Ad-Dawaa JOURNAL OF PHARMACY

ISSN 2987-4157

V0l. 2 No. 1 Page 35-49 DOI : 10.52221/dwj.v1i1.225

Concentration Ratio of Gelatine and Polyvinylpyrrolidone as Binder on Physical Properties of Red (*Zingiber officinale* Rosc.) Extract Lozenges

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ABSTRACT

Lozenges have the requisite tablets hardness value 7-14 Kgf, to achieve it using gelatine as suitable binder. Gelatine makes granules with bad flow time. PVP make granules with better flow time but it takes large quantity to reach hardness lozenges. This study aims at determining the effect of concentration ratio of gelatine and PVP as binder on the physical properties of red-ginger extract lozenges. Lozenges made using wet granulation method in variation of the concentration of gelatine and PVP as follows 1:1, 1:2, 1:3, 1:4 and 1:5. Hardness test results obtained from the formula 1 to formula 5 are 9, 14, 16, 13 and 12 Kgf and friability test results are 0,4%, 0,7%, 0,2%, 0,3% and 0,6%. The combination of gelatine and PVP as binder can provide meaningful difference in hardness and friability tablet.

Keywords : Red-ginger extract, Lozenges.

INTRODUCTION

Ginger as one of the most used herbs in food around the world has a wide range of medicinal uses. Medicinal use of ginger includes carminative, antiemetic, spasmolytic, antiflatulent, antitussive, hepato-protective, antiplatelet aggregation and hypolipidemic effects. Ginger has a strong odour generated by a mixture of phenolic compounds capable of stimulating thermogenic receptors so that give antiemetic effect (Heinrich et al. 2009). Generally herbal preparations of red ginger are consumed in the form of instant powder. The use of instant powder form in the treatment less practical, to be more practical and effective in its use need to be developed dosage form (Anonymous 2012).

Lozenge dosage form is a practical choice of dosage form to develop a dosage form containing red ginger. Lozenge is a solid preparation that will dissolve or break down slowly in the mouth (Agoes 2008). There are two types of lozenge that are widely used ie hard candy lozenges and compressed tablet lozenges (Peters 1989). For compressed tablet lozenges can be made by direct compression, dry granulation or wet granulation. The method of wet granulation has the advantage to facilitate the agglomeration process in the formula, so that it will be achieved the physical properties of tablet and tablet mass is good (Siregar and Wikarsa 2010).

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

As a natural binding agent can be used types of starch, gum, tragacanth and gelatine. Gelatine has a characteristic that inhibits the time of disintegration so suitable for use as a binder on lozenge (Voigt 1995). Gelatine can be used as a binder tablet formula in the form of a solution with a content of 2-10% (Anwar 2012). The use of gelatine as a binder on wet granulation can

produce poor granule flow properties (Hamed et al. 2005). Gelatine from natural sources that have viscous properties that can increase the size of granules cause increased granular flow time. This property can be improved by combining a natural binder with a synthetic binder (Agubata et al. 2012).

Synthetic binders which can be used in lozenge compression one of them is polyvinylpyrrolidone (PVP). As a binder in tablets, PVP can be used in the range 0.5-5% (Rowe et al. 2009). The use of PVP as a lozenge binder requires a large amount. In previous research results the use of 3% PVP in the formula yielded a hardness of 6.23 Kgf (Sari and Astuti 2010). It takes as much as 10% PVP to produce hardness of lozenge ginger extract with optimum hardness of 14.63 kg (Mutmainah 2005). While the use of combination of PVP as much as 4.7% and gelatine as much as 9.3% obtained physical properties of tablets that fit the requirements of tablet hardness of 13.04 Kgf and tablet fragility 0.215% (Liauw 2012). In this research, combination of PVP and gelatine will be studied for extract of ginger as active ingredient. It aimed obtaining optimum combination to get maximum hardness and minimum fragility on ginger extract lozenges.

Based on the above description, research the effect of gelatine and PVP combination on the physical properties of lozenge red ginger extract with gelatine in the range of 4.0-6.7% and PVP content in the range of 1.3-4% using wet granulation method was conducted. The combination of gelatine and PVP was performed in various concentrations of 1: 1 in the formula I, 1: 2 in the formula II, 1: 3 in the formula III, 1: 4 in the formula IV and 1: 5 in the formula V. The combination of Gelatine Vs PVP was not 0:1, 1:1, and 1:0, due to in orientation trial formula combination with gelatine under 4% didn't meet the high requirement of lozenges hardness. The quality of lozenge was assessed on the basic of physical property: evaluation of tablet mass, that is compressibility test, flow time, angle of repose, particle size distribution; and lozenge evaluation that is, organoleptic, weight uniformity test, size uniformity test, hardness test and friability test (Siregar and Wikarsa 2010).

