UNDERGRADUATE THESIS
FORMULATION OF LOZENGES FROM THE ETHANOL EXTRACT OF MISWAK *(Salvadora persica* L.*)* USING THE DIRECT COMPRESS METHOD

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ABSTRAK

FORMULASI TABLET HISAP EKSTRAK ETANOL KAYU SIWAK (*Salvadora Persica* L.) DENGAN METODE KEMPA LANGSUNG

Siwak *(Salvadora persica* L.*)* diteliti memiliki efektifitas sebagai antibakteri pada mulut. Semakin berkembangnya teknologi, kayu siwak jarang digunakan dan beralih pada media yang lebih modern seperti alat gosok gigi beserta bahan pembersih pastanya maupun cairan pembersih mulut, dengan ini peneliti membuat formulasi sediaan tablet hisap sebagai inovasi baru untuk mempermudah anak-anak dan orang tua yang sukar menelan obat. Penelitian ini dilakukan untuk mengetahui pengaruh variasi konsentrasi pada pengikat *Hidroxypropil Cellulose* (HPC-SSL-SFP) yang dibuat dalam 3 formulasi yang berbeda yaitu formula A 7,5%, formulasi B 10%, dan formula C 12,5%. Evaluasi massa cetak tablet yang dilakukan meliputi pengukuran uji kandungan lembab, laju alir, sudut henti dan kompresibilitas. Pengujian tablet hisap meliputi pengujian keseragaman bobot, kekerasan, friabilitas dan uji waktu hancur. Metode kempa langsung yaitu metode yang digunakan pada pembuatan tablet hisap dengan menganalisis halal bahan yang digunakan. Hasil evaluasi sifat fisik tablet dianalisa dengan statistik menggunakan uji One Way ANOVA menunjukan bahwa terdapat pengaruh pada kekerasan, kerapuhan dan waktu hancur dengan variasi pengikat HPC-SSL-SFP. Formula terbaik yaitu formula C yaitu dengan konsentrasi HPC-SSL-SFP 12,5% yang memiliki kekerasan paling tinggi yaitu 12,92 kg, kerapuhan 0,21 % dan waktu hancur yang lebih singkat dari formula A dan B yaitu 10,22 menit.

Kata kunci: Kayu Siwak, Kempa Langsung, Tablet Hisap.

ABSTRACT

FORMULATION OF LOZENGES FROM THE ETHANOL EXTRACT OF MISWAK *(Salvadora persica* L.*)* USING THE DIRECT COMPRESS METHOD

Miswak *(Salvadora persica* L.) has been studied as an antibacterial effect on the mouth. As technology develops, *miswak* is rarely used and shifts to more modern media such as toothbrushes and cleaning agents as well as oral cleansing fluids. With this the research made lozenges as an innovation to make it easier for children and parents who are difficult to swallow the drug. This study was conducted to determine the effect of variations in concentration on the Hydroxypropyl Cellulose (HPC-SSL-SFP) binder made in 3 different formulations namely formula A 7.5%, formulation B 10%, and formulation C 12.5%. The granule evaluation carried out included measurements of the moisture content test, flow rate, stop corner and compressibility. Testing of lozenges includes testing weight uniformity, hardness, friability and disintegration test. The direct compress method is the method used in making lozenges by analyzing the halal materials used. The results of evaluating the physical properties of tablets which analyzed by statistics using the One Way ANOVA test shows that there was an influence on hardness, friability and disintegration time with variations in the binding of the HPC-SSL-SFP. The best formula is formula C with the concentration of HPC-SSL-SFP 12.5% has the highest hardness of 12.92 kg, friability of 0.21% and shorter disintegration time of formula A and B which is 10.22 minutes.

Keywords: ***Miswak, Direct Compress, Lozenges.***

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PRELIMINARY

1.1 Background of the Study

Islam is a religion that regulates all aspects of life including how to maintain cleanliness and health. Hygiene and health of the body need to be considered especially in the mouth. The mouth is one of the main digestive organs of food because it is the place where food enters the stomach. Food scraps that are not cleaned, this will lead to the appearance of bacteria that damage teeth and cause unpleasant odors (Apriansi, 2017).

The practice of the Sunnah which is most often and most pleasantly carried out by the Messenger of Allāh is a civet. Wearing *miswak* is a simple and light work, but has very many benefits both worldly and hereafter. As the words of the Prophet Muhammad:

السِّوَاكَ مَطْهَرَةٌ لِلْفَمِّ مَرْضَاةٌ لِلرَّبِّ (رواه أحمد)

> Meaning*: "Miswak is cleanliness for the mouth and pleasure for Rabb" (H.R. Ahmad in Irwaul Ghalil no. 66 and Syarhul Mumti '1/120 and Taisir' Alam 1/62).*

The above hadith explains that *miswak* has benefits both worldly and hereafter. The benefits of *miswak* are worldly in the form of oral hygiene, health, freshness, teeth whitening, eliminating bad breath and others. While the benefits that are hereafter are *ittiba'* (following) to the Prophet Muhammad SAW and getting pleasure from Allah *Subhanahu wata'ala* (Ahmad, 2013).

Miswak *(Salvadora persica* L.) is a green leafy halofit plant that is usually used by Muslims to clean teeth. The Ulema said that women and certain people are allowed to use other media besides *miswak* because the gums and teeth of women and children are very soft, they are afraid that if they use *miswak*, then in order to continue to get the Sunnah he must

intend to use *miswak* even if he is allowed to use other media than *miswak*. (Maulana, 2008; Zaki, 2015).

Some studies suggest that *miswak* has antibacterial properties against *Streptococcus mutants, Streptococcus aureus, Streptococcus pyogenes, and Candida albicans.* (Abdel, *et al.*, 2002; Al-Bayati and Sulaiman, 2008). With the development of modern science and technology, *miswak* has rarely been used and switched to toothbrush media or tools plus cleaning agents or toothpaste. Besides, it is also found now oral cleansing fluids commonly used after brushing your teeth to increase dental hygiene and freshness of the mouth.

The pharmaceutical preparations made in this study were lozenges. The suction tablet has a local effect on the mouth and its use is found for the prevention and treatment of oral and jaw chamber infections as a drug predominantly antiseptic, disinfectant, analgesic and oral anesthetic. (Lachman, 1994; Voight, 1994). Making lozenges is intended to provide a form of treatment that can be easily given to children or parents who find it difficult to swallow whole drugs, and can mask the unpleasant or bitter taste of the drug (Voight, 1994).

Binder is the most important element in making lozenges. Hydroxypropyl Cellulose (HPC-SSL-SFP) is the latest variant of HPC which has a special low viscosity with very fine particle size (super fine powder) which was developed to provide excellent tablet properties in the direct press method (Muria, 2012).

Research on lozenges was made in three formulations which varied the concentration of Hydroxypropyl Cellulose (HPC-SSL-SFP) as a binder using the direct compress method. Research by (Muria, 2012) stated that the formulation of lozenges of betel leaf extract using binder (HPC-SSL-SFP) obtained the best formulation at a concentration of 10%, but the optimum concentration of the physical properties of *miswak* extract produced on *miswak* extract tablets was not known.

1.2 Formulation of the Problem

Based on the research background, the formulation of the research problems are as follows:

1. Can the ethanol extract of Miswak *(Salvadora persica* L.) be formulated into lozenges in the form of a direct compress method so that lozenges can be obtained to meet physical quality requirements?
2. What is the effect of the variation of the concentration of Hydroxypropyl Cellulose (HPC-SSL-SFP) as a dry binder on hardness, friability, and disintegration of lozenges in the ethanol extract of *miswak*?
3. Which formulation is the best among the three variations of the concentration of HPC-SSL-SFP binder on the lozenges of the *miswak* ethanol extract?

1.3 Research Objectives

Based on the formulation of the problem, the objectives of this study are:

1. Knowing that the ethanol extract of Miswak *(Salvadora persica* L.) can be formulated into lozenges in the form of direct compressing so that lozenges can be obtained to meet physical quality requirements.
2. Knowing the effect of variations in the concentration of Hydroxypropyl Cellulose (HPC-SSL-SFP) as a dry binder on hardness, friability, and disintegration of lozenges in ethanol extract of *miswak*.
3. Knowing the most optimum formulation among the three variations of the concentration of Hydroxypropyl Cellulose (HPC-SSL-SFP) binder on lozenges of ethanol extract of *miswak*.

1.4 Benefits of Research

1.4..1 Theoretical Benefits

The benefits of this research theoretically for the University is that the results of the research can be a useful academic document to be

used as a reference for further research, while for female students the results of this study can be a reference for further research.

1.4.2 Practical Benefits

The practical benefits of this research are:

1. For industry, research can be a development of the traditional drug industry with a new formulation of lozenges made from active extracts of *miswak* stem.
2. For the community, this research can be an important information for the use of *miswak* formulations as antibacterial in the mouth.

CHAPTER II

LITERATURE REVIEW

2.1 Previous Research

Research by Zainab, *et al.* (2004), entitled "Uji Antibakteri Siwak (*Salvadora persica* Linn.) terhadap *Streptococcus mutans* dan *Bacteroides belaninogenicus"* found that the MIC results of *miswak* extract against *Streptococcus mutant* bacteria were 6.25% and *Bacteroides melaninogenicus* were 3.12%.

Research by Mansoor, *et al.* (2011) entitled "Pharmacological Profile of Salvadora Persica" found that the results of acute oral toxicity show that S. persica extract is safe up to a dose of 5 g/kg weight of mice and extracts given orally show no analgesic, anti-inflammatory activity, not the occurrence of CNS depressants and confirms the results and safe pharmacological profile in the use of *miswak*.

Abe's research, *et al.* (2011) showed that the manufacture of tablets using the direct compression method with HPC-SSL-SFP binder can produce tablets with high hardness values and produce low friability at concentrations (3%, 5%, and 7%) as dry binders. The research conducted by Muria (2012) with the title "Formulasi Tablet Hisap Ekstrak Etanol Daun Sirih *(Piper betle L.)* menggunakan Metode Kempa Langsung dengan Variasi *Hidroxypropil Cellulose* (HPC-SSL-SFP) Sebagai Pengikat" found that the use of HPC-SSL-SFP dry binders in making lozenges using the compress method directly gets the best formula, that is in accordance with the physical and chemical properties of the tablet at a concentration of 10%.

Research by Mumtihanah and Amaliah (2018) entitled "Formulasi *Hazard Candy Lozenges* dari Ekstrak Bubuk Siwak *(Salvadora persica* L.) untuk Mengatasi Bau Mulut" showed that *miswak* can be made into lozenges and ethanol extract of *miswak (Salvadora persica* L.) is pharmaceutically stable whiich has an activity as an antibacterial bad breath.

