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FORMULATION OF CHEWABLE TABLET PREPARATIONS FROM THE COMBINATION OF *Azadirachta Indica* A. Juss. AND *Gynura Procumbens* (Merr.)

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ABSTRACT

Azadirachta indica A. Juss. and *Gynura procumbens* (Merr.) are one type of potential medicinal plants because they have various properties. One of the properties of these two plants is as an antioxidant. The combination of the two plants has a strong category of antioxidant activity, does not cause death and physical changes in test animals. This study aimed to make an antioxidant chewable Tablet containing a combination of *Azadirachta indica* A. Juss. and *Gynura procumbens* (Merr.) extract with a variation of mannitol-sorbitol as a filler. This variation has the advantage of covering the bitter taste of the active substance so that it is expected to provide a pleasant taste and is easy to swallow. The extract obtained was formulated into chewable Tablets with variations of mannitol-sorbitol (90%:10%), (80%:20%), and (70%:30%). The method used is wet granulation. The granules obtained were tested for their physical properties, namely flow velocity, angle of repose, and compressibility. The physical properties of the Tablets tested included uniformity of weight, size, hardness, friability, disintegration time, quality of taste, shape, and odor. Based on the test results of the physical properties of the granules, the three formulas met the requirements. While the physical properties of Tablets that do not meet the criteria are uniformity of size and disintegration time. This research concludes that the extracts *Azadirachta indica* A. Juss. and *Gynura procumbens* (Merr.) be formulated into chewable Tablets where formula two with variations of mannitol:sorbitol (80:20%) is the best formula by fulfilling 9 of 11 requirements.

Keywords: *Azadirachta indica* A. Juss; *Gynura procumbens* (Merr.); Chewable tablets

1. INTRODUCTION

Antioxidants from natural ingredients are starting to get a lot of attention they are considered to have fewer side effects than synthetic antioxidants (Ahmeda et al., 2009). Various natural ingredients containing antioxidants including *Azadirachta indica* A. Juss. and *Gynura procumbens* (Merr). Studies on the antioxidant activity of the two plants have been carried out, including the study conducted by Pratama (2019) reported a combination of ethanol extract of *Azadirachta indica* A. Juss. Meanwhile, the *Gynura procumbens* (Merr.) has the best antioxidant activity in the ratio of 75:25 (*Azadirachta indica* A. Juss: *Gynura procumbens* (Merr.)) with IC50 67.407 µg/mL. Given the unavailability of a combination of the two extracts in preparation, the researchers are interested in trying to make a combination preparation in the form of chewable Tablets with sweet fillers to mask the bitter taste of the extract.

A chewable tablet is a Tablet which use is intended for chewing. The chewable Tablet should taste good, be easy to swallow, and do not leave a bitter taste. The chewable Tablet has more advantages compared to other solid oral preparations such as better bioavailability, bypassing the disintegration process, resulting in increased dissolution, patient comfort since they do not need water to take the drug, fast onset time, increased patient acceptance (children), and more unique.

Meanwhile, the shortcomings of chewable tablet are bad taste and high concentration levels of active substances. Thus, the formulator needs more detailed consideration in the development of the main formulation to produce chewable Tablets with the expected taste (Siregar, 2010).

Suitable fillers for chewable tablet preparations are mannitol and sorbitol. Mannitol provides a mild sweet taste liked by many patients (Ansel, 1989). Whereas, sorbitol has good compressibility (Rowe et al., 2006). The use of a combination of mannitol-sorbitol fillers has been proven to produce chewable tablets that meet the standard tablet requirements (Uwamaretatyalovi, 2010).

This research is expected to contribute to the pharmaceutical sector by developing the potential of Indonesian medicinal plants. The combination of *Azadirachta indica* A. Juss. and *Gynura procumbens* (Merr) extract has been proven to have antioxidant activity and has the potential to be developed into antioxidant preparations to be more easily accepted by the public. From the results of this study, it will be directed to the development of antioxidant chewable tablet formulations containing herbal ingredients.

2. METHODS

2.1. Material and instrument

The instruments used include the maceration vessel, rotary evaporator (Horizontal Rotary Evaporator | B-One RE-2000 HN), disintegration tester (Type ZT222, Include Basket type A 6 test stations), friability tester (TAR 120), hardness tester (YD 1), tap density (SVM), moisturizer analysis (MB90 90g x 0,001g / 0,01%), analytical scales, calipers, Tablet printing machines (local large punch), mortars, and stampers. The materials needed in this study were Azadirachta indica A. Juss. and Gynura procumbens (Merr), 70% ethanol, distilled water, aerosil, mannitol, sorbitol, povidone, mg stearate, and aspartame.

