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FORMULATION OF MUCOADHESIVE TABLETS WITH FULLY GELATINIZED MODIFIED DALUGA (CYRTOSPERMA MERKUSII) MATRIX USING SIMPLEX LATTICE DESIGN METHOD

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starch could used as ingredient fillers, binders and crushers in tablet manufacture. Amylum is also defined as carbohydrates from from plant, as results photosynthesis, which is stored in part certain plant as backup food starch is mixture two type structure different polysaccharides that is contains (17-20) % amylose and (80-83) % amylopectin. Destination study this is for know the formulation of mucoadhesive tablets with fully gelatinized modified daluga (cyrtosperma merkusii) matrix using simplex lattice design method. Quantitative Test Methods that aim for count yield starch and qualitative tests aimed at for knowing content polysaccharides in starch. Iodine test on amylose will show color blue, and on amylopectin. Character test result data physique granules and tablets as well as release ranitidine of tablets analyzed with using the Design-Expert® software, so that obtained the contour plot of each test results. Determination of the optimum formula begins with determine the optimized parameters that is speed flow, tablet hardness, tablet friability, floating time and speed release ranitidine HCl

KEYWORDS *mucoadhesive tablets, gelatinized modified daluga (cyrtosperma merkusii), simplex lattice design method*

INTRODUCTION

Starch can be used as a filler, binder, and disintegrant in the manufacture of tablets (Sari et al., 2012). Starch is also defined as carbohydrates derived from plants, as a result of photosynthesis, which is stored in certain parts of the plant as food reserves. Physical modification of starch daluga (*Cyrtosperma Merkusi)* can be

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done through a *fully gelatinized process* or what is known as *fully gelatinized daluga daluga* (FGDS). Modification of FGDS was carried out by heating daluga starch above its gelatinization temperature. The *fully gelatinized process* can cause amylose to break down, resulting in more amylopectin components and an increase in *gelling ability*, larger particle size and higher particle density. The gel formed from the development of this matrix acts as a reservoir/gel barrier on the outer surface which is able to produce controlled release preparations (Sulaiman et al., 2011) .

Controlled release of the active substance in the digestive tract can be achieved by several methods namely *floating systems, high density systems, mucoadhesive systems*, ***extendable*** **or** ***expandable systems*** **and** ***superporous hydrogels*****. METHOCEL K4M® is a hygroscopic matrix that will increase the hardness of the matrix and easily release the drug substance in** the dissolution medium. METHOCEL K4M® apart from having hygroscopic properties, it is also hydrophilic, so that in large concentrations it will be easier to interact with the dissolution media (Soemarie and Maulita, 2012).

One of the branches of pharmacy that covers the treatment of animals or commonly known as veterinary pharmacy. Treatment in animals differs from humans due to the physiological differences between the two. The drug delivery system in animals has a very important role so that the drug can work optimally according to indications and produce the expected response (Ramadhani, 2017).

In this study, a mylum daluga was physically modified through a *fully gelatinized process* then tested for the physical and chemical characteristics of the starch produced, then the optimum proportion of the FGDS matrix was combined with METHOCEL K4M® and magnesium stearate which were used as excipients in tablets. mucoadhesive with the active substance ranitidine HCl.

The proportion of FGDS, METHOCEL K4M® and magnesium stearate greatly affects the mucoadhesive system that will be formed and the release of the drug. These problems can be overcome by an optimization technique approach. One of the optimization methods that can be used to determine the optimum proportion of a mixture of materials is the SLD (*simplex latice design*) method.

RESEARCH METHOD

MODIFIED FULLY GELATINIZED DALUGA DALUGA *(FGDS)*

Starch daluga *fully gelatinized* made with the modified process condition parameters that have been optimized (Table 1). The ratio of starch: aquadest is with a ratio of 1: 1 (w/v). The mixture is then stirred until a homogeneous suspension is formed. The suspension was heated at 80 ^{o}C for 15 minutes until a thick mass was formed. The viscous mass was dried in *an oven* at a temperature of 60 ^{o}C for 48 hours, after drying it was then ground and sieved using a 20 mesh.

Table 1
Fully gelatinized daluga daluga (FGDS) process conditions

Parameter	Process Condition
fully gelatinized temperature	80 ^{o}C
heating time	15 minutes
oven temperature	60 ^{o}C
old *oven*	48 hours

TESTING CHARACTERISTICS OF DALUGA FULLY GELATINIZED STARCH

A. MORPHOLOGY OF STARCH

A certain amount of starch is placed on a glass object. Then add 1-2 drops of distilled water. Observations of the hilum, lamellae and arrangement of corn starch were carried out under a microscope with a magnification of 400x .

