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Word count:	3,951
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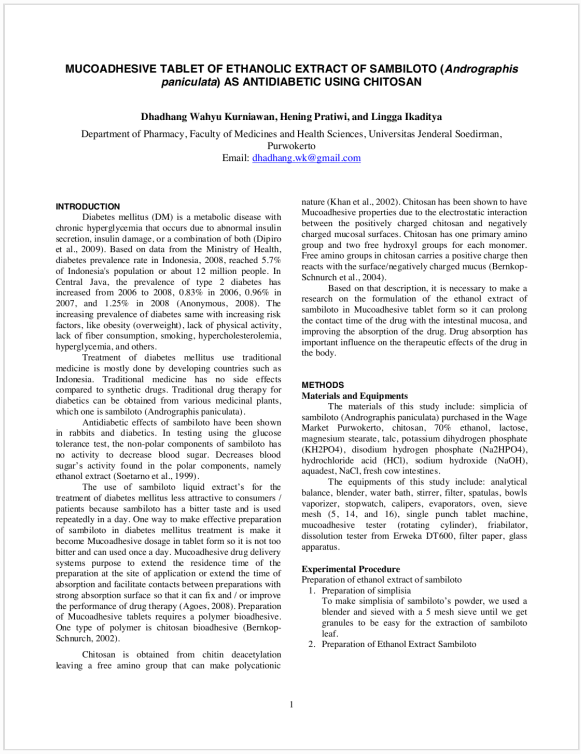

MUCOADHESIVE TABLET OF ETHANOLIC EXTRACT OF SAMBILOTO (*Andrographis paniculata*) AS ANTIDIABETIC USING CHITOSAN

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INTRODUCTION

Diabetes mellitus (DM) is a metabolic disease with chronic hyperglycemia that occurs due to abnormal insulin secretion, insulin damage, or a combination of both (Dipiro et al., 2009). Based on data from the Ministry of Health, diabetes prevalence rate in Indonesia, 2008, reached 5.7% of Indonesia's population or about 12 million people. In Central Java, the prevalence of type 2 diabetes has increased from 2006 to 2008, 0.83% in 2006, 0.96% in 2007, and 1.25% in 2008 (Anonymous, 2008). The increasing prevalence of diabetes same with increasing risk factors, like obesity (overweight), lack of physical activity, lack of fiber consumption, smoking, hypercholesterolemia, hyperglycemia, and others.

Treatment of diabetes mellitus use traditional medicine is mostly done by developing countries such as Indonesia. Traditional medicine has no side effects compared to synthetic drugs. Traditional drug therapy for diabetics can be obtained from various medicinal plants, which one is sambiloto (Andrographis paniculata).

Antidiabetic effects of sambiloto have been shown in rabbits and diabetics. In testing using the glucose tolerance test, the non-polar components of sambiloto has no activity to decrease blood sugar. Decreases blood sugar's activity found in the polar components, namely ethanol extract (Soetarno et al., 1999).

The use of sambiloto liquid extract's for the treatment of diabetes mellitus less attractive to consumers / patients because sambiloto has a bitter taste and is used repeatedly in a day. One way to make effective preparation of sambiloto in diabetes mellitus treatment is make it become Mucoadhesive dosage in tablet form so it is not too bitter and can used once a day. Mucoadhesive drug delivery systems purpose to extend the residence time of the preparation at the site of application or extend the time of absorption and facilitate contacts between preparations with strong absorption surface so that it can fix and / or improve the performance of drug therapy (Agnes, 2008). Preparation of Mucoadhesive tablets requires a polymer bioadhesive. One type of polymer is chitosan bioadhesive (Bernkop-Schnurch, 2002).

