temperature of 40 - 60 ° for ± 2 h until the granules were dry with a moisture content below 5 %. Next, the dried granules were sieved using a 1 mm sieve.

Granule characteristic test

Organoleptic test

An organoleptic test was carried out to determine the physical appearance of the dry extract by determining the assessment through visual observation of color, taste, and smell.

Flow properties test

The flow properties test was carried out by flowing as much as 25 g of granules in a glass funnel with a simple lid at the bottom. After that, the time taken for the granules to leave the funnel was recorded after the funnel cover was opened. The flow rate is calculated by dividing the mass of the powder by the time it takes the powder to leave the funnel. The calculation of the angle of repose is measured from the ratio between the height and the radius of the cone of powder coming out of the funnel [20]. Granules that have good flowability and are free have a flow rate of 10 s [21]. A good flow rate is not less than 4 g/s [22]. The angle of repose is calculated using the following formula:

Tan (α) = powder height (cm)/powder radius (cm)

Density and compressibility index

The real specific gravity test was carried out by measuring ± 25 g of extract granules into a measuring cup. Meanwhile, the compressive density test was carried out by measuring ± 25 g of extract granules into a measuring cup (there should be no shaking in pouring), leveling the surface of the powder, and reading the volume of powder in the measuring cup as a real volume. Then it was knocked using a tapped density tool with 500 beats and the first beat read as the volume of the powder (A). The second knocking was repeated 1250 times and the volume of the powder produced by the second tap was read as volume (B). If the difference between volume (B) and volume (A) was not more than 2 cm^3 then A was a compressed volume, but if the difference between the 2 volumes was more than 2 cm^3 then the beat was repeated as above until a volume that remains by the requirements (not more than 2 cm^3). For the calculation of % compressibility can be calculated using the following formula:

% Compressibility = Compressed density – Real density/Compressed Density × 100%

Particle size distribution test

The degree of fineness test was carried out by passing 100 g of powder on a sieve with certain sizes arranged sequentially from the largest hole size to the smallest hole and given mechanical vibration. The particles distributed on the sieve were then calculated by weighing the sieve and the powder in it minus the weight of the empty sieve [20].

Moisture content test

The moisture content of the granules was tested using a *moisture analyzer*. The examination was carried out by weighing as much as 0.5 g of granules which had been levelled and placed in a sample container from the moisture content balance. Position the heating lamp just above the material. Then the % MC of the granule will be known. The drying process is said to be perfect if after 3 experiments a constant weight of the material is obtained. The moisture content in good granules is between 2 - 5 % [18].

Determination of total flavonoid level

1) Preparation of test solution for granules Approximately 0.3 - 0.4 g of granules were added with 25 mL ethanol P and stirred using a magnetic stirrer for 30 min. Then the solution was filtered.

2) Preparation of comparison solution A ± 25 mg of comparator was added ± 20 mL ethanol and stirred homogeneously. Then the comparison solution was diluted to 50, 100, 150, 200, 250, and 300 g/mL.

3) Procedure Each 0.5 mL of test solution and reference series solution was added with 1.5 mL ethanol P, 0.1 mL aluminum chloride P 10 %, 0.1 mL of 1M sodium acetate, and 2.8 mL of water. Then each solution was shaken and allowed to stand for 30 min at room temperature and measured the maximum wavelength. The blank was measured in the same way, without the addition of aluminum chloride, then made a calibration curve and calculated the concentration of the test solution.

Results and discussion

In this study, a drying agent (Cab-O-Sil) was used in dry extracts to reduce their hygroscopicity and as an adsorbent. The concentration of Cab-O-Sil was optimized at 3 concentrations, 5, 10, and 20 % (**Table 1**), and Cab-O-Sil at 5 and 10 % could not flow. However, Cab-O-Sil at 20 % had a flow rate of 0.367 g/s and an angle of repose of 7.885 °. Cab-O-Sil as a drying agent in high concentration affects the compatibility of powder and the process of releasing the active ingredients in the extract because the bounding between extract and drying agent becomes strong and the therapeutic effect is not achieved. Thus, the concentration of 5 % Cab-O-Sil was chosen.

Table 1 Granule preparation formula.

Composition	Formula		
	A	**B**	**C**
Dried extract of *E. serratus* L.	50 g	50 g	50 g
Cab-O-Sil	5 %	10 %	20 %
PVP K-30	3 %	5 %	5 %

A binder (PVP K-30) was added in granules to increase the cohesiveness of the bonds between particles and increase the magnification of the particles in the granulation process. PVP K-30 has good binding capacity and low viscosity, so it has good distribution in granules and good homogeneity. In addition, PVP at 5 % produced granules with good compression power [23,24]. So in this formula, the difference in concentration of 3 and 5 % was used and wet granulation was used to improve the flow properties and compatibility of the material [24].