B. IDENTIFICATION OF STARCH

Quantitative test which aims to calculate the yield of starch and qualitative test which aims to determine the content of polysaccharides in starch. Iodine test on amylose will show a blue color, and on amylopectin will show a blue color

DETERMINATION OF THE OPTIMUM FORMULA BASED ON THE OBTAINED EQUATION

Based on the data on the results of the physical properties test and the release of ranitidine HCl from the slow-release tablet preparation with a *floating system*, it will be possible to calculate the coefficients of b1, b2, b3, b12, b23, b13 for each test result. Next is to determine the equation and create a profile of each parameter tested using the Design-Expert ® *software*, from each *contour plot a superimposed* curve is made so that the optimum formula area is obtained.

IN VIVO *TESTING*

The *in vivo study* was carried out with *a single dose crossover design* that previously had ethical clearance as shown in Table 3, using 5 rats. In the first week, rats 1, 3 and 5 were given orally with conventional ranitidine HCl tablets, while rats 2 and 4 were given *mucoadhesive tablets.* ranitidine HCl. At week 2-3 all test animals were rested. At week 4 mice 1, 3 and 5 were given *mucoadhesive tablets* , mice 2 and 4 were given conventional tablets (Mayer et al., 1990) .

Table 2
In vivo test research design mucoadhesive tablets ranitidine HCl

Rat	1st week	Week 2-3	4th week
1	kindergarten	-	TF
2	TF	-	kindergarten
3	kindergarten	-	TF
4	TF	-	kindergarten
5	kindergarten	-	TF

Information:
TF = ranitidine HCl *mucoadhesive tablets* administered orally
TK = conventional tablets of ranitidine HCl given orally
\- = indicates *washout time*

RESULT ANALYSIS

Data on the results of the physical properties of granules and tablets as well as the release of ranitidine from tablets were analyzed using the Design-Expert ® *software*, in order to obtain *a contour plot* of each test result. Determination of the

optimum formula begins with determining the optimized parameters, namely flow rate, tablet hardness, tablet friability, *floating time* and release rate of ranitidine HCl. Each test parameter is given a value and the desired target or *goal*, from each *contour plot a superimposed* curve is made so that the optimum formula area is obtained.

The results of the dissolution test data were made with a curve of the relationship between the amount of drug dissolution *versus* time and the root of time, the regression equation was sought. The correlation coefficient values of drug dissolution *versus* time and the roots of time were compared to determine the kinetics and mechanism of drug release from tablet preparations. The *slope value* of the regression equation is the rate of drug release. Drug release kinetics modeling was made according to: *zero order kinetics*, *first order kinetics*, Higuchi, Korsemeyer-Peppas and *curve fitting* with WinSAAM. The data from the dissolution test also calculated the values of f2 (*similarity factor*) and f1 (*difference factor*).

in vivo absorption test results curves for the relationship between drug levels in the blood *versus* time. The calculated parameters include: AUC, C max, t max, t½ elimination and K elimination. The data from the *in vitro* and *in vivo tests* were then analyzed for correlation *in vitro - in vivo* (IVIVC). *Relative* bioavailability is calculated by equation 3.6.

F = (AUC *mini floating* tablet /AUC conventional tablet) X 100% ……. (3.6)

The pharmacokinetic parameter data obtained from *floating mini* tablets and conventional tablets were analyzed by *paired sample test* with a 95% confidence level (Rosa et al., 1994) .

RESULTS AND DISCUSSION

DETERMINATION

The daluga tubers used in this study were obtained from the Tabanan area of Bali. The results of the determination of daluga tubers (Figure 16.) with the Latin name *Cyrtosperma merkusi* Schott including plants belonging to the family Araceae Juss The results of the determination are stated in the letter ID number ELSA 53531 on August 16, 2022 (Appendix 1.). The determination or identification of plants was carried out in the characterization laboratory of the Bali-BRIN Eka Karya Botanical Gardens. Determination is done to find out the truth of the identity of the plant, thus errors in the collection of materials to be studied can be avoided.

Figure 1
Cyrtosperma merkusi Schott

DALUGA STARCH EXTRACT

The starch extraction process resulted in a *Native daluga daluga (NDS) yield* of 30.79% with a water content of 9.38%. yield The NDS resulting from this process is greater than the yield obtained by Wathoni (2016) which is 15.69%. This difference is caused by differences in the harvesting age of the daluga tubers used. In this study, the daluga tubers used were 10-11 months old, while those used by Wathoni (2016) were 4-5 months old.

Yield is an important value in product manufacture. Yield parameters are important to determine the economic value and effectiveness of a product or material process. The greater the yield, the higher the economic value of the product, as well as the value of the effectiveness of the product.

Making starch Natural (*Native Daluga*)

Natural starch is made by peeling the daluga tubers and then washing them with clean water. After that, the daluga was crushed using a blender with distilled water using the ratio of daluga:aquadest (2:1) w/v. The purpose of using a blender is to create a mechanical collision between the solvent, namely water and daluga tubers, so that the water is pushed in and the release of primary metabolites will be even greater. After that, the results are squeezed and filtered using flannel. The next process is allowed to stand for 24 hours until a precipitate is formed. The goal is that starch can settle and not remain in the filtrate so that the resulting starch yield will be better (Kiptiyah et al., 2021).

