The Effect of Concentration Ratio of Gelatine and Polyvinylpyrrolidone as Binders on the Physical Properties of Red Ginger (*Zingiber officinale* Rosc.) Extract Lozenges

Inding Gusmayadi, Priyanto

Faculty of Pharmacy and Sciences Universitas Muhammadiyah Prof. DR. HAMKA, Indonesia

Keywords: Red ginger extract, Lozenge.

Abstract: Lozenges require the tablet hardness of 7-14 Kgf to be a suitable binder. Gelatine can be used to meet the requirement as it creates granules with bad flow time. PVP produces granules with better flow time but it takes a large quantity to reach the lozenges hardness desired. This study aimed to determine the effect of the concentration ratio of gelatine and PVP as binders on the physical properties of red-ginger extract lozenges. Lozenges made employing the wet granulation method following the ratio of gelatine and PVP of 1:1, 1:2, 1:3, 1:4 and 1:5. The hardness test results of the formula 1 to 5 are 9, 14, 16, 13 and 12 Kgf respectively and the friability test results were 0,4%, 0,7%, 0,2%, 0,3% and 0,6% accordingly. The combination of gelatine and PVP as binders provide a significant difference in the hardness and friability of the tablets.

1 INTRODUCTION

Ginger, one of the most commonly used herbs in food worldwide, has a wide range of medicinal uses including carminative, antiemetic, spasmolytic, antiflatulent, antitussive, hepato-protective, anti-platelet aggregation and hypolipidemic effects. Ginger has a strong odour generated by a mixture of phenolic compounds that can stimulate thermogenic receptors leading to the antiemetic effect (Heinrich *et al*. 2009). Generally, herbal preparations of red ginger are consumed as the instant powder. The use of instant powder in the treatment is less practical and therefore the dosage form needs to be developed to be more practical and effective (Badan Pengawasan Obat and Makanan Republik Indonesia 2012).

The lozenge is a practical choice to develop a dosage form of red ginger. The lozenge is a solid preparation that will dissolve or break down slowly in the mouth (Agoes 2008). Two types of lozenges are widely used, i.e. hard candy and compressed tablet lozenges (Peters 1989). Compressed tablet lozenges can be created using direct compression, dry granulation or wet granulation. The wet granulation method benefits to facilitate the agglomeration process in the formula so that it will result in the excellent physical properties and mass of the tablets (Siregar and Wikarsa 2010).

The differences in physical properties of lozenges and conventional tablets are the hardness of 7-14 Kgf, the diameter of 0.625-0.75 inches and the weight range of 1.5-4.0 grams. The pre-formulation of lozenge excipients should be filler, sweetener, lubricant, glidant, flavoring agent and binder to produce the good quality of lozenge physical properties required (Hadisoewignyo and Fudholi 2013, Siregar and Wikarsa 2010). The binder is an excipient in a tablet formula providing a cohesive force between particles thus compromising a compact and robust structure (Anwar 2012). The binding effect in the lozenge component is essential to produce greater hardness compared to the level of conventional tablet hardness. The bonding agent is divided into two groups: the synthetic and the natural binder.

The natural binding agents that can be used are starch, gum, tragacanth and gelatine. Gelatine has a characteristic that inhibits the disintegration time and thus it is suitable to be used as a binder on a lozenge (Voigt 1995). Gelatine solution of 2-10% can be used as a binder of the tablet formula (Anwar 2012). The use of gelatine as a binder on a wet granulation can produce poor granule flows (Hamed

Gusmayadi, I. and Priyanto, .
The Effect of Concentration Ratio of Gelatine and Polyvinylpyrrolidone as Binders on the Physical Properties of Red Ginger (Zingiber officinale Rosc.) Extract Lozenges.
DOI: 10.5220/0008240901470153
In *Proceedings of the 1st Muhammadiyah International Conference on Health and Pharmaceutical Development (MICH-PhD 2018)*, pages 147-153
ISBN: 978-989-758-349-0

et al. 2005). The viscous properties of natural-sourced gelatine can increase the size of granules which in turn increases the granular flow time. This property can be improved by combining a natural and a synthetic binder (Agubata *et al*. 2012).