The organoleptic test was carried out by color, taste, and smell of granules. Formula A had a dark brown, while formulas B and C were whitish brown with the smell of each formula was a strong odor. Formulas A, B, and C had a slightly bitter taste (**Table 2**).

Table 2 Organoleptic test results for granules extract of *Elaeocarpus serratus* L.

Formula	Flavour	Colour	Smell
Formula A (Powder with Cab-O-Sil 5 % + PVP K-30 3 %)	Slightly bitter taste	Dark brown	Special strong extract
Formula B (Powder with Cab-O-Sil 5 % + PVP K-30 5 %)	Slightly bitter taste	whitish brown	Special strong extract
Formula C (Powder with Cab-O-Sil 20 % + PVP K-30 5 %)	Slightly bitter taste	whitish brown	Special strong extract

The flow properties test was carried out by flowing 25 g of granules through a standard funnel with 3 repetitions. The requirement for a good granule flow time was < 10 s. Based on the results (**Table 3**), formula B had the best flow rate, followed by formulas A and C. Differences in the use and types of fillers affected the mass flow rate of the powder and there was a significant difference between formulas A, B, and C with a value of 0.000 ($p < 0.05$). It indicated that there was an effect of using Cab-O-Sil and PVP K-30 in the granulation process on the flow rate of the preparation. The result of the angle of repose test (**Table 4**) showed that formula C had the best angle compared to formulas A and B and the best range between 25 - 30 °. If the angle of repose < 25 ° indicates that the material can flow freely. The statistical calculations were carried out using the one-way ANOVA method and obtained a significant value of 0.000 ($p < 0.05$).

Table 3 Average flow velocity test results.

Formula	Average flow time (s)	Average flow rate (g/s)
Formula A (Powder with Cab-O-Sil 5 % + PVP K-30 3 %)	2.92	8.58 ± 0.000
Formula B (Powder with Cab-O-Sil 5 % + PVP K-30 5 %)	2.30	10.90 ± 0.000
Formula C (Powder with Cab-O-Sil 20 % + PVP K-30 5 %)	1.41	7.20 ± 0.029

Table 4 Test results mean angle of repose (α).

Formula	Average angle of repose (°)
Formula A (Powder with Cab-O-Sil 5 % + PVP K-30 3 %)	24.07 ± 0.548
Formula B (Powder with Cab-O-Sil 5 % + PVP K-30 5 %)	25.41 ± 0.000
Formula C (Powder with Cab-O-Sil 20 % + PVP K-30 5 %)	18.00 ± 0.000

The density and compressibility test were carried out by calculating the mass of several granules per volume of granules in a measuring cup before tapping and after tapping using tapped density (**Table 5**). Based on the compressibility index test, it was known that there are differences in the value of each formula, this was due to the presence of additional ingredients with different concentrations of use in each formula. Their difference caused differences in moisture content in each formula and the shape and size of the granules. Granules that had a compressibility index in the range of 11 - 15 % had good flow properties. The compressibility test meets the requirements if their percent value is < 20 % [25]. The size of the compressibility index in a formula is also influenced by the shape and size of the granules that are affected by additives. Based on the measurement of the water content test, formula B showed a higher water content than formulas A and C. The moisture content affected the compressibility index and mass flow properties of the granules. The high moisture content causes the cohesive force to be stronger so that the granules are increasingly difficult to flow [26]. The Cab-O-Sil concentration of formula C was very large (20 %) and had a fairly high hygroscopicity, causing formula C to be more moist than formulas A and B. Therefore, formula A has an index better compressibility than formulas B and C.

Table 5 Test results of real specific gravity, incompressible density and compressibility index.

Formula	Real density	Compressed density	Compressibility Index (%)
Formula A (Powder with Cab-O-Sil 5 % + PVP K-30 3 %)	0.3166 g/mL	0.3733 g/mL	15.19 %
Formula B (Powder with Cab-O-Sil 5 % + PVP K-30 5 %)	0.4315 g/mL	0.5006 g/mL	13.80 %
Formula C (Powder with Cab-O-Sil 20 % + PVP K-30 5 %)	0.2703 g/mL	0.3030 g/mL	10.79 %

The particle size distribution test is carried out using a stratified sieve which is carried out by mechanical vibration. Based on **Figures 1** and **2**, it was known that formula A had a smaller average particle size than formula B, so the finer particle size, the flow rate will decrease. This is due to the greater cohesiveness between particles. The distribution of granule particle size affects the flowability of granules and the variation in the weight. Fine powder is needed to fill the void between particles and to help form physical bonds that act as bridges between larger particles.

