Formulation and Characterization of SNEDDS of Dayak Onion Extract with Comparative Variation of Surfactants, Co-Surfactants, and Palm Oil

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Abstract

Self-Nanoemulsifying Drug Delivery System (SNEDDS) is a thermodynamically stable drug administration unit with the capacity to increase the solubility of active pharmaceutical ingredients (API) and bioavailability. In addition, dayak onion extract is an active ingredient developed to increase the effectiveness of therapy. The aims to formulate, characterize, and investigate stability. Moreover, the HLB approach was used to formulate SNEDDS from dayak onion extract, with a component ratio of palm oil, a combination of surfactants (hydrophilic Tween 80, Tween 20) and lipophilic (Span 20 and Transcutol) and PEG 400 as co-surfactants. A total of sixty formulas were used, with an HLB range of 11-15 and a ratio of 1:8:1, 1:7:2, and 2:7:1, followed by evaluating product characteristics. Furthermore, two formulas were selected, including F13 (HLB 13) and F34 (HLB 14), at ratios 1:8:1 and 1:7:2. The results showed particle size ranging from 10-200 nm, percent transmittance of <90%, while the viscosity and pH values were stable at various dilutions. The evaluation for thermodynamics indicates an unstable preparation. Therefore the SNEDDS formula of dayak onion extract using long-chain triglycerides (palm oil) was ineffective.

Keywords: *SNEDDS, self-nano emulsification, characteristic test, palm oil, HLB, dayak onion (Eleutherine palmifolia).*

Introduction

The development of formulation technology has attracted many researchers as an effort to produce new drugs with ideal properties by considering molecular ion balance, hydrophilic-lipophilic equilibrium, biopharmaceutical processes, metabolism and biodegradation, drug-receptor affinity, physiological considerations, and the biocompatibility of the system as the main factors influencing the development of formulation technology. Commonly done in research is about nanotechnology (Martien *et al.*, 2012). Nanoemulsion is a thermodynamically stable preparation, transparent dispersion of oil and water stabilized by the interfacial film of surfactant and co-surfactant molecules and has a droplet size of less than 100 nm (Shafiq-un-nabi *et al.*, 2007).

Self-Nanoemulsifiying Drug Delivery System (SNEEDS) is one of the developments of nanoemulsion delivery systems that can penetrate cell tissue by considering the physicochemical properties of the active ingredients and additives in the formulation so that they affect the resulting nanoemulsion preparations, such as droplet size, size distribution, and emulsification time. (Date *et al.,* 2010). The components of SNEEDS are influenced by the oil phase, surfactant, and co-surfactant (Huda *et al.*, 2016).

The oil component in this preparation is the primary carrier of the active substance. It is a determinant of the droplet size of the emulsion formed. The oil used is palm oil (Elaeisguineensis Jacq). Palm oil is a food oil with dominant long-chain fatty acids, which are essential to reduce unsaturation, prevent oxidative degradation, and affect drug solubility in water (Marpaung, 2014).

The next component, namely surfactants, reduces the size of droplets or emulsion droplets and stabilizes the active substance at the absorption site. There is no deposition in the gastrointestinal tract. The surfactants used were Transcutol, Span 20, Tween 80, and Tween 20. Co-surfactants function to assist surfactants in finding the surface tension of water and oil, increasing dissolution, and improving active substances' absorption (Marpaung, 2014). The co-surfactant used is PEG with stable properties, easily soluble in warm water, non-toxic.

The number of comparisons between oil, surfactant, and co-surfactant in this study used three ratios of variation between the three constituent components, namely 1:8:1, 1:7:2, 2:7:1. It is also influenced by the HLB value to get the most stable SNEDDS. SNEDDS with HLB between 11-15 is a stable vulnerability in the manufacture of SNEDDS systems (Winarti*et al.*, 2016).

The natural extract preparations that have been developed produce therapeutic effectiveness with large enough doses, low solubility, and less than optimal oral bioavailability. SNEDDS is used to increase the absorption and bioavailability of drugs in the body, especially for low solubility in water (Nasr *et al.,* 2016). The utilization of natural materials in this research uses dayak onion extract with naphthoquinone secondary metabolite compounds that have bioactivity as anticancer. The purpose of this research is expected to be an innovation for the development of drug delivery systems with extracts of natural ingredients using various concentrations of surfactants-co-surfactants with the oil used to improve the bioavailability of active substances in the body.

Materials and Methods

Materials

The materials used in this study were dayak onion extract, palm oil, Tween 80 (Merck, Germany), Transcutol (Gattefose, France), Tween 20, Span 20, PEG 400 (Bratachem, Indonesia), Ethanol, HCl, NaOH, KH2PO4 pro analysis (Merck, Germany).

