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FORMULATION AND CHARACTERIZATION OF GLIMEPIRIDE MUCOADHESIVE GRANULES WITH SODIUM ALGINATE POLYMER

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ABSTRACT: The mucoadhesive drug delivery system is a drug delivery system in which drugs, along with bioadhesive polymers, are designed to contact longer in the mucous membrane of the gastrointestinal tract. This study aims to formulate glimepiride with sodium alginate polymer to produce granules in mucoadhesive form, the influence of sodium alginate on the characteristics of Glimepirid mucoadhesive granules, and the dissolution profile of Glimepiride mucoadhesive granules. The preparation is made with three formulas with various comparisons. The manufacture of granules is carried out through wet granulation. Characterization of mucoadhesive granules is performed by *Scanning Electron Microscopy* (SEM). Determination of levels of Glimepiride active substances and mucoadhesive granules with HPLC: ZA 99.2566%, F1 100.8666%, F2 101.01%, F3 100.8733%. The dissolution profile shows an increase in the rate of dissolution, which is 7.4013% for pure glimepiride and successive formulas FI 8.155%; FII 7.6644% and FIII 7.9942%. The mucoadhesive ability of formula III is the highest compared to other formulas, namely 96% (in vitro mucoadhesive test) and 68.67% (wash-off test). It can be concluded Glimepirid formulation with sodium alginate polymer can produce mucoadhesive preparations
Keywords: Mucoadhesive, Glimepyrid, Sodium Alginate, Granule

1. Introduction

The mucoadhesive drug delivery system is a drug delivery system in which drugs together with bioadhesive polymers are designed to be able to contact longer in the mucous membrane in the digestive tract so as to provide benefits in the pharmacokinetics and pharmacodynamics of the drug. Glimepirid has been recognized by the FDA as an oral antidiabetic drug. Glimepiride have a short half-life of 3.4 ±0.7 hours. This short half-life makes the use 2 -3 times a day at a dose of 2.5 – 10 mg per day (Febryanto, *et al*., 2014). Diabetic diseases can affect the timing of gastric emptying. Oral use of slow-release dosage form of glimepiride will release the active ingredients slowly so that the drug can be continuously released at the place of its absorption, namely in the upper stomach. This method will be effective in achieving the effect of hypoglycemic.

Polymers should not be toxic and unabsorbed, rapidly related (*adhesive)* to wet organs, and release the drug in a controlled manner (Agoes, 2001). Sodium alginate is a polysaccharide extracted from brown algae or produced by bacteria, containing D-manuronic acid and L-guluronic acid. The contact of alginates with divalent cations (such as calcium ions in calcium chloride solution) instantly induces ion polymerization at the alginate interface through cation bonding with guluronic acid units resulting in a three-dimensional crosslinking with *the eggbox* structure. (Suciati, *et al*., 2011). Sodium alginate is used in slow-release preparations because it can inhibit the release of drugs in tablets and suspensions in water.

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2. Material

High-Performance Liquid Chromatography (HPLC) (Hitachi, Tokyo, Japan), vibration sieve, volumeter tap, wash off test kit (desintegrator tester), dissolution test equipment (Copley Scientific Type NE4-COPD, Nottingham, United Kindom), Scanning Electron Microscopy (SEM) (Hitachi S-3400N, Tokyo, Japan), pH meter (Hanna instrument HI 2211), Sonicator (Branson) , in vitro bioadhesive test equipment. Glimepirid (PT. Asian Semarang), Na Alginat (Shandong Jiejing) , Amilum manihot (PT. Bratachem), Lactose (PT. Bratachem), Ethanol (PT. Bratachem), Sodium Hydroxide (PT. Bratachem), Potassium Dihydrogen Phosphate (KH2PO4) (Merck), Physiological Sodium Chloride (NaCl) (Merck), Liquid Paraffin, Distilled Water (PT. Bratachem), Acetonitrile grade HPLC (Merck), Aquabidestilata grade HPLC (PT. Bratachem), Methanol grade HPLC (PT. Bratachem) and mucous membranes of the intestines and stomach (derived from white rabbits that are satisfied for 1 day before testing).

