Formulation of *Sechium edule* Extract Effervescent Granule with the Variation of Citric Acid, Tartrate Acid and Sodium Bicarbonate

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Abstract: The *Sechium edule* fruit is traditionally proven to contain antiulcer. Thus, it is necessary to develop dosage formulations. An effervescent granule is chosen as an alternative form of drug delivery, considering its dosage preparation may apply simply within a short amount of time. This study aims to discover the composition of the mixture of citric acid, tartrate acid, and sodium bicarbonate met the physical test requirement for effervescent granule. Effervescent granules are made by wet granulation technique (the mixture of alkali-acid) by <25% of relative humidity on 20-25^{o}C temperature. There are three effervescent granule formulas, consisting a different portions composition of citric acid, tartrate acid, and sodium bicarbonate: formula I = (2.5 :5:15); formula II = (2.25:4.5:16.88); and formula III = (2:4:18). Physical test on granules consists of flow rate test, moisture content, time of dissolution, pH and organoleptic. Following trials performed on Formulas I, II, and III of effervescent granule, the granules flow time of each formula are:1.48;1.53;1.48 seconds moisture content: 3.40; 3.62; 3.50%, time of solubility : 4.37; 4.25; 3.65 minutes, pH: 6.62; 6.54; 6.59, and likeness survey: (Colour=1.93; 1.90;2,0.Scent=2.0; 1.93; 2.07. Flavour=1.76; 2.06; 2.13). Those three formulas met the good physical test requirement, except on the moisture content. Formula III go the most preference on colour, scent and taste.

1 INTRODUCTION

Sechium edule is one of the plants used for traditional medicine. *Sechium edule* has many potentials as a drug to treat some diseases; one of them is as an antiulcer (Kamble *et al*., 2008). The fruits and leaves of *Sechium edule* contain saponins and flavonoids. Besides that, the fruit also contains alkaloids and tannins, while the leaves contain flavonoids and polyphenols (Gandhu *et al*., 2012). The fruit also contains saponins, alkaloids and tannins, while the leaves contain saponins, flavonoids and polyphenols (Pratiwi, 2011). The active ingredients in the contents of *Sechium edule* that function as antiulcer are the tannin, flavonoid, and alkaloid compounds contained in the skin and fruit of *Sechium edule* (Hagerman, 2000).

In Rofifah's research (2016), the extract of the *Sechium edule* has antiulcer effect at the dose of 300 mg/kg BW when administered to a rat. Converted into a human the dose, it equals 3.360 mg for single use. With such a large dose of use, it is necessary to develop a formulation to produce an appropriate dosage form acceptable to the patient. Effervescent granules are chosen as an alternative dosage form because of the advantages of these dosage forms. First, they are easy to use; the preparation of the solution with the right dosage of the drug can be done in fast, convenient time. Second, it can provide a refreshing delicious sensation because of carbonate, which can help improve the taste (Allen, 2002).

Effervescent granule processing is generally derived from the acid combination of citric acid-tartaric acid rather than just one acid because the use of single acid alone would be difficult. When using only citric acid, it will produce a mixture of adhesives and difficult for granulation. When only tartrate acid is used, the resulting granule will easily lose its strength, easy to clot and will produce a fast effervescent reaction (Ansel, 1989). Sodium bicarbonate is used as the alkali reaction and acts to neutralize the citric acid and tartaric acid and can produce foam and liberate carbon dioxide gas and is completely soluble in water (Pulungan *et al*., 2004). The acid mixture (citric acid-tartaric acid) and alkali (sodium bicarbonate) in effervescent granule extract of the *Sechium edule* aims to provide sparkle or taste

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effects such as soda drinks that take place quite rapidly and produce a clear solution (Pulungan *et al*., 2004). Therefore, the drug given in the form of an effervescent granule with a mixture of citric acid, tartaric acid and sodium bicarbonate will provide a refreshingly delicious taste sensation (Ansel, 1989). The objective of this research is to find out the composition of citric acid, tartrate, and sodium bicarbonate mixture which meets the physical requirement of effervescent granule extract of squash fruit (*Sechium edule*).

2 MATERIALS AND METHOD

2.1 Materials

The materials used in this research are *Sechium edule* obtained from farmers' group of Mount Sindoro, Parakan, Temanggung, Central Java, ethanol 96%, ethanol 70%, HCl 2 N, ammonia, Mayer reagent, $FeCl_3$, citric acid, tartaric acid, sodium bicarbonate, lactose, aspartame, and PVP.