2.2 Theoretical Basis

2.2.1. Miswak Plants

Miswak plant classification in the study of Tjitrosoepomo (1998), namely:

Divisio	: Embryophyta
Sub Divisi	: Spermatophyta
Class	: Dicotyledons
Sub Class	: Eudicotiledons
Ordo	: Brassicales
Family	: Salvadoraceae
Genus	: Salvadora
Species	: *Salvadora persica* Linn

Figure 2.1 Miswak Tree (Salvadora persica) (Sher, *et al*., 2010)

According to Sher, *et al*. (2010), *Miswak (Salvadora persica* L.) is a halofit plant that has green leaves and lives in extreme environments, ranging from very dry environments to very high salinity environments. This plant is a shrub with a maximum height of seven meters.

Research conducted by Putra, (2011) explained that the main *miswak* was covered in very thick branches and its growth was toward all directions, until the branches reached the ground. The shape of the leaves is *oblong elliptic* (like eggs) to round with a size of 3x7 cm, dark green, rather thick, the apex is tapered to rounded, narrowed sharply, the base generally narrows, there are clear leaf borders, leaf bones up to

10 mm long, and arranged in pairs. The flower color ranges from green to yellowish, very small, easily separated from the stem and there are from the axial part to the stem with many flower branches as long as 10 cm. Fruit is spherical, fleshy, has a diameter of 5-10 mm, colored pink to bronze and semitransparent when it is ripe.

Figure 2.2 Forms of Stems, Leaves, Flowers, and Fruits (Sher *et al*., 2010)

Distribution of *miswak* is mostly found in deserts, wide fields, grasslands and river banks. *Miswak* can survive in environments that are very dry and resistant to salt and can be found in coastal areas. *Miswak* can grow in high-range areas ranging from 0-1800 m above sea level (masl). *Miswak* can also be grown on clay, sand and black soil (Putra, 2011).

Miswak contains terpenoids, alkaloids, tannins, flavonoids, glycosides, sterols, sodium chloride, potassium chloride, sulfate, nitrate, thiocyanate, salvadorin, oleic, cyanogenic, resin, silica, vitamin C, saponins, linoleic, stearate acid, benzyl-isothyosine, trimethylamine, beta-sitosterol, sweetic acid, high mineral content of 27.6%, sulfur, abundant fluoride, chlorine-containing salts (Al-Sadhan and Almas 1999; Darout, *et al*., 2000; Ahmed *et al*., 2008; Amalia *et al*, 2018).

Miswak is a plant that is widely found in the Middle East and is usually used as a cleanser for teeth and mouth. The part used for wearing *miswak* is in the form of stems, twigs and roots (Noumi,

2004; Amalia *et al*, 2018). Research done by (Apriansi, 2017) also stated that *miswak* is used as a mouth cleanser because it has several ingredients of chemicals and bile substances that function to resist decay and clean teeth.

The chemical content of *miswak* extract is extremely effective in removing plaque and breaking down the virulence of pathogenic periodontal bacteria. The natural anionic content of *miswak* is believed to be an effective antimicrobial for inhibiting and killing microorganisms. One example is terpenoids as antibacterial which inhibits bacterial growth by disrupting the process of forming membranes or cell walls so that the membrane or cell wall of bacteria is not fully formed and also inhibits protein synthesis and soluble in lipids so that it can be easier to penetrate the cell wall (Amalia , 2018). Besides terpenoids, there are also alkaloid compounds and tannins, the mechanism of action of alkaloids as antibacterial is by disrupting the constituent components of peptidoglycan in bacterial cells, so that the cell wall layer is not formed intact and causes cell death. While the mechanism of action of tannins causes lysis in bacteria because it has a target on polypeptide cell walls so that cell walls are not fully formed and tannins have the ability to activate bacterial enzymes and interfere with the passage of proteins on cell membranes.

According to the study by (Putra, 2011), it was found that *miswak* has the ability as an antibacterial as well as the ability as antifungal, antiplasmodium, antiplaque, antiperiopathy, anticaries, anti-inflammatory, diuretic, antiulcer, antihelmin, dental cleanser, antirheumatic, cough and asthma, laxative, repair damaged gastric mucosa and increase low cholesterol levels in the plasma.

2.2.2 Extraction

Simplicia according to (Ministry of Health-RI, 2000) is a natural material used for drugs that have not undergone any processing, and it is also stated that simplicia is a dried material. Simplicia consists of

vegetable simplicia, animal simplicia and pelican simplicia or minerals.

a. Vegetable simplicia is simplicia in the form of whole plants, plant parts or plant exudates. Plant exudates are the contents of cells that spontaneously come out of their cells or vegetable substances which in a certain way are separated from the plants.
b. Animal simplicia is simplicia in the form of whole animals, animal parts or useful substances produced by animals and not yet in the form of chemicals.
c. Pelic acid or minerals are those that have not been processed or have been processed simply and are pure chemicals.

Extracts are viscous preparations obtained by extracting active compounds from vegetable simplicia or animal simplicia using appropriate solvents, then all or almost all solvents are evaporated and the remaining mass is needed to meet the prescribed standards (Ministry of Health-RI, 2000). Based on the nature of the extract it is grouped into 3 namely dilute extract (extractum tennue), viscous extract (extractum spissum) and dried extract (extractum siccum). Dilute extracts are preparations that have concentrations such as honey and can be poured. Viscous extracts are preparations in cold condition and cannot be poured while dry extracts are preparations that have concentrations of water content not more than 5% (Voight, 1994; Arum, 2012).

Extraction is a technique to attract active compounds from simplicia or techniques to separate dissolved material from plant tissue using suitable solvents. Selection of solvents is an important thing in making extracts, because active compounds in plants have certain affinity for solvents (Singh, 2002; Muria, 2012). Extracts can be made in several stages, namely making simplicia powder, adding solvent, purifying extracts from unwanted compounds, and drying extracts from these solvents (Ministry of Health, 2000).

The cold extraction method has two ways, namely the maceration and percolation method. The maceration method is a process of extracting simplicia using solvents with several shuffling or stirring at room temperature (room). The percolation method is an extraction method which is always new to perfect a solvent that is generally carried out at room temperature. This process consists of material development, intermediate maceration stage, continuous percolation stage until extracts (percolates) are obtained which are 1-5 times the amount of material (Muria, 2012).

2.2.3 Lozenges

Tablets are solid preparations which contain medicinal ingredients with or without additives. Tablets are the most widely used dosage forms and some tablets are made by pressing which gives high pressure to powder or granules using steel molds. Tablets can be made in various sizes, shapes and surface markings depending on the design of the mold (Ministry of Health-RI, 2014).

Tablet dosage forms have advantages such as: having dose accuracy, practical presentation, low cost of production, easy packaging, long-term storage, and easy to carry everywhere (Banker and Anderson 1986).

Lozenges are solid preparations containing one or more medicinal ingredients, generally with scented and sweet ingredients, and can make the tablet dissolve or slowly dissolve in the mouth. Suction tablets are generally intended to treat local irritations or infections of the mouth or throat, but can also contain active ingredients intended for systemic adsorption after being swallowed. The example of additional materials in the manufacture of lozenges is a binder. Binder is a critical factor in making lozenges, because the work of lozenges is intended to dissolve in the mouth slowly (Ministry of Health-RI, 2014; Chabib *et al*., 2010).

The difference between lozenges and conventional tablets is located in the organoleptic properties, non-disintegration properties, and extended dissolution rates on the tongue. The lozenges is designed with a slow release in the mouth so that this situation must develop a mixture of added flavors that can cover unpleasant sensations caused by the active substance. The hardness of lozenges must also be greater than conventional tablets because the lozenges are formulated to dissolve in the mouth slowly. Therefore high pressure and larger binding materials are needed (Siregar J.P. and Wikarsa, 2015).

There are three types of the methods of making compression tablets in general, ,namely:

1) Wet Granulation Method

   The wet granulation method is the process of adding liquid to a powder or powder mixture in a container equipped with stirring which results in agglomeration or granule (Siregar, 2010). This method is a method that is often used in making compression tablets. The granule is made by adding a liquid-shaped binder to the powder mixture, and then the mass of moist powder is ground and sifted to obtain the desired size of the granule. The drying process is used to remove moisture from the granule (Ansel, 1989).

   The weakness of this method is that the use of a binding solution containing water can damage the active substance through hydrolysis reactions. Degradation of active substances that have thermolabile properties can also occur due to the drying process in granules (Jones, 2008).

2) Dry Granulation Method

   The dry granulation method is formed by adding a binder to the drug powder mixture, by compacting large amounts of mass from the powder mixture, then breaking it down and making fragments into small granule masses (Haifa, 2013). This method is used specifically for materials that cannot be processed using a

wet granulation method because of their high sensitivity to water vapour and drying requires high temperature (Ansel, 1989).

The purpose of this method is to obtain granules that can flow freely for the manufacture of tablets. Dry granulation is made by directly pressing all the added material formulations with high pressure using a compactor machine (Siregar, 2010). The weakness of this method is that when the mixing process occurs segregation of each component, after the slugging process there is a lot of dust or fine particles (fines) and sieving can inhibit the flow rate of granules and tablets produced from dry granulation have a low hardness (Jones, 2008).

3) Direct Compress Method

The direct compress method is used for processes where the tablets are pressed directly from the powder mixture of the active substance and the corresponding excipients (fillers, disintegrates and lubricants) that flow uniformly into the press hole and form sturdy solids. This method is the most energy efficient, fastest and most economical method for producing a tablet compared to wet granulation or dry granulation methods (Siregar, 2010).

The press is directly termed as a general process for the manufacture of tablets that are compressed when there is no pre-treatment or only a small treatment is needed before entering the ingredients into the tablet machine. Some materials in this method have important binding characteristics (Haifa, 2013).

The method of pressing directly applies to drugs that have low to moderate doses and for drugs with large doses that are difficult to press directly because in general the material of attraction between molecules is weak and is enveloped by a membrane of gas that is absorbed tends to inhibit compaction, while for drugs with low doses or being with auxiliary materials that have good flow and compressibility properties can provide ease in the pressing process directly (Lachman, 1994). The physical properties of each filler are critical, and a slight change can

change the nature of the flow and press so that it is not suitable for direct pressing (Ministry of Health-RI, 1995).

The advantage of this method is that it is practical because the stages of the process are few and the process is dry which allows the medicinal material to be sensitive to moisture and heat to be compressed using the direct compress method (Lachman, 1994). The obstacle of this method is the technical constraints such as handling powders to meet the standard criteria of the nature of water and the specified compactibility. It is very difficult to obtain a powder mixture with a high degree of homogeneity. Another obstacle is the addition of color because it can allow the formation of spots on tablets (Aulton, 2002).