3. Method

3.1 Mucoadhesive Granule Manufacturing

Mucoadhesive granules are made in three formulas (F1, F2, F3), each containing Sodium Alginate in various comparisons as in Table 1. The manufacture of granules is carried out in a wet granulated manner. Put the lactose in the lump, add sodium alginate in various ratios, and put the group leid glimepiride until homogeneous, then put the mucilage amylum little by little until a mass can be formed that can be clenched. Then sifted with a *mesh* sieve 16, spread evenly over the aluminum foil, and put in the oven for ±6 hours at a temperature of 40^{o}C until the granules dry (Lachman, *et al*., 1994).

Table 1. Glimepiride Mucoadhesive Granule Formulation with Sodium Alginate

Material	Formula (gram)		
	F1	F2	F3
Glimepiride	0,5	0,5	0,5
Sodium Alginate	0,75	1	1,25
Lactose	1	1	1
Amylum Manihot	qs	qs	qs
total	6	6	6

3.2 Particle Size Distribution

The granules created are determined by the particle size distribution using a fibration sieve. Carried out by weighing as much as ± 3 g of granules placed in a sieve arranged decreasingly from the size of the most significant sieve hole to the smallest, and the sieving machine is run for 10 minutes. The granules left on each sieve are weighed and carried out three times for each formula (Halim, 2012).

3.3 Evaluation of Mucoadhesive Granules

Specific gravity, Compound gravity, True specific gravity, Hausner factor, Compressibility, Porosity, Flow Rate, and Avalanche Angle

3.4 Characterization of Granule Physics with Scanning Electron Microscopy (SEM)

The powder sample is placed on an aluminum sample holder and coated with gold with a thickness of 10 mm. The sample was then observed with various magnifications of the SEM tool. The voltage is set at 10 kV, and the current is 12 mA. This analysis showed the morphology of the particle form of a single compound of glimepiride, Na Alginate, and each of the mucoadhesive formulas.

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3.5 Glimepiride Levels Determination with HPLC

a. Chromatography conditions

Colom : Phenomenec / ODS C18 (4.6 x 150 mm)
Mobile phase : Aquabidestilata: Methanol (40: 60)
Flow Rate :1.1 mL/min
Injection Volume : 20 µL
Temperature : 25 ^{o}C
Detektor : UV λ (200-400 nm)
Retention time : 5 minutes

b. Motion phase optimization

The phase of motion to be used is Aquabidestilata : Methanol with 3 variations of aquabidestilata comparison: Methanol (50:50), (60:40) and (40:60). A combination of mobile phase and flow rate is selected that provides the best separation, based on symmetrical peaks, peak height, area area and retention time.

c. Manufacture of Glimepiride mother liquor

Glimepirid 500 µg/mL mother liquor dissolved in the mobile phase

d. Creation of calibration curves

Glimepirid solution concentration series 2 µg/mL, 4 µg/mL, 6 µg/mL, 8 µg/mL, and 10 µg/mL. Each solution is filtered with a membrane filter pore size of 0.45 µm. Put into the sample tube then determine the area with HPLC and determine the regression equation. (Harahap, *et al*., 2006)

f. Manufacture of mucoadhesive formula test solution

Each formula is weighed 50 mg equivalent, then dissolved with phosphate buffer into a 100 mL measuring flask, suffice the volume to the limit mark (concentration 500 µg/mL). From the mother liquor, 500 µg/mL is prepared from a solution with a concentration of 10 µg/mL. The solution is filtered using a membrane filter pore size of 0.45 µm. Furthermore, the chromatogram is measured with HPLC according to optimum analysis conditions. Measurements were made by three repetitions.

3.6 Glimepiride Mucoadhesive Dissolution Profile Determination

The dissolution test is carried out using a *type II dissolutionon tester*, namely the paddle type. With a solution medium with a phosphate pH of 6.8 as much as 900 mL and a temperature set at 37±0.5^{o}C. Then the equivalent test powder of 20 mg is put into the container and rotated at a speed of 50 rpm. The dissolution solution is pipetted 5 mL at minutes 5, 10, 30, 45, 60, 90, 120, 180, 240, 300 and 360. The absorption of the piped solution of the dissolution medium is measured at the maximum wavelength. Dissected glimepiride levels at each time were calculated using a calibration curve. (Bhanja, *et al*., 2013).

3.7 Mukoadhesif Test (in vitro)

Using the gastric mucosa and intestines of rabbits. The stomach and intestines of rabbits are washed with physiological NaCl solution then immersed in artificial gastric and intestinal juices, respectively. The gastric organs are opened and cut approximately 3 x 2 cm and the intestinal organs are split and cut approximately 7 cm, placed on aluminum supports, then placed in cylindrical cells with a slope of 45 ºC. A total of 20 granules are placed on the tissue and left in contact for 20 minutes. Then the cylindrical cells are set at a slope position of 45 ºC.

