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FORMULATION AND CHARACTERIZATION OF NANOEMULSION FROM TRADITIONAL EXTRACTS FOR ANTIDIABETIC

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ABSTRACT
Diabetes is a degenerative disease with the highest number of sufferers in the world. Traditional medicine naturally uses extracts of plants and animals in great demand. Curse fish or snakehead fish (Channa striata), elephant lempuyang (Zingiber zerumbet L) and rambutan rind (Nephelium lappaceum) are proven to have active ingredients of albumin, quercetin and geraniin as anti-diabetics. Disadvantages of these active compounds, namely having low solubility, permeability and stability, causing a decrease in bioavailability. Self Nano Emulsifying Drug Delivery System (SNEDDS) is a form of nanoemulsion and is a solution for delivering active compounds to increase permeability, stability and solubility of active compounds. The formula was made using olive oil as the oil phase, PEG 400 as the cosurfactant, span 80, tween 20 and tween 80 as the surfactant. The research aims to obtain the optimum nanoemulsion formula using the HLB method. Percent transmittance and emulsification time are used to determine the optimum formula. The selected formula was further tested with a particle size analyzer, zeta potential, PDI. Based on the 30 formulas that were made, F9 was the chosen formula with an HLB value of 15 with the oil, surfactant, cosurfactant phases at a ratio of 8:1:1. Formula F9 has an emulsification time of 18.76 seconds, a transmittance of 97.8%. The particle size test results were 196.2 nm and -30.1 zeta potential values. The research results showed that SNEDDS preparations were able to form nanoemulsions spontaneously and had good characteristics.

Keywords: channa; hlb; nanoemultion; nephelium; snedds; zingiber

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INTRODUCTION

Indonesia is one of the countries with the most population in the world, followed by the large number of diabetics, namely as many as 8.5 million and was ranked 7th in the world in 2013 and is expected to increase to 14.1 million in 2035 (BPS, 2017; IDF Atlas, 2019). Traditional medicine is one of the most popular degenerative disease therapies in Indonesia. Curse fish or snakehead fish (Channa striata) is a type of freshwater fish that has a high protein content compared to other fish (Asfar et al., 2014; Prasetyo et al., 2012). The percentage of protein in snakehead fish is 11.62% higher than other types of fresh fish, such as toman fish and betutu fish (Nurilmala et al., 2021). The largest type of protein found in snakehead fish extract is albumin with a total amount of 64.61% of the total protein content in snakehead fish (Mustafa et al., 2012). The high albumin content in snakehead fish is useful for regenerating the islets of Langerhans which are found in the pancreas organ significantly in diabetes therapy (Aisyatussoffi & Abdulghani, 2013). Islets of Langerhans are composed of 60-80% of the

mass of beta cells that function in secreting insulin (Clark, 2004). Increased improvement in the islets of Langerhans can be assumed to be an increase in insulin secretion improvement (Abdulgani et al., 2014). Elephant lempuyang extract (ELG) contains several active substances such as zerumbon, flavonoids, quercetin and kaempferol which have anti-diabetic activity by inhibiting the alpha-glucosidase enzyme (Chigurupati et al., 2019). Rambutan fruit peel extract (EKBR) contains a number of secondary metabolites, one of which is geraniin and corilagin which function to inhibit the enzymes α-glucosidase and α-amylase which can hydrolyze carbohydrates (Ajish et al., 2015; Malini et al., 2011). Based on research conducted by (Sulistia, 2017) the combination of the three traditional medicines showed a significant decrease in blood sugar levels in wistar rats.

The high protein content in snakehead fish has disadvantages, namely bioavailability and low absorption due to enzyme degradation under the influence of stomach acid and rapid clearance from the digestive tract (Tejasari, 2005; Zhang et al., 2012). Nano emulsion is defined as a delivery system for active ingredients together with oil as a carrier by utilizing a nanotechnology system. Instability under thermodynamic conditions is a drawback in nanoemulsion formulations and can be corrected by the Self-Nanoemulsifying Drug Delivery System (SNEDDS) (Rehman et al., 2017).

SNEDDS as the anhydrous form of n in the form of a mixture of oil, surfactants, cosurfactants and active substances. According to (Li et al., 2011; Shen et al., 2016), the ability of SNEDDS to help increase the bioavailability, permeability, stability, solubility of active substances in the stomach and intestines. (Makadia et al., 2013; Rane & Anderson, 2008; Winarti et al., 2016) states that these mixtures form nano emulsions which spontaneously result from interactions with gastric fluid water through mild agitation. SNEDDS spread easily in the gastrointestinal tract, the presence of movement from the stomach and intestinal tract provides the agitation necessary for emulsification (Nazzal et al., 2002). Nanoemulsions are widely used as delivery systems for active substances with BCS III and IV classifications such as proteins that have low solubility and permeability. The formation of nanoemulsion droplets with an oil-in-water system can increase drug absorption, because they can be well emulsified (Venkata Ramana Rao & Shao, 2008). So, the aim of the researchers was to find out more about the study of the SNEDDS formulation of a combination of snakehead fish meal (SIG), elephant tempuyang extract (ELG) and rambutan skin extract (EKBR).

