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Formulation and Physical Evaluation of *Orthosiphon aristatus* Leaf Extract Granule Preparation as Herbal Beverage Candidate

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ABSTRACT

Developing *Orthosiphon aristatus* (Blume) Miq. leaf extract of purple varieties into granule dosage forms is expected to facilitate consumption, storage, and can extend the shelf life of the product. This study aims to develop the formulation and evaluation of granule preparations of *O. aristatus* leaf extract of purple varieties, with a comparison of lactose and maltodextrin fillers to produce the best formula. The granule dosage forms were prepared using wet granulation method. Furthermore, the variation of granule preparation formula consists of F1 (extract with lactose), F2 (extract with maltodextrin), F3 (extract with a combination of lactose and maltodextrin 1:1), F4 (freeze dried extract with lactose), F5 (freeze dried extract with maltodextrin), and F6 (freeze dried extract with a combination of lactose and maltodextrin 1:1). The physical evaluation of granules comprised moisture content testing, flowability, compressibility index, particle size distribution, and granule dissolving time. Results from the physical evaluation of granules over 28 days of storage indicated that all six formulas met the criteria for good granules, with F3 emerging as the optimal formula due to its superior physical stability and visually appealing appearance upon dissolution. To conclude, this study demonstrates that *O. aristatus* leaf extract can be effectively formulated into instant granule preparations suitable for herbal beverage or alternative medicine. Moreover, by modifying the filler material, the physical stability of the granule preparation can be maintained.

Keywords: Lactose; Maltodextrin; *Orthosiphon aristatus* (Blume) Miq; Wet granulation

INTRODUCTION

Consuming traditional medicine is starting to be widely used for alternative therapy as a natural treatment for several therapies (Welz et al., 2018). The advancement of modern pharmaceutical technology encourages the transformation of traditional medicine research into pharmaceutical technology in several pharmaceutical dosage form. Therefore, this transformation aims to enhance the efficiency and effectiveness of traditional medicine usage, while also striving to ensure uniformity in the content of active efficacy ingredients, and also to enhance patient compliance with treatment. One of the plants that has the potential to be developed in traditional medicine is *Orthosiphon aristatus* (Blume) Miq (Chai et al., 2014).

O. aristatus plants have been known to have pharmacological activities as antioxidant, anti-inflammatory, antimicrobial, anti-angiogenic, antihypertensive, analgesic, hepatoprotective and hypoglycaemic (Chai et al., 2014). Traditionally used to treat several health problems, one of which helps the problem of difficulty urinating, diabetes, rheumatism, arthritis, gouty arthritis and kidney diseases (Alshehade et al., 2023). *O. aristatus* plants are classified into three varieties based on their flower morphology: the purple variety, the white-purple variety and the white variety (Febjislami et al., 2019). It is known that rosmarinic acid, eupatorin and sinensetin are the three main types of secondary metabolite compounds in *O. aristatus* (Guo et al., 2019). Purple varieties contain the most secondary metabolite compounds when compared to white varieties and have the highest rosmarinic acid and sinensetin levels, while white-purple varieties have the highest levels of eupatorine (Faramayuda et al., 2021).

The extract obtained from the extraction process for direct consumption with a certain dose is still not considered to be the best solution, because it provides an unattractive appearance and texture of clay and even a bitter taste that may appear due to extracts containing a mixture of several components in it. Consequently, it can interfere with comfort in use as an alternative therapy for a disease. To address these limitations, there's a necessity for advancement into more modern pharmaceutical technology. Developing the extract into a dosage form holds promise in creating a more effective and efficient preparation of natural ingredients, ultimately enhancing c

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comfort and safety in its use. One of the efforts made is to make it into a granule dosage form.

Granules are multiunit preparations in the form of agglomerates of powder particles. Granulation is the process of transforming the shape of small particles (powders) into large lumps (granules) of a certain size. Granulation methods consist of wet granulation and dry granulation. This study uses the wet granulation method, the advantages of wet granulation include being able to modify the properties of the formulation material to overcome the shortcomings of the material, since the granules produced tend to be rounder than powders, have better flow properties, ensure better content uniformity especially for low dose drugs (Shanmugam, 2015). Granule dosage form is relatively more practical, stable to moisture, and easy to consume for steeping beverages (Wardhana et al., 2021).