2.2 Methods

2.2.1 Preparation of Sechium edule Extract

One kilogram of *Sechium edule* crude simplicia granules was performed by maceration using 96% ethanol solvent of 5 L stirred with intermittent shaking for 3 hours at 400 rpm for 72 hours (3 days). The maceration results are evaporated over the waterbath at 50-60°C until a thickened extract is obtained, then placed in a dark container and stored in a cool place for further use. The evaluations of the extract of the *Sechium edule* include:

- Calculation of yield of the extract: the extract yield of the *Sechium edule* is calculated by comparing the initial weight of the simplisia and the final weight of the extract produced.
- Organoleptic extract of *Sechium edule*: organoleptic test includes the observation of colour, smell, taste and consistency of the extract.
- The moisture content of *Sechium edule* extract: the moisture content of the extract was tested using a Halogen Moisture Analyzer with heating at 105°C for 15 minutes, the percentage content of the sample will be automatically listed. Good moisture content does not exceed 10% (Depkes RI, 2000).
- Identification of flavonoids, alkaloids, and tannins: this identification was performed by tube test method using the appropriate reagents for the class of compounds to be tested i.e. flavonoids, alkaloids, and tannins. Ammonia vapour reagents are used for the examination of flavonoids (Robinson, 1995). Mayer reagent is used to detect alkaloid compounds and then observe the presence or absence of precipitation (Mojab *et al*., 2003). The $FeCl_3$ reactor is used for the examination of polyphenols (tannins) by observing the colour of the result solution (Sri *et al.*, 2014).

2.2.2 Making Effervescent *Sechium edule* Granule

Effervescent granules were made using a wet granulation method. Separated between acidic components and alkalic components. Effervescent granules are made under special conditions of 25% relative humidity at 20-25°C (Siregar, 2007). All ingredients on the formula were sieved with a sieve mesh size 50 and dried earlier in the oven for 1 hour then weighed according to the formula. The acid mixture consisted of dry extract of *Sechium edule*, citric acid, tartaric acid, aspartame, lactose and PVP, dripped with 96% ethanol to form a mass that can be clenched, sieved with sieve mesh size 14, dried in an oven at 50 °C for 3 hours. Dry granules are sifted back with sieve mesh size 16. The alkalic components (Sodium bicarbonate mixed with residual lactose, and residual PVP) were dripped with 96% ethanol to form a mass that can be clenched, sieved with mesh no. 14, dried in an oven at 50 ° C for 3 hours. Dry granules are sieved back with mesh sieves size 16. Acid components and alkalic components are mixed in special room conditions (temperature 20-25^{0}C with 25% relative humidity (RH)) until they became homogeneous. The mixture was packed in an airtight container. The granules obtained were evaluated. The organoleptic examination includes examination of colour, flavour and taste. The formulation of granule can be seen in Table 1.

Table 1: Effervescent granule formulation of *Sechium edule* (@ 50 g)

Ingredients	Formula I (g)	Formula II (g)	Formula III (g)
Dried Sechium edule extract (Viscousextract:Lactose (1: 5))	20.16	20.16	20.16
Citric Acid	2.5	2.25	2
Tartaric acid	5	4.5	4
Sodium bicarbonate	15	16.88	18
Polyvinyl pyrrolidone (PVP)	1.5	1.5	1.5
Aspartame	2	2	2
Lactose ad 50 g	3.84	5.43	4.68

Note :
F I: Mixtures Citric acid, tartaric acid, and sodium bicarbonate: (2.5 g: 5 g: 15 g)
F II: Mixture Citric acid, tartaric acid, and sodium bicarbonate: (2.25 g: 4.5 g: 16.88 g)
F III: Mixture Citric acid, tartaric acid, and sodium bicarbonate: (2 g: 4 g: 18 g)

2.2.3 Physical Characteristics of Effervescent Granules Abstract

- Effervescent granule flow time test

Weighed a total of 50 g, mass of granules were inserted into the flowmeter. The time required for the granules to flow through the lid of the funnel opening was recorded. Testing was done five times. Good flow time requirement <10 g/ sec (Voigt, 1995).

