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THE FORMULATION OF SELF-NANOEMULSIFYING DRUG DELIVERY SYSTEM OF ETHANOL EXTRACT OF *Marsilea crenata* C. Presl. LEAVES

B. Ma'arif[1], Y. Tamara[1], F. A. S. Al-Azzam[1], R. Azzahara[1], F. Rizki[1], H. Sugihantoro[1], N. Maulina[1,✉] and M. Agil[2]

[1]Department of Pharmacy, Faculty of Medicine and Health Science, Maulana Malik Ibrahim State Islamic University, Malang-65144, Indonesia

[2]Department of Pharmaceutical Science, Faculty of Pharmacy, Universitas Airlangga, Surabaya-60155, Indonesia

✉Corresponding Author: novia.maulina@uin-malang.ac.id

ABSTRACT

Marsilea crenata C. Presl. contains phytoestrogens, which have structures or activity similar to estrogen and could potentially be utilized as a neuroprotector in an estrogen deficiency disease. This study aims to utilize *M. crenata* in the formulation of SNEDDS as a neuroprotector. The dosage form chosen aims to maintain stability and effectiveness because of its multi-compound properties. *M. crenata* was extracted using ethanol, then formulated into four SNEDDS formulas, and then characterization was done, which included physical quality (organoleptic and pH), particle size, polydispersity index, transmittance percentage, and Scanning Electron Microscope (SEM) analysis. The results showed that the four formulas produced a homogenous yellow color with a distinctive odor formulation; the values of the pH, particle size, polydispersity index, and transmittance percentage were still in the allowable range; and the SEM analysis showed that SNEDDS particles dominated with a spherical shape of particles. It can be concluded that the ethanol extract of *M. crenata* leaves can be formulated into SNEDDS and the best SNEDDS formulation was formula B at 100 ppm extract concentration which had the smallest particle size, smallest polydispersity index, and the largest transmission percentage.

Keywords: Green Clover, SNEDDS, Dosage Form Development, Characterization, SEM.

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INTRODUCTION

Green clover (*Marsilea crenata* C. Presl.) is an aquatic plant that is usually utilized as an ingredient for traditional dishes in Surabaya, East Java Province, Indonesia. In aquatic conditions, *M. crenata* grows on vines with stalks that can reach 20 cm. Four dark green leaflets that are on average 2.5 cm long and 2.3 cm wide make up the *M. crenata* leaf. In some of the previous studies, *M. crenata* leaves were known to contain phytoestrogen compounds that have a neuroprotective effect.[1,2] Phytoestrogens are plant compounds that have a structure similar to estrogen or can replace the function of estrogen in maintaining homeostasis in the body's organs, including the brain[2,3], so they have the potential as an alternative treatment for neurodegenerative diseases due to estrogen deficiency.[4] The research of Ma'arif *et al.,* 2019 showed that *M. crenata* is known to be able to reduce the expression of MHC II in HMC-3 microglia cells so that it can be used as a neuroprotector.[5] However, there are problems that may arise from drugs derived from natural ingredients, namely variations in the content of compounds that can affect stability, which in turn affects the effectiveness of the drug.[6] The multi-compounds found in the extract, which are natural components, can interfere with the stability of the solution form and induce competition between compounds during the absorption process. The high molecular size and the simple digestion of chemicals in the stomach also affect the stability of natural components.[7,8] The lipid-based self-nano emulsifying drug delivery system

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(SNEDDS), which has emerged as a method to increase oral solubility, dissolution, and absorption for drugs that are insoluble in water, as in the majority of ingredients found in nature, can therefore be used as a dosage form of *M. crenata* leaves extract as nanoparticles.[9,10] The isotropic blend of oils, surfactants, cosurfactants, and active chemicals that make up SNEDDS, which have a particle size of less than 100 nm, create nano emulsions in the digestive system following oral administration.[11] Age-related neurodegenerative illnesses commonly cause a variety of problems in older person, including an increase in mortality from neuropsychiatric disorders.[12] Based on that, this study focuses on the purpose of creating herbal supplements using *M. crenata* with the SNEDDS delivery method as dosage form to maintain stability and effectiveness because of its multi-compound properties. It is anticipated that the creation of *M. crenata* herbal supplements with the SNEDDS delivery method will result in nano-products of *M. crenata* supplements with neuroprotective characteristics, especially for the elderly.