Previous research explained the development of granule preparation formulations based on herbal ingredients using the wet granulation method obtained more efficient results in making granules that have lower sensitivity to moisture (De Souza et al., 2009). Furthermore, related research also reported that granule preparations are suitable for clinical application due to their safety and easy of control, production, and management as consistent medical products, in contrast to boiled herbs (decoction). The formulation of granule preparations that can be used as herbal-based brewed health drinks generally requires several additional ingredients, including binding agents, filling agents, crushing agents and sweetening agents (Jassim et al., 2018).

This study uses lactose and maltodextrin excipients as a comparison for fillers, both of which are easily soluble in water and relatively cheaper. The purpose of adding maltodextrin as a filler is to enlarge the volume, quicken the drying process, and increase the dissolution rate of instant beverages (Yanti et al., 2022), while lactose can be neutral which hardly reacts with all medicinal ingredients, and also help increase a good flow rate and is physically and chemically stable (Dominici et al., 2022).

Therefore, this study aims to develop formulations and physical evaluation of granule preparations of *O. aristatus* leaf extract purple varieties with a comparison of lactose and maltodextrin fillers to produce the best formula, which is expected to be a candidate for herbal beverages or as an alternative herbal-based treatment.

MATERIALS AND METHODS

Materials

The apparatus used include glassware commonly used in laboratories, analytical balances, macerator, oven, rotary evaporator, moisture analyzer (Amstech), Tapped Density Tester (TDTF ZS-2E), Flowability Tester (CS-2), and Shieve shaker. The materials used were purple varieties of *O. aristatus* leaves which were gathered from The Manoko Medicinal Plant Garden, Lembang, West Java and have been determined at Jatinangor Herbarium, Plant Taxonomy Laboratory, University of Padjadjaran (No. 23/HB/05/2023), water extract of *O. aristatus* leaf (freeze dried), 70% ethanol, and the materials used in the formulation are of pharmaceutical grade, which are lactose, maltodextrin, PVP K30 (polyvinyl pyrrolidone), sodium starch glycolate, and sucralose obtained from Brataco Chemika Indonesia.

Extract Preparation of *O. aristatus* Leaf Purple Variety

Maceration was carried out using 70% ethanol as a solvent, in a ratio of 1:4 (crude drug: solvent). The mixture was allowed to stand for 10-18 hours with occasional manual stirring at selected times. The obtained extract was concentrated using a rotary evaporator.

Extract Preparation of *O. aristatus* Leaf Purple Variety (Freeze-dried)

The *O. aristatus* leaves that had been cleaned and sorted were blended using a slow juicer with water solvent in a ratio of 1:1. Following a 60-mesh sieve filter, the filtrate was collected, put in an Erlenmeyer, and frozen for a period of 24 hours at -80°C. In addition, the procedure of freeze drying was executed for 48 hours at a temperature of -50°C (Tukiran et al., 2021).

Formulation of Granule Preparations of *O. aristatus* Leaf Extract

Preparation of granule formulations of *O. aristatus* leaf extract can be done using wet granulation method with modifications (De Souza et al., 2009). Granules were obtained by weighing each ingredient according to a predetermined quantity, as presented in Table I. The filling material was put into a mortar, *O. aristatus* extract added and crushed until homogeneous, then added other excipients according to the formula, dripped with 96% ethanol with crushed until homogeneous and the mass are clenched. The mixed mass was sieved using a 14- mesh sieve and then put into the oven at ±40^{0}C for 15 minutes. After obtaining the

Table I. Formulation of granule preparations of *O. aristatus* leaf extract purple variety

Materials	(% w/w)					
	F1	F2	F3	F4	F5	F6
Ethanol extract of *O. aristatus* leaf	5	5	5	-	-	-
Water extract of *O. aristatus* leaf (freeze dried)	-	-	-	5	5	5
PVP K30	5	5	5	5	5	5
Sucralose	0,2	0,2	0,2	0,2	0,2	0,2
Sodium Starch Glycolate	4	4	4	4	4	4
Maltodextrin	-	85,8	42,9	-	85,8	42,9
Lactose	85,8	-	42,9	85,8	-	42,9

dry granule mass, it was sieved again using an 18-mesh sieve. The resulting granules were stored in a tightly closed container and given silica.

Physical Evaluation of Granule Preparation of *O. aristatus* Leaf Extract

Organoleptic

The organoleptic observation was carried out by observing the granule preparation starting from the aroma, shape, color, and taste. The test was carried out by placing a number of granules on a cup and observing the shape, color, aroma and taste (Rani et al., 2021).

