



PHYSICAL CHARACTERISTICS OF TABLET COMBINING GRANULES WITH DUTCH TEAK EXTRACT (*GUAZUMA ULMIFOLIA* (L.)) AND GREEN TEA EXTRACT (*CAMELIA SINENSIS* (L.) O.K) WITH AVOCADO STARCH (*PERSEA AMERICANA* MILL.) AS BINDING AGENT

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ABSTRACT

Dutch teak *Guazuma ulmifolia* (L.) and green tea (*Camelia sinensis* (L.) O.K) are known for their use as anti-obesity agents. The Dutch teak and green tea extract are produced through remaseration using 70% of alcohol. Avocado seed contains amylose and amylopectin compounds. Amylose content enables the extract to absorb water and has a good expanding capacity, which makes it possible to be employed as tablet break-apart agent. Amylopectin on the other hand, has the ability to form aggregate through inter-particle binding, therefore, it serves as a binding agent. The research is aimed at understanding the effect of avocado starch as a binding agent toward tablet's physical characteristics, including weight homogeneity, hardness, friability, and break-apart time. Tablet is produced through wet granulation process with avocado starch as the binding agents (on 4 formulas) and two other agents, serving as control agent, namely PVP and gelatin. The obtained data is analyzed theoretically by comparing the result with the existing literature and statistically employing ANOVA one-way test, with 95% level of trust. Tablet with the best quality is produced from formula group of avocado starch with 5% concentration. As the concentration of avocado starch goes up, the flow time also runs up, as well as the humidity level, hardness and break-apart time on granule, Dutch teak extract, and green tea extract. A significant difference among the six formula occurs on the test of hardness, friability, break-apart time, and some size homogeneity tests, which is indicated by the value of $p < 0.05$.

KEYWORDS: Avocado starch; binding agents; Dutch teak; green tea.

INTRODUCTION

Tablet is the most popular medicine in pharmacy industry. This product is most commonly found in the market and its formula is developing rapidly. During the process of formulation, a tablet comprises the mixture of an active substance and other substances which serve different purposes. One of the additional substances is the binder agent. Binder agent can be added from a solid or liquid form in wet granulation, aiming to form granulation agent or to ensure tablet's cohesiveness. The measurement of binder agent should be perfect; an excessive use of binder agent produces an overly wet and solid granule, on the other hand, deficiency of binder agent would ensure poor cohesiveness; the tablet breaks apart and causes *capping*.^[1]

A limited availability of excipients for national pharmacy industry resulted in a significant increase in medicine price, whereas Indonesia has relatively unlimited source of raw material. One of the most popular materials of

excipient agent is plant starch.^[2] Many studies indicate that many plant starches can be used as an excipient agent. One of them is avocado starch, which is reportedly added as a break-apart agent of Paracetamol.^[3] Another study suggested that durian starch can be added to Ketoprofen tablets, as a binder-agent, and serves the purpose better than cassava starch.^[4]

Avocado seed is a good alternative for some reasons. Firstly, it contains a relatively high amount of starch, which is 23%.^[5] The seed also contains polyphenols, which serves as antioxidant. Extract of avocado seed has 30% of inhibitory power against oxidation.^[6] The main compound of avocado seed contains amilose and amylopectin. Amilose content ensures better water absorb and its swelling power makes it a better break-apart agent. Amylopectin is stickier and tends to turn into a gel when it is held suspended with water. Amylopectin forms an aggregate through inter-particle binding, which makes it possible for it to become a binder-agent. The main problem in employing avocado starch is dealing

with its colour-changing behaviour; because it turns to brown when it is crushed, the produced starch will also maintain the colour. A way to turn the colour into white is by adding sodium metabisulfite ($\text{Na}_2\text{S}_2\text{O}_3$).^[7] The starch has a relatively high affinity against water; as the result, the starch absorbs water which allows it to expand and break apart.

Obesity is a condition in which an abnormal build up of fat takes place in the body. The determination of this condition is drawn considering the body mass index (BMI). BMI is a person's weight in kilograms divided by the square of height in meters. BMI 30 is considered obesity, while BMI 25 is considered excessive body weight.^[9] Obesity is a global pandemic and is established by World Health Organization (WHO) as the biggest chronic disease in adult.

The Dutch Teak is known for its efficacy in weight loss. Various studies have been drawn on this particular tree, especially regarding the effect of its dry leaves extract. A dose of 0.0056 g/200g body weight of a rat shows success in losing weight of the rat. Dutch teak decreases the amount of abdominal fat for 27.06% ($p < 0.1$), while its comparison group, the lovastatin succeeded in losing 8.68%.^[12] There are other plants known for its efficacy to generate weight loss. Green tea nowadays is getting more and more popular for its useful property. Green tea contains a high amount of tannin, ranging between 30-40%. Tannin in green tea belongs to a polyphenol compound, namely catekin, especially epigallocatechin-3-gallate.^[13] Proven helpful as an anti-diarrhea, green tea also helps to generate weight loss, as the result of its catekin content.^[14] Therefore, combining the useful agent contained in both plants would make an anti-obesity product expected to generate a synergic effect in weight loss.