The resulting precipitate was then washed using distilled water until the yield was obtained in accordance with the description of daluga, which was white and odorless. The precipitate has a smooth but soft texture because it still contains water, so it is dried in an oven at a temperature of 50 C to dry so that the starch produced is protected from the growth of microorganisms (Kiptiyah et al., 2021). The starch produced after drying is in the form of dry lumps with a fine texture. Sifting was carried out using a mesh sieve number 100 to obtain a fine powder in accordance with the starch requirements in the Indonesian Pharmacopoeia Edition IV.

Making starch *Fully Gelatinized*

The manufacture of *fully gelatinized starch* was made using natural starch (*native daluga*) obtained and added with distilled water with a ratio of starch:aquadest (1:1) w/v. After that, it was heated with steam at 80°C for 15 minutes. A temperature of 80°C is used because natural starch is gelatinized at a temperature of 68.18°C, so to make *fully gelatinized starch*, a temperature above the gelatinized temperature is used but does not damage the amylose and amylopectin content found in starch (Putra *et al*., 2018). The result of heating is a bone white gel which is then dried in an oven at 60°C for 48 hours. The results of heating from *fully gelanitized starch* obtained a hard shape so that it was necessary to reduce the particle size, then grind and sieve with a 20mesh sieve.

Preliminary Test starch Natural and Modified

Identification starch

Identification starch aim for ensure as well as identify that materials used is starch (Arisanti et al., 2014). Identification test results starch natural and starch *fully gelatinized* show results positive with formation color blue old purplish (appendix

3). Formed color the caused because bonded amylose _ with iodine will produce color blue and bound amylopectin with iodine Give Bluish Violet Color Or Purple (Priyanta Etc., 2012).

Organoleptic Test

Organoleptic test conducted for knowing characteristic physique later starch customized with Indonesian Pharmacopoeia IV edition. Test this cover color, smell, and taste. Results show that starch natural and starch *fully gelatinized* have same feature that is colored white, no smells, and doesn't taste (appendix 4). That thing already in accordance with Indonesian Pharmacopeia IV edition (Depkes RI, 1995).

Microscopic Test

Microscopic test aim for observe fragment identifier which is component Specific starch (Partiwisari et al., 2014). The results of observations on starch (attachment 5) have in accordance with Indonesian Pharmacopoeia IV, namely has a hilus located in the middle in the form of point, straight line and branch three as well as lamellae that are not clear (Depkes RI, 1995). starch daluga *fully gelatinized* has more many arrangement starch the crowd compared with starch experience because existence heating on gelatinization process starch, so that occur damage bond the hydrogen working maintain structure granule starch. Damage bond hydrogen on starch cause water to enter by slowly to in marked granule with development granules. Besides that, warm up could increase swelling starch so that amylose go out and amylopectin permanent trapped in matrix amylose and causes gel formation and push formation arrangement granule clustered starch (Arisanti et al ., 2014).

Macroscopic Test

Macroscopic test conducted for knowing characteristics and size from starch natural and *fully gelatinized*. Test this use sieve graded with mesh no. 20, 40, 60 and 80. Based on results obtained _ namely in appendix 4, starch experience capable sieved on mesh sieve no. 80 is 97.7 grams out of 100 grams. That thing already in accordance with Indonesian Pharmacopoeia IV edition that starch daluga shaped very fine powder capable of pass sieve mesh no. 80. That thing because starch experience not yet experience change size particle, so that still in form the powder. Form powder this classified as fines because could cause *capping* when printed into tablets (Sari et al., 2012).

starch *fully gelatinized* belong to powder Rough because capable sieved on a mesh sieve no.20 and many retained on the mesh sieve no. 40. Starch *fully gelatinized* belong to powder Rough because already experience treatment addition in the form of a gelatinization process namely the process of gel formation due to existence addition of water and heating which causes granule expand and shape something mass thick. Gelatination Process produce starch with more size large (Sari et al., 2012).