2.2. Extraction

Azadirachta indica A. Juss. and *Gynura procumbens* (Merr) were sorted dry. After that, the simplicia was chopped and powdered. The powder was macerated separately using technical 70% ethanol with a powder ratio simplicia:ethanol of 1:10. After 24 hours, the extract was filtered and separated from the filtrate. Then, the remaseration was done by soaking the residue twice. The filtrate obtained was concentrated into a thick extract (Astuti & Agustiyani, 2019).

2.3. Preparation of dry extract

The vicious extracts of *Azadirachta indica* A. Juss. and *Gynura procumbens* (Merr) were thawed with a little distilled water before being crushed in a sterile mortar along with the addition of an aerosil with a ratio of 2:1 by weight of the thick extract. The mass is flattened and dried in a drying cabinet with a temperature of 40oC. After 24 hours, it was crushed and sieved with a sieve no. 120 to the same size (Pratama, 2019).

2.4. Preparation of chewable granular Tables

All ingredients were weighed and put the dry extracts of *Azadirachta indica* A. Juss. and *Gynura procumbens* (Merr) of 25:75 (150mg:37.5mg) into the mortar until became homogeneous (Pratama, 2019). Mannitol, sorbitol, and aspartame were then added little by little and then crushed until homogeneous. After that, povidone and mg stearate were added and crushed until homogeneous. Distilled water was added to moist into the mass which can be clenched into a fist and sieved with a 12-mesh sieve. Then, it was put in a drying cabinet for 24 hours and then sieved again with a 16 mesh sieve until a granular mass formed (Astuti & Agustiyani, 2019).

2.5. Chewable Tablet dosage formulations

The granules that have been evaluated were then added with a lubricating agent, namely mg stearate before being crushed to make them homogeneous. Granules were printed into Tablets with a Tablet printing machine. Chewable Tablet formula had various fillers, mannitol, and

sorbitol in FI (90%:10%), FII (80%:20%), FIII (70%:30%) (**Table 1**). The weight of each 600 mg Tablet was 200 Tablets per formula. The following is the chewable Tablet from the extract of *Azadirachta indica* A. Juss. and *Gynura procumbens* (Merr).

Table 1. The formula of the chewable for the combination of the extract of *Azadirachta indica* A. Juss. and *Gynura procumbens* (Merr) (Uwamaretatyalovi, 2010; Yetti et al., 2015)

Material	FI (mg)	FII mg)	FIII mg)	Description
Extract + aerosil (2:1)	394	394	394	Active substance
Mannitol	139.5	124	108.5	Filler
Sorbitol	15.5	31	46.5	Filler
Povidone	30	30	30	Binder
Mg Stearate	15	15	15	Slipper
Aspartame	6	6	6	Sweetener

2.6. Formula Evaluation (Granule)

2.6.1. Flow velocity

The flow velocity test aims to determine the distribution of particle size in the granules which might affect the flow properties of the granules. 100 grams of granules were put into the funnel, with a closed bottom. Then, the lid of the funnel was opened and the granules were melted out until they run out. The time required for granules to get out of the funnel was calculated (Hadisoewignyo & Fudholi, 2013).

2.6.2. Angle of repose

The angle of repose is the maximum possible angle between the surface of a powder pile and the horizontal plane after being treated. Piles of granules that have been flowed during the flow velocity inspection in this study were calculated for the height and diameter. Then the angle of repose was calculated using the formula of $\tan \alpha = h/r$ (Agoes, 2012).

2.6.3. Compressibility

The compressibility test was carried out to see the change in granule volume due to shock and vibration that might occur in the tabling process. A measuring cup was used to calculate the ratio between the actual compressible density divided by the compressed density in percent (Hadisoewignyo & Fudholi, 2013).

2.7. Formula Evaluation (Tablet)

2.7.1. Uniformity of weight

20 dust-free Tablets were calculated their average weight by weighing the Tablets one by one. Each weight was recorded and then the weight deviation for each Tablet was calculated. A good criterion was obtained if from 20 Tablets there was one Tablet which weight deviates from an average of more than 10% and 2 Tablets were not more than 5% (Kesehatan, 1979).