Moisture Content

The measurement of moisture content was executed by weighing the sample as much as 5 g, sprinkled evenly on an aluminum pan and inserted into the moisture analyzer and set at a temperature of $\pm 70^0$C. The percentage of moisture content is obtained until the tool is finished from the measurement (Husni et al., 2011).

Flow Rate and Angle of Repose

The flow rate test and the measurement of the angle of repose were carried out by weighing a sample of 50 g, then put into the funnel on the flow ability tester. The funnel cover was opened along with the calculation of time using a stopwatch until all the granules flowed out which was collected above the container. The time required by the granule to flow was recorded. To determine the angle of repose, the height of peak and base circle diameter of the granule mound were recorded (Carr, 1965; Mirhosseini & Amid, 2013). The angle of repose is calculated using the formula below:

$$Angle\ of\ repose\ (tan\ \theta) = \frac{H}{R} \quad \text{.....(1)}$$

H is the height of the cone formed after full flow and R is the radius of the cone used to determine the angle of repose.

Compressibility Index

The percentage of compressibility index was obtained by weighing a sample of 50 g, putting it into a 100 mL measuring cup, then measuring its volume (*Vo*). The cup containing samples was then tapped 10, 500 and 1250 times using a Tapped Density Tester, thus obtaining the tapped volume (*Vf*) (Carr, 1965; Mirhosseini & Amid, 2013). *Vo* is the bulk density and *Vf* the final tapped volume. The compressibility index was then calculated using the following formula:

$$Compressibility\ index\ (\%) = \frac{Tapped\ density - Bulk\ density}{Tapped\ density}\ x\ 100 \quad \text{.....(2)}$$

Particle Size Distribution

Particle size distribution was determined by weighing a 50 g sample of granules, which were then placed into a sieve shaker equipped with a standard sifter containing a suitable pan and lid. The sieves were shaken in a horizontal rotation direction for 20 minutes, then carefully weighed the amount of granules left in each sieve with different sizes and in the collection pans (Kemenkes RI, 2020).

Granule Dissolving Time Test

The granule dissolving time test was conducted by weighing a number of several samples and dissolving them in water at a ratio of 1:10 (sample of solvent), with constant stirring using a magnetic stirrer at 50°C and a speed of 120 rpm. Subsequently, the dissolution time of the sample in water was measured using a stopwatch. The optimal dissolution time for the granules, as per previous studies(Husni et al., 2011; Kusuma et al., 2018), is less than 5 minutes.

RESULTS

The organoleptic observation of the ethanol extract of *O. aristatus* leaf ethanol extract showed that the extract was a very thick liquid, dark green

in color, had a distinctive aroma, and a bitter taste. Meanwhile, the water extract of *O. aristatus* leaf (freeze dried) showed a liquid form with a viscosity below the ethanol extract of *O. aristatus* leaf, dark green in color, had a distinctive aroma, and a bitter taste.

Organoleptic

The organoleptic observation of *O. aristatus* leaf extract granules showed that F1, F2, and F3 showed yellow color, no aroma and sweet taste. While for F4, F5, and F6 granules show greenish-yellow color, no aroma, and sweet taste (see Figure 1). The physical color difference of granules produced from the extract base form was influenced from the granulation process and was expected from the color mixture of excipients used which is common. The formation of solids by granulation can introduce color variations in the granule (N'Dri-Stempfer et al., 2004).

Moisture Content

The measurement of moisture content was carried out to ensure that the granules that have been prepared can qualify for good moisture content and to minimize the occurrence of microbial growth. Moisture content is also a factor determining the quality of granules that allow microbial contamination and can damage the physical and chemical stability of the material (Jung et al., 2018). The results of the moisture content measurement (see Figure 2a), showing that the different fillers in the preparation of granules affected the moisture content of the granules produced, where the moisture content of granules with maltodextrin fillers was higher than the moisture content of granules with lactose fillers and a combination of lactose-maltodextrin (1:1). This is comparable to a study of Nawatila *et al*., (2020), which shows that granule preparations with maltodextrin fillers had high enough moisture which is slightly hygroscopic. However, the granule preparations of *O. aristatus* leaf extract from the six formulas meet the criteria for granules that have a moisture content of not more than 10% (BPOM RI, 2019).