Granules that have been attached to gastric tissue are diluted with artificial gastric juices for 5 minutes at a speed of 22 mL/min. For granules attached to the intestines, diluted with artificial intestinal fluid for 5 minutes at a rate of 22 mL/min. The mucoadhesive test aims to see the ability of granules to adhere to the stomach and intestines in a static state (Suryani *et al*., 2009).

3.8 Wash Off Test

This test aims to look at the ability of granules attached to the gastric and intestinal mucosa for a period of 2 hours in a dynamic state. The cleaned gastric and intestinal mucosal tissues are glued to the object glass and

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then plastered with granules as many as 20 granules evenly, then placed on a glass tube and put into a disintegration test kit. The tool is moved up and down 30 times per minute. The medium used is artificial gastric and intestinal juices with a temperature of 37 ºC ± 5 ºC. The number of granules that are still attached is seen and calculated for 2 hours (Indrawati *et al*., 2005)

4. Result and Discussion

Glimepiride, raw material is carried out according to the requirements listed in the 2014 edition of the Indonesian Pharmacopoeia V. The examination includes shape, color, taste, smell, and identification. The results show that the Glimepirid used has met the requirements. Glimepiride is a white crystalline powder, odorless, slightly bitter, have a yellowish-white color. Identification by determination of the maximum wavelength of the glimepiride with a UV spectrophotometer in a dissolution medium solvent with a concentration of 10 µm/mL obtained 232.8 nm with an uptake of 0.561. From the results of the wavelength identification, Glimepirid has met the requirements, namely a wavelength of 233 nm. The average level of glimepiride using HPLC was obtained at 99.2566%, which met the requirements in the 98.0 % -102.0% range.

Inspection of raw materials of Na Alginate is carried out according to the requirements listed in the *Handbook of Pharmaceutical Excipients (6th edition)*. The examination includes shape, color, and smell. The results showed that the Na Alginate used had met the requirements. Na Alginate is powdered, tasteless, odorless, and has a pale yellowish-white color.

Particle size distribution can affect the flow properties of the granule because the smaller the particle size of the granule, the granule has good flow properties. Glimepiride and mucoadhesive granule particle size distributions are shown in figure 1.

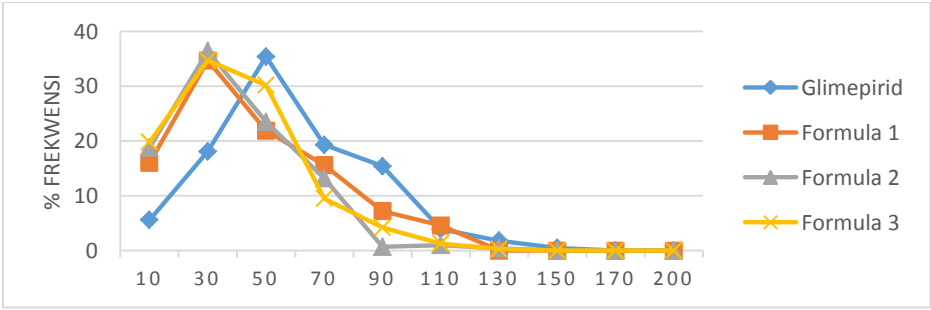

Figure 1. Particle Size Distribution Comparison Curve

Evaluation results of the F1, F2, and F3 granules show that Glimepirid mucoadhesive granules have good flow properties. Hausner factor in determining the flow or free-flowing properties of a powder or granule, if the value ≥ 1, it can be stated that the granule has good flow properties (Halim, 2012). % good porosity of a granule value is small than 50% because the smaller the porosity results in an increase in the number of drugs that will increase the effectiveness of the drug work (Halim, 2012). A large angle of 30˚ has poor flow properties, while a slight angle of 30˚ has good flow properties.