Methods

Optimization of the SNEDDS Formulation Design Using the HLB Method

SNEDDS components consist of palm oil, surfactants (Tween 80, Tween 20, Span 20, and Transcutol), and co-surfactants (PEG 400). The ratio of the formula to 1:8:1, 1:7:2, 2:7:1. Two hydrophilic surfactants (Tween 80, Tween 20) were mixed with two lipophilic surfactants (Span 20 and Transcutol) to form 4 binary combinations of surfactants with an HLB range of 11-15

(Table 1). The HLB mix of each surfactant mixture is calculated by the following equation (Winarti*et al.*, 2016):

$$HLBmix = f_A HLB_A + f_B HLB_B$$

HLB_A dan HLB_B : surfactant value of A dan B
fA : weight fraction of surfactant A
fB : weight fraction of surfactant B

Tabel 1. Formula based on HLB and Component Ratio

Formula	HLB mix ratio	Mix Surfaktan (% b/b)				Component Ratio
		Tween 80/ Span 20	Tween 80/ Transcutol	Tween 20/ Span 20	Tween 20/ Transcutol	
F1	11	30,00/50,00	-	-	-	
F2	12	42,50/37,50	-	-	-	
F3	13	55,00/25,00	-	-	-	
F4	14	67,50/12,50	-	-	-	
F5	15	80,00/0,00	-	-	-	
F6	11	-	50,37/29,63	-	-	
F7	12	-	57,77/22,23	-	-	
F8	13	-	65,20/14,80	-	-	
F9	14	-	72,60/7,10	-	-	
F10	15	-	80,00/0,00	-	-	1:8:1
F11	11	-	-	23,70/56,30	-	
F12	12	-	-	33,58/46,42	-	
F13	13	-	-	43,46/36,54	-	
F14	14	-	-	53,30/26,70	-	
F15	15	-	-	63,21/16,79	-	
F16	11	-	-	-	43,52/36,48	
F17	12	-	-	-	49,92/30,80	
F18	13	-	-	-	56,32/23,68	
F19	14	-	-	-	62,72/17,80	
F20	15	-	-	-	69,12/10,88	
F21	11	26,25/43,75	-	-	-	
F22	12	37,2/32,80	-	-	-	
F23	13	48,13/21,87	-	-	-	
F24	14	59,1/10,90	-	-	-	
F25	15	70,00/0,00	-	-	-	
F26	11	-	44,07/25,93	-	-	
F27	12	-	50,56/19,44	-	-	1:7:2
F28	13	-	57,04/12,96	-	-	
F29	14	-	63,52/6,48	-	-	
F30	15	-	70,00/0,00	-	-	
F31	11	-	-	20,74/49,26	-	
F32	12	-	-	29,40/40,60	-	
F33	13	-	-	38,02/31,98	-	
F34	14	-	-	46,67/23,33	-	

F35	15	-	-	55,31/14,69	-	
F36	11	-	-	-	38,08/31,92	
F37	12	-	-	-	43,68/26,32	
F38	13	-	-	-	49,28/20,72	
F39	14	-	-	-	54,88/15,12	
F40	15	-	-	-	60,48/9,52	
F41	11	26,25/43,75	-	-	-	
F42	12	37,20/32,8	-	-	-	
F43	13	48,13/21,87	-	-	-	
F44	14	59,10/10,90	-	-	-	
F45	15	70,00/0,00	-	-	-	
F46	11	-	44,07/25,93	-	-	
F47	12	-	50,56/19,44	-	-	
F48	13	-	57,04/12,96	-	-	
F49	14	-	63,52/6,48	-	-	
F50	15	-	70,00/0,00	-	-	2:7:1
F51	11	-	-	20,74/49,26	-	
F52	12	-	-	29,40/40,60	-	
F53	13	-	-	38,02/31,98	-	
F54	14	-	-	46,67/23,33	-	
F55	15	-	-	55,31/14,69	-	
F56	11	-	-	-	38,08/31,92	
F57	12	-	-	-	43,68/26,32	
F58	13	-	-	-	49,28/20,72	
F59	14	-	-	-	54,88/15,12	
F60	15	-	-	-	60,48/9,52	

SNEDDS Preparation

The preparation of SNEDDS, namely hydrophilic and lipophilic surfactants, was stirred at 300 rpm for 10 minutes. Co-surfactant PEG 400 was added and stirred for 10 minutes, finally added oil little by little and stirred for 10 minutes. SNEDDS were stored for 24 hours and observed for phase separation. The most stable preparation with the lowest surfactant composition, the highest oil component, and the highest HLB was chosen as the SNEDDS formula for dayak onion extract (Winarti *et al.,* 2016).

Preparation of SNEDDS Bawang Dayak Extract

The design of the optimized SNEDDS formula consisting of oil, surfactant, and co-surfactant added 50 mg of dayak onion extract, then mixed until homogeneous with a magnetic stirrer LAB MS-H (Heidolph, Germany) for 10 minutes and stored at 25^{o}C for further characterization.
SNEDDS Characteristic Test of dayak onion extract.