EXPERIMENTAL

Plant Material

M. crenata was collected in the Benowo district, Surabaya, Indonesia, in January 2022 and identified in UPT Materia Medica, Batu, Indonesia, in January 2022 with Letter of Determination number 74/133/102.20-A/2022 and specimen number 1a-17b-18a-1. The leaves were dried and ground in order to retain their green color.

Chemical Material

Miglyol (capric oil), tween 80, and propylene glycol were purchased from Sigma-Aldrich (Darmstadt, Germany). Virgin coconut oil (VCO) was purchased from Bimala (West Java, Indonesia).

Extraction

A total of 325 g of dry powder of *M. crenata* leaves was extracted with 96% ethanol as solvent using ultrasonic-assisted extraction (UAE) methods (Sonica 5300EP S3). This process was repeated, collecting all the supernatants, which were finally evaporated in a rotary evaporator (Heidolph Hei-VAP G3).

Formulation

The four formulas use a ratio of oil phase: surfactant: cosurfactant in 1:7:2 (formula A) and 1:8:1 (formula B) for the VCO as oil phase and 2:5:3 (formula C) and 1:7:2 (formula D) for the miglyol as oil phase. All formulas use tween 80 as a surfactant and propylene glycol as a cosurfactant. Each formula's 30 mL of formulation was prepared. Table-1 displays the components of the SNEDDS formula for ethanol extract of *M. crenata* leaves.

Table-1: Formula for SNEDDS 96% Ethanol Extract of *M. crenata* Leaves

Formula	Ingredient	Function	Ratio	Amount				
				F1	F2	F3	F4	F5
A	*M. crenata* Extract	Active ingredients	-	10 ppm	25 ppm	50 ppm	75 ppm	100 ppm
	VCO	Oil Phase	1	3 mL	3 mL	3 mL	3 mL	3 mL
	Tween 80	Surfactant	7	21 mL	21 mL	21 mL	21 mL	21 mL
	Propylene Glycol	Cosurfactant	2	6 mL	6 mL	6 mL	6 mL	6 mL
B	*M. crenata* Extract	Active ingredients	-	10 ppm	25 ppm	50 ppm	75 ppm	100 ppm
	VCO	Oil Phase	1	3 mL	3 mL	3 mL	3 mL	3 mL
	Tween 80	Surfactant	8	24 mL	24 mL	24 mL	24 mL	24 mL
	Propylene Glycol	Cosurfactant	1	3 mL	3 mL	3 mL	3 mL	3 mL
C	*M. crenata* Extract	Active ingredients	-	10 ppm	25 ppm	50 ppm	75 ppm	100 ppm
	Myglyol	Oil Phase	2	6 mL	6 mL	6 mL	6 mL	6 mL
	Tween 80	Surfactant	5	15 mL	15 mL	15 mL	15 mL	15 mL

	Propylene Glycol	Cosurfactant	3	9 mL	9 mL	9 mL	9 mL	9 mL
D	*M. crenata* Extract	Active ingredients	-	10 ppm	25 ppm	50 ppm	75 ppm	100 ppm
	Myglyol	Oil Phase	1	3 mL	3 mL	3 mL	3 mL	3 mL
	Tween 80	Surfactant	7	21 mL	21 mL	21 mL	21 mL	21 mL
	Propylene Glycol	Cosurfactant	2	6 mL	6 mL	6 mL	6 mL	6 mL

The oil phase, surfactant, and cosurfactant were homogenized for 30 minutes, then dissolved in 5 mL of each concentration of extract before being homogenized using a vortex (Barnstead Thermolyne) for 4 minutes. The mixture was then cooked in a water bath (Memmert) at 37°C for 15 minutes before being sonicated (Branson 3800) for 5 minutes. The prepared formulas were next put to the characteristic test.