Test for Amylose and Amylopectin Levels

Content test amylose and amylopectin aim for determine content amylose and amylopectin in starch natural and *fully gelatinized*. Test earn starch experience contains 37.25% amylose and 62.75% amylopectin, while starch *fully gelatinized* contains 25.12% amylose and 74.88% amylopectin. Test results show that existence

upgrade amount amylopectin in starch *fully gelatinized*. That thing because starch at the moment undergo a *fully gelatinized process* cause amylose broken and components amylopectin more a lot (Kalogianni *et al*., 2004). Decrease rate amylose caused because happening disconnection bond glucoside in the chain amylose, where? chain the is composer part big area easy amorphous entered the water. When done heating in the modification process, water enters to in area amorphous and result weak bond hydrogen Among chain amylose and amylopectin. Weakness bond the result in the damage crystallinity starch that causes rupture granule starch so that component amylose will go out from granule starch and components amylopectin will trapped in the structure matrix amylose (Soebagio and Sriwidodo, 2009)

pH test

test on starch aim for knowing starch pH value natural and fully *gelatinized* produced already in accordance range namely starch pH experience namely 4-8 and starch pH pregelatin namely 4.5-7 (Rowe *et al*., 2009). Test results show that starch natural and *fully gelatinized* already enter good pH range (appendix 8). Results obtained show that starch experience have a higher pH low compared starch *fully gelatinized* because in the gelatinization process molecule amylose pushed out. Amylose have chain shaped the helix part inside contains H atoms. Reduced molecule amylose in starch cause decline the number of H atoms so that the starch pH will increases, so that in the process of storage will stable and able endure longer (Arisanti et al., 2014).

Moisture Test

The water content is the amount of water contained in declared material _ in percent. High water content could cause starch attached to the surface *die* and *punch* at the moment tablet printing. Besides that, high water content could trigger existence reaction enzymatic nor growth microbes that cause occur decay or degradation the compounds present in starch so that could influence stability starch moment storage (Arisanti et al., 2014). The results of the water content test show that starch experience nor starch *fully gelatinized* already enter condition water content is 15% (w/w) (Depkes RI, 1995).

The test results show there is difference water level is starch *fully gelatinized* have more water content low compared starch natural (Appendix 9). That thing because the gelatinization process which causes bond hydrogen Among chain amylose and amylopectin weakened and damaged. It's broken bond hydrogen cause during the drying process starch, more water easy miss from group hydroxyl starch and cause drop water content of starch (Arisanti et al., 2014).

and Ethanol Solubility

Test water solubility aims for see solubility starch in water. Solubility test results good starch experience nor starch *fully gelatinized* show that starch no dissolved (appendix 10). starch shaped particle solid and network the molecule bound through bond hydrogen. In cold water, the particles no will dissolve and break. With existence increase temperature and stirring will produce debilitating energy bond hydrogen, so that water can absorbed by the granules starch and become like a gel. Test solubility ethanol obtained results starch natural and starch

fully gelatinized no dissolve. Ethanol is also hard late in starch because particle solid starch, however if heated will into a gel (Putra *et al*., 2018).

***Fourier Transform Infrared* (FTIR) Spectra**

Fourier Transform Infrared (FTIR) spectra were used to identify functional groups organic compounds. The principle of FTIR is based on the interaction between the vibrational energy levels (vibration), the vibrations of atoms bonded in the **molecules by absorbing** *infrared* electromagnetic wave radiation. The results of the FTIR test are in the form of a spectrum (attachment 11). Starch daluga is a compound composed of several components, namely amylose and amylopectin which are composed of CH, CO, and OH bonds. In natural starch, the CH alkane functional group was detected at a wave number of 2891.3 cm $^{-1}$ with an absorption frequency of 2800-2900 cm $^{-1}$. The absorption peak of 1159.22 cm $^{-1}$ was detected by CO bonds with an absorption frequency of 1000-1300 cm $^{-1}$. The alcohol OH functional group was detected at a wave number of 3550.95 cm $^{-1}$ with an absorption frequency of 3200-3600 cm $^{-1}$. Meanwhile, in *fully gelatinized starch* no OH functional group was detected and CH alkane group was detected at wave number 2883.58 cm $^{-1}$ and CO functional group at absorption peak 1134.14 cm $^{-1}$. The CH bond is an identification of the presence of an aldehyde functional group, where the aldehyde group is one of the constituent groups of glucose. Glucose is the basic structure of the formation of amylose and amylopectin molecules (Kasmawati, 2018). The OH functional group was not detected in *fully gelatinized starch* due to a modification process in starch that is *fully gelatinized*, resulting in a weakened and damaged hydrogen bond structure (Arisanti et al., 2014).

Test Metal Weight (Pb, Cd, Fe, As)

Metal heavy could cause effect to health for man depending on the part bound body metal. Metal weight that is poison inside body will endanger health even cause death (Zulharmita et al., 2017). Test metal heavy aim for knowing amount Pb, Cd, Fe, and As content in starch. Test results show that starch natural and starch *fully gelatinized* no contains Cd (Cadmium) and As (Arsenic). Condition good Pb content that is no more than 1 mg/kg (SNI, 1994). Result of the Pb (Lead) content has been Fulfill requirements ie 0.1998 mg/kg on starch natural and 1 mg/kg on starch *fully gelatinized*. Besides that, condition good Fe content that is no more than 3 mg/kg (Sumakul, 2019). The content of Fe (Iron) in starch natural and starch *fully gelatinized* already Fulfill good requirements that is of 0.2603 mg/kg on starch natural and by 0.3445 mg/kg in starch *fully gelatinized*. Existence content metals (Pb and Fe) due to because storage as well as effect environment like soil, water, and air during the manufacturing process starch (Zulharmita et al., 2017).