One of the synthetic binders that can be used in lozenge compression is polyvinylpyrrolidone (PVP) in the range 0.5-5% (Rowe *et al*. 2009). A large amount PVP is needed to be used as a lozenge binder. Previous research reported that 3% of PVP in the formula yielded a hardness of 6.23 Kgf (Sari and Astuti 2010). It takes 10% of PVP to produce the optimum lozenge ginger extract hardness of 14.63 kg (Mutmainah 2005), while the combination of PVP (4.7%) and gelatine (9.3%) creates the physical properties of tablets fitting the tablet hardness and fragility requirements of 13.04 Kgf and 0.215% respectively (Liauw 2012). This research examined the combination of PVP and gelatine for ginger extract as an active ingredient. It aimed to obtain the optimum combination to achieve the maximum hardness and the minimum fragility on ginger extract lozenges.

Based on the previous review, this research investigated the effect of gelatine (4.0-6.7%) and PVP (1.3-4%) combination on the physical properties of red ginger extract lozenge employing wet granulation method. The combination of gelatine and PVP was performed in various concentrations of 1: 1 (formula I), 1: 2 (formula II), 1: 3 (formula III), 1: 4 (formula IV) and 1: 5 (formula V). The combination of Gelatine and PVP was not 0:1, 1:1, and 1:0 due to the trial results of the combination of gelatine less than 4% did not meet the requirement of lozenges hardness. The quality of lozenges was assessed based on the physical properties: (1) the evaluation of the tablet mass includes the compressibility test, the flow time, the angle of repose, the particle size distribution; and (2) lozenge evaluation includes the organoleptic, the weight uniformity, the size uniformity, the hardness and friability test (Siregar and Wikarsa 2010).

2 MATERIALS AND METHOD

2.1 Materials

Materials used included the dry red ginger extract (PT Haldin Pacific Semesta), PVP K-30 (Kimia Farma), gelatine (Kimia Farma), dextrose (Kimia Farma), mannitol (Kimia Farma), Talc (Kimia Farma), and Magnesium Stearate (Kimia Farma).

Table 1: Lozenges Formula.

Materials	Formula (%)				
	1	2	3	4	5
Ginger Extract	30	30	30	30	30
Dextrose	20	20	20	20	20
PVP	4	2,7	2	1,6	1,3
Gelatine	4	5,3	6	6,4	6,7
Magnesium Stearate	1	1	1	1	1
Talc	2	2	2	2	2
Mannitol ad	100	100	100	100	100

2.2 Methods

2.2.1 Lozenges Formula

Lozenges were made in five formulas namely F1, F2, F3, F4 and F5. The five formulas had different ratios of gelatine and PVP combinations as the binding agents of 1000 mg tablet (see Table 1).

2.2.2 Lozenges Production

All materials were prepared and weighed. The red ginger extract was put into the container, the mannitol and dextrose were added and stirred resulting in a homogeneous mixture. The PVP solution was prepared by dissolving it in the 70% ethanol (1: 5) and the gelatine solution was prepared by hydrating the gelatine in cold water (1:2) for 24 hours before mixing and heating. PVP solution and gelatine solution were added in warm conditions slowly and stirred to be homogeneous and mass was wet enough could be formed into granules.

The mass was sieved using a 12-mesh sieve and then put into an oven at ± 50 ° C for ± 24 hours. The granules were then sieved back with an 18-mesh sieve. The magnesium stearate and talc were added and mixed homogeneously. The granule evaluation was then conducted. The granules were prepared and put into the hopper. The tablet weight and hardness were set. The lower punch was set if the hardness was less than 7.0-14 Kgf. The upper punch was set if the tablet weight was less than 1000 mg. The engine ran until all granules transform into tablets.

2.2.3 The Evaluation of Extract, Granules, and Tablets

The evaluation of dried red ginger extract included the organoleptic, loss on drying, ash residue, solubility, particle size and phytochemical extract tests.

The evaluation of granules included the flow time, the angle of repose, the compressibility, the granule size distribution and the loss on drying.

The lozenge evaluation included the organoleptic, uniformity size, weight uniformity, tablet fragility and tablet hardness tests.