SNEDDS Formula Characterization

Physical Quality Test

Physical quality tests, including organoleptic and pH tests. Organoleptic tests were done to use the human senses to look at the physical properties of the formulas. The formulas homogeneity, color, and odor were among the parameters that were identified. A digital pH meter was used to conduct the pH test (Laqua Horiba PH1100). The formulas to be studied were applied to the bulb, and the resulting pH was noted.[13]

Particle Size Test and Polydispersity Index

The 10 mL of distilled water were used to dissolve 1 mL of the SNEDDS formulas. For one minute, the mixture was vortexed. Next, it was put in a cuvette that was free of fat and foam. Then, put the cuvette containing the sample into the sample holder. The instrument used was particle size analyzer (PSA) (Micotrac Nanotrac Wave II) was turned on, and the test was carried out for 10 minutes. Next will be generated particle size data.

Transmittance Percentage Test

The transmittance percentage test was carried out by taking 100 µL of the formulas, which were then added to distilled water until the final volume reached 5 mL. The mixture was homogenized using a vortex for 1 minute. Furthermore, the percent transmittance was measured using a spectrophotometer UV-Vis (Shimadzu) at a wavelength of 650 nm.[14] These measurements were carried out using an aquadest as blank so that the level of clarity of the SNEDDS system could be known.[15]

Scanning Electron Microscope (SEM) Analysis

The SNEDDS droplet was observed by a scanning electron microscope. SNEDDS was placed on a carbon tip and given absolute ethanol so that the liquid evaporated quickly. It was then made conductive, and the size of the SNEDDS droplets was observed at SEM magnifications of 100x, 20,000x, and 80,000x.[16]

RESULTS AND DISCUSSION

Extraction

The extraction process produced 55.16 g of 96% ethanol extract of *M. crenata* leaves. The yield obtained was 16.97%.

Formulation

Two different types of oil phases were used in the formulation of SNEDDS: miglyol and VCO. It is anticipated that both types of oil phases will create SNEDDS with good stability. Miglyol was used because it cannot be easily oxidized and VCO was used since it resists damage from exposure to air, light, or heat.[17,18] Tween 80 was used in the production of SNEDDS in addition to the oil phase since it is a nonionic surfactant, which is thought to lower the possibility of harmful consequences. Additionally, tween 80 has a Hydrophilic-Lipophilic Balance (HLB) value of 15, making it appropriate for the creation of stable oil-in-water emulsions even in single use.[19] According to earlier studies, tween 80 has a superior emulsification rate than span 80. In addition, propylene glycol offers improved emulsification than PEG 400. Tween 80 and the active ingredient can be more easily dissolved in an oil basis when propylene glycol is used as a

cosurfactant. Additional research has demonstrated that the mixture of tween 80 and propylene glycol can create snedds with nano-size and properties that fall within the desired range.[14,20] The use of propylene glycol as cosurfactant because it can improve the absorption of the medication too. The results were a flawlessly blended and homogenous mixture of SNEDDS base and a 96% ethanol extract of *M. crenata* leaves that can be seen in Fig.-1.[21]

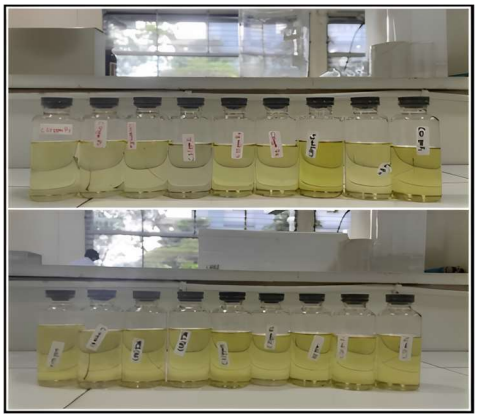

Fig.-1: Physical Appearance of the SNEDDS Formula of 96% Ethanol Extract of *M. crenata* Leaves

SNEDDS Formula Characterization

Physical Quality Test

In the physical quality test, the organoleptic test aims to evaluate how the formulated SNEDDS appears, and the pH test aims to ensure that the SNEDDS product does not irritate the digestive tract when taken orally, so the pH value must be within the range of values.[22] The physical appearance can be observed in Fig.-1 and the results of physical quality testing, including organoleptic test results and pH test results can be seen in Table-2.