Table 2. Evaluation of Glimepiride mucoadhesive granules

Granule evaluation	Mucoadhesive granule formula		
	F1	F2	F3
Real breed weight	0,9966 g/mL	0,87 g/mL	0,8866 g/mL
Compressed breed weight	1,0666 g/mL	1,1266 g/mL	1,0233 g/mL

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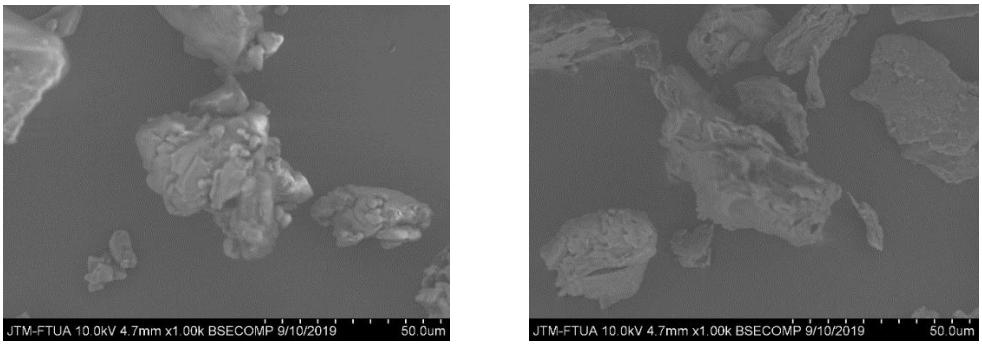
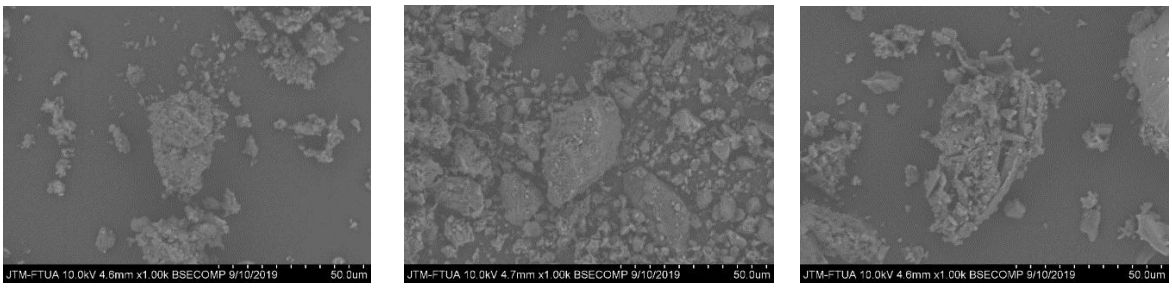
Correct breed weight	1,0266 g/mL	0,87 g/mL	0,5766 g/mL
Factor Hausner	1,0766 g/mL	1,29 g/mL	1,1633 g/mL
% komprebilitas	6,4 %	22,3133%	13,6366 %
Porosity	-37,3 %	-13 %	-56 %
Flow rate	34.3833 g/s	27.99 g/s	37.3166 g/s
Landslide angle	10,60°	16,75°	13,66°.

Scanning Electron Microscopy (SEM) is a tool that can view a sample's surface morphology microscopically and provide information about the surface texture of the sample (Gennaro, 1985). At SEM magnification 1000 times, Glimepyrids are seen as solids that are irregularly rectangular in shape and small cubes. Na Alginate looks like elongated and folded flakes (Figure 2). F2 and F3 are still visible cube shapes, squares, and flakes that are elongated, which means they can still be distinguished, which are glimepiride and sodium alginate (Figure 3). The principle of this SEM analysis is to see if the active substance has been dispersed with polymers so that we can no longer distinguish between them. This shows that F1 has been dispersed between the active substance (glimepiride) and the polymer (sodium alginate).



(a) (b)

Figure 2. Morphology of (a) Glimepiride, (b) Sodium Alginate



(a) (b) (c)

Figure 3. Morphology of granule mucoadhesive (a) Formula 1, (b) Formula 2, (c) Formula 3

The glimepiride levels in mucoadhesive granules were determined using High-Performance Liquid Chromatography (HPLC). The determination of the level begins with the determination of the maximum wavelength at a concentration of 4 µg / mL and obtains a maximum wavelength of 233.60 nm with an absorbent value of 0.313. In determining the level of the active substance, optimization must first be carried out on the

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phase of motion to be used. Optimization can be seen from the resulting retention time and the good separation of substances (Harmita, 2004). The mobile phase used is a mixture of methanol – aqua bidestilata in several ratios of 50:50, 60:40, and 40:60. A combination of 40:60 motion phases was chosen because it results in good separation.