3 RESULTS AND DISCUSSION

The dry extract obtained from PT. Haldin was then determined. The result of the extract determination from LIPI Cibinong showed that the dry extract observed was Red Ginger which belongs to the Zingiberaceae tribe. The result of the organoleptic test on the dry red ginger extract is the fine yellow-brown powder with spicy taste and red ginger specific smell. The LOD test to examine the moisture of the dry extract of red ginger was conducted to prevent the powder become moist which can accelerate the microbial growth. The LOD test result was 5,61%. This shows that the moisture of the extract meets the requirements, i.e. no more than 10% (Departemen Kesehatan RI 1980).

The LOD extract test used a moisture balance employing the gravimetric principle. This tool measured the moist in the extracts that evaporated from the heat generated by the appliance. The extract moisture may be due to the water or organic solvents used during the extraction process. So, it is not specific to measure the water in the extract. If the extract is made using an organic solvent, the tool can detect the remaining solvent in the extract as the amount produced. The results showed that the water in the extract was 5.6%. Based on Hadisoewignyo and Fudholi (2013), the extract classifies into the non-hygroscopic category (<10%).

The residual test of dry red ginger extract ash aimed to investigate the inorganic impurities in the extract. The larger ash in the material shows the higher mineral in the material. According to Departemen Kesehatan RI (1980), the residual ash requirement of excellent red ginger rhizome extract should be no more than 5.0%. The results showed that the ash residue obtained was 4.7%, so it can be concluded that the dry ginger extract meets the requirements of the excellent ash content.

Table 2: The results of evaluation of red ginger extract.

Parameter	Results
Organoleptic	Color : Yellow-Brown
	Odor : Specific Ginger Odor
	Taste : Spicy
	Form : Fine Powder
LOD	5,61 %
Ash Residue	4,6912%
Solubility	100 mg dissolve in 1,73 mL of water
Particle size	93,79% passing the 80-mesh sieve
	80,47% passing the 100-mesh sieve
Flavonoid	+
Saponin	+
Tannin	-
Phenol	+
Triterpenoid	-
Steroid	-

The results of the phytochemical screening test showed that the red ginger extract contained the alkaloid, flavonoid, saponin, terpenoid, and glycoside compounds. The purpose of the test is to examine the active substance of the gingerol compound, a phenol-derived compound. This compound does not break when it is processed at temperatures below 70℃ but it will be converted into shogaol compounds that increase the spicy flavour of the red ginger extract (Heinrich *et al.* 2009). Due to the stability of this compound indicated by the spicy flavour and the same spot on the TLC test, it can be concluded that the extract as an active substance does not suffer damage during

Table 3: The results of the granule evaluation.

Formula	Flow Time (g/sec)	Angle of Repose	Compressibility (%)	LOD (%)	Granule Size (μm)
F1	10,21 ± 0,17	28º58"	2,7 ± 0,36	3,70 ± 0,16	826
F2	9,51 ± 0,37	27º01"	2,6 ± 0,09	3,45 ± 0,29	817
F3	9,09 ± 0,14	27º38"	2,5 ± 0,43	3,27 ± 0,23	798
F4	9,74 ± 0,18	27º51"	2,6 ± 0,26	3,28 ± 0,15	813
F5	10,76 ± 0,67	30º41"	2,8 ± 0,51	4,38 ± 0,45	859

the granule drying process and can be used to produce tablet employing the wet granulation method.

The solubility test was performed to determine the solubility of the extract. The solubility test was carried out using water as a solvent resulting in 100 mg of ginger extract dissolved in 1.73 mL of water. It can be concluded that one part of the extract is soluble in 17 parts of waters (1:17). The solubility nature of the extract is soluble in water (Departemen Kesehatan RI 1979). Based on the result of particle size analysis (table 2), it was found that 93,79% of the dried red ginger extract can pass through the 80-mesh sieve and 80,47% of the extract can pass through the 100-mesh sieve. The amount of extract that can pass through 80-mesh sieve in the test is larger than the certificate analysis of 80%.

In this study, the dry ginger extract is used. Based on the amount of rendemen dry extract that is 49.5%. The dose of the red ginger extract according to Zick *et al.* (2008) is 150 mg. Thus, this study uses 300 mg per tablet.

3.1 The Results of Granule Evaluation

The purpose of the granule evaluation is to examine the quality of granules in each formula concerning the excellent granule requirements meeting the requirements for the compression process to tablets.