Table-2: The Results of the Physical Quality Test of the SNEDDS Formulas

Formula	Concentration	Replication	Organoleptic Results			pH
			Color	Smell	Homogeneity	
A	10 ppm	R1	Bright yellow	Typical weak	Homogeneous	8.67
		R2	Bright yellow	Typical weak	Homogeneous	
		R3	Bright yellow	Typical weak	Homogeneous	
	25 ppm	R1	Dark yellow	Typical weak	Homogeneous	8.52
		R2	Dark yellow	Typical weak	Homogeneous	
		R3	Dark yellow	Typical weak	Homogeneous	
	50 ppm	R1	Dark yellow	Typical medium	Homogeneous	8.13
		R2	Dark yellow	Typical medium	Homogeneous	
		R3	Dark yellow	Typical medium	Homogeneous	
	75 ppm	R1	Dark yellow	Typical medium	Homogeneous	8.40
		R2	Dark yellow	Typical medium	Homogeneous	
		R3	Dark yellow	Typical medium	Homogeneous	
	100 ppm	R1	Dark yellow	Typical medium	Homogeneous	8.51
		R2	Dark yellow	Typical medium	Homogeneous	
		R3	Dark yellow	Typical medium	Homogeneous	
B	10 ppm	R1	Bright yellow	Typical medium	Homogeneous	8.00
		R2	Bright yellow	Typical medium	Homogeneous	
		R3	Bright yellow	Typical weak	Homogeneous	
	25 ppm	R1	Bright yellow	Typical weak	Homogeneous	8.18
		R2	Bright yellow	Typical medium	Homogeneous	
		R3	Bright yellow	Typical medium	Homogeneous	
	50 ppm	R1	Bright yellow	Typical weak	Homogeneous	8.43
		R2	Bright yellow	Typical weak	Homogeneous	
		R3	Bright yellow	Typical medium	Homogeneous	

	75 ppm	R1	Dark yellow	Typical medium	Homogeneous	7.76
		R2	Dark yellow	Typical medium	Homogeneous	
		R3	Dark yellow	Typical medium	Homogeneous	
	100 ppm	R1	Dark yellow	Typical medium	Homogeneous	8.06
		R2	Dark yellow	Typical medium	Homogeneous	
		R3	Dark yellow	Typical medium	Homogeneous	
C	10 ppm	R1	Bright yellow	Typical weak	Homogeneous	8.65
		R2	Bright yellow	Typical weak	Homogeneous	
		R3	Bright yellow	Typical weak	Homogeneous	
	25 ppm	R1	Bright yellow	Typical weak	Homogeneous	8.68
		R2	Bright yellow	Typical weak	Homogeneous	
		R3	Bright yellow	Typical weak	Homogeneous	
	50 ppm	R1	Dark yellow	Typical medium	Homogeneous	9.35
		R2	Dark yellow	Typical medium	Homogeneous	
		R3	Dark yellow	Typical medium	Homogeneous	
	75 ppm	R1	Dark yellow	Typical medium	Homogeneous	8.59
		R2	Dark yellow	Typical medium	Homogeneous	
		R3	Dark yellow	Typical medium	Homogeneous	
	100 ppm	R1	Dark yellow	Typical medium	Homogeneous	9.05
		R2	Dark yellow	Typical medium	Homogeneous	
		R3	Dark yellow	Typical medium	Homogeneous	
D	10 ppm	R1	Bright yellow	Typical weak	Homogeneous	8.06
		R2	Bright yellow	Strong special	Homogeneous	
		R3	Bright yellow	Typical weak	Homogeneous	
	25 ppm	R1	Bright yellow	Typical medium	Homogeneous	7.59
		R2	Bright yellow	Typical medium	Homogeneous	
		R3	Bright yellow	Typical weak	Homogeneous	
	50 ppm	R1	Bright yellow	Strong special	Homogeneous	7.59
		R2	Bright yellow	Typical medium	Homogeneous	
		R3	Bright yellow	Typical weak	Homogeneous	
	75 ppm	R1	Bright yellow	Typical weak	Homogeneous	8.00
		R2	Bright yellow	Typical weak	Homogeneous	
		R3	Bright yellow	Typical medium	Homogeneous	
	100 ppm	R1	Bright yellow	Typical medium	Homogeneous	7.93
		R2	Bright yellow	Typical medium	Homogeneous	
		R3	Bright yellow	Typical medium	Homogeneous	