The materials used in this study include; avocado seed (*Persea americana*, Mill), Dutch teak dry leave extract, dry green tea extract, PVP, gelatin, aerosol, magnesium stearat, and talcum. The study employs some tools, including; water steamer, stove, flannel fabric, vaporizer

cup, spatula, horn spoon, parchment, analytical scales, stainless steel container, sieve number 40,14 and 16, thermometer, measuring cup, beaker glass, stirring rod, oven, stopwatch, flower tester, Jolting Volumeter, tablet machine, calipers, hardness tester, friability tester, humidity balance and pH meter.

MATERIAL AND METHODS

Extract Preparation

The extract is produced by macerating, using 70% of ethanol. Measure 100 g of simplicia powder and put them into macerating vessel, then add 1000 ml of 70% ethanol. Leave it for 6 hours and stir them every 30 minutes for 5 minutes then leave it for 24 hours. Filter the mixture using flannel fabric and filtering paper, and pour them into macerating container. Simplicia waste is added with more solvent using the same type and measurement. Repeat the process twice, with the total three days of immersion. The macerate is collected and vaporized with water-bath until the expected denseness is gained.

Preparation of Avocado Starch

The following are the procedures of making avocado starch^[5,8]

1. Peel the seed skin using a knife.
2. Wash the seed with flowing water.
3. Chop the seed.
4. Soak the seed with 200 ppm of sodium metabisulfite for 24 hours with the ratio 1 : 5
5. Grind the seed using a blender with 1 : 1 water ratio.
6. Use a fabric to filter the mixture.
7. Wash the seed pulp 3 times using distilled water.
8. Suspend it in a decanter for 6 – 12 hours until the starch is perfectly sedimentary.
9. Separate the sediment from the solution, then dry the sediment with an oven on 50°C
10. Grind the dry starch and sieve.

Granule and Tablet Formulation

The tablet is produced through various processes, using wet granulation method, the procedures are as follows:

Chart 1: Formula Dutch Teak Extract and Green Tea with Avocado Starch Tablet.

Materials	FA	FB	FI	FII	FIII	FIV
Dutch Teak Extract (mg)	100	100	100	100	100	100
Green tea extract (mg)	33.33	33.33	33.33	33.33	33.33	33.33
Avocado starch (%)	-	-	5	10	20	30
PVP (%)	5	-	-	-	-	-
Gelatin (%)	-	2	-	-	-	-
Talcum (%)	1	1	1	1	1	1
Magnesium stearat (%)	1	1	1	1	1	1
Avicel PH101 - lactose ad	650	650	650	650	650	650

Tablets Preparation

Mix the Dutch teak extract, green tea extract, and other additional substances into a container, then add mucilage avocado starch, with 10%, 20%, and 30% concentration

to each formula, while stir and push the mixture, until the mixture breaks away when a moderate press is given. Mix the granulate component and sieve the mixture using no. 12 sieve. Once the humidity granules are

drawn, dry them using an oven on 40° - 50° C for 30 minutes. After the process, use no. 16 sieve to draw smaller granules. Add magnesium stearat and talcum and stir until the mixture is homogene. Do a test on the granules, including flow time test and granule compressibility test. Finally, the tablet can be produced using a mold or the machine.

Granule Tests

Flow Time Test

Measure the mass of 50 g, and put it in the flower tester and keep it close. Then, open the cap and let the mass flow, count the time of flow using a stopwatch. Repeat the step three times and calculate the average time. The best flow time is ≥ 10 gram/second.

Compressibility Test

Put the 50mL of mass into the measuring cup; in which a bulk density tester will be installed, note the initial volume. Turn the tester on, count 100 beats, and note the final volume. Keep the procedure until a constant result is obtained. If compressibility index is somewhere between 11 – 15 %, the mass has good compressibility quality.

Angle of Repose

Measure the mass for 50gr and put it inside flower tester and close the tester. Open the cap, let the mass flow. Measure the height of the formed stack of powder and the diameter. Count the measurement using angle of repose formula. The angle between 25°-35° indicates a special nature of flow.

Humidity Test

Measure 5g of granules and heat it inside drying machine on 105° C for 2 hours. The humidity level of granule should not be over 2-4%.

Tablet Test

Visual Test

The test is conducted by determining some parameters, including size, form, color, scent, surface shape, consistency, and physical defect.

Weight Homogeneity Test

Choose 20 tablets randomly, and carefully measure each and every one of them and calculate the weight average.

Chart 1 Granule Test Result.