***X-Ray Diffraction* (XRD)**

X-Ray Diffraction conducted for knowing level crystallinity starch based on peak diffraction. There are 3 patterns diffraction X- ray on starch that is The XRD pattern in type A has peak diffraction strong around 15º and 23º as well as peak that is not perfect about 17º and 18º; The type B XRD pattern has peak diffraction strongest around 17º as well as a number of peak small around 15º , 20º, 22º, and 24º, and peak special at 5.6º; whereas The type C XRD pattern has nature mixture from type A and type B i.e have peak strongest around 17º and 23º as well

as a number of peak small about 5.6º and 15º (Triwitono et al., 2017). Based on pattern the resulting diffraction could concluded that pattern diffraction starch experience that is XRD pattern in type A because have peak strong diffraction at 15º and 23º and peaks that are not perfect at 17º and 18, whereas starch *fully gelatinized* no have peak perfect diffraction (appendix 12). Peak diffraction relate close with nature crystallinity from starch (level amylose and amylopectin). Starch is ingredient semicrystalline containing area crystalline and amorphous. starch *fully gelatinized* have level more crystallinity low compared starch natural. That thing caused because increase content amylopectin due to the modification process. The more many amylopectin, then area amorphous will the more broad and cause area crystalline the more narrow. starch arranged from amylopectin located in the region amorphous and amylose which are in the region crystalline. (Haryani et al., 2022).

***Scanning Electron Microscope* (SEM)**

Scanning Electron Microscope (SEM) is a a microscope designed electrons _ for observe surface object by direct with magnification 10-3,000,000 times. Test this aim for see form surface starch with resolution high. Results show that starch experience shaped particle small no hollow and regular. Whereas starch *fully gelatinized* shaped particle big hollow and amorphous (appendix 13). This thing caused by the modification process because content amylose and amylopectin play a role in control size and shape granules (Sakinah and Kurniawansyah, 2018).

Physical Properties Test starch Natural and Amylum Modification

Flow Properties Test

a. Flow Time

Flow time is time required amount granule for flow pass declared funnel as a lot flowing powder each unit time (Elisabeth et al., 2018). Time test results flow show that on starch experience no could flow pass funnel (appendix 14). That thing because size small particles so that cause no existence cavity air between particles. Meanwhile, in starch *fully gelatinized* have nature good flow ie 12.29 ± 0.09 g/ second and already enter range of 4 gram/ second (Sari et al ., 2012).

b. Angle of Still

The angle of repose is corner formed Among -shaped powder cone with field flat. Measurement silent corner done with compare Among tall cone powder formed with diameter (Rohmani and Rosyanti, 2019). Test results angle of repose in starch experience show that starch no capable pass the funnel that causes angle of repose no could calculated. Meanwhile, in starch *fully gelatinized* generated angle of repose is 26.21º ± 0.30 (appendix 14). The result already enter range good still angle i.e. 25˚-30˚ (Arisanti et al., 2014).

Compressibility Test

Compressibility test aim for determine nature materials that can shape stable and compact mass when given pressure (Nurjanatun and Balfas, 2019). Results show that starch experience have index compressibility as big as 21.60 ± 0.47%, while starch *fully gelatinized* has index compressibility of 12.49 ± 1.56% (appendix 15). Compressibility value starch experience morebig compared with starch *fully* gelatinized because starch experience have size more particles small compared starch *fully* gelatinized. Compressibility value affected by distribution size particles. The more small size particle so score score resulting compressibility the more big.

If seen from nature the flow, the more small score compressibility so nature flow will the more good (Sari et al., 2012).

Making Granule

Granules were made by wet granulation method. Wet granulation is a process of mixing the active substance and excipient particles into larger particles by adding the right amount of binder liquid so that a moist mass can be granulated. The principle of this method is to wet the mass or mixture of active substances and excipients with a binder solution until a certain level of wetness is obtained (Gopalan and Gozali, 2018).