Additives are medicinal ingredients that have several special properties to be made into a drug preparation, taking into account the various effects of the drug, the performance of the drug, the chemical properties of the drug and its organoleptic. The use of additional ingredients in lozenges is based on the effects on the quality of lozenges produced such as hardness, taste, erosion, disintegration and granule flow characteristics. (Lachman, 1994; Haifa, 2013). Additional ingredients for the formula for lozenges are:

1) Fillers

   The filler material is used in tablet formulations to increase the mass of tablets containing low active ingredients so as to allow the printing and compounding of very small amounts of drugs, and the use of fillers as additional ingredients to have the required size or mass (Voight, 1994; Jones, 2008) In addition fillers can also improve the power of cohesion so that it can spur flow or can be pressed directly. Fillers must also be inert or neutral, physically and chemically stable, both in combination with various other components (Banker and Anderson, 1986; Lachman, 1994; Putrisari, 2009).

Some fillers are commonly used in the direct compress method because they have compression properties, good flow and sweet taste namely sucrose, xylitol, agglomerated a-lactose, dextrose, mannitol, sorbitol, microcrystalline cellulose (Banker and Anderson, 1986).

2) Binder

Binding material is the material needed to provide adhesion to the mass of powder during granulation and provide cohesion properties that have been present in the filler so that it can form a compact tablet structure after printing and increasing the durability of the tablet. Therefore the binder guarantees the union of several powder particles in granular granules. The binding material can be added to the dry form material, liquid or solution, depending on the method of making tablets (Ministry of Health-RI, 1995).

The function of the binder is to increase the medicinal ingredients with other auxiliary materials so that good granules can be obtained and can produce tablets that are compact and not broken. Binder is also a major component that contributes to tablet hardness, but depends on the type and concentration of the binding material used (Parrot, 1971; Lachman, 1994).

Some examples of commonly used binders are Hydroxypropyl Cellulose, Microcrystalline Cellulose (Ceolus PH-101), L-HPC, PVP-PVA, natural polymers (starch, gelatin, Arabic gum, alginate acid), synthesis polymers (polyvinyl pyrrolidone, methylcellulose, HPMC, Na CMC, ethyl cellulose, and sugar (glucose, sucrose, sorbitol) (Muria, 2012; Siregar 2010).

3) Lubricant material

Lubricant material is a material used to spur the flow of powder or granules by reducing friction between particles, and so that the tablet is not attached to the mold. Lubricant materials can also fulfil some different functions and are grouped into glidant,

lubricant and antiadherent materials (Lachman, 1994; Voight, 1994).

Some lubricating materials that are often used in the manufacture of tablets include: talc, magnesium stearate, stearate acid, calcium salts, sodium stearate, Lycopodium, fat, liquid paraffin, aerosol starch, glyceryl behenate, PEG and sodium lauryl sulfate (Jones, 2008; Voight, 1994).

4) Sweetener ingredients

Sweeteners or flavourings are extremely important in making lozenges because what is felt to be mouthed when smoked is strongly related to consumer acceptance and affects the quality of the product (Peters, 1989). The use of sweeteners is limited mainly to tablets that are chewed or smoked. Some fillers that can be used as sweeteners such as: sucrose, dextrose, mannitol and sorbitol (Lachman, 1994).

In lozenges, tablet occupancy in the oral cavity requires that formulators develop not only products with pleasant flavor additions, but the addition of sweetness to the product can also cover the bitter base that the formulation might have (Siregar, 2010).

2.2.4 Evaluation of Granule Tablet

According to (Gibson, 2004) understanding the unique properties of powder systems such as moisture content, flow properties, stationary angles and compressibility is needed in the formulation and production of rational tablets.

1) Moist content

Examination of moist content is extremely important because it can affect the physical and chemical properties of the tablets produced. The moisture level requirements for lozenges should not be dry with the remaining 2-5% moisture (Voight, 1994).

2) Flow rate

Flow rate is the time needed by a number of granules and powders to flow in a tool. Granules that have good flow will flow from a container with a time of no less than 10 seconds. Flow velocity is influenced by particle size and shape, surface conditions, humidity, and addition of pelican material (Voight, 1994).

3) Stop corner

Stop corner is the corner that occurs between cone-shaped particles and horizontal fields. The size is influenced by the shape and humidity of the granule. If the corner $<30^{o}$, it shows that the granule can flow freely and if the angle $\geq 40^{o}$ it shows that the flow properties of the granule is not good (Voight, 1994).

4) Compressibility test

Compressibility shows the volume of a number of granules powder due to pounding or tabs and vibration. Factors that influence are particles size, density and shape. The smaller the index of determination, the smaller the flow properties. The standard of good granule compressibility is <15% (Voight, 1994).

2.2.5. Evaluation of Lozenges

Evaluation of lozzenges aims to determine the quality of tablets and ensure that tablets made meet the standards required for the quality of tablets before they are marketed. Quality tests include a physical examination of tablets, namely uniformity of weight, tablet hardness, friability, disintegration time and organoleptic examination performed to determine the taste of lozenges that have been formulated (Muria, 2012; Arum, 2012).

1) Weight uniformity

Weight uniformity is influenced by the flow properties of the granule mixture in the compression chamber filling process. Granules with good flow properties have a uniform ability to

fill the compression space so that the variation in tablet weight decreases. The uniformity of tablet weight can also be influenced by the condition of tablet machines that are not good (Arum, 2012).

The uniformity of the preparation is defined as the degree of uniformity in the amount of active substance in the preparation unit. This uniformity can also be viewed from the weights in each preparation. A total of 10 to 20 tablets are weighed one by one then calculated the percentage of existing deviations (Ministry of Health-RI, 2014).

2) Tablet hardness

The hardness of the tablet shows the resistance of the tablet to various mechanical shocks during packing and transporting. In general, the greater the pressure applied to the mass of powder or granule, the harder the tablet is produced, although the properties of each additional material can also determine the hardness of the tablet. The hardness requirement for lozenges is that it can withstand pressures of 30-50 kg per inch2 or above 10 kg per cm3 (Voight, 2014).

3) Tablet friability

The friability of the tablet is the ability of the tablet to withstand scratches and mechanical shocks during manufacture, packaging, and shipping. The friability of tablets is related to the physical strength of the tablet surface. A tool for measuring tablet rigidity is called a friabilator. Tablets can still be tolerated if the tablet only has a heavy loss between 0.5% to 1% (Voight, 1994).

4) Disintegration Time

Disintegration time is the time needed for lozenges to dissolve or erode slowly in the oral cavity within 5-10 minutes. The lozenges are expected to have a local effect on the mouth and oesophagus (Siregar, 2010; Lachman, 1994).

2.2.6. Additional Material Monographs

Additional materials used in the manufacture of lozenges according to the Indonesian Ministry of Health-RI, 1995; Rowe *et al*., 2009) are:

1) Mannitol (Direct compressed)
   - Chemical name: D-Mannitol
   - Molecular formula: $C_6H_{14}O_6$
   - Description: Crystal powder or free-flowing granule, white, odorless, sweet taste.
   - Uses: Sweeteners on tablets used for the direct compress method.
2) Hydroxypropyl cellulose (HPC-SSL-SFP)
   - Chemical name: Cellulose, 2-hydroxypropyl ether
   - Molecular formula: $CH_2CH\ (OH)\ CH_3$
   - Description: Hydroxypropyl cellulose is a white or yellow powder, tasteless and smelly.
   - Uses: Hydroxypropil cellulose as a dry binder and can be used for low concentrations and is beneficial for active ingredients with poor compressibility.
3) Magnesium stearate
   - Chemical name: Octadecanoic magnesium acid salt
   - Molecular formula: $C_{36}H_{70}MgO_4$
   - Description: Forms fine white powder with a distinctive weak odor and is easily attached to the skin.
   - Uses: The main function of magnesium stearate is as a lubricant in making capsules and tablets at a concentration of 0.25-5%.
4) Talcum
   - Chemical name: Talcum
   - Molecular formula: $Mg_6\ (Si_2O_5)_4\ (OH)_4$
   - Description: Powder form is extremely fine, white or gray-white, shiny and easily attached to the skin.
   - Usefulness: Apart from having a function as a lubricant, talkum also

functions as glidant and antiadherent, used with a concentration of 1-10%.

5) Lactose (Agglomerated a-lactose monohydrate)
   - Chemical name: lactose monohydrate
   - Molecular formula: $C_{12}H_{22}O_{11}H2O$
   - Description: Lactose is a white powder or crystal, odourless and has a sweet taste equivalent to 20% sucrose.
   - Use: filler material on tablets is used for the direct press method.

6) Avicel PH 102
   - Chemical name: Microcel PH 102, cellulose microcrystalline
   - Molecular formula: $(C_6H_{10}O_5)n$
   - Description: Fine powder form, white, odourless, tasteless.
   - Use: As a filler or destroyer.

2.2.7. Halal Product Analysis

The legal halal basis for products in Islamic sharia is found in the Word of Allah SWT:

يَٰٓأَيُّهَا ٱلنَّاسُ كُلُواْ مِمَّا فِى ٱلۡأَرۡضِ حَلَٰلٗا طَيِّبٗا وَلَا تَتَّبِعُواْ خُطُوَٰتِ ٱلشَّيۡطَٰنِۚ إِنَّهُۥ لَكُمۡ عَدُوّٞ مُّبِينٌ (البقرة : ١٦٨)

Meaning: *O mankind, eat from whatever is on earth [that is] lawful and good and do not follow the footsteps of Satan. Indeed, he is to you a clear enemy. (QS. Al-Baqarah: 168).*

Based on the letter of Al Baqarah above, Allah commands the believers to eat *halal* food while information related to raw materials and additional materials in a product needs attention from producers and consumers because this information will provide additional knowledge to the public about raw materials that are *halal* or *subhat.*