The granule loss on drying (LOD) test aims to investigate how many volatile materials include water in the drying process and to determine the moisture of the granules. The results (table 3) showed that the same ratio (1:1) in F1 resulting a greater LOD value than F2, while F5 had the biggest LOD value. This is due to the amount of solvent in each formula. In a ratio of 1:1, the amount of PVP used was more than the other formulas, requiring more ethanol. Although the nature of ethanol was more volatile than water as a gelatine solvent, a large amount of gelatine in F5 may affect the PVP character to be more sensitive to moisture (Siregar and Wikarsa 2010).

Therefore, F5 with the highest gelatine concentration had the highest LOD value. The LOD values in F2, F3 and F4 were not significantly different since the PVP concentration was not as large as F1, and the gelatine concentration was not as large as F5. The results of the LOD value test of granules in all formulas meet the requirements of 3-5% (Voigt 1995). The LOD value of the granules may affect the nature of the tablet produced. It is concerned that the large LOD value may contribute to the attachment of granules on the punch at the time of printing which in turn can affect the weight and size of the tablet produced (Siregar and Wikarsa 2010).

The results of the granule flow time test of the five formulas met the requirements of the flow time. While the ratio of 1:1 and 1:5 did not meet the requirements of flow time because of the inappropriate amount of the binding material, F1 was lack of gelatine and F5 contained too much of gelatine. The inappropriate amount of the binder will reduce the bonding between the granules particles (cohesive force), consequently the particle size is not good enough and the granules are difficult to flow (Anwar 2002). The results showed that F3 has the best flow properties, indicating that the 1:3 binder ratio is the best ratio to obtain the optimal granule cohesive force so that the granules can flow smoothly. Flow time is also affected by the moisture of the granules.

The repose of the angle test aimed to examine the flow properties of the granules when subjected to the tableting process. The angle of repose is the fixed angle between the cone-shaped particles and the horizontal plane. The results presented that the angle of repose in the five formulas were different. The difference may be affected by the cohesiveness of the granules caused by the binder. The shape, size and moisture of the granules influence the magnitude of the repose angle. The value of repose angle ranges from 25^{o} to 45^{o} (Siregar and Wikarsa 2010).

The five formulas met the requirements of the repose angle. It can be concluded that the binder ratio of F1 and F2 had decreased up to F3. However, there was an increase in the granular repose angles in F4 and F5 because of the lack of cohesiveness among granules affected by the comparison of the binder concentration. The measurement of the granular particle size distribution to determine the granule size and depth was necessary because it can affect the mixing process. Based on the results of the study, the granules left in the 18-24 sieve was the heaviest. According to Agoes *et al*. (2008), the use of gelatine solution in the formula affects the size of the granules. The amount of gelatine solution negatively influences the size of the granules. A relatively small size granule has smaller internal porosity contributing to the greater cohesion force and causes the granules to pass the mesh size of the larger sieve hardly. The larger particles of granules tend to separate from the smaller particles and move downward while small particles will rise (Lachman *et al*. 2003).

The addition of gelatine concentration to F4 and F5 did not result in smaller granule size, as shown in Figure 5, the number of granules left increased in 18-mesh sieves. It can be concluded that the addition of the gelatine concentration to F4 and F5 increases the granular size caused by an unbalanced binder ratio. The larger gelatine concentration in the binder combination can lead to an increase in the sensitivity of PVP as a binder (Anwar 2012), to decrease the performance of the binder combination. The size of the granules that generally falls on the 12-20 sieve is 840-1680 μm (Agoes 2012).

The large granule size will decrease the granule mass density. Smaller granules can form a more compact mass than larger granules (Banker and Anderson 1994). The result of the granular compressibility index test after the determination on 100 ml granule for F1 to F5 satisfied the requirement of good flow property category, the compressibility ≤ 20% (Agoes 2012). The granular density influences the compressibility of the granules leading to the decreased internal porosity of the granules to increase the hardness of the tablets produced (Anwar 2012). The granules compressibility of F1 was 2.7% after the addition of 4% gelatine concentration. The addition of gelatine concentration at F2 decreased the compressibility value to 2.6% and 2.5% in F3. The addition of gelatine concentration in F4 and F5 further increased the percentage of granular compressibility because the addition of excess gelatine concentration can disrupt the performance of PVP. Thus, the cohesive forces between the granules and the decreased porosity of the granules increased the compressibility values in F4 and F5.