The formula's result also exhibits homogenous dispersion. As a whole, it had a yellow color and a distinctive smell of ester, according to the results of the organoleptic test. Its yellow color was created by the tween 80 colors. This was because the concentration of tween 80 was higher than other excipients, allowing it to provide a more dominant color to the resultant product.[23] The percentage of extract present in SNEDDS can also influence how intensely the yellow color was produced. The 96% ethanol extract of *M. crenata* leaves with a higher concentration can result in a somewhat darker yellow. Several formulas have a yellow color with variable intensity, according to the results of the organoleptic test. The findings of the pH tests reveal that the pH of the SNEDDS formulas was fairly variable, but the majority were within the permitted range. An allowed SNEDDS formulation has a pH value between 6.5 and 9.[24] The pH value of the SNEDDS formulas can be affected to the point that it exceeds the range of acceptable pH values at high enough extract concentrations, specifically 50 ppm and 100 ppm.[25] This was possible because the pH value can be changed by several things, such as the type and concentration of the extract used, the type of surfactant, and other excipients.

Particle Size Test and Polydispersity Index

The ideal particle size for SNEDDS is below 200 nm. The polydispersity index shows the uniform size distribution of the SNEDDS particles. The polydispersity index demonstrates the homogeneity of SNEDDS

particle size. The smaller the polydispersity index value, the more uniform the SNEDDS particle size.[21,26] The results of the PSA tests on the particle size and polydispersity index are shown in Table-3.

Table-3: Particle Size Test Results and Polydispersity Index of the SNEDDS Formulas

Formula	Concentration	Particle Size (nm) ± SD	Polydispersity Index (mV) ± SD
A	10 ppm	10.92 ± 0.15	0.0530 ± 0.0002
	25 ppm	11.46 ± 0.10	0.0614 ± 0.0030
	50 ppm	11.36 ± 0.05	0.0690 ± 0.0009
	75 ppm	11.66 ± 0.02	0.0545 ± 0.0031
	100 ppm	11.74 ± 0.12	0.0618 ± 0.0117
B	10 ppm	10.97 ± 0.11	0.0463 ± 0.0052
	25 ppm	11.20 ± 0.09	0.0449 ± 0.0036
	50 ppm	11.67 ± 0.07	0.0516 ± 0.0021
	75 ppm	11.05 ± 0.06	0.0343 ± 0.0244
	100 ppm	10.63 ± 0.09	0.0616 ± 0.0059
C	10 ppm	156.77 ± 1.57	0.1999 ± 0.0291
	25 ppm	175.20 ± 3.82	0.1779 ± 0.1019
	50 ppm	161.00 ± 5.56	0.1873 ± 0.0308
	75 ppm	122.95 ± 4.74	0.2422 ± 0.1651
	100 ppm	214.55 ± 7.00	0.1467 ± 0.0659
D	10 ppm	11.84 ± 0.06	0.0538 ± 0.0059
	25 ppm	12.02 ± 0.15	0.0602 ± 0.0045
	50 ppm	11.99 ± 0.08	0.0516 ± 0.0015
	75 ppm	11.87 ± 0.04	0.2398 ± 0.3050
	100 ppm	11.77 ± 0.10	0.0294 ± 0.0353

The result showed that all formulas A, B, and D have particle sizes between 10 and 12 nm. Still, this Fig. falls within a desirable particle size range. Only concentrations of 10 ppm to 75 ppm, not all sizes in formula C are <200 nm. The particle size of Formula C at a concentration of 100 ppm is larger than the desirable range of 214.55 nm. The composition of the constituent materials can have an impact on the particle size of SNEDDS formulations. The higher the concentration of oils and extracts used; the more surfactants are required. The smallest particle size in formulas A and B, which both contain a VCO oil phase, was 100 ppm. There is a difference between formulas A and B due to the higher tween 80 content in formula B. The oil phase in formulas C and D was miglyol with a different concentration, and also different concentration of tween 80. Because of the higher miglyol concentration in formula C, the particle size results were in the hundreds. In contrast to the other formulations, formula C contains the highest oil concentration, but it also uses a lower concentration of surfactant. As a result, the surfactant is unable to completely cover the oil phase. Furthermore, the high concentration of extract in the oil phase influences the particle size of the formula. The smallest particle size results for the formula using VCO was formula B at 100 ppm concentration of extract, but the smallest particle size result for the formula using miglyol was formula D at 100 ppm concentration of extract. When these two data sets were compared, formula B at 100 ppm had the smallest particle size. These two formulas contain the same concentrations of the oil phase and surfactant. This shows that the oil phase can also influence droplet size, which is connected to the oil phase's surfactant solubility. In a study by Mustika *et al.* 2019, the combination of VCO and tween 80 provided SNEDDS results with nanoparticle sizes. In a study by Sahumena *et al.* 2019, the VCO oil phase and the surfactant tween 80 both produced the best formula results.[14,19,27] When making SNEDDS, droplet size is very important because it affects the rate of drug release and absorption as well as the bioavailability and stability in vivo of smaller droplets with a larger surface area. The result of the polydispersity index value of all the SNEDDS formulas was less than 0.7. Formulas A, B, C, and D have polydispersity index values ranging from 0.0063 to 0.592, which still satisfy the criteria for a high polydispersity index value. This shows that the size of the SNEDDS particles was the same all over. The distribution method of the polydispersity index value is <0.05 for monodisperse, <0.08 for almost monodisperse, 0.08 to 0.7 for the highest performance, and >0.7 for extremely polydisperse, which exhibits a wide variety of particle sizes and the potential for sedimentation.[26,28] The polydispersity index value with the lowest value in formulas A