METHOD

This research utilizes equipment in the form of analytical balances, porcelain and petri dishes, rotary evaporators, waterbaths, Buchner funnels, cuvettes, vortexes, homogenizers, UV-Vis spectrophotometers, test tubes, measuring cups, micropipettes, proppipets, conical flasks, pipettes, beakers. chemistry, stirrer, spoon, centrifuge, magnetic stirrer, stirrer, ultrasonicator, thermometer, pH meter, stopwatch and particle size analyzer. Meanwhile, the researchers used materials in the form of snakehead fish powder (CV Jadiid), elephant lempuyang rhizome, rambutan rind, 96% ethanol, distilled water, aqua demineralization, filter paper, PEG 4000, olive oil, tween 20, tween 80, CaCl2, HCl 37%, KCl, MgCl2, NaCHO3 and NaCl. Processing of samples of lempuyang rhizome (Zingiber zerumbet L) and rind of rambutan fruit (Nephelium lappaceum) were obtained from Pasar Gede, Surakarta, Central Java, Indonesia. Extract preparation was carried out with each dry sample taken as much as 5 kg and macerated using 96% ethanol solvent.

The SNEDDS formulation template was made by mixing the surfactant ratios of Tween and Span with mixed HLB values of 11 to 15. The comparison ratios were divided into 8:1:1, 7:2:1, 7:1:2 for 30 formulas. Thirty samples that had been prepared were tested for the stability of the mixture by allowing it to stand for 24 hours and observing the separation of the solution. Stable and separation-free formulations were selected for emulsification and transmission rate tests. The selected SNEDDS formulation is combined with SIG, EKBR and ELG. Tests performed on the formula were evaluation of emulsification time, spectrophotometric transmittance, thermodynamic stability, phase and stability studies, dilution strength, droplet size analysis, Poly Dispersity Index (PDI), and Zeta Potential.

RESULTS

Based on the 30 SNEDDS model formulations performed, two of them were stable and separation did not occur at room temperature for 24 hours. F5 is a formulation with HLB surfactant 13 and F9 is a formulation with surfactant HLB 15. This condition is in line with the theory (Egito et al., 2018; ICI Americas Inc., 1984) which explains the HLB value for non-ionic surfactants of more than 12 is the recommended value . Research (Buya et al., 2020) explains that emulsification of HLB can occur spontaneously in media with a particle size of less than 200 nm after being dispersed in water. Evaluation of emulsification time and spectral transmission was carried out on F5 and F9. The time on the F9 emulsifier was shown to be better, namely 15.74 seconds compared to F5 of 26.22 seconds. In the spectral transmission test, F9 gave better results (94.2%) compared to F5 (93.8%). In other words, the higher the HLB value, the faster the emulsification time and the higher the percentage of spectral transmission at F9. In conclusion, the greater absorption power can be digested along with the fast emulsification time of the SNEDDS formulation. This was shown in the emulsification time of the SNEDDS F9 system of less than 1 minute (Wijayanti et al., 2019). F9 is the best SNEDDS formulation to be combined with the active ingredients SIG, ELG and EKBR. The evaluation of the observations made on F9 is related to the operating principle.

Observations for 24 hours at F9 showed that the sample was stable and no separator was found. The purpose of emulsification is to calculate the time required for dissolving the SNEDDS and the combination of SIG, EKBR and ELG. The media needed are three types and different. Khan et.al (2015) explained the dissolution function in different media with the aim of knowing the dissolution ability of SNEDDS under acidic and basic pH conditions. Acidic pH refers to the stomach and alkaline pH refers to the intestines. The three media used by researchers include Aquades, AGF (Artificial Gastric Fluid) and AIF (Artificial Intestinal Fluid). As a result, in the first medium or Aquades media, the emulsification time was 18.76 seconds. The second media AGF is 11.13 seconds. The third medium is AIF 11.51 seconds. The transmittance evaluation results obtained 97.8%. In other words, the transmittance of SNEDDS is close to the transmittance of aquadest by 100%. So, the particle size is getting closer to the nanometer due to the higher transmittance value (Wijayanti et al., 2019). The results of the thermodynamic stability test did not experience a complete separation of the formula, immersion or creaming and cracking. This means that the formula used is stable during the test and storage process at -20 to 2°C and 25°C. The results of the phase separation test and stability study showed no precipitate was found in the main media. That is, this phase separation is clear which has been proven in vitro.