The glimepiride calibration curve is made by making the solution series into several concentrations, namely 2 µg/mL, 4 µg/mL, 6 µg/mL, 8 µg/mL, and 10 µg/mL dissolved. The analysis method is validated against linearity, LOD, LOQ, precision, and accuracy. From the analysis results, the linear regression equation y = 1661192.3 + 201081.15x with the value r = 0.9956. Where the established linearity requirement is r = ±0.9998 (Harahap *et al*., 2006), this shows a linear relationship between concentration and area. LOD and LOQ, respectively, are 1.0103 ppm and 3.3676 ppm.

Determination of glimepiride levels of each formula F1, F2, and F3 respectively 100.87%, 101.01%, 100.87%. The regression equation calculates the determination of the pure glimepiride level of each formula. The results of determining the levels obtained are in accordance with the requirements listed in the Indonesian Pharmacopoeia V edition (2014), where the glimepiride content in the granule is not less than 98.0% and not more than 102.0%

The determination of the dissolution profile of glimepiride and each formula was carried out using a dissolution medium with a pH of 7.4 phosphates as much as 900 mL, according to the official book of the Indonesian Pharmacopoeia V edition (2014). Determination of the maximum absorption wavelength of glimepiride in the dissolution medium using a solution with a concentration of 10 µg/mL obtained a maximum absorption wavelength of 232.80 nm with an absorbent of 0.561. The calibration curve obtained from the concentration of 4 µg/mL, 6 µg/mL, 8 µg/mL, 10 µg/mL, and 12 µg/mL obtained the line equation y = 0.05098x + 0.05964 with the value r = 0.99992. Dissolution efficiency is a suitable parameter for *in-vitro* dissolution evaluation. The dissolution efficiency value is the AUC (*Area Under Curve*) value of the number of dissolution drugs per unit of time. The calculation of the average dissolution efficiency shows the values of pure glycemia = 7.4013 %, F1 = 8.155 %, F2 = 7.6644 %, and F3 = 7.9942 %. These data indicate that formula 3 has a higher efficiency. The results of this dissolution confirm the results of SEM and mucoadhesive tests.

Mucoadhesive evaluation of Glimepirid granules with Sodium Alginate in the stomach was obtained at F1 = 94 %, F2 = 95.33 %, and F3 = 96 %. In the mucoadhesive test of Glimepirid granules with Sodium Alginate in the intestine, the results of F1 = 36 %, F2 = 42.67 %, and F3 = 51.33%. This suggests that the comparison of the use of sodium alginate polymers with various concentrations can affect the granules attached to the gastric mucosa and intestines. The data obtained indicate that using a polymer Sodium Alginate with a higher concentration results in better mucoadhesive properties. Sodium Alginate has mucoadhesive properties, but its ability to expand and solubility is not good at low pH. Amylum Manihot has excellent inflatability but high solubility at low pH, so it cannot control the release of the preparation (Suciati *et al*., 2011).

The Glimepiride granule wash-off test with Nartium Alginate also used rabbit gastric and intestinal mucosal tissue. This test was carried out for 2 hours, and after more than 2 hours, the integrity of the mucous tissue was no longer feasible for subsequent testing. The test results of glimepiride granules attached to the rabbit gastric mucosa in formulas 1, 2, and 3 were 39.33%, 43.33%, and 68.67%. While in the intestinal mucosa, it is 0.67%, 1.33%, and 4%. This shows that after 2 hours, the number of granules attached to the stomach can be seen in formula 3 with 68.67% compared to sticking to the intestines. This means that sodium alginate has great mucoadhesive power in the gastric mucosa.

Theoretically, mucoadhesive can occur due to good contact between the bioadhesive polymer and the membrane, namely by wetting or developing a bioadhesive polymer, then penetrating the bioadhesive polymer into the tissue mucus gap, and then weak chemical bonds such as hydrogen bonds between polymers and mucus occur (Indrawati *et al*., 2005).

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5. Conclusion

Formulations of glimepiride with sodium alginate polymers can produce mucoadhesive preparations. F3 has a greater ability to attach to the gastric mucosa compared to other formulas, which is 96%. The use of sodium alginate polymers in mucoadhesive preparations of glimepiride affects the physicochemical characteristics of glimepiride. The influence of the use of sodium alginate on the dissolution rate of the mucoadhesive granules of glimepiride can be seen as an increase in the dissolution rate of pure glimepiride and formulas.

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