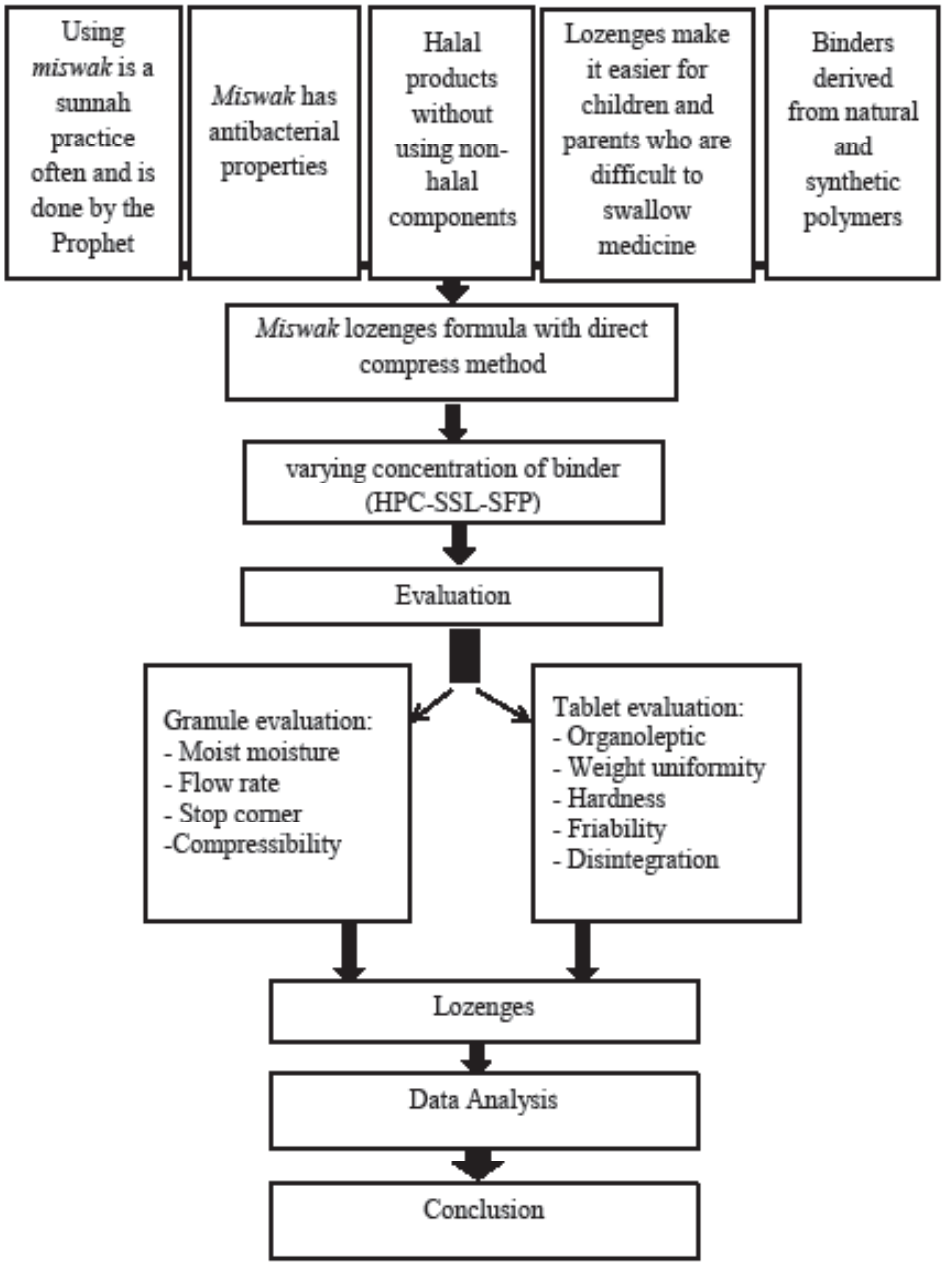
Halal products are products that meet halal requirements both in terms of production and materials used. The manufacture of drugs also has a critical point especially in the materials used. One of the

critical points is the use of alcohol as a solvent. The legal provisions for alcohol use according to the Indonesian Ulema Council are the use of *non-khamar* industrial alcohol or ethanol (whether it is the result of chemical synthesis or the results of non-chemical fermentation industries) for the production of food, beverage, cosmetics, and pharmaceutical products. if it is not medically harmful (Ministry of Religion, 2003).

In the selection of ingredients for drug formulations, there are at least three aspects that must be considered, namely:

1. Not made from unclean ingredients (for medicine)
2. Not made of unclean ingredients (external medicine and internal medicine)
3. Not contaminated by unclean materials (in the process of production, storage and distribution).

2.3 Conceptual Framework



CHAPTER III

RESEARCH METHODS

3.1 Place and Time of Research

This research was conducted at the Laboratory of Pharmaceutical Chemistry at the University of Darussalam Gontor and Pharmaceutical Laboratory of the University of Muhammadiyah Surakarta. The study lasted approximately five months from November 2018 until March 2019.

3.2 Equipments and Materials Research

The tools used in this research are: Tools Printers tablet, blender, sieve mesh 44, a rotary evaporator, water bath, oven, climatic oven, mortar pestle, analytical balance, measuring cups, moisture analyzer (Ohaus MB 45), flowmeter, stopwatch, volunometer (Dual Density Tapped type-DTD 22), disintegration tester, digital hardness tester (Stokes Mosanto Scale 0-20 kg) and friabilator (Erweka type of FY 20).

The materials used are: *Miswak* (PT. Siwak-F), *Hidroxypropyl cellulose* (HPC-SSL-SFP) (Nisso PT. Lawsim Zecha), 96% ethanol (Mitra Medika), mannitol Direct Compress (PT. Signa Husada), avicel PH 102 (BRATACO).

3.3 Design of Experiments

This research is of the experimental category. Free variables used are concentration on *Hidroxypropyl cellulose* binding, whereas the binding variable binding is the physical nature of the tablets hardness, friability of the tablets and disintegration time. The lozenges of dry *miswak* extract tablets formualtions the *miswak* is made in 3 formulations with different concentration variations in ingredients and sweetener binding as follows.

Table 3.1 Formulations Draft of Lozenges of Dry Extract *Miswak*

Material	The Function of Material	Formula (%)		
		A	B	C
The ethanol extract *Miswak* stem 1:2	Active substances	10	10	10
Hidroxypropil Cellulose (HPC-SSL-SFP)	Fastener	7,5	10	12,5
Mannitol	Sweetener	40	40	40
Mg Stearate	Lubricant	1	1	1
Talcum	Antiadheren	1	1	1
Avicel PH 102	Filler	10	10	10
Agglomerated a-lactose monohydrate	Filler	Add 100	Add 100	Add 100

Descriptions:

Dosage in ethanol *miswak* extract formula is determined by reference to the study (Akhtar *et al,* 2011) that the 10% effective concentration of the extract as an antimicrobial when using clinically using human saliva and indicates that that significant cuts in the bacterium *Streptococcus mutans*. Whereas, according to research conducted by Zainab (2014) states that the results of the *Miswak* extract MIC against the bacteria *Streptococcus mutans* test by 6.25% and against *Bacteroides melaninogenicus* 3:12%. MIC is the minimum concentration of test compounds capable of inhibiting growth microbial.

Concentration 10% = 10 g in 100 g= 10000 100000 mg

Preparations to be made = lozanges 500 mg

Dose in tablet dosage= 500 hundred thousandths x 10000 = 50 mg

3.4 Stages of Research

3.4.1. Determination of Plant

The *miswak* was obtained from Saudi Arabia which then in determination to ensure the truth and identity of plants so that errors can be minimised. The determination is carried out in the Department of Pharmaceutical Biology University of Gajah Mada Yogyakarta.

3.4.2. Manufacturing Simplicia Miswak

Manufacturing of Rod Simplicia *Miswak* is done by washing the *miswak* to clean the stem and dry it through unclear, then the dried rods are cut into small pieces and blended into powder to expand surface making it possible to dissolve its full potential. The already obtained is powder sifted using a mesh size 44.

3.4.3. The Making of Viscous Extracts

The process of extraction is done by the method of maceration using solvent ethanol 96%. Maceration was chosen because the process is simpler and does not damage the compounds which are not heat resistant. Simplicia *miswak* steeped for 5 days with stirring ±3 times a day. The result of maceration then evaporated using a rotary evaporator at a temperature of binding C and 60^{o}C using a waterbath.

3.4.4. The Making of Dry Extract Powder

Viscous *miswak* extract is added adsorbent Aerosil 1:2 by comparison, then extract the condensed crushed in a mortar until the dry powder extract obtained *miswak*.

3.4.5. Analysis of Halal Ingredients

Analysis of halal ingredients in the formulation of lozenges of *miswak* ethanol extracts was done by analyzing the origin of the materials to be used and viewed from three aspects related to halal pharmacologically namely:

1. Not made from *haram* materials
2. Not made from the unclean
3. Not contaminated by haram ingredients

3.4.6. Making Lozenges

The making of the lozenges in each formula is with mass per tablet 500 mg. All materials to be used are weighed, then the extract of dried *miswak* is crushed together with sweeteners material namely manitol. Add HPC as a dry binder, as well as lactose and stirring until the mixture is homogeneous. Improve the nature of flow with lubrication and adhesive added with talcum and magnesium stearate. Before being pressed into a tablet, be evaluated of the granule. The evaluation was also done on a tablet in accordance with the procedures set out in this research.

3.4.7. Evaluation of Granule

a. Moist Content

Moist content is intended to prevent from dust that can cause the growth of mold and microbes. Evaluation of moisture content which is done by as much as 3 grams of the powder is incorporated into the tool to analyze its moisture. The requirement levels of moist powder is incorporated into the tool to analyze moisture. The requirement levels of moist powder that is contained is on 2-5% (1994 Voight).

b. Flow Rate

Flow rate is intended to specify the nature of the prevailing flow corner of the slope of the flow. To measure the flow rate, the researcher used tools mass flowmeter by means of as many as 100 gram. Tablets are then placed in a container and funnel-shaped tool is run. The amount of time becomes a print by the granule to be able to pass through the funnel is calculated (Voight, 1994).

$$\text{Flow Rate} = \frac{\text{Mass of Powder (g)}}{\text{Flow Time(second)}}$$

Table 3.2 Flow Rate and Flow Properties

Flow Rate	Flow Properties
>10	Free Flowing
4-10	Easy Flowing
1,6-4	Cohesive
<1,6	Very Cohesive

c. Stop Corner

Evaluation stop corner was done by inserting the tool mass flowmeter, then the mass forms a cone at the base of the funnel, the measured height (h) and the radius of the cone (r) (Voight, 1994).