and B was formula B at 75 ppm concentration of extract. The polydispersity index value with the lowest value between formulas C and D was formula D at 100 ppm concentration of extract. The smaller particle size can have an impact on the polydispersity index value, which implies that the final distribution is also homogeneous. Indicators of homogenous globules and a restricted particle size distribution include a low polydispersity index. Because a higher polydispersity index value indicates that the particles created are not homogeneous, the formula will soon flocculate, the smaller the polydispersity index value, the more stable the formula of a formulation made.[28] Based on the results of the tests, the formulas B with VCO oil phase and formula D with miglyol oil phase were found to have the best particle size and polydispersity index. Based on the results of particle size and polydispersity index, formula B was the best formula when these two formulas were compared.

Transmittance Percentage Test

The transmittance percentage test is a procedure used to assess the clarity of a formulation utilizing a spectrophotometer as the testing tool. A rough notion of the tiny droplet size in the nanometer range can be obtained from the percentage transmittance number that is near 100%. Emulsion droplet size affects the rate and amount of drug release and absorption, making it a crucial component of self-emulsification performance.[29] Table-4 contains the results of the transmittance percentage test of the SNEDDS formulas of 96% ethanol extract of *M. crenata* leaves.

Table-4: Transmittance Percentage Test Results of the SNEDDS Formulas

Formula	Concentration	Percentage of Transmittance (%) ± SD
A	10 ppm	99.16 ± 0.13
	25 ppm	98.78 ± 0.26
	50 ppm	98.86 ± 0.00
	75 ppm	97.72 ± 0.23
	100 ppm	96.90 ± 0.46
B	10 ppm	99.16 ± 0.13
	25 ppm	99.01 ± 0.13
	50 ppm	99.01 ± 0.13
	75 ppm	98.93 ± 0.26
	100 ppm	99.62 ± 0.23
C	10 ppm	79.83 ± 1.40
	25 ppm	76.89 ± 7.98
	50 ppm	94.07 ± 2.67
	75 ppm	89.82 ± 1.87
	100 ppm	88.64 ± 9.18
D	10 ppm	99.16 ± 0.13
	25 ppm	99.01 ± 0.13
	50 ppm	98.86 ± 0.23
	75 ppm	98.70 ± 0.13
	100 ppm	98.55 ± 0.13

The results of the percent transmittance for all formulas A, B, and D and formula C at 50 ppm concentration of extract meet the standards with a transmittance value of > 90% to produce a visually clear dispersion, as can be seen from Table-4. A decent transmittance percentage must be greater than 90%.[30] The transmittance value of the formula C at 10 ppm, 25 ppm, 75 ppm, and 100 ppm concentrations of the extract as 90%, as shown by the formula's turbidity. Turbid dispersion reduces transmission because it spreads incident radiation more widely, resulting in low transmittance levels.[31] The transmittance value in formula C was quite low since the globule size does not approach the nanoscale size, which is known to be the case when formula C uses the greatest concentration of the oil phase. The size of the globules generated was significantly influenced by the amount of oil phase utilized, which has an impact on the formula's transmittance value. Excessive oil phase concentration results in larger globules, this is due to interfacial film distortion caused by oil droplet penetration into the surfactant chain, which affects the curvature of the globule surface and leads to an increase in size.[32] The presence of more emulsifiers in the emulsification