TOOLS AND MATERIALS

Materials used include dried red ginger extract (PT Haldin Pacific Semesta), PVP K-30 (Kimia Farma), gelatine (Kimia Farma), dextrose (Kimia Farma), mannitol (Kimia Farma), Talc (Kimia

Farma), Magnesium Stearat (Kimia Farma).

METHODS

Lozenges Formula

Lozenges were made in 5 formulas namely F1, F2, F3, F4 and F5. The five formulas are distinguished in the comparison of gelatine and PVP combinations as binding agents with a weight of 1000 mg / tablet (see Table 1).

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 Stearat	1	1	1	1	1
Talc	2	2	2	2	2
Mannitol ad	100	100	100	100	100

Lozenges Making

All materials were prepared, then weighed. Red ginger extract was put into the container, added mannitol and dextrose, and stirred until homogeneous. The PVP solution was prepared by dissolving it in 70% ethanol (1: 5) and the gelatine solution was prepared by hydration of gelatine in cold water (1: 2) for 24 hours then mixed and heated. PVP solution and gelatine solution are added in warm conditions bit by bit, stirred until homogeneous and banana breaking mass is formed.

The mass was sieved with a 12-mesh sieve, then fed into an oven at ± 50 ° C for ± 24 hours. The granules are sieved back with 18-mesh sieves. Magnesium stearate and talc are added and mixed homogeneously. Perform granule evaluation. The granules are prepared and put into the hopper. The tablet weight and hardness are 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

runs until the granules run out into a tablet.

Evaluation of Extract, Granules, and Tablets

Evaluation of dried red ginger extract included organoleptic, loss on drying test, ash residue test, solubility test, particle size test and phytochemical extract test.

Evaluation of granules includes flow time, angle of repose, compressibility, granule size distribution and loss on drying. Lozenge evaluation includes organoleptic test, uniformity size, weight uniformity, tablet fragility and tablet hardness.

Table 2. Results of Evaluation of Red Ginger Extract

Parameter	Results
Organoleptic	Colour : 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% pass of mesh 80 sieve
	80,47% pass of mesh 100 sieve
Flavonoid	+
Saponin	+
Tannin	-
Phenol	+
Triterpenoid	-
Steroid	-

RESULTS

The dried extract obtained from PT. Haldin was then determined. The result of extract determination from LIPI Cibinong showed that the red ginger dry extract observed was Red Ginger (Zingiber officinale Roscoe) which belongs to Zingiberaceae tribe. The results of organoleptic test on dried red ginger extract in the form of fine powder yellow brown with spicy flavour and red ginger specific smell. LOD test to know the moisture content of dry extract of red ginger so that can prevent powder become moist which can accelerate microbial growth. LOD test result was 5,61%. This shows that the extract had a moisture that meets the requirements, i.e. no more than 10% (Anonymous 1980).

The LOD extract test uses a moisture balance with the principle of gravimetry. This tool measures the moist content contained in extracts that evaporate from heat generated by the

appliance. The extract moisture can be due to water or organic solvents used during the extraction process. So, it is not specific to measure the water content in the extract. If the extract is made with an organic solvent, the tool can detect the remaining solvent in the extract as the amount produced. The results showed that the water content of the extract was 5.6%. Based on Hadisoewignyo and Fudholi (2013), the extract belongs to the non-hygroscopic category (<10%).

On the residual test of dried red ginger extract ash, aims to see the presence of inorganic impurities in dry red ginger extract. The larger the ash of a material shows the higher the mineral content of the material. According to Anonymous (1980), the requirements of residual ash of good red ginger rhizome extract no more than 5.0%. From the results of test value of ash residue obtained by 4.7%, so it can be concluded that the dry extract of ginger meets the requirements of good ash content.

The results of the phytochemical screening test showed that red ginger extract contained alkaloid, flavonoid, saponin, terpenoid, and glycoside compounds. The purpose of the phytochemical screening test is to know the gingerol compound, which is a phenol derived compound, which is an active substance. This compound does not break when processed at temperatures below 70℃ but will be converted into shogaol compounds that will increase the spicy flavour of red ginger extract (Heinrich et al. 2009). Due to the stability of this compound which was known from the spicy flavour and with appearing same spot-on TLC test, it can be concluded that the extract as an active substance does not suffer damage during the granule drying process and can be done making tablet with wet granulation.