2.7.2. Uniformity of size

20 Tablets were taken randomly and measured their thickness and diameter one by one using a caliper. The average diameter and thickness of the Tablets from these measurements were calculated. Tablets are said to be good in terms of size uniformity if the average diameter of the Tablets was more than 3 times the thickness of the average Tablets and not less than 1 1/3 times the thickness of the average Tablets (Kesehatan, 1979).

2.7.3. Hardness

10 Tablets were prepared and measured using a hardness tester. A good chewable Tablet has a hardness level of 4-7kp (kilopond) where 1 kp is equal to 1kg (Sulaiman, 2007).

2.7.4. Friability

At least 20 Tablets weighing at least 6 g should be weighed accurately. The Tablets were rotated in a friability tester for 100 rounds, dusted, and weighed again. The percentage of friability is determined from weight loss (Siregar, 2010).

2.7.5. Disintegration time

Tablets were placed in an open pipe in the basket using a machine. The basket was raised and lowered in the dyeing liquid with a frequency of 39-32 times fluctuating per minute. The disintegration time of a good crewable Tablet is no more than 30 minutes (Siregar, 2010).

2.7.6. Quality of taste, shape, and odor

The response test for the quality taste, shape, and odor was carried out on 20 respondents asked to rate the Tablets in terms of taste, shape, and odor. The taste and odor quality tests had 5 indicators, namely very good, tasty, quite tasty, not good, not good at all while the odor quality test had 5 indicators, very attractive, interesting, quite interesting, less attractive, not interesting.

3. RESULTS AND DISCUSSION

This section is the most important section of your article. The analysis or results of the research should clear and concise. The results should summarize (scientific) findings rather than providing data in great detail. Please highlight differences between your results or findings and the previous publications by other researchers. For Tables you need to sound the Table.

3.1. Extraction

The simplicia extraction of Azadirachta indica A. Juss. and *Gynura procumbens* (Merr) was 178.70 g with a yield of 8.50% and 181.51 g with a yield of 8.64%. The water content of the *Azadirachta indica* A. Jus was 2.54% and that of the *Gynura procumbens* (Merr) extract was 5.52%. The organoleptic results of the extract obtained can be seen in **Table 2**.

Table 2. Organoleptic extracts of *Azadirachta indica* A. Juss. and *Gynura procumbens* (Merr)

No	Parameter	Azadirachta indica extract	Gynura procumbens extract
1.	Color	Blackish green	Blackish green
2.	Texture	Thick, sticky	Thick, sticky
3.	Smell	Typical odortic	Typical odortic
4.	Taste	Bitter, chelate	Bitter, chelate

3.2. Dry extract

The dry extract obtained was formulated with the ingredients according to the formula from dry granules with the moisture content of formula 1 (3.57%), formula 2 (4.1%), and formula 3 (5.46%).

3.3. Observation of granule physical properties

3.3.1. Flow velocity

Granules and flow properties might be directly proportional, indicating that the granules will be good if the flow properties are also good. Thus, the filling time in the print space will be constant (Parrot, 1970). The results of the granule flow velocity observations presented in **Table 3** show that the granule flow velocities in the formula 1, 2, and 3 were 5.32 g/s, 4.73 g/s, and 4.85 g/s respectively. From these results, the flow velocity shows good granule properties since it was still within the specified range of Aulton (2002), which is 4-10g/s. Of the three formulas, the one with the best flow velocity was the formula I for it had the highest flow velocity and made the granules easier to glow. This is due to the influence of the water content of formula 1, which is at least 3.57%. The lower the water content, the faster the flow rate. The presence of slight friction with the die wall also causes the granules to flow more easily (Hadi et al., 2014).

3.3.2. Angle of repose

The angle of repose between $28^o - 42^o$ indicates good flow properties or good granule quality (Carstensen, 1997). The data obtained from the observation of the angle of repose in formulas 1, 2, and 3 were 32.0877^o, 35.1263^o, 29.6095^o. From these results, all formulas had an angle of repose between $28^o - 42^o$ which indicates the angle of repose of the three-formula showed food flow properties.