Table l2
The design of the mucoadhesive tablet formula using the simplex lattice design method which is processed computationally using Design Expert software

Run	Ingredients (mg)/tablet		
	FGDS (X_1)	HPMC K4M (X_2)	Mg stearate (X_3)
1	76.67	36.67	6.67
2*	80.00	40.00	0.00
3	78.33	33.33	8.33
4 #	75.00	35.00	10.00
5	80.00	35.00	5.00
6*	80.00	40.00	0.00
7 –	80.00	30.00	10.00
8 –	80.00	30.00	10.00
9 –	70.00	40.00	10.00
10 –	70.00	40.00	10.00
11	75.00	40.00	5.00
12	78.00	38.33	3.33
13 #	75.00	35.00	10.00

Physical Properties Test Granule

Particle Size Distribution

The particle size distribution test uses the most commonly used method, namely the sieving method because it is cheap and simple. This method serves to measure the particle size distribution by using a sieve *mesh* arranged in succession, where the coarsest sieve mesh is placed at the top (Jannah et al., 2018; Mulyadi et al., 2011). The importance of this test because the particle size can affect the flow rate of a granule. The finer the particle size, the lower the flow rate. Granules that are more distributed at a certain size indicate the quality of the granules (particle size uniformity) is quite good as a raw material for tablet printing. The results showed that all formulas had a particle size distribution with a *mesh size of* 20 and the most retained by a 40 *mesh sieve* (appendix 19). This is because the granulation process is carried out using a 20 *mesh sieve*. The concentration of the binder affects the particle diameter, so that more binders will produce small particle diameters and fewer fines (Mulyadi et al., 2011).

Compressibility

Compressibility testing aims to measure the density of the granules to facilitate tablet printing because tablets that have a good percent compressibility will be easier to compress. The results of the compressibility test show that the percent compressibility index of all formulas meets the requirements well, which is below 20%. The size of the compressibility is influenced by the shape of the granules and the size of the granules (Devi et al., 2018; Yulisani et al., 2020). The smaller compressibility percentage indicates the ease of granules in tablet compression so that a more compact tablet is produced compared to formulations that have a high compressibility percent. Compressibility will also affect the flowability of the granules. The presence of wetting can increase the compressibility of the granules. This is due to the strong bonds between particles so that the granules can be well compressed (Devi et al., 2018).

Flow time

Flow time is the time required for a number of granules to flow through the funnel which is expressed as the amount of powder flowing per unit time. The results of the flow time test showed that all the formulas had met the good requirements, namely 10 grams/second. The nature of the flow is influenced by the shape of the particles as well as the size of the particles. Good granules are granules that can flow freely so they can be compressed into tablet preparations. The smaller the concentration of the binder, the more the particle size makes it difficult for the granules to flow freely (Elisabeth et al., 2018). Granules with poor flow will cause the flow of granules from the *hopper* to the *die* is not perfect, as a result the resulting tablet weight is not constant (Putra et al., 2019)

Quiet angle

The angle of repose is a fixed angle that occurs between the pile of conical particles and the horizontal plane when a certain amount of powder is poured into the measuring device. The granules will form a cone, the flatter the resulting cone, the smaller the angle of repose is (Husni et al., 2020; Mulyadi et al., 2011). The results of the angle of repose test show that all formulas have entered the requirements of a good angle of repose, namely the angle of repose if 30° then the powder is able to flow well, but if 40° then the flow properties are not good. The smaller the angle of repose the better the flow properties of the granules so that the tablets have a uniform weight uniformity. The value of the angle of repose is related to the flow time, where the faster the flow, the smaller the angle of repose formed (Rohmani and Rosyanti, 2019).

Granule moisture content

The moisture content test was carried out to determine the amount of volatile substances including water contained in the instant granules due to the heating process that occurred in the granules at the time of drying (Husni et al, 2020). The results obtained from testing the moisture content of the granules are that all formulas have entered the criteria for a good granule moisture content of 5% so that it will produce good and stable granules during storage (Rowe *et al*., 2009).

Tablet Manufacturing

Making tablets is seen based on the results of testing the physical properties of the granules. Based on the test results, all formulas have met all the requirements

so that they can be compressed into tablets because they are in a good range of requirements. Tablet printing uses a *single punch* set up. The main requirement for making tablets is that the components are easy to compress and flow easily. Tablet components that have good flow properties and compressibility index will experience changes in shape and volume more when given an external mechanical force (Lachman et al., 1994).

CONCLUSION

Modification starch Becomes Fully gelatinized starch can be used as mucoadhesive tablet excipients. That thing proven in research this that is fully gelatinized starch has size more particles big compared starch experience so that cause fully gelatinized starch has nature more flow good. Flow properties take effect to mucoadhesive tablet manufacture because good granule that is granules that can be flow free so that could compressed Becomes tablet preparation.

Combination of FGDS, HPMC K4M and mg stearate give influence to hardness test response Y = (+0.056374) (A) + (+0.035041) (B)+ (-0.021404) (C), brittleness test response Y = (-1.37491E-005) (A) + (+2.18064E-005) (B) + (+3.46251E-005) (C), mucoadhesive test response Y = (+0.12141) (A) + (+0.068080)(B) + (-0.091920)(C) and response to dissolution test Y = (-0.023471) (A) + (+0.073374) (B) + (+0.46146) (C). Combination results of FGDS, HPMC K4M, and mg stearate with comparison (300:150:105) set as the optimal formula with desirability value 0929; with score prediction violence 19.921; brittleness 0.036; mucoadhesive 36,985; and dissolution 52.419.