Flow Rate Test

The flow rate test aims to establish the ability of the flow speed of a mixture of materials and determine the cohesiveness of the powder mixture. The results of the flow rate test on the 28th day of each formula showed F1 (6.3 g/s ± 0.13); F2 (5.0 g/s ± 0.21); F3 (7.8 g/s ± 0.13); F4 (6.9 g/s ± 0.07); F5 (7.4 g/s ± 0.14) and F6 (6.0 g/s ± 0.05). The flow rate test results of the six formulas as a whole from the beginning of manufacture to the last test have a flow rate in the range of 4.0 - 8.0 g/s which indicates good flowability. A good flow rate time value is above 4 g/s (Aulton, 2002), and good granule flow is if the time required to flow 100 grams is no more than 10 seconds (Carr, 1965).

Dissolving Time of Granule

The granule dissolving time test aims to determine how long it requires for the granule to dissolve completely in water. The results of testing the dissolving time of *O. aristatus* extract granule preparations (see Figure 2b). The dissolving time obtained for the six formulas shows that all formulas meet the criteria for good granule dissolving time, where the granules completely dissolve in less than 5 minutes (Yanti et al., 2023). The selection of excipients in the form of water-soluble components is also a consideration in the preparation of instant granules, because it can produce granules that dissolve easily and not produce sediments (van der Merwe et al., 2020).

Angle of Repose

The measurement of the angle of repose aims to determine the flow properties of the granule. The measurement results of the angle of repose of *O. aristatus* leaf extract granule preparations from the six formulas (see Figure 3). which showed good granule flow properties during 28 days storage at room temperature with a value of less than 32°. The good flow properties if the angle of repose value was in the range of 25° to 35° and if the angle value was more than 45° then the granule flow properties are declared poor, as presented in Table II. The angle of repose value is influenced by particle size, the larger the particle size, the smaller the angle of repose and indicates the better the granule flows (Florenly et al., 2023).

Compressibility Index

The measurement of the compressibility index percentage aims to determine the granule's properties in forming a stable and compact mass when given a certain pressure, and becomes a parameter to forecast the powder flow characteristics. The compressibility index was determined by measuring the bulk volume and final tapped volume of the granule. The results of the compressibility index measurement of *O. aristatus* leaf extract granule preparations (see Figure 3), where F3 and F5 can be said to be stable during 28 days storage at room temperature by showing a compressibility index percentage below 20% which is included in the "fair" flow properties category compared to other formulas (see Table II). However, if traced to measurements on each

Figure 1. Physical appearance of granule preparations that contain ethanol extract of *O. aristatus* leaf (F1, F2, F3), and water extract of *O. aristatus* leaf (F4, F5, F6) as herbal beverage candidates.

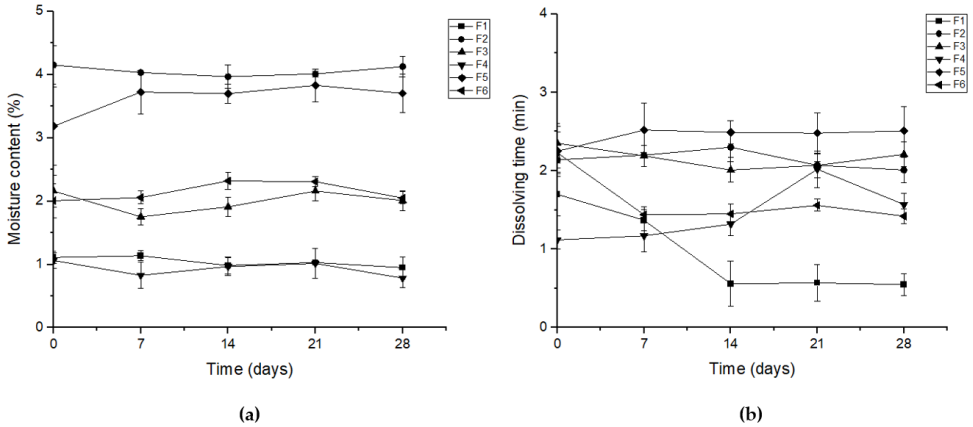

Figure 2. Evaluation of granule preparation of *O. aristatus* leaf extract on (a) moisture content, and (b) granule dissolving time during 28 days storage at room temperature.