3.2 Results of Lozenge Evaluation

The purpose of the tablet evaluation is to examine the quality of tablets in each formula concerning the requirements of good tablets. The tablet evaluation includes colour, shape, taste, weight uniformity, uniformity size, tablet hardness and tablet fragility. Details of tablet evaluation results can be seen in Table IV.

The obtained lozenges of all formulas were brownish white, oval and spicy-sweet. The oval shape is adjusted to the availability of the punch for a tablet weight of 1 gram. Tablets shape generally are round but it can also be oval or other shapes. In the pharmaceutical industry, tablet shape is used as a product characteristic (Agoes 2012). Spicy taste on lozenge was evident because of the lack use of sweetener. In addition, the heating can change the gingerol to be spicier yet it does not reduce the pharmacological effects of the active substances (Heinrich *et al*. 2009). Lozenges dissolve slowly inside the mouth, so the formula having the highest hardness lasts longer in the mouth. The spicy after-taste of the tablets in the F3 with the hardness of 15.95 Kgf had the most unpleasant taste. F5 obtained the most delicious taste with a hardness of 12.31 Kgf and had the largest amount of gelatine. Gelatine as a natural ingredient in the lozenge formula can improve the characteristics and texture of the lozenge surface when dissolving in the oral cavity (Siregar and Wikarsa 2010).

The tablet produced showed color patches. Striking and uniformly dispersed dark areas on the surface of the tablet were due to the different color of the active substance and other tablet excipients. Such spots may arise due to the use of natural materials in the lozenge formula (Badan Pengawas Obat dan Makanan 2012). In addition, the use of dextrose in the formula can contribute to the brownish color if the temperatures given is above 37ºC (Siregar and Wikarsa 2010).

The tablet weight uniformity test was performed by testing the weights of 20 tablets per formula. The

Table 4: The red ginger lozenge test results.

Evaluation	F1	F2	F3	F4	F5
Organoleptic:					
a. Shape	Oval	Oval	Oval	Oval	Oval
b. Smell	Specific	Specific	Specific	Specific	Specific
c. Color	White Brownish	White Brownish	White Brownish	White Brownish	White Brownish
Thick (mm)	5,75 ± 0,01	5,75 ± 0,02	5,75 ± 0,01	5,75 ± 0,02	5,75 ± 0,02
Length (mm)	23,05	23,05	23,05	23,05	23,05
Width (mm)	10,45	10,45	10,45	10,45	10,45
Weigh (g)	1,008 ± 0,01	1,035 ± 0,01	1,030 ± 0,01	1,027 ± 0,01	1,025 ± 0,01
Friability (%)	0,442 ± 0,01	0,674 ± 0,01	0,174 ± 0,01	0,337 ± 0,01	0,571 ± 0,01
Hardness (Kgf)	9,01 ± 0,71	14,15 ± 0,80	15,95 ± 0,76	13,45 ± 0,87	12,31 ± 0,68

results of the test for F1 to F5 fulfilled the requirement as no two tablets having a weight deviation of 5% from the mean tablet weight and no one tablet having weight deviation of 10% from the average weight (Departemen Kesehatan RI 1979).

The tablet size uniformity test was performed by measuring the width, length and thickness of the tablet. There was no difference in length and width of the lozenges as they were determined by the size of the punch. If there was a difference in length and width of the tablet, it might be due to the moisture of granules causing a granule attached to the punch. However, there were differences in the thickness of the tablets due to the rise and fall of punch in the die hole. This study used a single punch tablet machine with only a pair of punch. The downward movement of the bottom punch along with the up movement of punch to a certain distance during the process of filling the die hole resulted in the granule down due to the gravitational effect. The distance between the punch can be different, therefore there was a thickness difference in the tablets produced yet it was not significant.