Formula	Condition	FA	FB	FI	FII	FIII	FIV
Flow time	≥ 10 g/det	20	12.25	14.28	6.16	5.85	5.32
Compressibility	≤ 22 %	10	16	14	8	16.27	10
Humidity	2 – 4%	3.56	2.65	2.55	3.35	3.77	5.15

Notes:

FA : tablet with 5 % PVP binder.

FB : tablet with 2 % gelatin binder.

FI : tablet with 5 % avocado starch.

FII : tablet with 10 % avocado starch.

Calculate the relative standard deviation or its variation coefficient.

Size Homogeneity Test

Take 20 tablets randomly, measure the thickness and diameter. Thickness can be obtained using the stirring rod, while the diameter is obtained during the process of hardness test, the diameter appears before the hardness measurement. Calculate the average of thickness and diameter. The diameter should not be 3 times larger than the thickness of 1 1/3 measurement of the tablet.

Hardness Test

10 tablets are chosen randomly, measure the hardness using *hardness tester*, and calculate the average. The minimum force of pressure is $4 \text{ kg/cm}^2 - 8 \text{ kg/cm}^2$.

Friability Test

Measure 10 tablets, and put them inside *friability tester* and roll the machine 100 times. Clean the tablets and measure the tablets once again. The weight loss should be somewhere between 0.5% until 1 %.

Disintegration Time Test

Break-apart time test is conducted using break-apart time tester. Choose 6 tablets and put them inside a container. Fill the container with 600 ml of distilled water on 37 ± 5 °C. Watch the time it takes for the tablet to completely break apart. The time should not be more than 15 minutes.

RESULT AND DISCUSSION

Dutch Teak extract and green tea extract used in this study are thick and have solid green color. In order to simplify the process of formulation, the thick extract is firstly dried using lactose, where the ratio of extract: binder is 1:2.

Therefore, there are two types of binder agents in this study, namely avicel pH101 and lactose. The study is conducted on 6 formulas; 2 of the formulas use the most common agents, which are gelatin and PVP, while the other 4 use avocado starch with 4 different concentration, 5%, 10%, 20%, and 30%.

FIII: tablet with 20 % avocado starch.

FIV: tablet with 30 % avocado starch.

The result suggests that there are only three granules on flow time test that meet the qualifications; formula A, B,

and I. Compressibility test on all formulas suggests that all formulas are qualified, while moist level test on six formulas, there is only one formula - formula IV - that does not meet the qualification.

The result on the nature of flow test suggests that three out of six formulas meet the characteristics of flow. The nature of flow influences the mass of tablet. Formula II, III and IV have a low nature of flow, hence, they consequently suffer a bigger weight deviation than formula A, B, and I.

The result of compressibility test suggests that all formulas meet the qualification, evidently because all of the formulas' compressibility tests are less than 20%. Sieve process using type 16 sieve causes size reduction in dried granules. As the result, it produces denser bulk. The density of bulk increases in circular particles and also in smaller granules.^[15]

Humidity test on granules suggests that not every formula meet the humidity standard, which ranging from 2 – 4 %. Humidity level determines the tableting process. If total dryness happens, granulate loses its binding capacity.^[1] High level of humidity resulted in stronger binding capacity, because the area of contact between particles increase; as the result, it is more difficult for the granules to flow.

The result of visual test on the combination of Dutch teak extract and green tea extract shows that all formulas are not homogenous. The tablets are circular, have different types of green, and there are green spots on the surface. This happens because the extract is built up of a different color than the color of other additional

substances. Tablet from plant extracts usually suffers from color homogeneity problem on its surface.

For uncoated tablets with an average weight of > 300 m, FI III requires that there are only two tablets deviated by 5% of the average weight and none of the tablets could deviate more than 10% of the average weight. The result is obtained through 20 times measurements. The weight homogeneity test result suggests that all formulas meet the requirements of weight homogeneity.

The result of size homogeneity test suggests that all formulas are qualified. According to FI III, the diameter of tablet should not be more than 3 times or less than 1/3 of thickness measurement. The thickness will be constant if the granule has a relatively consistent size of particle and size of distribution if punch tool has consistent length and if the mold is clean and in good condition.^[15]

The hardness test result suggests that all formulas are eligible, which are minimally 4 kg/cm². The hardness factor may vary as the result of a difference in tension given by the press machine, the hardness level goes up as the bigger the pressure given to the tablet.

The result of friability test suggests that all formulas are eligible, which means the tablets do not suffer weight loss less than 0.5 - 1%. The friability of the tablet is influenced by the hardness level.

Disintegration test suggests that all formulas are eligible, which means it does not take up more than 15 minutes. The time is affected by the degree of hardness. The time is longer if the hardness is high. The hardness level is affected by break-apart level.^[15]

Chart 3 Inter-group Test Result.