- Effervescent granule moisture content

Five gram mass of granules inserted into the moisture balance tool at 105^{0}C for 15 minutes. After 15 minutes, the percentages (%) of water levels will automatically displayed on the tool display. The requirements of good effervescent moisture content granules levels are 0.4-0.7% (Fausett *et al*., 2000).

- Soluble time of effervescent granule

The effervescent granules weighed 5 g was then inserted into 200 mL of water. Time recording is required until the granules dissolve. Requirements for good effervescent granule time of less than 5 minutes result in a clear solution (Siregar, 2007).

- pH of granule effervescent

The effervescent solution was prepared by weighing 5 g of mass of granules dissolved in 200 mL of water. pH meter calibration was performed by first using buffer solution of pH 4.0 and pH 7.0. Once calibrated, the electric pH meter was dipped into effervescent solution that no longer have gas bubbles. the pH value obtained was noted. The pH of effervescent solution is said to be good if the pH is close to neutral i.e. 6-7 (Widayanti *et al*., 2012).

- Hedonic test

Hedonic test was administered to 30 panel lists age 17 years and above, healthy and had no disorder around the mouth that can affect the taste. They had been instructed not to consume food or drink prior to the test that could affect the assessment. They were asked to taste and assess the taste, smell and colour of the 5 g effervescent granule samples which had been diluted with 200 mL water. The panellists were expected to fill in the provided questionnaires.

2.3 Data Analysis

The result of granule physical characteristics test was statistically analyzed using one way ANOVA. This was followed by LSD test with 95% confidence level to know the significant difference between test result formula.

3 RESULT AND DISCUSSION

3.1. Simplicia and *Sechium edule* Extract

The *Sechium edule* are dried in the sun for 1 day and continued to be dried in the oven at 50°C for 2 days to reduce the moisture content. The use of the oven as a dryer means that the dried *Sechium edule* are evenly dried and the drying time is faster because it is not affected by weather conditions and protected from UV damage (Sulistyani and Eka, 2011). The powder of simplicia obtained from 20 Kg of squash is 1000 g of crude simplicia powder.

The *Sechium edule* extract is prepared by maseration method. The solvent used in this study was 96% ethanol because the content of the active substance of the *Sechium edule* had a good solubility in ethanol (Firdous *et al*., 2012). The maceration was performed with a ratio of 1000 g of simplicia of *Sechium edule* and 5 L of ethanol 96% per 1 time maceration. From the extract that was obtained thick extract 194.626 g from 1000 g of simplicia with yield of extract 19.463%. The result of organoleptic examination of *Sechium edule* extract is dark brownish green colour extract, unique smell of aromatic extract, bitter extract flavour and slightly thickened extract form.

The identification of the compounds contained in the extract of the *Sechium edule* is done by tube test. The tests include flavonoids, alkaloids, and tannins. Flavonoid test obtained positive results by passing the extract that has been dripped on filter paper with ammonia vapour. Filter paper turns yellow due to flavonoid reaction with ammonia vapour to form salt and a kinoid structure on ring B that will create double bonds that conjugated longer so that it will increase the colour intensity (Robinson, 1995). In the alkaloid test, positive result of alkaloid with Mayer's reagent was characterized by turbidity and formed a little white precipitate. The nitrogen in the alkaloids reacts with the K^+ metal ions from the tetraiodomerkurat (II) potassium to form the potassium-alkaloid complex precipitation (Marliana, 2005). In the tannin test, a positive result was obtained by adding the $FeCl_3$ reagent to form a blackish-green colour. The formation of blackish-green colour on the extract after being added with $FeCl_3$ is because tannin will form complex compounds with Fe^{3+} ions (Mangunwardoyo *et al*., 2008).

3.2. Granulation

Formulation of effervescent granule extract of *Sechium edule* with a mixture of citric acid, tartaric acid, sodium bicarbonate and other excipients of the three formulas is a modified obtained from the trial results. Manufacture of effervescent granules with wet granulation method has the advantage of making a simple, quick and homogeneous granule produced (Parikh, 2005). Effervescent granules are prepared by separating the acid and the alkali components to prevent reaction between acid-base components when mixed in wet conditions (Parikh, 2005). Citric acid and tartaric acid act as the source of acid, sodium bicarbonate as the alkali source, PVP as the binder, aspartame as the sweetener, and lactose as the filler. All the processes were performed; both formulations and physical properties of effervescent granules were performed in a special room with RH of 25% and temperature of 20-25ºC (Siregar, 2007).