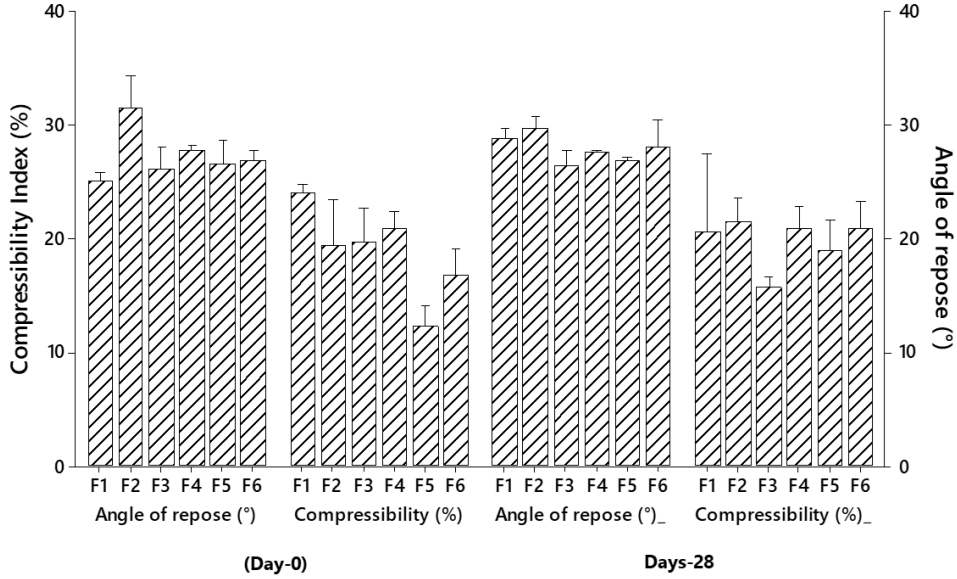

Figure 3. Evaluation of granule preparation of *O. aristatus* leaf extract on the compressibility index (%) and angle of repose (°) in the first and the final measurement of granule preparation.

week, the data were not attached. In F3, the results of measuring the percentage of compressibility index results starting from the day of preparation of the granule until the third week showed "fair" flow properties with a compressibility index of ≤20%, and in the last week showed "good" flow

Table II. Flow properties based on compressibility index and angle of repose (Carr, 1965)

Compressibility index (%)	Flow properties	Angle of repose (°)
≤10	Excellent	25 – 30
11 – 15	Good	31 – 35
16 – 20	Fair	36 – 40
21 – 25	Passable	41 – 45
26 – 31	Poor	46 – 55
32 – 37	Very poor	56 – 65
>38	Very, very poor	>66

properties with a compressibility index of 15%. However, on the other hand, in F5, the measuring results the percentage of compressibility index on the day of preparation of granules showed "good" flow properties with a compressibility index of 12%, and in the first week to the fourth or last week showed "fair" flow properties with a compressibility index of ≤20%. Based on the results of the last measurement of the percentage of compressibility index of the six formulas, F3 shows the lowest percentage value of compressibility index with the content of filler material combination of lactose - maltodextrin (1:1), which showed good granule flow properties.

Particle Size Distribution

The particle size distribution aims to determine the uniformity of granule size with a sieving method that classifies granules based on passing or not passing through a sieve with a certain diameter size. The results of measuring the particle size distribution of granule preparations of *O. aristatus* leaf extract during 28 days storage at room temperature (see Figure 4), which shows that, the particle size distribution of F1 dominated the granule size in the range of 212-250 µm (40%), while the particle size distribution of F2, F3, F5 and F6 dominates the granule size in the range of 600-710 µm (36 - 47%), and the particle size distribution of F4 dominates the granule size in the range of 212 – 250 µm (34%). The sieving process to estimate particle size distribution is normally intended to use at least 80 % of particles larger than 75 µm (Council of Europe, 2019).

DISCUSSION

Preparation of granule formulations containing *O. aristatus* leaf extract was made by wet granulation method. This method was chosen because it has the capability of binders to facilitate particle binding and forming agglomerates, improve flow and compressibility properties, has better distribution and uniformity of substances than the direct method (Dürig & Karan, 2021), wet granulation can prevent segregation of components of the mixture, and can increase the dissolution rates of active substances with the addition of appropriate solvents and binders (Shanmugam, 2015).

After the extract of *O. aristatus* leaf was formulated in granule preparation, the physical stability of the preparation was evaluated. The purpose of evaluating the physical properties of granules is to determine the quality and collect data that can help in supporting the quality control of materials, and produce high-quality pharmaceutical preparations, and improve product performance. (Anacleto et al., 2018; Cui et al., 2022).