1. Transmittan Percent Test

Measurement of percent (%) transmittance of SNEDDS was carried out using a UV-Vis 1800 spectrophotometer (Shimadzu, Germany). Measurement by taking 100 L of each formula then diluted with distilled water to 100 mL. The mixture was homogenized with a magnetic stirrer at 200 rpm. SNEDDS was measured at a wavelength of 650 nm to determine the percent transmittance (Nasr *et al.*, 2016).

2. Emulsification Time Test

The SNEDDS formula was evaluated visually to determine the emulsification time using a magnetic stirrer. A total of 100 L of SNEDDS was dropped into a beaker containing 100 mL of simulated gastric fluid (SGF) without enzymes pH 1.2 ± 0.05 and simulated intestinal fluid (SIF) at pH 6.8 ± 0.05 without enzyme (Ren *et al.*, 2009), temperature 37ºC with stirring 200 rpm. The time for emulsification was determined as the SNEDDS time to form a homogeneous mixture after mixing (Basalius*etal.*, 2010).

3. Particle Size Measurement

SNEDDSparticles were measured using the Microtrac Nanotrac wave II Particle Size Analyzer (PSA). Take 100 L of SNEDDS, then put it into a cuvette. The cuvette used must be free of foam and grease. The cuvette that has been filled with the sample is inserted into the sample holder. The tool is turned on, and the particle size menu is selected.

4. pH measurement

The pH measurement of each formula was carried out using a calibrated digital pH meter pH-700. Take 5 mL of SNEDDS, the electrode is inserted into the SNEDDS, and the number indicated by the pH meter is recorded (Annisa*et al.*, 2016).

5. Viscosity Measurement

Viscosity measurements were carried out to see the viscosity of SNEDDS produced due to the influence of the addition of other ingredients such as surfactants and the power of manufacturing techniques. Viscosity measure meant using a Brookfield cone and plate viscosimeter. A stationary plate forms the bottom of the movable sample cup and is filled with 0.5 mL-2.0 mL SNEDDS. The system is accurate within ± 1.0% of the fulls clearance. Reproducibility ± 0.2%. The tool works in a temperature range of 0-100oC (Zhao *et al.*, 2015).

6. Dilution with Various Media

The stability of the dayak onion extract in nanoemulsion after dilution with water, SGF, and SIF was examined by monitoring the concentration of whole dayak onion extract during incubation at room temperature. SNEDDS were added to 100 mL of distilled water, artificial intestinal fluid (SIF), and artificial gastric fluid (SGF). The mixture was then homogenized with a vortex for 2 minutes (Ren *et al.*, 2009) (Astuti*et al.*, 2018).

7. ThermodynamicStability

Heating-cooling Cycle

The test was carried out by taking 2 mL of SNEDDS diluted with 10 ml of aquadest and stored at 4°C and 45°C for 48 hours. The temperature was exchanged for each preparation. Physical damage to the SNEDDS preparation was observed (Winarti*et al.*, 2016).

Freeze-Thaw Cycle

The test was carried out by taking 2mL of SNEDDS, diluting with 10ml of aquadest, and stored at -20°C and 25°C for 48 hours. The temperature was exchanged for each preparation. Physical damage to the SNEDDS preparation was observed (Winarti*et al.*, 2016).

Centrifugation

Thermodynamic testing of 10 mL SNEDDS was carried out using a Hettich Rotofix 32 centrifuge at 3500 rpm for 30 minutes. Then the SNEDDS were stored at -20ºC and the others at 25ºC. Stability observations were carried out after 24 hours of storage (Winarti*et al.*, 2016).

Result and Discussion

Optimization of the composition of the SNEDDS material was carried out by mixing the ratio of surfactants (Tween 80, Tween 20, Span 20, and Transcutol) and co-surfactants (Transcutol) with palm oil as a carrier oil with an HLB range of 11-15 which is a stable HLB in SNEDDS (Syukri *et al.*, 2019). Palm oil is an extended chain oil group that has the advantage of increasing drug transport through lymphatics, thereby reducing first-pass metabolism, but its ability to emulsify compared to medium-chain triglycerides, diglycerides, or fatty acid esters (Sapra*et al.*, 2012). The use of HLB ranges from 11-15 because this value shows O/W droplets, and the higher the HLB value, the more hydrophilic nanoemulsion preparations are obtained. Furthermore, the ratios of 1:8:1, 1:7:2, and 2:7:1 to determine the stable formulation of SNEDDS. The comparison between the amount of surfactant by mixing hydrophilic and hydrophobic surfactants to form nanoemulsions with better characteristics and affect the surface tension of the preparation (Debnath *et al.*, 2011).

