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CHARACTERISTICS NANOPARTICLE OF PROPOLIS ETHANOL EXTRACTS WITH VARIATIONS OF CHITOSAN-SODIUM ALGINAT Santi Sinala1* , Marianti A.Manggau2 , Sartini3 1Department of Pharmacy, Makassar Health Ministry Polytechnic 2Department of Pharmacy, Hasanuudin University 3Department of Pharmacy, Hasanuudin University Submitted: Revised: Accepted: * Corresponding author Santi Sinala E-mail: santisinala@poltekkes-mks.ac.id _ABSTRACT Nanoencapsulation technology has many advantages, which include important roles in drug delivery and protection of bioactive components that have perishable stability, one of which is polyphenol compounds. Propolis which contains high levels of polyphenol compounds has been used as an antioxidant for various diseases.

By making nanoparticles from propolis, it can maintain the stability of polyphenol compounds from propolis and increase the effect of treatment through optimal delivery. Nanoformulations containing ethanol extract of propolis were absorbed by chitosan-sodium alginate using an ionotropic pre-gelation method. Optimization is carried out at various concentrations of chitosan, namely 0.05%; 0.075%; 0.1% and 0.125% , with the use of the same sodium alginate concentration which is 0.0063%.

Testing of nanoparticle characteristics includes particle size and morphology and adsorption efficiency (EE) consisting of total flavonoid and total polyphenol values. The increase in chitosan polymer is directly proportional to the increase in particle size, but does not occur in the absorption efficiency value. The 0.05% chitosan formula showed the absorption of polyphenol compounds at 99.41% with particle sizes of 259.12 nm Key words: Propolis, Nanoparticles, Chitosan-Sodium Alginate, Absorption Efficiency _ _ INTRODUCTION Nature has prepared ingredients that contain substances that have the potential as antioxidant agents. One of them is propolis. Propolis is a resin

material collected by bees mixed with saliva.

Propolis is used by bees as a defense for survival (Pietta, 2002). Propolis contains many secondary metabolites that can be used as antioxidants including polyphenols (flavonoids, phenolic acids and esters), terpenoids, amino acids and steroids (Kumazawa et al., 2004).

This polyphenol content can inhibit specific enzymes, stimulate several hormones and neurotransmitters, fight free radicals and prevent the growth of microorganisms (Cao et al, 2004; Sforcin, 2007). In drug delivery systems, nanoencapsulation acts as a carrier (carrier) by absorbing, encapsulating, or attaching the drug in the matrix to protect bioactive components (polyphenols, micronutrients, enzymes, and antioxidants) (Mohanraj and Chen, 2006).

Through the encapsulation of these molecules in nano carriers, the solubility and stability of the drug can be increased and can control the release of the drug in the workplace (Moghimi, 2006). Small-sized nano-encapsulation materials, which are around 50-500 nm, can overcome biological barriers that help permeate and diffuse in achieving cellular recapture (Brigger et al ., 2002).

Several studies have been conducted on nanoencapsulation technology including Hollmer (2012) who conducted tests on mice and reported increased effectiveness and reduced toxicity from cancer treatment of the head and neck when using nanoencapsulation as a drug carrier. Radovic et al . (2012) reported that nanoencapsulation containing antibiotics can kill bacteria because of high doses in the workplace and sustained release.

One ingredient in making nanoencapsulation is chitosan and sodium alginate. Chitosan, a polysaccharide consisting of glucosamine units and acetilglucosamine units. Chitosan is biocompatible, biodegradable and non-toxic when used as a drug carrier orally. In addition, chitosan also prolongs the contact time of active substances with epithelial tissue and expands absorption by opening the tight junction of the epithelium.