$\alpha = \text{arc tan } \frac{2h}{d}$

Description: h = height of the printed mass cone tablet

R = radius of printed mass cone tablet

Table 3.3 Categories of Powder Flow Based on Stop Corner

Stop Corner	Category Flow
<25	Very Good
25-30	Good
30-40	Enough
>40	Very Bad

d. Compressibility

Test compressibility according to (Voight, 1994) is performed with an instrument called volunometer. Terms % of good compressibility is 5-15%. Percent compressibility can be calculated using the formula:

$$\% \text{ compressibility} = \frac{V1 - V2}{V1} \times 100\%$$

Table 3.4 Compressibility Index and the Nature Flow

% Compressibility	Nature Flow
5-15	Very Good
16-18	Good
19-23	Enough
24-33	Bad
34-40	Very Bad
>40	Worse

3.4.8. Evaluation of Lozenges

a. Organoleptic Examination

Examination of the organoleptic includes the tablet form, colour or smell, and the aroma of tablets taste. Colour is not uniform and the existence of a disability on a tablet in addition to its aesthetic value can also give rise to the perception of the existence of varicosity of the content and quality of the product is bad (Ansel, 1989).

b. Uniformity of Test Weights

Test of weight uniformity with weighing 20 heavy tablet is done carefully and calculate the average weight of the tablets. The test conditions of the uniformity of weights is done if the average weight is more than 300 mg. Weigh one by one if no more than two tablets these di it weight of deviate from the average of 5%. And no one does it weigh deviate from the average weights more than 10% (Ministry of Health-RI, 2014).

c. Test Hardness

Tablet hardness test was performed by using digital hardness tester. How to test the hardness of tablets, namely to be tested is paced with the horizontal position, the tool is calibrated to the position of 0.00. Rotate the tool until the tablet is broken and then see the scale printed on the tool. The experiment was conducted four times and calculate the price of a full (Voight, 1994).

d. Test Friability

Friability test, that is, by way of considering 10 tablets is taken randomly and cleaned of the dust, and then laid into 4 minutes fribiliator speed round tool of 25 rounds *per*- minute. A tablet has been weighed tested and then weighed. The requirment in the test friability is <1% (Voight, 1994).

e. Disintegration

Disintegration is done by how tablet is taken at randomly and put individual commandments themselves in each of the tubes of the basket, and then set time limit; the basket was made and observed all the tablets. All of the tablets should be crushed or dissolved perfectly. When 1 or 2 tablets were not decimated perfectly then repeat with 12 other tablets. There should not be less than 18 tablets that should be crushed perfectly (Ministry of Health-RI, 1995).

3.5 Data Analysis

The data obtained were analyzed statistically using one way ANOVA test. For the distribution of the data is gaussian with the standard of belief 95%.

CHAPTER IV

RESULTS AND DISCUSSION

4.1 Results of Plant Determination

The results of the examination of determination is carried out at the Department of Pharmacy-Biology at Gajah Mada University Yogyakarta it showed that the types of plants used in this study were the type of *miswak* (Salvadora persica Linn) with the tribe of Salvadoraceae.

4.2 Results of Making *Miswak* Viscous Extract

The extract of *miswak* was obtained through maceration using ethanol 96% solvent. The choice of maceration method for extracting active compounds on *miswak* is an extraction method that does not damage compounds, not heat resistant and are simple and tend to be more practical than percolation and socletation methods. Also, the maceration method is carried out using 96% ethanol solvent, which is a volatile polar compound that is well used as extract solvents (Amalia *et al*, 2018).

The maceration process was carried out for 5 days by soaking 1 kg of *miswak* powder with 96% ethanol and stirring ± three times a day; the remaining pulp was carried out repeatedly until the clear filtrate was obtained. The extract was then evaporated with a rotary evaporator at 60^{o}C and concentrated with a water bath at 60^{o}C to increase the number of dissolved compounds. The viscous extract obtained is 40 grams.

The results of organoleptic examination of *miswak* extract obtained a viscous liquid with blackish brown color and has a distinctive aroma of *miswak* and has a bitter taste. The purpose of this examination is to find out the physical properties of the extract produced. The following are the results of organoleptic examinations:

Table 4.1 Organoleptic Examination of *Miswak* Extract

No.	Parameter	Results
1.	Form	Viscous liquid
2.	Coluor	Blackish brown
3.	Smell	Typical
4.	Taste	Bitter

4.3 Results of Making Miswak Dry Extract

The viscous extract of *miswak* is not easy to formulate into several tablets, with the viscous extract being converted into the dry extract. The dried *miswak* extract was obtained through an aerosil drying process in a ratio of 1: 2, because the hygroscopic extract of the adsorbent was used to overcome these obstacles and had the aim to shorten the drying time because the adsorbent material had a function to bind water contained in viscous extracts (Muria, 2012) The results of *miswak* extract in the climatic oven at a temperature of 60^{o}C and Rh 30 for 2 hours to reduce the moisture content in dried extract of *miswak*.

The results of the organoleptic examination on dried extracts of *miswak* were obtained fine powder in the colour of light brown, flavoured with typical *miswak* and has a bitter taste. The test results for the moist content of dried *miswak* extract were 7.53%.

Table 4.2 Parameter Results of Miswak Dry Extract

Type of Characterization	Result
A. Specific Parameters •Identity	Dried *miswak* extract
•Organoleptic : 1.Form 2.Color 3.Smell 4.Taste	 Fine powder Light brown Typical strong Bitter
B. Parameter Nonspesifik •Moist Content	 7,53 %

4.4 Results of Halal Analysis of Materials in Formulation

Table 4.3 Halal Analysis of Suction Tablet Formulation Materials

Material	Material Origin	Parameter			Information
		A	B	C	
Dried *miswak* extract	*Miswak* extracted with 96% ethanol	√	√	√	Mubah (MUI Fatwa)
HPC-SSL-SFP	Cellulose-based polymers which are organic compounds from plants (MUI, 2013)	√	√	√	Mubah (MUI Fatwa)
Mannitol	Types of sugar alcohol contained in fruits (Ministry of Religion, 2003)	√	√	√	Mubah (MUI Fatwa)
Avicel PH 102	Cellulose-based polymers which are organic compounds from plants (MUI, 2013)	√	√	√	Mubah (MUI Fatwa)
Magnesium Stearat	Derived from mining or quarrying materials (MUI, 2013)	√	√	√	Mubah (MUI Fatwa)
Talcum	Derived from mining or quarrying materials (MUI, 2013)	√	√	√	Mubah (MUI Fatwa)
Agglomerated a-lactose monohydrate	The source of these types of sugar comes from plants and milk. (Ministry of Religion, 2003)	√	√	√	Mubah (MUI Fatwa)

Information:

A = Not made from unclean ingredients (for internal medicine)

B = Not made of unclean ingredients (internal medicine and external medicine)

C= Not contaminated with unclean and unclean ingredients (in the process

of production, storage and distribution).

Making *miswak* viscous extract used 96% of ethanol. Ethanol which is also called ethyl alcohol with the chemical formula C_2H_5OH which has the properties of a colourless liquid that is volatile and slightly smelly (Ministry of Health, 2014). The function of ethanol is a solvent and the ethanol used is evaporated through evaporation and waterbath with the aim of removing the alcohol content contained therein.

The Indonesian Ulema Council (2009) concerning the legal provisions of alcohol explains that the use of *non-khamr* industrial ethanol (both the result of chemical synthesis and the results of *non-khamr* fermentation industries) for the production of drugs is allowed if it is not medically harmful then the law is changed. But the reason for the prohibition of ethanol if ethanol comes from the *khamr* industry because *khamr* is anything that can be intoxicating and the law is *haram*. Like the hadith of the Prophet Muhammad SAW:

عَنْ عَائِشَةَ رضي الله عنه قَالَ رَسُوْلُ اللهِ صلى الله عليه وسلم كُلُّ شَرَابٍ أَسْكَرَ فَهُوَ حَرَامٌ (رواه البخاري)

Meaning: *From Aisha RA said: Rasulullah SAW said: "Every intoxicating drink is haram".* (Narrated by Bukhari).

Based on the hadith, it can be concluded that the ethanol used in extraction that has been evaporated and mixed with drugs with small concentrations is not *haram*, because it does not have an effect.

Hydroxypropyl Cellulose (HPC-SSL-SFP) comes from PT. Lawsim Zecha is produced by PT. Nisso Soda Co. Ltd., Japan. The material is derived from plant-based non-ionic cellulose ether which is not included in unclean and unclean ingredients and is not produced from the results of the *khamr* industry, therefore according to the Indonesian Ulema Council the selection of materials fulfills the requirements of 3 predetermined parameter aspects and the law is valid for use medically and is not harmful (MUI, 2013).

Mannitol and agglomerated a-lactose monohydrate are from PT. Signa Husada, Jakarta. The material derived from these types of sugar comes from plants and milk which are not included in unclean ingredients and are not produced from the results of the *Khamr* industry, According to the MUI fatwa the selection of these materials fulfills the requirements of 3 predetermined parameter aspects and the law is changed be if it is not medically harmful (MUI, 2013).

Avicel PH 102, magnesium stearate and talcum are from PT. Brataco. Avicel PH 102 comes from cellulose-based polymers which are organic compounds derived from plants. Magnesium stearate and talcum are derived from mining materials or excavated which are not included in unclean ingredients and are not produced from the results of the *khamr* industry. According to the MUI fatwa the selection of these materials fulfilling the requirements of the 3 parameter aspects that have been determined and the law is changed to be used if it is not medically dangerous (MUI, 2013).

4.5 Making Lozenges

The lozenges used in this study were made using the direct compress method. The direct compress method has the advantage of making the tablet making process simple compared to other methods (wet and dry granulation) where there is no mechanical processing except only the process of mixing active substances with excipient substances. The stability of the active substance which is thermolabile and sensitive to moisture properties can be improved because it does not go through the process of wetting or drying during the powder and the process of making tablets is short so that it can save time during production (Muria, 2012 and Lachman, 1994).

The binder used in the manufacture of lozenges is Hydroxypropyl Cellulose (HPC-SSL-SFP), which is the latest variant of HPC which has a special low viscosity with super fine powder which is developed to provide excellent tablet properties on direct press method. In a study (Muria, 2012), it was shown that there was an effect of HPC-SSL-SFP on the physical properties of lozenges, especially on hardness which is a characteristic of

lozenges. Mannitol with a concentration of 40% is used as a sweetener, where mannitol has a sweetness level of about 50% of sucrose sweeteners and has cold properties when it is tasted and can cover the bitter taste of active substances in lozenges formulations (Rondonuwu *et al*, 2017).

The current study added Avicel PH 102 10% and agglomerated a-lactose monohydrate as fillers to improve flow properties. Research conducted by Handayani (2006) increased levels of Avicel PH 102 (10%, 15% and 20%) on orally disintegrating paracetamol tablets can increase violence, reduce fragility, and tend to accelerate disintegration time. Addition of agglomerated a-lactose monohydrate as a filler for the manufacture of tablets with direct compression methods is available in granulated lactose form to help improve poor flow properties (Rowe *et al*., 2009). Magnesium stearate and talc are added as lubricants and antiadherents to prevent the granule from sticking to the mold and can improve the flow properties of the tablet print mass (Dewi, 2018).