AGF value with a pH level of 1.2 and AIF with a pH level of 6.8. In other words, the oil phase is well covered in the nanoemulsion. The transmittance percentage results are described from a thorough test with very high and clear transmittance percent results at a retail of 100 to 1000 times. The formula is clear, transparent, and looks like a homogeneous single-phase liquid.

This result is in line with (Nasr et al., 2016) which describes that the higher the transmittance percentage, the smaller the particle size results in the SNEDDS formula particles.

Formula Code	Dilution Power	Replication	Percent Transmittance		
			Aquades	AGF (pH 1,2)	AIF (pH 6,8)
F9	100 times	R1	99,5	99	99,1
		R2	98,7	99,5	99,6
		R3	99,4	99,9	99,2
	1000 times	R1	95,6	98,9	99,0
		R2	99,5	99,2	99,1
		R3	98,8	98,2	98,2

The particle measurement test obtained a value of 196.2 nm. The magnitude of the particle size is less than 200 nm which has the positive side of being able to pass through the galvanic cell more easily. This plays an important role in the absorption and distribution of active substances (Baloch et al., 2019). The PDI test showed a result of 0.348. That is, the dispersion is high because the PDI value corresponds to the particle size distribution in the sample. Meanwhile, PDI values that are smaller or closer to 0 or between 0.05-0.7 are considered to have uniformity (Danaei et al., 2018). Potential zeta test value obtained -30.1 (stable charge). The reason is because the nano emulsion has a potential zeta value of more than +30 mV and less than +30 mV. In other words, the level of stability is relatively high with the electrostatic type. Whereas in (Gao et al., 2008; Ujilestari et al., 2018) states that the potential zeta test number is classified as sterically stable if it shows more than +20 mV and less than -20 mV.

DISCUSSION

The results of the extraction with the maceration process obtained 32.28 grams of viscous ECBR with a yield value of 6,456% while for ELG, 28.63 viscous extracts were produced with a yield value of 5,726%. The yield value obtained is still in accordance with the minimum limit for the yield obtained in an extraction according to the Indonesian Herbal Pharmacopoeia, which is not less than 5.5% (Ministry of Health of the Republic of Indonesia, 2017). Based on research conducted by (Winarti et al., 2016) fast emulsification time is the effect of the combination of surfactants and co-surfactants which are able to form an oil-water interface layer so that it can reduce its surface tension. The small globule size and the ability of the surfactant and co-surfactant mixture to envelop the globule can reduce the gravitational force and free energy, thereby increasing the thermodynamic stability of SNEDDS (Priani et al., 2020).

The absence of precipitation and phase separation indicates that the oil phase in the nanoemulsion is well covered by surfactants (tween 20 and span 80) and co-surfactant (PEG 400). PEG 400 succeeded in increasing the fluidity of the interface and getting into the layer between the surfactants, so that after the addition of the media, a transparent, clear nanoemulsion can be formed which is a sign of the formation of a spotty nanoemulsion between SNEDDS and the media. Tween 20 as a hydrophilic non-ionic surfactant can maintain the oil phase properly by reducing the surface tension between oil and water so that it cannot be affected by acidic (AGF) and electrolyte (AIF) conditions. PEG 400 is able to withstand changes in pH, reduce the fluidity of the oil and water interface and reduce free energy so as to prevent thermodynamic instability that can change pH and volume during drug absorption. The average of the SNEDDS particle size tests showed that it did not meet the requirements for nanoemulsion preparations, namely 20-200 nm (Date et al., 2010). The stability of SNEDDS also depends on the particle size. The smaller the particle size formed, the emulsion stability, drug absorption and bioavailability of the SNEDDS formula will increase (Ujilestari et al., 2018; Nandita et al., 2021). PDI is used to estimate the uniformity of particle distribution in solution (Clayton et al., 2016). A large PDI

value will correspond to a larger particle size distribution in the sample, while the smaller the PDI value is close to 0 or between 0.05-0.7, the more uniform the particle size is (Danaei et al., 2018).

Potential zeta testing was carried out to determine the surface charge of nanoemulsion droplets (Winarti et al., 2016). The potential zeta value is used as a parameter to determine the stability of the nanoemulsion and the surface charge of the colloidal particles (Nurdianti et al., 2017). A zeta potential value that is greater than 0 has the ability to make the preparation more stable because it will form an electric double layer as a separator between particles (Nandita et al., 2021). The minus value in the zeta potential number indicates that there are free fatty acids in the preparation which causes a large enough repulsion between droplets so that the droplets do not combine and the emulsion system becomes stable (Nugroho and Sari, 2018; Ujilestari et al., 2018).

CONCLUSION

The conclusion was formulated that SIG, ELG, and EKBR used in a combination of tween 20: span 80, PEG 400 and olive oil in the SNEDDS formula were able to form SNEDDS. Then, the properties evaluated showed the same results with a transmittance percentage of more than 90%, emulsification time of less than 2 minutes, and particle size of less than 200 nm with a good level of stability.

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