process may account for the increase in transmittance percentage with decreasing oil content. The clarity produced will also depend on how much surfactant is employed. This is shown by formulations using the VCO oil phase, such as formulas A and B, which show that formula B has a higher transmittance percentage than formula A. This is because formula B contains more surfactant than formula A does. The SNEDDS formulas will be clearer if the surfactant concentration is higher.[15,22] The capacity to lower the voltage of the oil phase by enclosing the oil phase increases with surfactant concentration, producing a clearer formula with a transmittance percentage close to 100%.[19] This also occurred in the formulas C and D that contained the miglyol oil phase, demonstrating that formula D had a higher transmittance percentage than formula C. Based on the percentage of transmittance, formula B is the best formula when the two formulas are compared.

Scanning Electron Microscope (SEM) Analysis

The morphological characterization of SNEDDS can be known through SEM analysis. The morphology is important to know because it describes the shape and size of particles. In this study, SEM analysis was used with an image magnification of 80,000x. The following is an image of SNEDDS morphology.

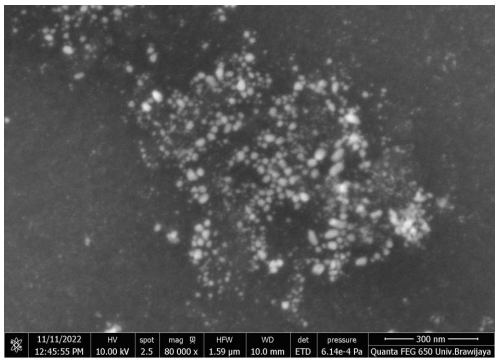

Fig.-2: Morphology of the SNEDDS Formula of 96% Ethanol Extract of *M. crenata* Leaves

Based on the results of the SEM analysis above, it can be seen that the morphology of the SNEDDS formulations of 96% ethanol extract of *M. crenata* has various shapes and sizes. However, the dominating shape is an irregular spherical shape. This occurs due to the aggregation effect of nanoparticles and the presence of un-uniform particles.[33] Particle aggregation can occur due to prolonged storage.[34]

Determination of the Best Formula

The best formula, according to the characteristic test, was formula B. This was because formula B outperformed other formulations in terms of particle size, polydispersity index, and transmittance percentage. Due to its superior particle size, polydispersity index, and transmittance percentage compared to other B formulas, formula B at 100 ppm concentrations of the extract was demonstrated to be the best formula B in the findings of the properties of formula B. In this situation, particle size, polydispersity index, and transmittance percentage are more important than pH in determining the best formula since these three factors have a significant impact on how much and how quickly the active chemical can be released. This will also affect how well the medicine is absorbed, increasing its bioavailability and enabling it to have a more effective therapeutic effect.

CONCLUSION

The ethanol extract of *M. crenata* leaves can be well formulated into SNEDDS. The best formula was shown to be formula B at 100 ppm extract concentration, with a component ratio of 1:8:1 (VCO: tween 80: propylene glycol), and the volume of each component was 3 mL (VCO), 24 mL (tween 80), and 3 mL (propylene glycol), which has the best particle size, polydispersity index, and percent transmittance compared to other formulas.

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CONFLICT OF INTERESTS

There is no conflict of interest between the authors.

AUTHOR CONTRIBUTIONS

All the authors contributed significantly to this manuscript, participated in reviewing and editing, and approved the final draft for publication. The research profiles of the authors can be verified from their ORCID ids, given below:

B. Ma'arif http://orchid.org/0000-0001-9182-343X
Y. Tamara https://orcid.org/0009-0009-0032-4172
F.A.S. Al-Azzam https://orcid.org/0009-0007-9963-0553
R. Azzahara https://orcid.org/0009-0001-9942-8183
F. Rizki https://orcid.org/0009-0007-5949-1173
H. Sugihantoro http://orchid.org/0000-0001-5451-657X
N. Maulina https://orcid.org/0000-0002-7948-0101
M. Agil http://orchid.org/0000-0002-2300-9214

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