4.6 Results of Evaluation of Granule

The granule of lozenges of the *miswak* ethanol extract was evaluated by measuring the moisture content, flow rate, stop corner and compressibility. The four evaluations were carried out to find out whether the printed mass of tablets that had been made could meet the requirements according to the prescribed standards so that it was expected to produce good tablets.

Table 4.4 Evaluation of Granule Results

No.	Type of Testing	Formula		
		A	B	C
1.	Moist content (%) Terms: 2-5%	2	2,12	2,46
2.	Flow rate (g / sec) Terms: 4-10g / sec	8,34 ± 0,30	6,45 ± 0,29	5,38 ± 0,36
3.	Stop corner (degree) Terms: ≤ 40^{o}	31± 0,00	29 ± 0,00	28 ± 0,57

4.	Compressibility (%) Terms: 5- 18 %	8,5 ± 0,70	8 ± 0,00	6,5 ± 0,70

a. Moisture content

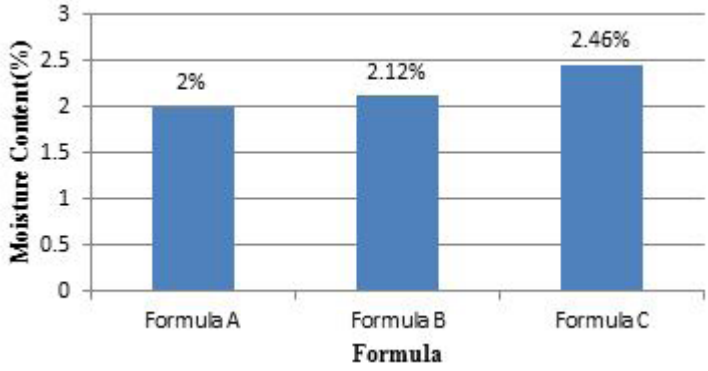


Figure 4.1 Moisture Content Test Results

Based on the results obtained, the printed mass of tablet formulations or granule from the three formulations fulfilled the moisture content test requirements, namely: 2%; 2.12% and 2.46%. The requirements for good moist content are 2% - 5% (Lachman, 1994). The moist content if ≤ 2% then the resulting tablet will be brittle or easily broken and if the moisture content is ≥ 5% then the resulting tablet will be too moist and result in the mass flow of the powder to be poor (Haifa, 2013).

b. Flow rate

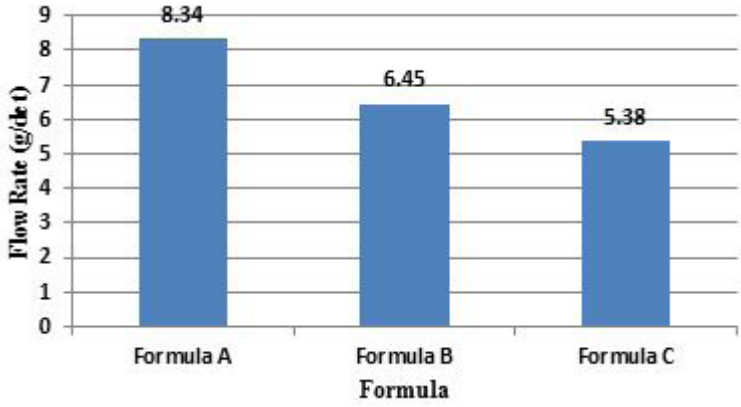


Figure 3.2 Flow Rate Test

The results of the flow rate test of the three formulas above are 8.34 g / sec, 6.45 g / sec and 5.38 g / sec, respectively. This shows that the flow rates of formulas A, B and C have met the requirements of a good flow rate of 4-10 g / sec (Aulton, 2002). The difference in the rate of flow that occurs can be affected by an increase in the concentration of the HPC-SSL-SFP binder because of the increasing number of fine particles in the tablet mass and the ingredients of agglomerated a-lactose monohydrate which are used to improve flow properties (Muria, 2011).

c. Stop corner

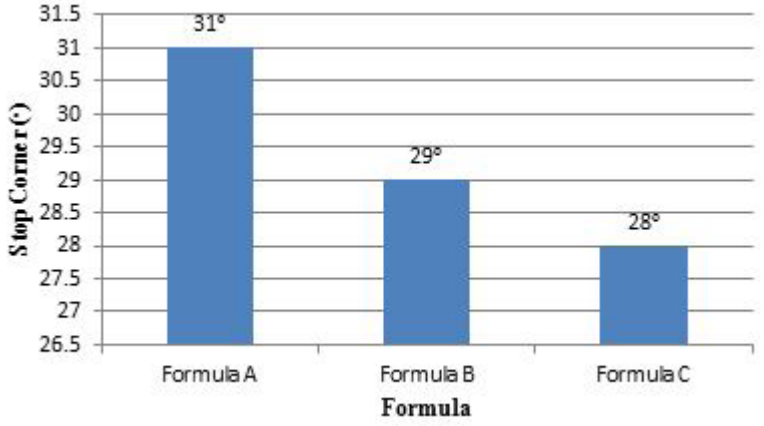


Figure 4.3 Stop Corner Test

In addition to testing the flow rate, the flow properties are also determined by the stop angle. The stop angle is a simple technique used to measure resistance to particle particles (Suciati, 2018). The data obtained shows that the stop angles of formulas A, B and C are 31°, 29° and 28° respectively, so that they have met the good stop angle requirement which is less than 45° (Dewi, 2018). Testing the speed of the flow rate and stop angle is important to know whether the print mass can flow well from the hopper on the tablet machine (Haifa, 2013).

d. Compressibility Test

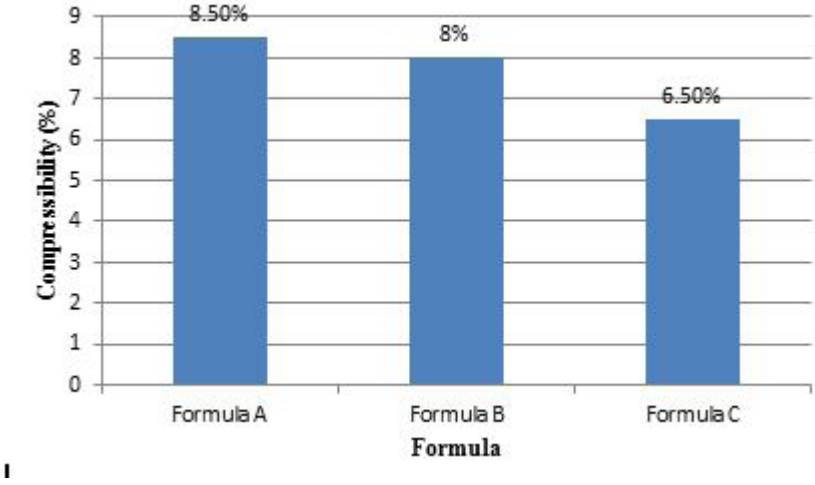


Figure 4.4 Compressibility Test

The compressibility test results of the three formulas are 8.5%, 8% and 6.5%. These results indicate that the three formulas above meet the requirements of less than 20% (Dewi, 2018). The higher the compressibility value, the more cohesive the powder and the flow characteristics become worse, then from the three formulas which have the lowest compressibility index in formula C, so there is a correlation between the increasing concentration of HPC-SSL-SFP and powder mass cohesiveness (Muria, 2011).

4.7 Results of Lozenges Evaluation

Lozenges with active ingredients of *miswak* extract were evaluated on each formula which included organoleptic evaluation, weight uniformity, brittleness hardness and tablet disintegration.

Table 4.5 Results of Evaluation Lozenges of *Miswak* Ethanol Extract

No	Evaluation of Lozenges	Formula		
		A	B	C
1.	Weight uniformity (mg)	498 ± 11,7	493 ± 3,21	481,1 ± 17,35
	Terms	There are no more than 2 tablets which deviate 5% from the average weight. And none of the tablets that deviate from the average weight of more than 10% (Ministry of Health, 2014)		
2.	Tablet hardness (kg)	10,13 ± 0,40	11,45 ± 0,51	12,92 ± 1,21
	Terms	>10 kg (Voight, 1994).		
3.	Friability (%)	0,62 ± 0,00	0,45 ± 0,14	0,21 ± 0,03
	Terms	No more than 0,8% (Voight, 1994).		
4.	Disintegration (minutes)	17,15 ± 0,04	14,23 ± 0,07	10,22 ± 0,07
	Terms	No more than 30 minutes (Lachman, 1994)		

a. Organoleptic Examination

Table 4.6 Results of Organoleptic Evaluation of Lozenges

No	**Organoleptic**	**Formula**		
		A	**B**	**C**
1.	Form	Round	Round	Round
2.	Colour	White with brown spots	White with brown spots	White with brown spots
4.	Aroma	Typical of Miswak	Typical of Miswak	Typical of Miswak
5.	Taste	Sweet	Sweet	Sweet

Observations of lozenges of organoleptic with active ingredients of *miswak* extract in each formula have the same characteristics, which are round, white with brown spots on each tablet, with a distinctive aroma of sweet taste.

b. Weight uniformity

Based on the test results, the weight uniformity of 20 tablets for each formula fulfilled the requirements, namely if one by one weighed no more than 2 tablets, each of which weighed 5% of the average weight and none of the tablets weighed 10% of the average weight (Ministry of Health-RI, 1979). The results of the average weights in appendix 7 state that the evaluations of the three formulas are: 498 mg, 4493 mg and 481.1 mg. This states that the ethanol extract lozenges have good uniformity in which good weight uniformity is influenced by the good or not the flow properties of tablets because the good flow properties will affect the volume of material entering the compression rag so that the resulting weight of the tablet is not too big (Haifa, 2013).

c. Hardness Test

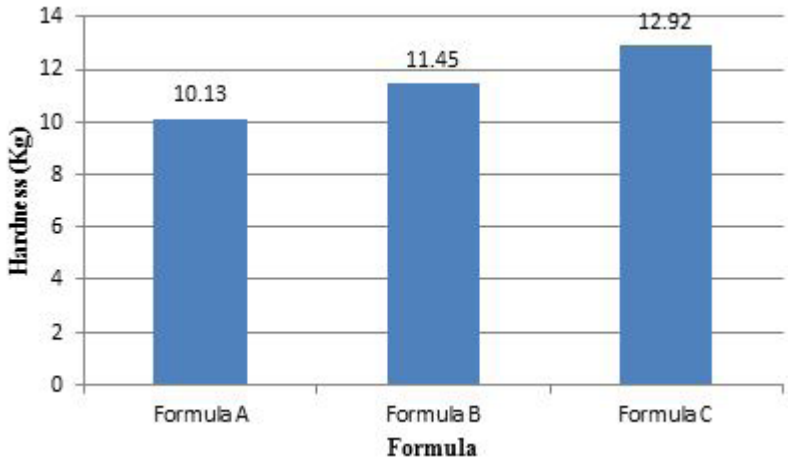


Figure 4.5 Results of Tablet Hardness Evaluation

Hardness is one of the most characteristic characteristics in lozenges, where lozenges have higher hardness than ordinary tablets (Muria, 2012).