Chitosan is obtained from chitin deacetylation leaving a free amino group that can make polycationic nature (Khan et al., 2002). Chitosan has been shown to have Mucoadhesive properties due to the electrostatic interaction between the positively charged chitosan and negatively charged mucosal surfaces. Chitosan has one primary amino group and two free hydroxyl groups for each monomer. Free amino groups in chitosan carries a positive charge then reacts with the surface/negatively charged mucus (Bernkop-Schnurch et al., 2004).

Based on that description, it is necessary to make a research on the formulation of the ethanol extract of sambiloto in Mucoadhesive tablet form so it can prolong the contact time of the drug with the intestinal mucosa, and improving the absorption of the drug. Drug absorption has important influence on the therapeutic effects of the drug in the body.

METHODS

Materials and Equipments

The materials of this study include: simplicia of sambiloto (Andrographis paniculata) purchased in the Wage Market Purwokerto, chitosan, 70% ethanol, lactose, magnesium stearate, talc, potassium dihydrogen phosphate (KH_2PO_4), disodium hydrogen phosphate (Na_2HPO_4), hydrochloride acid (HCl), sodium hydroxide (NaOH), aquadest, NaCl, fresh cow intestines.

The equipments of this study include: analytical balance, blender, water bath, stirrer, filter, spatulas, bowls vaporizer, stopwatch, calipers, evaporators, oven, sieve mesh (5, 14, and 16), single punch tablet machine, mucoadhesive tester (rotating cylinder), friabilator, dissolution tester from Erweka DT600, filter paper, glass apparatus.

Experimental Procedure

Preparation of ethanol extract of sambiloto

1. Preparation of simplisia
   To make simplisia of sambiloto's powder, we used a blender and sieved with a 5 mesh sieve until we get granules to be easy for the extraction of sambiloto leaf.
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2. Preparation of Ethanol Extract Sambiloto

The simplisia are macerated using 70% ethanol with ratio 1:4 in a closed container, then stirred and allowed to stand for 24 hours.

a) Every day after 24 hours, squeezed and filtered with filter paper and a Buchner funnel. Then squeezed again with 70% ethanol for 3 days.
b) Liquid maceration and pulp results mixed together.
c) The results of the extraction solvent was evaporated to help separate and extract condensed
d) The evaporated allowed for one day and concentrated on a water bath until a constant volume.

3. Preparation of Tablets

a. Tablet formulation

Preparation of ethanol extract of sambiloto granules made using wet granulation method by varying the amount of chitosan. The number of active substances used in the formulation is determined based on the dose that has been studied by Nugroho et al. (2012), which is 150 mg.

Table 1. Formula of tablets Ethanol Extract of sambiloto leaf

Materials	Formula			
	1	2	3	4
Ethanol extract of sambiloto (mg)	150	150	150	150
Chitosan (%)	20	40	60	80
Lactose (%)	77	77	77	77
Talk (%)	1	1	1	1
Mg-stearat (%)	2	2	2	2

b. Preparation of granules (granulation)

The phases of making granules were:

1) Ethanol extract of sambiloto, chitosan, lactose, talc, and Mg-stearate was weighed.
2) The ethanol extract was mixed with partially lactose, and then added to the chitosan. The materials are mixed and stir until homogeneous, then added residual lactose.
3) The result sieved using a 14 mesh sieve.
4) After become granules, spread out on a sheet of aluminum foil on a flat tray and dried in an oven at a temperature of 40 - 60°C.
5) The dried granules were sieved with a 16 mesh sieve.
6) Then magnesium stearate and talc as the outer phase is added to the granules, mixed until homogeneous.
7) Granules were prepared felted mass.

c. Examination of Flowing Properties of granules

Examinations of the flowing property of granules were observed by stationary angle and flowing time methods.