Chitosan here acts as a polycation polymer. While sodium alginate will act as a crosslinked polyanion polymer, which will eventually form nanoparticles (Hendrik et al. , 1996). Based on the background above, the problem that arises is how does the effect of chitosan concentration with sodium alginate in the formation of nanoencapsulation of ethanol extract of propolis MATERIALS AND MATERIALS The tools used are a set of maceration tools, analytical scales, rotary evaporators, water baths, sonicators, a set of freeze drying tools , homogenizer, centrifuges, scanning electron microscopy (SEM) 10

MA EVO, UV-Vis spectrophotometer, and Particle Size Analizer (PSA) While the ingredients used are propolis, n-hexane, acetic acid, 70% ethanol, aqua destillata, Folin reagent - Ciocalteau, 96% pa alcohol, Na 2 CO 3 , Quercetin, AlCl 3 , gallic acid, Sodium acetate, chitosan , sodium alginate, CaCl 2 . Sample 1 Raw material of propolis is put into the freezer until it freezes.

After freezing, propolis is cut into small pieces and pollinated, then extracted by multilevel maceration. The pollinated propolis was weighed as much as 300 g and then extracted by maceration with one liter of n-hexane for 10 x 24 hours with the help of a magnetic stirrer. The filtrate is then evaporated with a rotary evaporator until a thick n-hexane extract is obtained and dried in a desiccator vacuum.

The residue from n-hexane extraction was macerated with 70% ethanol as much as 500 ml for 6 x 24 hours with the help of a magnetic stirrer. The filtrate is then evaporated with a rotary evaporator and then dried in the freeze dryer to obtain a thick extract. Sample 2 Determination of total polyphenols was carried out by weighing 0.25 g of ethanol extract of propolis and dissolved with 50 ml of 80% ethanol (5000 µg / ml). 0.3

mL was taken from the dilution of the extract, then put in a 10 ml volumetric flask, added 96% pa ethanol as much as 1 mL and added Folin - Ciocalteau reagent (1: 1) as much as 100 µL and stirred. After that Na 2 CO 3 solution is added 7.5% and homogeneous stirring, then each volume is up to 5 mL. The mixture is left for 3 minutes and the solution is measured absorbance at a wavelength of 641.5 nm.

The concentration is calculated from the regression equation for standard gallic acid solutions. Sample 3 Total Flavonoid Test (Chang et al ., 2002) where e ethanol extract of propolis was weighed 0.25 g then dissolved in a flask measuring 50 ml with 80% ethanol. From the stock solution carefully piped 0.3 ml then added 1 ml of 96% ethanol and added 100 µl of AlCl 3 10% and 100 µl Sodium acetate 1.

The final volume is sufficient to 10 ml in a flask. After incubation for 25 minutes at room temperature, absorbance was measured at a wavelength of 422.5 nm. Concentration was calculated from the regression equation for standard quercetin solutions. Sample 3 Nanoencapsulation was made based on the formula in table 1. The method of making nanoencapsulation was adapted from the modified method of Chopra et al . (2012).

Weighed 1 g of propolis ethanol extract and dissolved it in 80% ethanol as much as 10 mL. The ethanol extract solution was then put dropwise into 470 ml of sodium alginate 0.0063% solution which was stirred using a magnetic stirrer for 30 minutes. The solution

is then sonicated for 15 minutes. 30 mL 0.9% CaCl 2 solution was added dropwise to the extracted alginate solution while stirring with a magnetic stirrer at a speed of 1000 rpm for 60 minutes to induce gelation.

Then 0.5% (0.5 g) chitosan solution in 1% acetic acid as much as 100 mL was added dropwise into the previous mixture while stirring with a magnetic stirrer at a speed of 1000 rpm for 90 minutes. The solution mixture was then centrifuged at a speed of 15000 rpm for 30 minutes. The precipitate was collected and then dried at 18 o C.

The supernatant was then analyzed to obtain the absorption efficiency value. After drying the nanoenkapsulation powder was weighed. The same treatment was carried out on each formula, namely chitosan 0.075%, 0.1% and 0.125%. Sample 4 Nanoencapsulation testing Observation of Size and Shape of Vesicles The particle size was analyzed using the Particle Size Analizer (PSA) tool and the surface morphology was measured using scanning electron microscopy (SEM).

Determination of Absorption Efficiency (EE) Determination of Concentration Total Flavonoid Levels Piped 5 ml of the supernatant solution resulting from centrifugation then added 1 ml of ethanol pa, 100 µL of AlCl 3 10% and 100 µL of sodium acetate 1 M. The volume was sufficient to 10 mL and left for 25 minutes. After being allowed to stand, the absorbance is measured at a wavelength of 422.5 nm.