The requirements for hardness of lozenges are >10 kg / cm^2 (Haifa, 2013). The table above states that the average hardness of the three formulas meets the requirements for tablet hardness, namely: 10.13 kg, 11.45 kg and 12.92 kg. The data shows that the greater the concentration of HPC-SSL-SFP used, the higher the yield of lozenges because it can increase the mass cohesiveness of the powder through the power of hydrogen formed from hydroxyl groups (-OH) attached to cellulose molecules (Muria, 2012). Data analysis which was carried out by one way ANOVA test found in Appendix 11, there were significant differences in formulations A, B and C. Significant values were <0.05, H0 was rejected, so there were differences in the three formulations.

d. Tablet friability

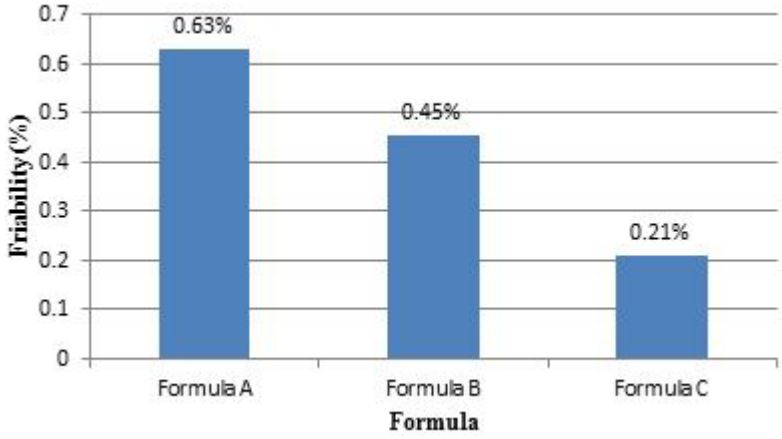


Figure 4.6 Results of Tablet Friability Test Evaluation

The evaluation results of fragility test of *miswak* extract lozenges fulfilled the requirements because the evaluation results of tablets were less than 0.8% which were 0.63%, 0.45% and 0.21% (Voight, 1994). The higher the concentration of binder, the higher hardness is obtained so that it is resistant to shocks during the manufacturing process, packing, transportation to the use of the consumer (Muria, 2011). The results of the SPSS test using one way ANOVA test found in Appendix 12 found that

there is a difference between the formulation and the significant value of 0.03, therefore the significance value <0.05, H0 is rejected, which means that there are differences from the three formulations.

e. Disintegration Test

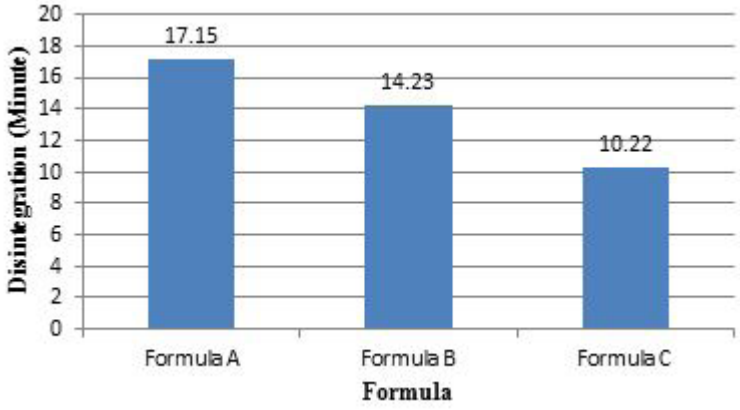


Figure 4.7 Results of Evaluation of Tablet Disintegration

The test results of the four disintegration times of the formula have a disintegration time, namely: 17.15 minutes, 14.23 minutes and 10.22 minutes. The disintegration time of the three formulas has met the requirements of slowly dissolving or eroding in less than 30 minutes (Lachman, 1994). From the data obtained there is a relationship between the disintegration time and the concentration of the use of HPC-SSL-SFP binder because the higher the concentration of the binder the shorter the crush time of the lozenges (Muria, 2012). It can be understood that HPC-SSL-SFP is a cellulose derivative compound that dissolves water so that the tablet is easily destroyed. Thus it can be explained that the variation in the concentration of the HPC-SSL-SFP binder can affect the crush time of the lozenges. The results of the SPSS test using the one way ANOVA test found in Appendix 13 show that there are differences between formulations A, B and C with significant values which can be 0.00, then H_0 is rejected which means there are differences in the three formulations.

CHAPTER V

CONCLUSIONS AND SUGGESTIONS

5.1 Conclusions

1. Ethanol extract of *miswak* (Salvadora persica L.) can be formulated into lozenges in the form of direct press and obtained lozenges that meet physical quality requirements.
2. Hydroxypropyl Cellulose (HPC-SSL-SFP) can affect the physical properties of lozenges such as hardness, brittleness and tablet disintegration. The difference in concentration of the three formulas was 7.5%, 10% and 12.5% with hardness of 10.13 kg, 11.45 kg and 12.92 kg, friability of 0.62%, 0.45%, 0.21 % and disintegration time of 17.15 minutes, 14.23 minutes and 10.22 minutes, the greater the concentration of HPC-SSL-SFP used, the harder the tablet produced and the crush time of the lozenges is shorter.
3. The lozenges of *miswak* ethanol extract with a binding concentration of 12.5% in formula C has the best criteria as lozenges with tablet hardness of 12.92 kg, friability of 0.21% and disintegration time of 10.22 minutes.

4.2 Suggestions

1. It is necessary to develop taste by combining or varying the sweetener formulation of lozenges of ethanol extract of *miswak* such as sucrose and sorbitol with special characteristics modified for the direct pressing method so that the tablet can be known as the best sweetener for lozenges.
2. Further research is done for in vitro and in vivo testing so that the lozenges of ethanol extract of *miswak* can be consumed by humans safely and beneficially.

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APPENDIXES

Appendix 1. Results of Determination of *Miswak* Plants (Salvadora persica L.)

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SURAT KETERANGAN
No.: 7. 7.1 /UN1/FFA/BF/PT/2019

Yth. : Irtizaqun Nabila 7 Januari 2019
NIM 362015712257
Prodi Farmasi
Fakultas Ilmu Kesehatan
Universitas Darussalam Gontor
Di Ngawi

Bersama ini kami sampaikan hasil identifikasi sampel yang Saudara kirimkan ke Departemen Biologi Farmasi, Fakultas Farmasi UGM, adalah :

No.Pendaftaran	Jenis	Suku
136	*Salvadora persica* L.	Salvadoraceae

Demikian, semoga dapat digunakan sebagaimana mestinya.

Mengetahui,
Dekan

Prof. Dr. Agung Endro Nugroho, M.Si.,Apt

Ketua Departemen Biologi Farmasi

Dr. Indah Purwantini, M.Si., Apt.

Appendix 2. Calculation of *Miswak* Extract Lozenges Formulation

1. *Miswak* extract (active substance) $= \frac{10}{100} \times 500 = 50\ mg$
2. HPC-SSL-SFP (binder)
   - Formula A $= \frac{7,5}{100} \times 500 = 37,5\ mg$
   - Formula B $= \frac{10}{100} \times 500 = 50\ mg$
   - Formula C $= \frac{12,5}{100} \times 500 = 62,5\ mg$
3. Manitol (sweetner) $= \frac{40}{100} \times 500 = 200\ mg$
4. Mg Stearat (lubricant) $= \frac{1}{100} \times 500 = 5\ mg$
5. Talk (Antiadheren) $= \frac{1}{100} \times 500 = 5\ mg$
6. Avicel PH 102 (filler) $= \frac{10}{100} \times 500 = 50\ mg$
7. Agglomerated a-lactose (filler)
   - Formula A $= \frac{30,5}{100} \times 500 = 152,5\ mg$
   - Formula B $= \frac{28}{100} \times 500 = 140\ mg$
   - Formula C $= \frac{25,5}{100} \times 500 = 127,5\ mg$

Appendix 3. Moist Content Test

Formula	Result
Formula A	2%
Formula B	2,47%
Formula C	2,03%

Appendix 4. Flow Rate Test

Formula	Trial			Mean ± SD
	1	2	3	
A	8,65	8,33	8,04	8,34 ± 0,30
B	6,63	6,11	6,62	6,45 ± 0,29
C	5,54	5,65	4,97	5,38 ± 0,36

Appendix 5. Stop Corner Test

Formula	Trial			Mean ± SD
	1	2	3	
A	31	31	31	31± 0,00
B	29	29	29	29 ± 0,00
C	29	28	28	28 ± 0,57

Appendix 6. Compressibility Test

Formula	Trial		Mean ± SD
	1	2	
A	9%	8%	8,5 % ± 0,70
B	8%	8%	8% ± 0,00
C	7%	6%	6,5% ± 0,70

Appendix 7. Weight Uniformity Test

No.	Formula A	Formula B	Formula C
	Weight	Weight	Weight
1	499 mg	495 mg	505 mg
2	478 mg	486 mg	500 mg
3	480 mg	492 mg	467 mg
4	497 mg	492 mg	486 mg
5	480 mg	490 mg	492 mg
6	498 mg	499 mg	470 mg
7	482 mg	494 mg	465 mg
8	506 mg	490 mg	503 mg
9	493 mg	492 mg	462 mg
10	514 mg	497 mg	466 mg
11	509 mg	495 mg	490 mg
12	509 mg	494 mg	501 mg
13	508 mg	495 mg	472 mg
14	493 mg	493 mg	485 mg
15	507 mg	490 mg	475 mg
16	495 mg	498 mg	471 mg
17	514 mg	496 mg	457 mg
18	512 mg	493 mg	459 mg
19	492 mg	490 mg	480 mg
20	495 mg	490 mg	516 mg
Mean	498 mg	493 mg	481,1 mg
SD	11,7	3,21	17,35

The average weight of formulation tablets A = 498 mg

- For deviations 5% = 5/100 x 498 = 24.9
  498 - 24,9 = 473,1
  498 + 24.9 = 522.9
  So heavy tablets with a 5% deviation between 473,1 - 522,9
- For a deviation of 10% = 10/100 x 498 = 49.8
  498 - 49.8 = 448.2
  498 - 49.8 = 547.2
  So the weight of the tablet with a 10% deviation between 448,2 - 547,2