1) Angle of repose Method

Angle of repose measurement is carried out by weighing 100 g of granules, the granules inserted into the funnel flow time test standing at a height H above the graph paper in the horizontal plane. Cover is opened so that the granules out and placed on a flat surface (Carstensen, 1977). Measurements replicated three times. Angle of repose can be calculated by the formula:

$$\text{Tan } \alpha = \frac{H}{R} \text{ atau } \alpha = \text{arc tan } \frac{H}{R}$$

Description: α = stationary angle
H = height
R = radius or ½ d

2) Flowing time

The flow time measurement method is done by weighing 100 g of granules, the granules then inserted into the funnel that closed. Cover is opened and the granules allowed to flow until the end. Calculated flow time granule. The granules have good flow properties when it has a flow time of no more than 10 seconds (Fudholi, 1983). Measurement of flow time was replicated three times.

d. Tablet compression

Compression tablets using a single punch tablet machine to adjust the size and weight of the tablet mass. When the tool has finished setting, granules were prepared and then inserted through the hopper and the machine starts (Voigt, 1994).

e. Evaluation of Tablets

1) Physical Characteristic

Tests of physical characteristic descriptively include testing for uniformity of color, presence or absence of odor, surface shape, consistency, and presence or absence of physical defects (damage).

2) Uniformity of size

Each formula is taken 20 tablets, then the tablet's diameter and tablet's thickness was measured using calipers and analyzed with the standard of uniformity in the size of the tablet edition of Indonesian Pharmacopoeia III (Anonymous, 1979).

3) Weight uniformity

Each formula is taken 20 tablets, and tablets that free from dust, weighed and the average weight was calculated, and then matched with a table percentage weight deviation allowed in the third edition of the Indonesian Pharmacopoeia (Anonymous, 1979).

4) Hardness test

Each formula is taken 10 tablets, then one by one tablet is placed in the middle to the hardness tester, first scale on the zero

position, and then the tool rotated slowly until the tablet breaks. Read scale achieved when broken or crushed tablets (Voight, 1994). Hardness is expressed in kilograms. The tablet has a hardness between 4 kg to 10 kg (Parrott, 1971).

5) Friability (fragility)

According Agoes (2006), 20 tablets of each formula that free from dust, placed in friabilator. Friabilator run 4 minutes or 100 times a round. Tablets were taken and cleaned of particles attached, by weight, calculated the percentage in weight. The total weight of the tested tablets should not be reduced by more than 1 % of the initial weight of the test. Testing was replicated three times.

Friability test results can be calculated using the following equation:

$$F\% = \frac{(Wo - Wt)}{Wo} \times 100\%$$

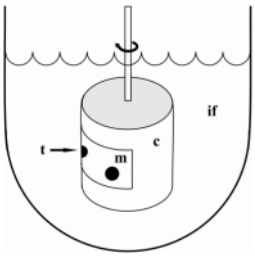
Description:

W0 = initial weight of the tablet before intervened friabilator

Wt = weight of tablet after intervened friabilator

f. In vitro evaluation of mucoadhesive properties by the rotating cylinder method

Tablet attached to the pressure of 500 Pa in the intestinal mucosa of cow, which was attached to a stainless steel cylinder (diameter 4.4 cm, height 5.1 cm, the 4-cylinder, USP XXVI) using cyanoacrylate adhesive. The cylinder is placed in the dissolution apparatus according to USP, entirely immersed in the dissolution medium of 100 mM phosphate buffer pH 6.8, at a temperature of 37°C and stirred at 100 rpm. Testing tools can be seen in picture 1. Tablet test apart, disintegrated and/or eroded observed for a period of 10 hours (Bernkop-Schnurch, 2002).



Picture 1. Testing system scheme which is used to evaluate the properties of mucoadhesive tablets based on various polymers. c: cylinder, if: intestinal fluid, m: bovine intestinal mucosa, t: tablets (Bernkop-Schnurch, 2002).

g. Data analysis

Data results of testing the physical properties of granules and tablets compared to physical evaluation requirements of tablets according to the third edition of the Pharmacopoeia of Indonesia (1979), Indonesia Pharmacopeia IV edition (1995), and related literature .