Total Polyphenol Levels Piped 5 ml of the supernatant solution resulting from centrifugation then added 1 ml of ethanol pa, 100 µL of Folin - Ciocalteau (1: 1) and 100 µL of Na 2 CO 3 solution 7.5% . The volume is sufficient to 10 mL and left for 3 minutes. After being immobilized, the absorbance is measured at a wave length of 641.5 nm.

Calculation of Absorption Effectiveness (EE) The percentage of gallic acid absorption is calculated from the following formula: EE = Qt-Qs Qt x 100% EE is entrapment efficiency , Qt is the amount of gallic acid in the ethanol extract of propolis added, Qs is the amount of gallic acid detected in the supernatant. RESULTS AND DISCUSSION In this study the active substances contained in propolis are withdrawn by means of multilevel maceration, where propolis is macerated with n-hexane several days until it is clear to attract non-polar substances such as fat and tannins which are mostly found in propolis.

After that, the residue was first released from n-hexane, then macerated with 70% ethanol to attract polar compounds in the form of flavonoids and phenolic compounds. The results of extraction in the form of rendamen and total flavonoid test and total polyphenols can be seen in table 2. From table 2 , the data obtained for the weight of n-hexane extract as much as 145.80 grams, with a rendition

of 48.6% and 70% ethanol extract as much as 45.06 grams with a rendition of 15.02%. The ethanol extract obtained is brown and has a distinctive odor. An active substance to reach its working target requires a carrier.

This choice of carrier is very important. In this study examined the carrier that can form a nanoparticle. One of the nanoparticle forming materials is chitosan and sodium alginate. Chitosan is a natural polymer that is biodegradable, non-toxic and non-irritant. The use of chitosan has the advantage of increasing drug absorption because chitosan can open the tight junction (Henrik et al ., 1996).

The interaction of amine groups protonated with cell membranes causes opening while tight junction (Rodrigues et al ., 2012). This property causes chitosan to facilitate the parasellular transport of hydrophilic compounds. The effect of chitosan in the tight junction opening is temporary, so it does not cause permanent epithelial damage or is not toxic.

The method of making nanoparticles used in this study is the ionotropic gelation method (polyelectrolyte coaservation or complexation method). In the ionic gelation method, polysaccharides (chitosan) are dissolved in a weak acid medium, then added dropwise with constant stirring in solutions containing other counterions (Racovita et al ., 2009).

The basis of this method is the nature of chitosan which experiences a liquid-gel transition due to ionic interactions with polyanion. This interaction occurs between positively charged chitosan ammonium groups with a crosslinker (Dounighi et al ., 2012). Nanoparticles are formed by constant stirring at room temperature.

Electrostatic interactions between crossing anions and chitosan determine the nature of the nanoparticles produced. This interaction depends on the molecular structure of anions, surface charge and molecular concentration, pH of chitosan solution, and physical properties of chitosan (Gupta and Jabrail, 2007). The physical properties of chitosan include molecular weight and degree of deacetylation.

The advantage of the ionic gelation method is that it can be carried out under mild conditions, does not require organic solvents, can increase drug loading capacity , and form nanoparticles with a hydrophilic environment (Agnihotri et al ., 2004). Chitosan used in this study is medium chain chitosan (200-800 cps) because it has the best encapsulation efficiency.

Sodium alginate is a negative anion used to stabilize the formed nanoparticles

(Sarmento et al ., 2006). Before sodium alginate is reacted with chitosan, sodium alginate is first mixed with calcium cloride solution. Calcium ions from calcium clorida will react with guluronic acid units from alginate to form an 'egg-box' structure.

This shows that nanoparticles can be formed by wrapping negatively charged calcium alginate complexes in a pre-gel state with cationic polymers such as chitosan, and it is the pre-gel state that is very important to allow ionic interactions between alginate, calcium and cationic polymers such as chitosan to form nanoparticles (Ping et al ., 2006). The results of making nanoenkapsulation powder from chitosan-alginate can be seen in Figure 1.