3.3.3. Compressibility

The smaller the compressibility, the better the flow properties. The compressibility value according to Aulton (2002) is divided into two, special and good. It is special if the compressibility value is <12%. It is good if the compressibility value is 12-16%. From the observations, it was found that the compressibility values in formulas 1, 2, and 3 were 2%, 5%, and 2% respectively. Thus, the three formulas had special compressibility values and the granules can be pressed into Tablets.

3.4. Observation of Tablets physical properties

3.4.1. Uniformity of weight

From the observations (**Table 3**), it shows that all formulas met the requirements for Tablet uniformity since no more than 2 Tablets which deviated from the average weight and the percentage of deviation was not more than 5% (Kesehatan, 1979). Uniformity of weight is a very important parameter in the quality of the Tablets produced. The uniformity of weight is also affected by the filling of the granules on the die. When several granules are inserted into the die, the pressing might determine the uniformity of the resulting weight. Thus, anything that can change the filling process of the press holes can change the weight of the Tablet and cause weight variations (Siregar, 2010).

Table 3. The results of the weight uniformity test

Formula	N	$\bar{x}$ ± SE (mg)
F1	20	674 ± 1.88
F2	20	620.5 ± 1.94
F3	20	607.4 ± 2.01

Description: N=Number of Tablets, $\bar{x}$=Mean, SE=Standard error

3.4.2. Uniformity of size

The observation results presented in **Table 4** show that the measurement uniformity values in formulas 1, 2, and 3 were 3.64, 3.67, and 3.79, respectively. This indicates that all formulas did not meet the requirements set by the 3rd edition of the Indonesian Pharmacopoeia where a good uniformity is not more than 3 times and not less than 1 1/3 times the thickness of the average Tablet. This is probably due to the diameter of the Tablet which was too large making the size of the Tablet was not thick enough.

Table 4. The results of the size uniformity test

Formula	d mean	t mean	1 1/3t<d<3t
F1	1.32	0.36	0.48<1.32<1.08
F2	1.32	0.36	0.48<1.32<1.09
F3	1.31	0.35	0.46<1.31<1.05

Description: d=Diameter, t=Thickness

3.4.3. Hardness

From the observations (**Table 5**), it was found that the size uniformity values in formulas 1, 2, and 3 were 12.34kp, 6.73kp, and 5.57kp. These data show that formula I did not meet the requirements since the value was more than 7kp or in a very strict sense. This shows that the amount of mannitol might affect the hardness of the Tablet wherein formula 1 while the amount

of mannitol was more than sorbitol in formulas 2 and 3. Meanwhile, formula 2 and 3 had good hardness value since the mannitol content was less and the sorbitol content was more compared to formula 1.

Table 5. Tablet hardness test results

Formula	N	$\bar{x}$ ± SD (Kp)
F1	10	12.34 ± 2.22
F2	10	6.73 ± 1.10
F3	10	5.57 ± 0.96

Description: N=Number of Tablets, $\bar{x}$=Mean, SD=Standard deviation

3.4.4. Friability

The friability test was conducted to determine the ability of Tablets to prevent chipping and scratching during handling and shipping. From the observations (**Table 6**), it was found that the Tablet friability test values in formula 1, 2, and 3 were 1.40%, 2.07%, and 2.95%. Those three formulas met the requirements for the friability value for chewable Tablets, less than 4% (Siregar, 2010).

Table 6. The results of the friability test

Formula	Friability (%)
F1	0.47
F2	0.69
F3	0.98

3.4.5. Disintegration time

Time tests on chewable Tablets need to be done to show the ability of Tablets to integrate (Siregar, 2010). From the observations (**Table 7**), the disintegration time in formula 1, 2, and 3 was 45.09 minutes, 37.81 minutes, 41.67 minutes, respectively. The disintegration time of a good chewable Tablet is no more than 30 minutes (Siregar, 2010). Thus, none of the three chewable Tablet formulas met the requirements for good disintegration because all of them exceed 30 minutes.

Table 7. Results of the disintegration time test

Formula	Disintegration time (minute)
F1	45.09
F2	37.81
F3	41.67

The longest disintegration time occurred in formula 1, 45.09 minutes, possibly because the process of drying with formula 1 took faster than formulas 2 and 3. This reason is supported by a study conducted by Jayanti (2013), which stated that the drying time of granules could reduce Tablet hardness. This is comparable to the hardness and friability of the Tablet, where the formula one Tablet had the highest hardness, and the lowest friability took the longest disintegration time.