In this study, the physical appearance of the solution at the time of the granule dissolving time test shows a different color when dissolved in water, data not shown. Where F1, F2 and F3 are greenish yellow while F4, F5 and F6 are dark green. The color difference is thought to be due to differences in the use of solvents in the extraction process, in other studies also described by (Dirar et al., 2019; Zeroual et al., 2022) that differences in solvents and extraction methods used can affect extract yields and secondary metabolite content to biological activity. However, the resulting color remains the same and stable when testing during 28 days of storage. So the author does not discuss further because this study aims to produce the best formula for the development of herbal-based pharmaceutical preparations.

According to the particle size classification results obtained, it showed that all six formulas had a particle size above 75 µm. However, F3 was dominated by granule sizes in the range of 600 - 1000 µm (> 35-40%) that can be said to be stable during 28 days storage and was considered better because it had a dominance of larger particle sizes, this had a correlation with the results of the measurement of the angle of repose (< 30°) and the percentage of compressibility index (< 20%) and had a flow rate (7.8 g/s). This findings are in line with previous research which explains that, the value of the angle of repose is influenced by particle size, the larger the particle size (> 500-1000 µm) for instant granules (Belt & Aagaard, 2002; Budiati & Wicaksono, 2024), the angle of

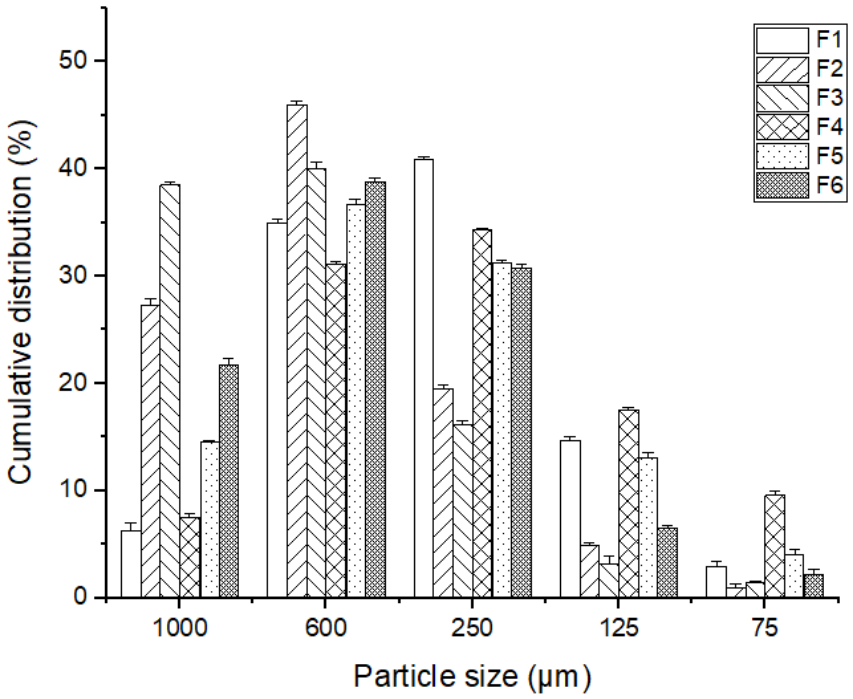

Figure 4. Evaluation of granule preparation of *O. aristatus* leaf extract on particle size distribution by sieving method

repose will be smaller and indicates good granule flow properties (Zhou et al., 2001). However, F1, F2, F4 and F6 have a compressibility index percentage value (>20%) and have a dwell angle (≥ 25-35°).

This study shows novelty by utilizing herbal potential of *O. aristatus* leaf which can be innovatively formulated into pharmaceutical instant granule dosage forms. These granules can serve as health herbal beverage or alternative medication. Through careful consideration of the filler and binder excipients as carriers in the formulation of the drug delivery system, this development is also expected to facilitate the packaging and consumption, storage and the possibility of shelf-life extension of the product.

CONCLUSION

This study proves that the extract of *Ortosiphon aristatus* (Blume) Miq. purple variety can be formulated in the dosage form of pharmaceutical granules, as evidenced by the physical evaluation results of granule preparations. All six formulas evaluated met the criteria of a high-quality granule. This finding suggests their potential utility as instant granule preparations for herbal beverage candidates or as alternative treatments for various diseases. Additionally, the modification of fillers in the formulation can maintain the physical stability of the granule preparations.

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