Figure 1 shows brown chitosan-alginate nanoparticles powder with fine and light powder. This brown color comes from the color of propolis ethanol extract. The results of testing nanop powder in the form of particle size and adsorption efficiency can be seen in table 3. While the results of nanoenkapsulation particle morphology can be seen in Figure 2.

From the results of nanoparticles with differences in the concentration of chitosan to sodium alginate 0.0063 mg and measurements obtained data that the smallest particle size of the four is formed by chitosan with a concentration of 0.05% with 99 absorption efficiency, 47% with a size of 259.12 nm.

This is supported by the results of SEM measurements that show the morphology of nanoparticle powder with a symmetrical sphere shape. The resulting morphology of powder is not significantly different from the morphology of nifedifin chitosan- sodium alginate powder (Ping et al ., 2008) which is also in the form of sperm.

The location of the difference is in the particle size produced, where the particle size of nifedifin chitosan-alginate ranges from 20-50 nm, while the particle size in this study is around 200-500 nm. This is due to differences in the tools used in making nanoparticles. However, this result is not much different when compared with the results of research from Chopra et al .

(2012) which produced particle size of streptomycin-chitosan-alginate ranging from 300-700 nm. From the particle size data, it can be seen that the greater the concentration of chitosan, the greater the size of the particles produced. This is because more chitosan wraps the polyphenol compounds of propolis so that the particle size gets thicker and bigger.

There are two data in obtaining absorption efficiency that is based on the total

content of flavonoids which is equivalent to quarsetin and the total content of polyphenols which is equivalent to gallic acid. The measurement of absorption efficiency obtained total flavonoid data with negative absorbance values ??so that the absorption efficiency cannot be calculated.

This shows that 100% quarsetin equivalent flavonoids are absorbed in chitosan-alginate nanoparticles. While the absorption efficiency for the total polyphenols on the four formulations obtained chitosan data 0.05% with EE value = 99.47%, chitosan 0.075% with EE value = 97.66%, chitosan 0.1% with EE value = 98.04% and chitosan 0.125% with EE value = 98.71%. These results indicate that 0.05% chitosan has the best EE among the four formulas. Because the total polyphenol data can be calculated, the total polyphenols are then used in the next calculation.

CONCLUSION Chitosan at a concentration of 0.05% has a particle size of 259.12 nm with adsorption efficiency of 99.47%. BIBLIOGRAPHY Agnihotri, S.A., Mallikarjuna, N.N., Aminabhavi, T.M. 2004. Recent Advances in Chitosan-based Micro-and Nanoparticles in Drug delivery, J. Control Rel 100, 5-28. Brigger I. Dubernet C. Couvreur P. 2002. Nanoparticles in cancer therapy and diagnosis. Adv Drug Deliv Rev 54:631–651 Cao, Y.H., Wang, Y.,

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Tabel 1. Nanoencapsulation formula Formula _Consentration b/v % _Ethanol Extract of Propolis (g) _ _ _Chitosan _Sodium Alginat _ _ _I _0.05 _0.0063 _1 _ _II _0.075 _0.0063 _1 _ _III _0.1 _0.0063 _1 _ _IV _0.125 _0.0063 _1 _ _ Tabel 2. The rendament value and total flavonoid and total polyphenols Extract _Weight (g) _Rendament (%) _Total Flavonoid (%) _Total Polyphenol (%) _ _n- heksan _145.8 _48.6

_- _- _ _etanol 70% _45.06 _15.02 _4.6984 _6.6428 _ _ Tabel 3. Results of testing of propolis ethanol extract nanoparticles powder Chitosan Concentration (%) _% EE _Particle Size (nm) _ _ _ _ _ _0,05 _99,47 _259,12 _ _0,075 _97,66 _270,34 _ _0,1 _98,04 _301,03 _ _0,125 _98,71 _327,45 _ _ / Gambar 1. Result of chitosan-alginate nanoparticles powder / Gambar 2.

SEM of chitosan-alginate nanoparticles in view-field 6,35 µm

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