The solubility test was performed to determine the solubility of the extract. The solubility test is carried out with water as a solvent. The result, 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 waters (1:17). Based on Anonymous (1979), the solubility nature of the extract is soluble in water. From the result of particle size analysis, it was found that the dried red ginger extract 93,79% can pass through mesh sieve 80 and 80,47% extract can pass through mesh sieve 100. The amount of extract that can pass through mesh sieve 80 on test result is bigger than the certificate analysis is 80%.

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

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Table 3. Results of 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

Table 4. 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. Colour	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

Evaluation	F1	F2	F3	F4	F5
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

DISCUSSION

The results of the granule flow time test of the 5 different formulas met the requirements of time flow. While the ratio of 1:1 and the ratio of 1:5 did not meet the requirements of flow time, which was caused by the amount of binding material that was not appropriate, in the F1 it was lack of gelatine and in the F5 it was too much of gelatine. If the amount of binder is not suitable will cause the bonding between particles (cohesive force) the granules are reduced, it causes the particle size is not good enough and the granules are difficult to flow (Anwar 2002). From the test results, F3 obtained the best flow properties, indicating that the 1:3 binder ratio was the ratio of the binder concentration which obtained the optimal granule cohesive force so that the granules were easy to flow. Flow time was also affected by moisture of granules.

The repose of angle test aimed at knowing the flow properties of granules when subjected to tableting process. The angle of repose is the fixed angle that occurs between the cone-shaped particles with the horizontal plane. From the research results obtained the angle of repose of the five formulas was different. The difference in the angle of repose may be affected by the cohesiveness of the granules caused by the binder. The magnitude of the angle of repose is affected by the shape, size and moisture of the granules. The value of angle of repose ranges from 25o to 45o (Siregar and Wikarsa 2010).

The five formulas met the requirements of the repose angle. From these results it can be concluded that the binder ratio of F1 and F2 had decreased up to F3. However, in F4 and F5 there was an increase in granular repose angle caused by lack of cohesiveness among granules due to comparison of binder concentration. Measurement of granular particle size distribution to determine granule size and granule depth, this was necessary because it can be affected the mixing process. From the results of the study, granules left in the sieve number 18-24 was the heaviest. According to Agoes et al. (2007), the use of gelatine solution in the formula affects the size of the granules. The greater the amount of gelatine solution the smaller the size of the granules. In the granule with a relatively small size then the internal porosity is also getting

smaller. Because the porosity of the granules is relatively small then the cohesion force is greater and causes the granules to hardly pass the mesh size of the larger sieve. Granules with larger particles tend to separate from smaller particles and move downward while small particles will rise upward (Lachman et al. 2003).

The addition of gelatine concentration to F4 and F5 did not result in a smaller granule size, as shown in Fig. 5 the number of granules left increased in mesh sieves 18. It can be concluded that the addition of gelatine concentration to F4 and F5 increases the granular size caused by an unbalanced binder ratio. Too much 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 combination of the binder. The size of the granules generally falls on the sieve number 12-20 with the particle size of 840-1680 µm (Agoes 2012).

Large granule size will result in decreased granule mass density. Smaller granules can form a more compact mass than large granules (Banker and Anderson 1994). The result of the test of granular compressibility index after determination on 100 ml granule of formula 1 to formula 5 met the requirement of good flow property category with% compressibility of ≤ 20% (Agoes 2012). Compressibility of the granules is affected by the granular density resulting in decreased internal porosity of the granules to increase the hardness of the resulting tablet (Anwar 2012). In F1 granules has a compressibility of 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. While the addition of gelatine concentration in F4 and F5 resulted in increased% granular compressibility again. This happens because the addition of excess gelatine concentration can disrupt the performance of PVP. Thus, the cohesive forces between the granules and the porosity of the granules decreased resulting in increased compressibility values in F4 and F5.

Results of Lozenge Evaluation

The purpose of the tablet evaluation is to know the quality of tablets in each formula in relation to the requirements of good tablets and meet the requirements. 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 have a brownish white colour, oval-shaped and has a

spicy sweet taste. The oval shape is adjusted to the availability of punch for a tablet weight of 1 gram. Tablets shape generally are round but can also be oval and other shapes. In the pharmaceutical industry, tablet shape is used as a product characteristic (Agoes 2012). Spicy taste on lozenge still felt, because less optimal use of sweetener. In addition, heating of the extract can change the gingerol content to be spicier but does not reduce the pharmacological effects of the active substances (Heinrich et al. 2009). Lozenge dissolves slowly inside the mouth, so the formula that has the greatest hardness lasts longer in the mouth. Because the aftertaste produced by the tablet still feels spicy then formula 3 with a hardness of 15.95 Kgf has the most unpleasant taste. The formula 5 obtained the most delicious taste with a hardness of 12.31 Kgf and the largest amount of gelatine. Gelatine as a natural ingredient in lozenge formula can improve the characteristics and texture of the lozenge surface when dissolving in the oral cavity (Siregar and Wikarsa 2010).