The average weight of formulation tablets B = 493 mg

- For deviations 5% = 5/100 x 498 = 24.6
  493 - 24.6 = 468.4
  493 + 24.6 = 517.6
  So the weight of the tablet with a 5% deviation between 468.4 - 517.6
- For a deviation of 10% = 10/100 x 493 = 49.3
  493 - 49.3 = 468.4
  493 + 49.3 = 517.6
  So the weight of the tablet with a 10% deviation between 468.4 - 517.6

The average weight of formulation tablets C = 481.1

- For deviations 5% = 5/100 x 481,1 = 24,055
  481,1 - 24,055 = 457,045
  481,1 + 24,055 = 505, 155
  So the weight of the tablet with a 5% deviation between 457,045 -505,155
- For deviations 10% = 10/100 x 481,1 = 48.11
  481,1 - 48,11 = 432.99
  481,1 + 48,11 = 529, 21
  So the weight of the tablet with a 10% deviation between 432.99 - 529.21

Appendix 8. Tablet Hardness Test

No.	Hardness Test		
	Formula A	**Formula B**	**Formula C**
1	9,54	11,75	12,74
2	10,46	10,79	11,85
3	10,22	11,67	12,44
4	10,32	11,96	14,65
Mean	10,13	11,450	12,92
SD	0,40	0,51	1,21

Appendix 9. Lozenges Friability Test

Formula	**Initial Weight (gram)**	**Final Weight (gram)**	**Friability (%)**	**Mean (%)**	**SD**
A	5.04	5.01	0.63	0.62	0,00
	5.05	5.02	0.62		
B	4.84	4.81	0.55	0.45	0,14
	4.86	4.85	0.35		
C	4.84	4.82	0.23	0.21	0,03
	4.87	4.86	0.18		

Appendix 10. Lozenges Disintegration Test

No.	Disintegration (minute)		
	Formula A	**Formula B**	**Formula C**
1	17,10	14,15	10,14
2	17,10	14,15	10,14
3	17,15	14,24	10,24
4	17,15	14,24	10,24
5	17,20	14,31	10,30
6	17,20	14,31	10.30
Mean	17,15	14,23	10,22
SD	0,04	0,07	0,07

Appendix 11. One Way ANOVA SPSS Test Lozenges Hardness Data

ANOVA

Kekerasan

	Sum of Squares	Df	Mean Square	F	Sig.
Between Groups	15.513	2	7.757	12.244	.003
Within Groups	5.702	9	.634		
Total	21.215	11			

Multiple Comparisons

Dependent Variable: Kekerasan

	(I) Formulasi	(J) Formulasi	Mean Difference (I-J)	Std. Error	Sig.	95% Confidence Interval	
						Lower Bound	Upper Bound
LSD	Formulasi A	Formulasi B	-1.40750*	.56281	.034	-2.6807	-.1343
		Formulasi C	-2.78500*	.56281	.001	-4.0582	-1.5118
	Formulasi B	Formulasi A	1.40750*	.56281	.034	.1343	2.6807
		Formulasi C	-1.37750*	.56281	.037	-2.6507	-.1043
	Formulasi C	Formulasi A	2.78500*	.56281	.001	1.5118	4.0582
		Formulasi B	1.37750*	.56281	.037	.1043	2.6507

*. The mean difference is significant at the 0.05 level.

Kekerasan

	Formulasi	N	Subset for alpha = 0.05		
			1	2	3
Duncan[a]	Formulasi A	4	10.1350		
	Formulasi B	4		11.5425	
	Formulasi C	4			12.9200
	Sig.		1.000	1.000	1.000

Means for groups in homogeneous subsets are displayed.

a. Uses Harmonic Mean Sample Size = 4.000.

Appendix 12. One Way ANOVA SPSS Test Results for Lozenges Friability Data

ANOVA

Kerapuhan

	Sum of Squares	Df	Mean Square	F	Sig.
Between Groups	.178	2	.089	11.726	.038
Within Groups	.023	3	.008		
Total	.201	5			

Multiple Comparisons

Dependent Variable: Kerapuhan

	(I) Formulasi	(J) Formulasi	Mean Difference (I-J)	Std. Error	Sig.	95% Confidence Interval	
						Lower Bound	Upper Bound
LSD	Formulasi A	Formulasi B	.2751500	.0872236	.051	-.002434	.552734
		Formulasi C	.4204500*	.0872236	.017	.142866	.698034
	Formulasi B	Formulasi A	-.2751500	.0872236	.051	-.552734	.002434
		Formulasi C	.1453000	.0872236	.194	-.132284	.422884
	Formulasi C	Formulasi A	-.4204500*	.0872236	.017	-.698034	-.142866
		Formulasi B	-.1453000	.0872236	.194	-.422884	.132284

*. The mean difference is significant at the 0.05 level.

Kerapuhan

	Formulasi	N	Subset for alpha = 0.05	
			1	2
Duncan[a]	Formulasi C	2	.208850	
	Formulasi B	2	.354150	.354150
	Formulasi A	2		.629300
	Sig.		.194	.051

Means for groups in homogeneous subsets are displayed.

a. Uses Harmonic Mean Sample Size = 2.000.

Appendix 13. One Way ANOVA SPSS Test Data on Lozenges Disintegration

ANOVA

Waktu_hancur

	Sum of Squares	df	Mean Square	F	Sig.
Between Groups	144.986	2	72.493	17576.395	.000
Within Groups	.062	15	.004		
Total	145.048	17			

Multiple Comparisons

Dependent Variable:Waktu_hancur

	(I) Formulasi	(J) Formulasi	Mean Difference (I-J)	Std. Error	Sig.	95% Confidence Interval Lower Bound	95% Confidence Interval Upper Bound
LSD	1	2	2.91667*	.03708	.000	2.8376	2.9957
		3	6.92333*	.03708	.000	6.8443	7.0024
	2	1	-2.91667*	.03708	.000	-2.9957	-2.8376
		3	4.00667*	.03708	.000	3.9276	4.0857
	3	1	-6.92333*	.03708	.000	-7.0024	-6.8443
		2	-4.00667*	.03708	.000	-4.0857	-3.9276

*. The mean difference is significant at the 0.05 level.

Waktu_hancur

	Formulasi	N	Subset for alpha = 0.05 1	2	3
Duncan[a]	3	6	10.2267		
	2	6		14.2333	
	1	6			17.1500
	Sig.		1.000	1.000	1.000

Means for groups in homogeneous subsets are displayed.

a. Uses Harmonic Mean Sample Size = 6.000.

Appendix 14. Certificate of Material Analysis of HPC-SSL-SFP

Nisso NIPPON SODA CO.,LTD.
SHIN-OHTEMACHI BLG., 2-1, 2-CHOME OHTEMACHI
CHIYODA-KU, TOKYO 100-8165, JAPAN

CERTIFICATE OF ANALYSIS

This is to certify that under-mentioned commodity has been duly inspected by us and meets our standard in all respects.

Commodity	:	Hydroxypropyl Cellulose
CAS No.	:	9004-64-2
Grade	:	HPC-SSL-SFP
Lot No.	:	NEF-1121S
Manufacturing Date	:	June, 2015
Manufacturing Place	:	Nihongi Plant, 950, Fujisawa, Nakago-ku, Joetsu-Shi, Niigata, 949-2392, Japan
Expiry Date	:	May, 2020
Retest Date※	:	May, 2020

ANALYSIS RESULTS

Characteristics	Test Methods	Specifications	Results
Description	JP	White to yellowish white powder	Conforms
Identification(1)(2)(3)	JP	Conforms	Conforms
pH	JP	5.0-7.5	5.9
Viscosity (2% aqueous solution at 20°C)	JP	2.0-2.9 mPa·s	2.5 mPa·s
Clarity of solution	JP	Conforms	Conforms
Chloride	JP	Not more than 0.142 %	≦ 0.142 %
Sulfate	JP	Not more than 0.048 %	≦ 0.048 %
Heavy metals	Modified JP	Not more than 20 ppm	≦ 20 ppm
Arsenic	ICP-MS	Not more than 2 ppm	≦ 2 ppm
Loss on drying	JP	Not more than 5.0 %	1.1 %
Residue on ignition	JP	Not more than 0.5 %	0.2 %
Assay (Hydroxypropoxy group)	Modified JP	53.4-77.5 %	63.7 %
Particle size (45 μ m pass)	Air Sieve	Not less than 99 %	99.8 %

※ We do not perform retest for HPC, therefore we assure only expiry date.

This analysis is according to JP 16.

Class2 solvent, toluene listed in USP <467> is used for the manufacturing of Nisso HPC. The amount of toluene is monthly checked, using USP <467>. The obtained results are not more than 20ppm (LOQ) for the specification of 890ppm. There is no use of the organic solvents (chloroform; 1,4-dioxane; methylene chloride; tri-chloroethylene) during the manufacturing process of Nisso HPC, and no contaminant of during shipping or storage.

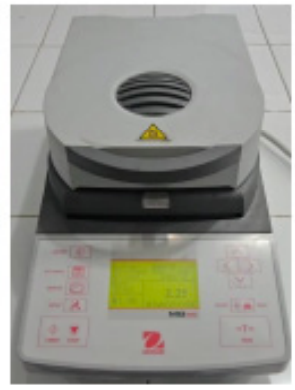
Issued By:
K. Miyashita Jan. 24. 2015
Q.C.Manager
Nihongi Plant
Nippon Soda Co.,Ltd.
Date

Reviewed By:
T. Hayashi Jun 25. 2015
Q.A.Sec.
Nihongi Plant
Nippon Soda Co.,Ltd.
Date

Appendix 15. Tools Used

Blender

sieve



Moisturizer Balance

Tablet Printing Tools

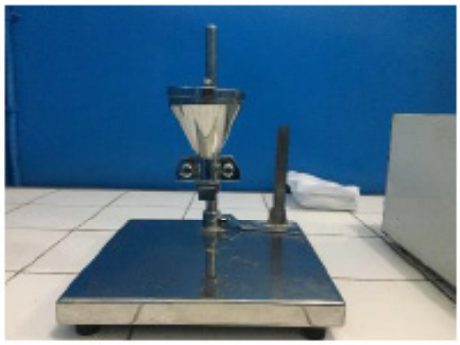
Hardness Tester

Friabilator

Analytical Balance

Disentegation Tester

Volumometer



Flowmeter

Oven

Evaporator

Waterbath

Appendix 16. Results of *Miswak* Lozenges Ethanol Extract

Tablet Formula A

Tablet Formula B

Tablet Formula C