The lozenge hardness requirement is 7-14 Kgf (Hadisoewignyo and Fudholi 2013). The results (tabble 4) reported that all formulas had different hardness values; F2 and F3 did not meet the requirements. The hardness of F2 and F3 exceeding the requirement were 14.15 and 15.95 Kgf respectively. The gelatine properties can draw water into its bonds, resulting in a more spherical and homogeneous granule and enhancing the cohesive force between granular particles which in turn increase the tablet hardness (Anwar 2012). The characteristic of PVP is that the higher concentration dissolved in alcohol, the stronger the liquid bridge formed; so that the drying process of the solid bridge formation is also stronger resulting in reduced granular porosity increasing the greater granule density and the tablet hardness (Siregar and Wikarsa 2010).

The addition of gelatine concentration on F4 and F5 decreased the tablet hardness. The interaction between PVP and gelatine in F4 and F5 can reduce the performance of the binder because of the second characteristic of the material. The gelatine properties of having a low melting point, easily melt when exposed to heat, causes the interaction with PVP tending to be sensitive to water vaporization (Anwar 2012). When it is exposed to the pressure on the machine, the tablet becomes moist and the bond strength between granular particles is decreased resulting in reduced tablet hardness (Siregar and Wikarsa 2010).

The tablet fragility test was performed to determine the tablet physical stability from mechanical shock effects during the manufacturing, packing and transportation process. The results of tablet fragility test obtained from F1 to F5 fulfilled the requirement that was below 0.8% (Voigt 1995) due to the character of the binder components. The properties of gelatine that can absorb water into its bonds, result in a more spherical and homogeneous granule and increase the cohesion force between granular particles leading to increase tablet hardness and decrease the tablet fragility value (Anwar 2012). The PVP characteristic is that the higher the concentration dissolved in alcohol, the stronger the liquid bridge is formed; thus, the process of drying solid bridge formation is also stronger which in turn reduce the granular porosity and increase the granule density leading to increase the tablet hardness and reduce the tablet fragility (Siregar and Wikarsa 2010).

The addition of gelatine concentration on F4 and F5 decreased the tablet fragility. The interaction between PVP and gelatine in F4 and F5 decrease the force of binding due to the gelatine (Anwar 2012). The more gelatine leads to the less tablet fragility. Therefore, tablet hardness decreases, and tablet fragility increases (Siregar and Wikarsa 2010).

Based on the results of the data analysis, there is a significant difference in each ratio of PVP and gelatine concentration as a binder against the tablet hardness and fragility. The results of the hardness test identified that the increased hardness and decreased fragility of the tablets were from the 1:1, 1:2 and 1:3 binding ratio. Also, there was a decrease of the hardness and an increase of fragility in the 1:4 and 1:5 binder ratio.

4 CONCLUSIONS

The comparison of gelatine and PVP concentration as the binding agent of red ginger lozenge provide significant differences in the tablet hardness and fragility. The ratio of gelatine and PVP concentrations in F3 with a ratio of 1:3 concentrations identified as the highest hardness value of 15.9 Kgf and the lowest vulnerability of 0.2%.

ACKNOWLEDGEMENTS

We would like to express our gratitude to Faculty of Pharmacy and Sciences of Universitas Muhammadiyah Prof. DR. HAMKA for the contribution in the Laboratory equipment and for joining on MICH-PHD International Seminar.

REFERENCES

Agoes G. 2008. Seri Farmasi Industri-1. Pengembangan Sediaan Farmasi, Edisi Revisi and Perluasan. Penerbit ITB. Bandung. Hlm. 286-335.

Agoes G. 2012. Seri Farmasi Industri-6: Sediaan Farmasi Padat. Penerbit ITB. Bandung. Hlm. 73-79,224-234,245.

Agubata C, Onunkwo GC, Ugwu CE, Chime SA. 2012. Physical and mechanical effects of starch-gelatin binary binder mixtures on sodium salicylate tablets, *Journal of Chemical and Pharmaceutical Research*, 4 (3), 1625-1628.

Agus S, Sudirman I, Feranses SP. 2007. Pengaruh Ukuran Granul terhadap Kadar Solutio Gelatin sebagai Bahan Pengikat terhadap Migrasi Vitamin B6. Jurnal PHARMACY, Fakultas Farmasi Universitas Muhammadiyah Purwokerto. Purwokerto. ISSN 1693-3591. Hlm 3-4.

Departemen Kesehatan RI. 1979. Farmakope Indonesia. Edisi III. Jakarta: Departemen Kesehatan RI; Hlm. 6, 7, 93, 354, 378, 535, 807, 840.