REFERENCES

Ansel HC 1989, Introduction to pharmaceutical preparations, University of Indonesia Press, Jakarta.

AOAC. 2000, *Official Methods of Analysis*, 17th Edition, Association of Official Analytical Chemists, Virginia.

Arisanti, CIS, Dewi, DPRP, and Prasetia, IGNJA 2014, Effect of Starch: Water Ratio on Specifications of *Fully Pregelatinized Daluga Starch (Manihot esculenta* Crantz), *Journal of Pharmacy Udayana*, **3** :1-8.

National Standardization Body. 1994, *Tapioca*, SNI 3451-1994, National Standardization Councils, Jakarta.

Badaring, DR, Sari, SPM, Wulan, W., and Lembang, SAR 2020, Test of Maja Leaf Extract (*Aegle marmelos* L.) on the Growth of *Escherichia coli* and *Staphylococcus aureus*, *Indonesian Journal of Fundamental Sciences*, **6** :16-26

Banne, Y., Ulaen, SP, and Lombeng, F. 2012, Banne, Y., Ulaen, SP, & Lombeng, F. (2012). Test of hardness, firmness, and disintegration time of several ranitidine tablets, *Jurnal Ilmiah Pharmacy (JIF)*, **3** :74-78.

Collett, JH and Moreton, RC 2002, *Modified Release Peroral Dosage Forms, in Pharmaceutics: The Science of Dosage Form Design*, 2nd edition. Churchill Livingstone, London.

Das, S., Duta, S. and Deka, S. 2008, A study of the anti-ulcer of the ethanolic extract of the leaves of psidium guajava on experimental animal models, *Thr Internet Journal of Pharmacology*, **7**.

Indonesian Ministry of Health. 1995, *Indonesian Pharmacopoeia*, Edition IV, Ministry of Health of the Republic of Indonesia, Jakarta.

Indonesian Ministry of Health. 2008, *Indonesian Herbal Pharmacopoeia*, Edition I, Ministry of Health of the Republic of Indonesia, Jakarta, Indonesia.

Devi, IAS, Shodiquna, QA, Eni, NWSD, Arisanti, CIS, Samirana, PO 2018, Optimization of Concentration of Polyvinyl Pyrolidone (PVP) as a Binding Material on Physical Properties of Bangle Rhizome Ethanol Extract Tablets (*Zingiber cassumunar* Roxb), *Udayana Journal of Pharmacy*, **7** :42-52.

Diniatik, 2015, Determination of Total Flavonoid Levels of Kepel Leaf (*Stelechocarpus Burahol* (Bl.) Hook F. & Th.) Ethanolic Extract Using Spectrophotometric Methods, *Scientific Journal of Pharmacy*, **3** :1-5.

Faizatun, SS, and Riyana, Y. 2007, Mucoadhesive Matrix Tablet Formulation of Diltiazem Hydrochloride Using Hydroxy Propyl Methyl Cellulose and Carbopol 940, *Indonesian Journal of Pharmaceutical Science*, **5** :53-58

Felicia, N., Widarta, IWR, and Yusasrini, NLA 2016, Effect of Leaf Aging and Processing Methods on Antioxidant Activity and Sensory Characteristics of Avocado Leaf Powder Herbal Tea (*Persea americana* Mill.), *Journal of Food Science and Technology (itepa)*, **5** : 85-94.

Feriadi, E., Muhtadi, A. and Barliana, MI 2018, Galing (*Cayratia trifolia* L.): A Study of Biological, Phytochemical, and Pharmacological Activities, *Journal of Pharmacy, Science, and Health*, **4** :1-5.

Gopalan, SV, and Gozali, D. 2018, Review of Articles: Formulation and Evaluation of Effervescent Granules and Tablets with Wet Granulation Method, Pharmacists, **16** :117-123.

Imanningsih, N. 2012, Gelatinization Profile of Several Flour Formulations for Estimating Cooking Properties, *Food Nutrition Researcher*, **35** :13-22.

Indrawati, T. 2011, *Delivery System for Oral Drugs Retained in the Stomach (Gastroretentive)* , ISTN Jakarta, Jakarta.

Kartikasari, D., Nurkhasanah, Suwijiyo, P. 2014, Characterization of Simplicia and Ethanol Extract of Bertoni Leaves (*Stevia rebaudiana*) from Three Growing Places, *Proceedings of the National Seminar on Recent Developments in the Utilization of Herbs as Preventive Agents in Cancer Therapy*, 149-150.

Kasmawati. 2018, Characteristics of *Edible Film* Corn Starch (*Zea mays* L.) with Addition of Glycerol and Extract of Temu Putih (*Curcuma zedoaria*), *Thesis* , Faculty of Science and Technology, Alauddin State Islamic University Makassar.