RESULTS AND DISCUSSION

Results of determination of plant stated that the plant is sambiloto with the scientific name of *Andrographis paniculata* (Burm f .) Nees. Dry powder of sambiloto was 1788 mg, obtained after the extraction process as much as 153 mg of extract thick, mean yield of extract of dried powder is 8.56%. Viscous extract obtained was then conducted organoleptic test. The results of ethanol extract of sambiloto organoleptic test are shown in Table 2.

Table 2. The results of organoleptic test ethanol extract of sambiloto

No.	Organoleptic parameters	Description
1.	Color	Black greenish
2.	Odor	typical
3.	Taste	bitter
4.	consistensy	condensed

Ethanol extract of sambiloto granules that made by wet granulation subsequent physical characteristic test, including flowing properties of granules and granules moisture content. Data of flowing properties of granules are presented in Table 3 .

Table 3. Test results of flowing properties of ethanol extract of sambiloto

Formula	Flowing time (seconds)	Stationary angle (x°)	Specification
F1	4,33 ± 0,08	26,14 ± 1,06	Eligible
F2	3,77 ± 0,10	25,24 ± 1,66	Eligible
F3	4,77 ± 0,12	24,10 ± 0,48	Eligible
F4	4,64 ± 0,08	23,57 ± 0,77	Eligible

* replicated 3 times.

Based on Table 3 , known that all formulas have the flowing time and repose angle qualified because 100 grams of ethanol extract of sambiloto granules flowing less than 10 seconds and repose angle less than or equal to 30º. Repose angle measurement shown that the higher amount of chitosan added, the smaller repose angle got. It means that the addition of chitosan effect on repose angle of granules.

Test of flowing time and repose angle describe the flowing properties of granules. Good flowing properties of the granules is essential to ensure efficient mixing and uniformity of weight (Siregar and Wikarsa, 2005).

Flowing properties are affected by particle size, particle shape, moisture granules, gravity and friction forces between particles. If a large particle size and spherical

shape as well as gravity and friction forces small, it will be faster and easier flowing. The more flat cone generated, then the smaller the tilt angle and the better of the flowing properties. Based on the results of the study, increased of chitosan will accelerate the flowing time. This is due to the formula with the higher chitosan concentration resulted in large granules, granules that are large will have little friction so the flowing time is small (Lachman et al., 1994; Voigt, 1995).

The results of the determination of moisture content of the ethanol extract of sambiloto granules can be seen in Table 4 .

Table 4. The results of the determination of moisture content of ethanol extract of sambiloto granules.

Formula	Initial weight (gram)	Final Weight (gram)	Moisture content (%)
1	5,00 ± 0,00	4,86 ± 0,00	2,92 ± 0,08
2	5,00 ± 0,00	4,85 ± 0,00	3,16 ± 0,09
3	5,00 ± 0,00	4,84 ± 0,00	3,31 ± 0,08
4	5,00 ± 0,00	4,83 ± 0,00	3,53 ± 0,09

* replicated 3 times

Based on the data in Table 4, shows that the granules of all formulas qualify moisture contents, because the content is in the range 2-4% moisture. According to Lachman et al., (1994) that the good moisture content of the granules is 2-4%.

The test results of physical characteristic ethanol extract of sambiloto tablet can be seen in Table 5. Physical characteristic showed that tablets produced relatively good. Greenish black color tablet, the younger of the formula 1 to formula 4, it is caused by increasing of chitosan. The more chitosan used in this study resulted in younger creamy white colored tablet produced.

Uniformity test results measure the ethanol extract of sambiloto tablets are presented in Table 6 .