3.3. Physical Properties of Effervescent Granule Extract of *Sechium edule*

Effervescent granules were tested for their physical properties using methods such as flow time test, moisture content test, soluble test, pH test, and Hedonic test. The test results can be seen in Table 2. The flow time of effervescent granule extract of *Sechium edule* from F I is shorter compared to F II and F III. This is due to F I that produced effervescent granules with larger particle size compared to other formulas (determined based on visual observations since they are not measured).

Table 2: Physical properties of granul effevescent extract of *Sechium edule*

No	Test Parameter		Value (X ± SD)		
			Formula I	**Formula II**	**Formula III**
1	Granule flow time (seconds)		1.47±0.20	1.53± 0.14	1.48 ± 0.10
2	Granule water content (%)		3.40 ± 0.34	3.62 ± 0.44	3.50 ± 0.63
3	Granule soluble time (minutes)		4.37 ± 0.12	4.25 ± 0.08	3.65±0.55*
4	pH value		6.62 ± 0.04	6.54 ± 0.08	6.59 ± 0.05
		Colour	1.93 ± 0.78	1.90 ± 0.71	2.00 ± 0.69
5	Hedonic test	Scent	2.00 ± 0.79	1.93 ± 0.74	2.07 ± 0.91
		Taste	1.77 ± 0.77	2.07 ± 0.74	2.13 ± 0.63

Description: * There is a difference with FI

According to Ansel (1989), one molecule of water per citrate acid molecule determines powder formation, whereas according to Voigt (1984), enlargement of particle size can generally improve flow characteristic or powder glide power. Differences in the concentration of citric acid and tartaric acid (1:2) used can affect the effervescent granular flow characteristic. The higher the acid concentration used, the better the flow characteristic (Widayanti *et al*., 2012). The flow time is influenced by the shape, size, porosity, density, and particle frictional forces and experimental conditions. Tartaric acid has a greater density than citric acid so that granules containing tartrate acid will have greater density. Large densities show large molecular weights that will flow more easily due to greater gravity (Anshory *et al*., 2007). According to Mohrle (1980), citric acid has a specific density value of 1.665 mg/mL, while tartaric acid has a specific density value of 1.7598 mg/mL. The statistical analysis of the three distributed formulas is 0.930 and the homogeneous data is 0.086. The result of statistical test shows that the three effervescent granule formulations that have been made have an average granule flow time which is not significantly different and less than 10 seconds. These results show that citric acid, tartaric acid, and sodium bicarbonate in the formula have no significant effect on granule flow time.

The moisture content of FI, FII, and FIII of effervescent granules in this study has not fulfilled the requirements of good effervescent granule water content i.e. 0.4-0.7% (Fausett *et al*., 2000). The moisture content was not achieved because of the limitations in the room where the effervescent produced has high relative humidity, causing the raw material from the effervescent to react quickly. Despite efforts to reduce the relative humidity of the room, room control can only reach 29% with a temperature of 29°C, whereas the room relative humidity for the preparation of effervescent preparations is 25% with a temperature of 20-25°C (Siregar, 2007).

This limitation makes the granules absorb moisture from the environment so that moisture content in the effervescent granule becomes high. Although the effervescent granule materials have been dried in the oven, effervescent granules produced cannot reach moist moisture of 0.4-0.7%. It is possible to achieve moisture content balance between the effervescent granule materials and the humidity of the manufacturing chamber (Budi and Lisa, 2007). The non-fulfilment of the effervescent granular moisture content will affect the flow characteristic and the dissolution rate (Widayanti *et al*., 2012). The ability of sodium bicarbonate to absorb moisture during storage is less than citric acid and tartaric acid, so the moisture contained in sodium bicarbonate is less than the moisture contained in citric acid and tartaric acid. Thus, the greater the amount of sodium bicarbonate used in the production of effervescent granules will further decrease the moisture content of effervescent granules produced.

The nature of citric acid that is hygroscopic also has the potential to absorb water vapour in the air. Sodium bicarbonate is not hygroscopic and at room temperature that has a moist content of less than 1% (Lindberg *et al*., 1992). From the statistical test obtained, the average of granule moisture content of the three formulas is not significantly different.