Test	Statistic Test	
	Sig	Result
Hardness	0.000	Different significant
Weight Homogeneity	0.890	Not different significant
Size Homogeneity	0.001	Different significant
Friability	0.000	Different significant

Hardness test is conducted using Kolmogorov-Smirnov testing method, showing a significant value of > 0.05, suggesting that the data shows a normal distribution. The result of hardness level is tested using Levene test, shows significant value of 0.057 ($p > 0.05$) which means hardness level of each formula group is homogenous. The distribution of data is normal and homogenous, the test is continued by conducting one – way parametric test ANOVA < the data shows significant result of 0.000 ($p < 0.05$) therefore, it can be concluded that a significant difference among six testing groups. The testing is followed by Hoc Test (LSD) to figure out groups with significant difference. The result suggests that there is a significant difference between 5 % PVP (FA) binding

agents and 2% gelatin and 5 % (FI) avocado start binding agents; the formula and 2% of gelatin binding agent, and 5% of avocado starch (FI); formula with 2% gelatin binding agent is different from the formula with 5% of avocado starch with 10%, 20%, and 30% concentration. Formula with 5% of binding agents is different from avocado starch with 10%, 20%, and 30% of binding agent, and formula with 10% of avocado starch is different from formula with 30% avocado starch.

Weight homogeneity test using Kolmogorov-Smirnov shows a significant value of > 0.05. It can be concluded that the data shows a normal distribution. Furthermore, the result of weight homogeneity test is tested using

Levene test, showing a significant value of 0.170 ($p > 0.05$). Therefore, it can be concluded that the homogeneity of weight of every formula group is homogenous. The distribution of data is normal and homogenous, the data is carried on using one-way parametric test ANOVA, which indicates a significant result of 0.890 ($p > 0.05$), therefore, it can be concluded that there is no significant distinction among six formula groups.

The size homogeneity test is conducted using Shapiro – Wilk testing method, which indicates that the homogeneity has a significant value of < 0.05 . It can be concluded that the data has a relatively abnormal distribution on 5% starch formula and 2% gelatin. The result of size homogeneity test is then tested using Levene testing, which shows a significant value of 0.053 ($p > 0.05$), which means the size homogeneity of every formula group is homogenous. The data distribution is abnormal but homogenous, and later it is tested using Kruskal Wallis test. The condition in Kruskal Wallis test is if $p \leq 0.05$ then H_a is accepted and H_0 is denied. The result of statistic test indicates a significant result of 0.001 ($p \leq 0.05$), which means based on the significant difference among six formula groups, the hypothesis is accepted. The test is carried on using Mann-Whitney test, to figure out the data variable with significant difference. The condition in Mann-Whitney U test establishes that if $p \leq 0.05$, H_a is accepted and H_0 is rejected. The result suggest that a significant difference takes place in formula with 5% PVP binding agent and 5% and 10% of avocado starch, the formula with 2% of gelatin binding agent is different from the formula with 5% avocado starch with 20% starch. The formula with 5% avocado starch is different from the one with 10% of avocado starch, while the formula with 20% of avocado starch is different from the one with 30% of avocado starch.

Friability test using Shapiro-Wilk test indicates that the friability shows a significant value of $p > 0.05$, which means that the data has a normal distribution. Furthermore, the result of friability test is treated using Levene test, and indicates the value of 0.157 ($p > 0.05$), it can be concluded that the friability of each formula group is homogenous. The test is carried on using one-way parametric test ANOVA, and the data shows a significant value of 0.000 ($p < 0.05$), which means that a significant difference occurs among six groups of formula. The test goes on using Post Hoc Test (LSD) to figure out the group with the most significant difference. The result suggests that a significant difference occurs between formula group avocado starch with 10%, 20%, and 30% concentration and 5% of avocado starch with 5% of PVP and 2% of gelatin, in formula group 5% of avocado starch with 5% PVP and 2% gelatin, and formula group of 5% PVP and 2% gelatin.

CONCLUSION

The result of evaluation on granule and Dutch teak extract and green tea extract which categorizes into six formula groups with including avocado starch (5%, 10%, 20%, and 30% concentration), 5% PVP and 2% gelatin, indicates that formula with 5% avocado starch produces the best physical quality of tablet, because the higher concentration of avocado extract, the more flow time, humidity level, hardness, break-apart time on the granule, and dutch teak extract and green tea extract. In addition, the result also suggested that among six formula groups, a significant difference occurs in hardness test, friability test, break-apart time, and some homogeneity test, indicated by the value of $p < 0.05$.

SUGGESTIONS

Researchers who pursue similar researches may try to change the concentration into less than 5%, coat can be used to cover/fix the color distribution, and find a formula which addresses the tablet hygroscopicity problem and find a necessary modification, such as adding aerosol into the formulation in order to fix the flow time.

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