Departemen Kesehatan RI. 1980. Materia Medika Indonesia. Jilid IV. Jakarta: Departemen Kesehatan RI; Hlm 78.

Badan Pengawasan Obat and Makanan Republik Indonesia. 2012. Pedoman Tenologi Formulasi Sediaan Berbasis Ekstrak. Volume 1. Jakarta: Badan Pengawasan Obat and Makanan Republik Indonesia; Hlm. 16- 18, 33 – 34.

Anwar E. 2012. Eksipien dalam Sediaan Farmasi Karakterisasi and Aplikasi. Cetakan pertama. Jakarta: PT. Dian Rakyat. Hlm.5, 26-92.

Banker GS and Anderson NR. 1994. Tablet. Editor: Lahman L. Teori and Praktek Farmasi Industri. Edisi III. Jilid II. Penerjemah: Suyatmi. UI Press. Jakarta. Hlm. 643-703.

Hadisoewignyo L and Fudholi A. 2013. Sediaan Solida. Yogyakarta: Pustaka Pelajar. Hlm.11,19,21,35.

Hamed E, Moe D. Khankari R. and Hontz J. 2005. Binder and solvent dalam: Handbook of Pharmaceutical Granulation Technology. Second edition. Taylor & Francis Group. London; Hlm. 109-119.

Heinrich M, Barners J, Gibbons S, Williamson EM. 2009. Farmakognosi and Fitoterapi. Alih bahasa Amalia H, Hadinata. Penerbit EGC. Jakarta. Hlm. 235 – 236.

Lachman L, Lieberman HA. 2003. Pharmaceutical Dosage Forms: Tablets Volume 2. United States of America, New York. Hlm. 254, 299-300, 330, 714.

Liauw NR. 2012. Optimasi Formula Lozenge ekstrak Rimpang Kencur (*Kaempferia galanga* L.) menggunakan kombinasi PVP K-30 dengan Gelatin Sebagai bahan Pengikat. Skripsi. Fakultas Farmasi Unika Mandala, Surabaya. Hlm. 50, 51,52,96.

Moore, R., Lopes, J., 1999. Paper templates. In *TEMPLATE'06, 1st International Conference on*

Mutmainah MD. 2005. Pengaruh PVP Sebagai Pengikat Terhadap Sifat Fisik Lozenge Ekstrak Jahe (*Zingiber officinale* Roxb). Skripsi. Fakultas Matematika and Ilmu Pengetahuan Alam Universitas Islam Indonesia, Jogjakarta.

Peters D. 1989. Medicated Lozenges, in: Lieberman HA, Lachman L.(eds), Pharmaceutical Dosage Form. Second edition. Volume 1. Marcel Dekker Inc. New York. Hlm. 419, 420.

Rowe RC, Sheskey JP, Quinn ME. 2009. Handbook of Pharmaceutical Exipient. Sixth Edition. The Pharmaceutical Press. London. Hlm. xxviii – 917.

Sari E, Astuti IY. 2010. Formulasi Tablet Kunyah Ekstrak Rimpang Jahe Merah (*Zingiber officinale* Roxb) dengan Bahan Pengisi Sorbitol and Laktosa and kontrol kualitasnya. Dalam Jurnal Farmasi Indonesia. Vol. 07 (02) ISSN 1693-3991. Hlm 67-75.

Siregar CJP, Wikarsa. 2010. Teknologi Farmasi Sediaan Tablet Dasar-Dasar Praktis. Universitas Indonesia Press. Jakarta. Hlm. 35, 193-195, 202, 505-523.

Voigt R. 1995. Buku Pelajaran Teknologi Farmasi. Edisi V. Penerjemah Soendani Noerono. UGM Press.Yogyakarta. Hlm. 160-161, 166, 168, 223, 564, 568, 570.

Zick S, Djuric Z, Ruffin MT, Litzinger AJ, Normolle DP, Alrawi DP, Alrawi S, Feng MR, Brenner DE. 2008. Pharmacokinetics of 6-gingerol, 8-gingerol, 10-gingerol and shogaol and conjugate metabolites in healthy human subjects. Cancer Epidemiol Biomarkers Prev. 17 (8): 1930-35.