Indonesian Ministry of Health. 2014, *Indonesian Pharmacopoeia*, Edition V, Ministry of Health of the Republic of Indonesia, Jakarta.

Kiptiyah, M., Rahmatullah, S., Wirasti, Waznah, U. 2021, Evaluation of the use of Canna Starch (*Canna Edulis* Kerr.) as a Binder in Moringa Leaf (Moringa

Oleifera L) Ethanol Extract Chewable Tablets Using the Wet Granulation Method, *National Seminar Health*, 1-20.

Mulyadi, MD, Astuti, IY, and Dhiani, BA 2011, Instant Granule Formulation of Buga Roselle (*Hibiscus sabdariffa* L.) Juice with Variations in Concentration of Povidone as Binder and Quality Control, *Pharmacy*, **8** :29-41.

Nurjanatun and Balfas, RF 2019, Test of Compressibility of Taro Starch Granules With Wet Granulation Method, *Journal of Pharmacy UMUS*, **1** :23-27.

Partiwisari, NPE, Astuti, KW, and Ariantari, NP 2014, Identification of Simplicia Bark of Cempaka Kuning (*Michelia champaca* L.) Macroscopically and Microscopically, *Journal of Pharmacy Udayana*, **3** :36-39.

Ramirez, YIC, Cruz, OM, Sanchez, CLDT, Corral, FJW, Flores, JB and Moroyoqui, FJC 2018, The structural characteristics of dalugaes and their functional properties, *CyTA Journal of Food*, **16** :1003-1017.

Ririn, NF, RY Dewi, BR Ferry. 2020, Breadfruit Starch Granule Flow Time Test with Wet Granulation Method, *Jophus Scientific Journal*, **1** : 1-4.

Robiyanto and Marsela, M. 2018, Antiulcer Potential of Noni Fruit Powder and Aloe Vera Leaf Peel on Macroscopic Appearance of the Stomach, *Education: Journal of Education*, **16** : 182-195.

Rohmani, S., and Rosyanti, H. 2019, Differences in Methods of Adding Intragranular-Extragranular Disintegrants on Physical Properties and Dissolution Profiles of Ibuprofen Tablets, *JPSCR: Journal of Pharmaceutical Science and Clinical Research*, **2** :95-108.

Siregar, CJP and Wikarsa, S. 2010, *Pharmaceutical Technology for Practical Basic Tablet Preparation*, EGC Medical Book Publisher, Jakarta.

Soebagio, B. and Sriwidodo, AAS 2009, Testing the Physicochemical Properties of Natural and Modified Durian Seed Starch by Acid Hydrolysis, Faculty of Pharmacy, Padjadjaran University, 2–7.

Susanti, HD 2012, Effect of Addition of Papaya Leaf Extract (*Carica papaya* L.) as *Coadministration* with Metmorphine in Tablet Preparations on Physical Properties and Dissolution of Tablets, *Thesis*, Sebelas Maret University, Surakarta.

Sutriyo, Khairunnisya, Mun'im, M, 2011, Formulation of Mucoadhesive Granules Combination of Neem (*Azadirachta Indica* A. Juss) and Turmeric (*Curcuna domestica* Val.) Bark Extract, *Pharmaceutical Science Magazine*, **2** :97-104.

Syamsuni. 2006, *Basic Pharmacy and Pharmacy Count*, EGC Medical Book Publisher, Jakarta.

Triwitono, P., Marsono, Y., Murdiati, A., Marseno, DW 2017, Isolation and Characterization of the Characteristics of Green Bean Starch (*Vigna radiata* L.) Several Indonesian Local Varieties, *AGRITECH*, **37** :192-198.

Utami, YP, Umar, AH, Syahruni, R., and Kadullah, I. 2017, Standardization of Simplicia and Ethanol Extract of Leilem Leaves (*Clerodendrum* minhassae Teisjm. & Binn.), *Journal of Pharmaceutical and Medicinal Sciences*, **2** :32–39.

Voigt, R. 1994, *Pharmaceutical Technology Textbook*, Gajah Mada University Press, Yogyakarta.

Wahyuni, R., Guswandi, and Rivai, H. 2014, Effect of Drying Method with Oven, Wind Dry and Direct Sunlight on the Quality of Sambiloto Herb Simplicia, *Higea Pharmaceutical Journal*, **6** : 126-133.

Wijayanti, NPAD, Dewi, LPMK, Astuti, KW and Fitri, NPE 2016, Optimization of

Zulharmita, Zulfaretna, M., and Misfadhila, S. 2017, Analysis of Heavy Metal Contamination in Herbal Medicines at Siti Rahmah Islamic Hospital Padang by Atomic Absorption Spectrophotometry, *Journal of Pharmacy Higea*, **9** :159-164