Tabel 5. The results of testing the physical characteristic of tablets

The characteristic	Formula			
	F1	F2	F3	F4
Color	Black greenish (thick)	Black greenish	Black greenish (young)	Black greenish (young)
Odor	Typical	Typical	Typical	Typical
Surface	Smooth and compact	Smooth and compact	Smooth and compact	Smooth and compact
Physicallly disabilities	None	None	None	None

Table 6. Test results of tablet size uniformity ethanol extract of sambiloto

Formula	Thick of tablet (mm)	Diameter of tablet (mm)	Spesification
F1	0,33 ± 0,00	1,31 ± 0,00	Eligible
F2	0,33 ± 0,00	1,31 ± 0,00	Eligible
F3	0,33 ± 0,00	1,31 ± 0,00	Eligible
F4	0,33 ± 0,00	1,31 ± 0,00	Eligible

Based on the data in Table 6, it is seen that all the tablets eligible with requirements of uniformity of size . Thus, the ethanol extract of sambiloto tablet can be declared to have good size uniformity. One good indicator is expressed tablet is a tablet that has a good size uniformity.

Tablet weight uniformity test results of ethanol extract of sambiloto can be seen in Table 7.

Table 7. The results of uniformity test of ethanol extract of sambiloto tablet

Formula	Weight (mg)	Coefficient of Variation (CV)	Spesification
F1	498,3 ± 6,59	1,32%	Eligible
F2	502,15 ± 7,34	1,46%	Eligible
F3	498,5 ± 6,46	1,30%	Eligible
F4	505,55 ± 6,75	1,33%	Eligible

Based on the data in Table 7, it is seen that all formula eligible weight uniformity, because none of the tablets deviated 5% and 10% of the average weight of the tablet and has a CV less than 5%. Tablets with a good weight uniformity can be assumed that the levels of active ingredient in the tablet as well uniform so that the therapeutic effect produced identical (Anonymous, 1979; Voigt, 1995).

The results of hardness test of the ethanol extract of sambiloto tablets are presented in Table 8.

Table 8. The results of hardness test of ethanol extract of sambiloto tablets

Formula	Hardness (kg)	Specification
F1	4,15 ± 0,24	Eligible
F2	4,05 ± 0,16	Eligible
F3	3,85 ± 0,24	Eligible
F4	3,65 ± 0,34	Eligible

Based on the data in Table 8, it is seen that all formulas eligible with tablet hardness scale between 4-10 kg (Anonymous, 1979). Hardness of formula 1 to formula 4 is getting smaller. Formula 1 with the highest levels of chitosan has the greatest hardness is 4.15 kg. Supposedly greater levels of chitosan will increase the bond between chitosan with other ingredients to produce a stronger bond and tablets are formed more compact and hard. But the results showed different results, this was caused by the size of the chitosan used larger than it should be. The size of

chitosan amorphous powder/powder causes compactibility less than the maximum.

The results of ethanol extract of sambiloto tablet friability test can be seen in Table 9.

Table 9. The results of friability test of ethanol extract of sambiloto tablets

Formula	Friability (%)	Specification
F1	0,62 ± 0,20	Eligible
F2	0,55 ± 0,08	Eligible
F3	0,60 ± 0,28	Eligible
F4	2,10 ± 2,25	None eligible

*replicated 3 times

Based on the data in Table 9, shows that the friability test of formula 1 to formula 3 were eligible, because of losses weight were not more than 1% (Banker and Anderson , 1994). Friability formula 4 wasn't eligible, because the amount of chitosan used was more than it should, where the size of chitosan was large, so tablet compactibility and hardness wasn't good. Compactibility and hardness of tablets are good enough to make the tablets brittle. Tablet which has a high hardness means have strong bond between particles, so it is not easily damaged by shocks.

Friability is a parameter to assess the resilience of the tablet to a variety of things that can cause damage to the surface of the tablet (Ansel, 1989). According to Voigt (1995) friability is expressed as the mass of the entire particle released from the tablet due to mechanical load testers . Friability expressed as a percent of friability which refers to the mass of the initial tablet before testing.

Friability test is very important because tablet that easily crushed into powder, flakey, and cracked in handling will loses its aesthetic value so the consumer won't accept it, it also can caused contamination at the site of the transport and packaging, and also caused variations in tablet weight and content uniformity (Banker and Anderson, 1994).