In the colour of the resulting tablet there are patches on the tablet. Spots with dark areas that are striking and dispersed uniformly on the surface of the tablet arise because the active substance that has a different colour with other tablet excipients. Such spots may arise due to the use of natural materials in the lozenge formula (Anonymous 2012). In addition, the use of dextrose in the formula can cause brownish colour if given temperatures above 37ºC (Siregar and Wikarsa 2010). The tablet weight uniformity test was performed by testing the weights of 20 tablets per formula. The result of uniform test of weight of tablet from formula 1 to formula 5 fulfilled the requirement because there were no 2 tablets that had a weight deviation of 5% from the mean tablet weight and no one tablet had deviation of 10% weight from average weight (Anonymous 1979).

The tablet size uniformity test is performed by measuring the width, length, and thickness of the tablet. There is no difference in length and width of the lozenge since the length and lozenge are determined by the size of the punch. If there is a difference in length and width of the tablet can be caused by moisture granules so that there is a granule attached to the punch. However, there are differences in the thickness of the tablets due to the rise and fall of punch in the die hole. In the study, used a single punch tablet machine that only has a pair of punch. The movement of bottom punch down along with the movement of punch up to a certain distance

during the process of filling the die hole resulted in the granule down as a gravitational effect. The distance formed between the punch can be different, therefore there is a thick difference in the resulting tablet, but the difference is not significant.

The lozenge hardness requirement is 7-14 Kgf (Hadisoewignyo and Fudholi 2013). From the results of the study, all formulas get different hardness values and F2 and F3 did not meet the requirements. The hardness of F2 the 14.15 and F3 15.95 Kgf exceed requirement. The properties of gelatine can draw water into its bonds, resulting in a more spherical and more homogeneous granule and enhancing the cohesive force between granular particles which leads to an increase in tablet hardness (Anwar 2012). The character of PVP is the greater concentration dissolved in alcohol, the liquid bridge is formed stronger, so that on the drying process of solid bridge formation is also stronger consequently granular porosity becomes reduced so that the granule density is greater so hardness tablet increases (Siregar and Wikarsa 2010).

While addition of gelatine concentration on F4 and F5 decrease hardness of tablet. The interaction between PVP and gelatine in F4 and F5 can decrease the performance of the binder, this is due to the presence of the second character of the material. The gelatine properties that have low melting point, easily melt when exposed to heat, then cause the interaction with PVP that tend to sensitively to water vapor (Anwar 2012). When exposed to pressure on the machine, the tablet becomes moist and can decrease the bond strength between granular particles, resulting in decreased tablet hardness (Siregar and Wikarsa 2010).

The tablet fragility test is performed to determine the tablet's physical stability from mechanical shock effects during the manufacturing, packing and transportation process. The results of fragile tablet test obtained from formula 1 to formula 5 fulfilled the requirement that is below 0.8% (Voigt 1995). This is due to the character of the binder component. The properties of gelatine can absorb water into its bonds, resulting in a more spherical and more homogeneous granule and increase the cohesion force between granular particles which leads to increased hardness of tablets and decrease the fragility value of tablets (Anwar 2012). The PVP characteristic is that the greater the concentration dissolved in alcohol the liquid bridge is formed stronger, so that in the process of drying solid bridge formation is also stronger consequently granular porosity becomes reduced so that the granule density is greater so that the hardness of tablet increases

and the fragility of the tablet decreases (Siregar and Wikarsa 2010).

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

From the results of the above data analysis, statistically shows that there is a significant difference in each ratio of PVP and gelatine concentration as a binder against hardness and fragility of tablets. From the results of hardness test, we found increased hardness of tablet and decreased % of fragility from 1:1, 1:2 and 1:3 binding ratio. And there was a decrease in the number of hardness and an increase of % fragility in the 1:4 and 1:5 binder ratio.

CONCLUSION

The result of this research can be concluded that the comparison of gelatine and PVP concentration as binding agent of red ginger lozenge can give significant difference in hardness and fragility of tablet. The ratio of gelatine and PVP concentrations in formula 3 with a ratio of 1: 3 concentrations found the highest hardness value of 15.9 Kgf and the lowest vulnerability of 0.2%.

ACKNOWLEDGEMENTS

Thank you to Faculty of Pharmacy and Sciences of Universitas Muhammadiyah Prof. DR. HAMKA for contribution in Laboratory equipment.

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