3.4.6. Quality of taste, shape, and odor

Figure 1 shows the chewable tablets. The data (**Figure 2**) obtained for the quality of taste and odor from formulas 1, 2, and 3 showed that the Tablets were quite tasty, where formula 2 was the most preferred by respondents for its taste quality. Meanwhile, formulas 2 and 3 got the same value for odor quality. Whereas, the quality of the shape was quite interesting where formula 2 got the most ratings. Tablets are said to meet the requirements if 50% of respondents say they like and can accept the Tablet's taste, shape, and odor (Hidayati et al., 2020).

Based on the results of the recapitulation (**Table 8**) regarding the physical properties test results of the chewable Tablets extracts of *Azadirachta indica* A. Juss. Meanwhile, the *Gynura*

procumbens (Merr.) with variations of mannitol sorbitol, the results showed that formula 1 with a concentration of 90% mannitol and 10% sorbitol met 7 out of 11 chewable Tablet requirements. Formula 2 with a concentration of 80% mannitol and 20% sorbitol met 9 out of 11 chewable Tablet requirements. Formula 3 with a concentration of 70% mannitol and 30% sorbitol met 8 out of 11 chewable Tablet requirements.

Figure 1. The chewable tablets

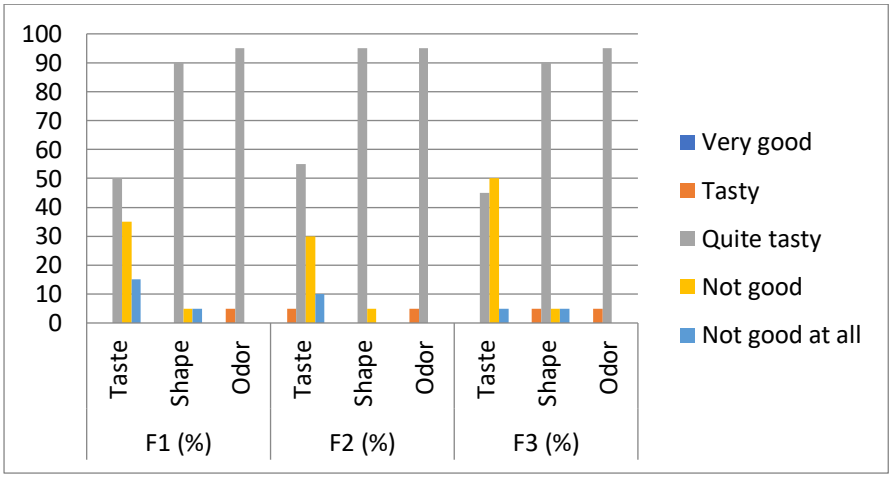

Figure 2. The results of the taste, shape, and odor response tests

Table 8. Recapitulation of results

Evaluation test	Chewable Tablet formulation		
	F1	F2	F3
Flow velocity (g/s)	Q	Q	Q
The angle of repose (o)	Q	Q	Q
Compressibility (%)	Q	Q	Q
Weight uniformity (%)	Q	Q	Q
Size uniformity (cm)	DQ	DQ	DQ
Hardness (Kp)	DQ	Q	Q
Friability (%)	Q	Q	Q
Disintegration time (minutes)	DQ	DQ	DQ
Taste quality (%)	DQ	Q	DQ
Shape quality (%)	Q	Q	Q
Odor quality (%)	Q	Q	Q
Total	7 Q	9 Q	8 Q
	4 DQ	2 DQ	3 DQ

Description: Q=Qualify, DQ=Doesn't Qualify

4. CONCLUSION

The extracts of Azadirachta indica A. Juss. and Gynura procumbens (Merr) can be formulated into chewable antioxidant Tablets with variations of mannitol-sorbitol as a filler where formula 2 with variations of mannitol:sorbitol of 80%:20% became the best formula by meeting 9 out of 11 physical requirements for chewable Tablets. The physical properties of the Tablets tested included flow velocitiy, angle of repose, compressibility, uniformity of weight and size, hardness,

friability, disintegration time, quality of taste, shape, and odor. It is necessary to carry out further testing related to other pharmacological activities of the chewable tablet preparation extract of Azadirachta indica A. Juss. and Gynura procumbens (Merr.).

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6. CONFLICT OF INTEREST

The author declares that there no competing conflicts of interest.

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