At the time of the tablet contacted with a solution of phosphate buffer pH 6.8, all formulas tablet looked swell and form a hydrogel, and stick/attached firmly to the intestinal mucosa. Adhesion of tablets on the intestinal mucosa can be seen in Picture 2 .

Picture 2. Adhesion to the intestinal mucosa tablet

Hydrophilic chitosan can undergo hydration contact with water and form a hydrogel that expands into a tablet formula (Varshosaz et al., 2006). Hydrogels are three-dimensional cross linked polymer chains that have the ability to hold water in the porous structure. This hydrogel is formed by the presence of hydrophilic functional groups, such as hydroxyl, amino, and carboxyl. In the chitosan structure, there is a hydroxyl group that can form a chitosan hydrogel (Mythri et al., 2011).

Tablet expands slowly because chitosan has the ability controlled hydration (Jain et al., 2008). Hydration is controlled to prevent the occurrence of excessive hydration. Excessive hydration would reduce the flexibility of the polymer chains due to the formation of cross linked polymer chains thereby limiting excessive interpenetration of polymer chains into the mucus and eventually will reduce mucoadhesive strength (Mythri et al., 2011).

In theory, this mucoadhesive phenomenon takes place in two steps. The first step is a contact between the polymer bioadhesive (chitosan) and mucus due to wetting and development of bioadhesive materials (chitosan). The second phase is consolidation, a process where bioadhesive polymer penetrate into crevices and surface mucus occurring chemical bonds between the polymer and mucin bioadhesive (Carvalho et al., 2010). Mucoadhesive properties test results in vitro are presented in Table 10 .

Table 10. The results of in vitro testing mucoadhesive properties tablets ethanol extract of sambiloto

Formula	Mucoadhesive properties
1	4,33 minute 25,67 seconds ± 0,58
2	8 minute 20 seconds ± 2,00
3	17,33 minute 18,33 seconds ± 2,52
4	23 minute 16,33 seconds ± 2,00

*replicated 3 times

Based on Table 10, it is seen that of formula 1 to formula 4 with the increasing of chitosan resulted in an increase in mucoadhesive properties. Formula 4 with the highest levels of chitosan having the greatest mucoadhesive properties that can be attached for 23 minutes 16.33 seconds, while the lowest adhesion owned by Formula 1 with the lowest levels of chitosan which can be attached for 4.33 minutes 25,67 seconds. This is due to the higher levels of chitosan used; the ability of bonding with mucin is stronger. Chitosan has hydroxyl groups that are responsible adhesion. Mucoadhesive properties possibbly caused by the formation of hydrogen bonds between the hydroxyl groups of the chitosan with mucus components and ionic bonds between atoms N in chitosan with the S atom of cysteine contained in the mucus layer (Majithiya et al., 2008; Sreenivas and Pai, 2008). Hydrogen bonds are the bound between the H atoms in the molecule which attracted by the highly electronegative atom, in example F, O, or N from adjacent molecules. While the ionic bond is a bound that is formed due to the difference in charge between the

two components, between chitosan and mucin (Petrucci, 1985). The higher levels of chitosan used, the stronger bond produced, so the mucoadhesive properties will be stronger (Majithiya et al., 2008).

CONCLUSION

Ethanol extract formula of sambiloto tablets made by using chitosan as a carrier qualify physical characteristic of tablets (physical appearance, uniformity of size, weight uniformity, hardness, and friability). Increased levels of chitosan on the ethanol extract of sambiloto tablets can improve mucoadhesive properties. Formula 4 with the highest levels of chitosan have the strongest mucoadhesive properties which can be attached for 23 minutes 16.33 seconds, while the lowest power possessed by the formula 1 with the lowest levels of chitosan which can be attached for 4.33 minutes 25.67 seconds.

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