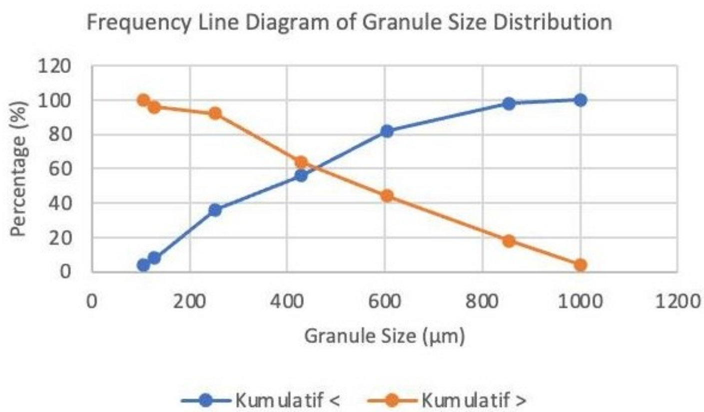

Figure 1 Frequency line diagram of the granule size distribution of formula A.

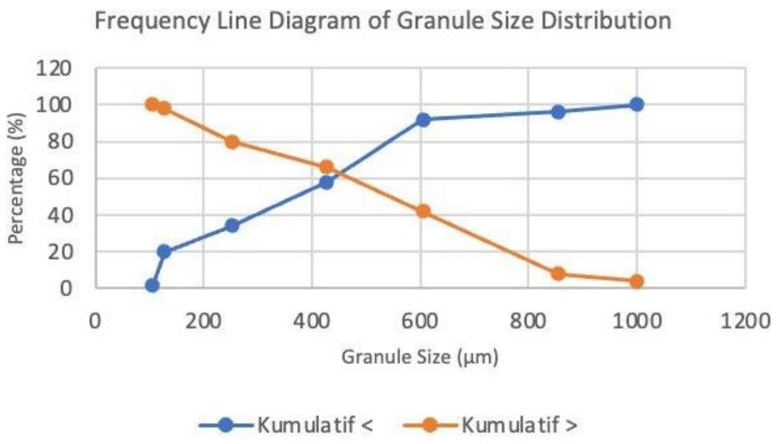

Figure 2 Frequency line diagram of the granule size distribution of formula B.

The moisture content test was carried out by inserting approximately 0.5 g of granules into the moisture analyzer. Based on **Table 6**, it was known that formula B had a greater moisture content than formulas A and C and met the % moisture content requirement between 2 - 5 % [18]. Their difference was due to the different concentrations of the drying agent and binder in each formula. High water content reduces the stability of a product, and the size of the moisture content affects the flow rate of the granules. The lower the moisture content had a higher low rate.

Table 6 Moisture content/MC test results (%).

Formula	Moisture content/ MC (%)
Formula A (Powder with Cab-O-Sil 5 % + PVP K-30 3 %)	2.83 ± 0.141
Formula B (Powder with Cab-O-Sil 5 % + PVP K-30 5 %)	4.36 ± 0.214
Formula C (Powder with Cab-O-Sil 20 % + PVP K-30 5 %)	3.51 ± 0.301

Determination of the total flavonoid was carried out using the spectrophotometric method. Based on **Table 7**, it was known that the rutin contained in both preparations, before granulation (dry extract) and after granulation (Formula A, B, and C). Formula C had a very small average level of total flavonoid (0.16 % w/w) because the concentration of Cab-O-Sil was quite high (20 %). It affects the release of compounds in the granules and the levels of the formula. The level of rutin in an extract of E. serratus L. was 1.26 % w/w [27].

Table 7 Test results for routine flavonoid levels.

Formula	% w/w average
Formula A (Powder with Cab-O-Sil 5 % + PVP K-30 3 %)	0.68 ± 0.017
Formula B (Powder with Cab-O-Sil 5 % + PVP K-30 5 %)	0.66 ± 0.044
Formula C (Powder with Cab-O-Sil 20 % + PVP K-30 5 %)	0.16 ± 0.006

Conclusions

The physical and chemical characteristics of the 3 granule formulas meet the requirements and formula B was the most optimal formula (5 % Cab-O-Sil and PVP K-30) with a slightly bitter taste, whitish brown color, a strong characteristic odor, flow rate (10.90 ± 0.000) g/s, angle of repose (25.41 ± 0.000) °, % moisture content (4.36 ± 0.214) %, compressibility index 13.80 %, particle average distribution 1772.04 µm, and percent of routine flavonoid content was (0.66 ± 0.044) % w/w.

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