The soluble time of FI, FII, and FIII of effervescent granules in this study fulfilled the requirement of good soluble time i.e. less than 5 minutes. The process of dissolution of effervescent granules begins with the penetration of water into the effervescent granules. The presence of water penetration into the effervescent granules will produce acid and alkali reactions that will produce CO_2 gas. In the presence of CO_2 gas, the process of breaking the granules will be faster and indirectly accelerate the process of dissolving granules in water.

The binder used in this study was PVP 3%. PVP has hydrophilic properties that will facilitate the penetration of water into the effervescent granules, which will accelerate the dissolution of effervescent granules in the water. According to Rizal and Widya (2014), the citric acid contains water when reacting with sodium bicarbonate containing carbon dioxide gas then it will produce sodium citrate, water and carbon dioxide gases three times faster that can help solubility. This is supported by Nugroho (1999) who states that the presence of carbon dioxide gases produced help solubility without involving manual stirring on condition that all components are highly soluble in water. Based on a study conducted by Hayu (2015), the combination of citric acid and tartaric acid had a significant effect on the dissolving time of the effervescent tablets made. The higher the tartaric acid in the tablet, the higher the solubility (quick to dissolve). This occurs because citric acid has lower solubility than tartaric acid, and tartaric acid can react with sodium bicarbonate which can accelerate the solubility of effervescent tablets. According to Mandagi *et al*. (2015), the greater the concentration of sodium bicarbonate and the smaller percentage of citric acid in the effervescent formula, the faster the soluble time in water. Otherwise, the less sodium bicarbonate, the greater percentage of citric acid in the formula the longer the granule dissolves in water. This is because sodium bicarbonate acts as a destroyer of effervescent granules in water so that it can dissolve completely without stirring and when sodium bicarbonate reacts with water it carbonates (Dwijayanti, 2009). Alkali effect is greater than the acid mixture effect. Thus it is predicted that the base is more dominant in determining the effervescent granule soluble time. Comparing soluble time between F I and F III, there was a significant difference due to differences in the composition of citric acid, tartaric acid and sodium bicarbonate.

The pH test needs to be done because if the effervescent solution that is formed is too acidic it can irritate the stomach whereas if it has too much alkaline it will have bitter taste and bad taste. pH values of F I, F II, and F III of effervescent granules in this study are qualified as good pH values, ranging from 6.54 to 6.62. The pH of effervescent solution is said to be good if the pH is close to neutral i.e. 6-7 (Widayanti *et al.,* 2012). The statistical results show that the three formulas have different granule pH values not significant.

The hedonic test is a test method used to measure the level of preference of a product using a rating sheet (Singh-Ackbarali and Maharaj, 2014). Assessment categories consist of 4 levels namely (1) do not like; (2) somewhat like; (3) like, and (4) like very much. To know whether there is a difference between treatments an analysis of variance needs to be done seen from the value of F arithmetic compared with the value of F table. If the value of F arithmetic > F table then the treatment is very different (significantly different). Considering that the difference level is significant, the test was continued with DMRT (Duncan Multiple Rating Test) method to know which treatment is the same or different (Itsagusman, 2013). The hedonic test was seen from 3 hedonic test parameters (colour, scent, and taste). The results of the tests indicate that the highest hedonic average score belongs to formula III in terms of colour (2.0), scent (2,07), and taste (2.13). The results of the analysis of the organoleptic colour, smell, and taste test varieties showed no significant differences between formulas I, II, and III. The conclusion of hedonic test for the colours, aromas, and flavours of these three formulas is that they have an average score of 2 which means they are in the category of "somewhat like". This means that based on the general panellist's response on the three formulas of effervescent granules they are less attracted to the colour, the smell of effervescent granule drink, and that the taste of effervescent granule drink extract of *Sechium edule* on the three formulas is too sweet. These results show that required the modification of effervescent granule formula is required to produce health drinks that is acceptable to the people.

4 CONCLUSIONS

The formula that produces the best effervescent granules of the best *Sechium edule* extract is formula III whose composition of the mixture of citric acid, tartaric acid, and sodium bicarbonate is 2: 4: 18. This best formula has physical properties of flow time of 1.48 seconds, water content of 3.50%, soluble time 3.65 minutes, pH 6.59, and has the highest degree of preference (colour 2.0, aroma 2.07, and taste 2.13).

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