The composition of the ingredients was mixed until homogeneous and not observed for 24 hours to determine the formula for the HLB value and a stable ratio indicated by the absence of phase separation. Preparations with a clear physical appearance and no phase separation will be selected next to be tested for physical characteristics of SNEDDS preparations. The resulting formula is 60 formulas using three ratio ratios of SNEDDS components. A formula with a clear appearance and no phase separation indicated a stable preparation in the formation of SNEDDS. From the optimization obtained 15 formulas namely F1, F2, F3, F4, F5, F10, F11, F12, F13, F21, F22, F31, F32, F33 and F34. The formula consists of surfactants tween 80 and span 20 with a ratio of surfactant oil and co-surfactant 1:8:1 (F1, F2, F3, F4, F5), surfactant tween 80, and transcutol 1:8:1 (F10).), surfactant tween 20 and span 20 ratio 1:8:1 (F11, F12, F13), surfactant tween 80 and span 20 ratio 1:7:2 (F21, F22), surfactant tween 20 and span 20 ratio 1:7 :2 (F31, F32, F33, F34). Of the 15 formulas, the ratios are 1:8:1 and 1:7:2, which can produce stable compositions when diluted, with good droplet sizes and meet the stability test requirements (Syukri*et al.*, 2019).

The 15 formulas were then tested for %transmittance to determine the level of clarity of the preparation using UV-VIS Instruments at a wavelength of 650nm. F13 and F34 were obtained at HLB 13 and 14, respectively, with a ratio of 1:8:1 and 1:7:2, which had %transmittance values >90% (Wirnarti*et al.*, 2018). Furthermore, both formulas were tested for emulsification time with dilution in SIF and SGF liquids. Both formed homogeneity with a value of <2 minutes (Winarti*et al.*, 2016). Then proceed to the particle size test on the preparation by diluting SGF and SIF. The range of values obtained is between 10-200 nm (Syukri*et al.*, 2016).

The preparation was carried out by mixing the composition of the SNEDDS material with a predetermined ratio in a stable formula, then homogenized and observed for 24 hours at room

temperature. In this case, the formula that is made is a formula that is stable at the time of optimization of SNEDDS without dayak onion extract, namely F13 and F34.

The selection of this formula will then be tested for the physical characteristics of the SNEDDS preparation by adding dayak onion extract to improve the bioavailability of the active substance in the body.

1. Transmittance Percent Test

The data from the percent transmittance test are in Table 2. This result shows a value that is far from the range, namely >90% (Sahumena, 2014). This result contradicts the research, which stated that the emulsion with transparent and clear preparation conditions had a transmittance value close to aquadest. It could be concluded that the emulsion droplet size value was 10-200 nm (Syukri*et al.*, 2016). SNEDDS, which has a low transmittance value, shows a larger particle size. A macroemulsion is formed to look cloudy because its solubility with water is very low (Syukri*et al.*, 2018).

The lack of clarity of SNEDDS, which can be indicated, is that the oil globules are not dispersed with the active ingredients and other components in a homogeneous and nano-sized manner (Nurdianti and Rahmiyanti, 2016). It can also be indicated that dayak onion extract, which has lipophilic properties, also affects the instability of the oil because of the amount of oil in the preparation increases. Increasing the amount of oil in the preparation can reduce the stability of the preparation if it is not accompanied by an increase in the amount of surfactant, which functions as a decrease in surface tension and can produce smaller globules (Nurdianti and Rahmiyanti, 2016). Both formulas are still being continued for other characteristic tests.

Tabel 2. Results of Transmittance Percent

Formula	HLB	Average ± SD
F13	13	49,90 ± 0,81
F34	14	53,85 ± 5,41

2. Particle Size Test

Droplet size characterization was carried out to determine the nanoemulsion droplet size. This particle size affects a larger interfacial surface area for drug absorption. The size of the nanoemulsion has a droplet size of less than 200 nm (Syukri *et al.*, 2019). The droplet size can be known through the appearance of the preparation. The more cloudy the preparation is, the more likely it is to have a large droplet size (Winarti *et al.*, 2016).

Table 3 in F13 shows that the particle size value when diluted follows the parameter value range, which is 10-200nm. However, at F34, the particle size value is below the parameter range or smaller than the parameter. The Polydispersity Index (PDI) value is also obtained in Table 4 if the value <1 indicates the uniformity of particle size is well-formed and uniform.

The size of the dispersed phase dramatically affects the appearance of the emulsion to be transparent or cloudy, and this is due to the size of the oil droplets dispersed in water. Suppose light passes through an emulsion system with very small droplet sizes. In that case, the light beam will be transmitted so that the color of the solution looks transparent and the resulting transmittance is more excellent (Sahumena, 2014).

Tabel 3. Result of Particle Size Test

Formula	HLB	Average ± SD (SGF (nm))	Average ± SD (SIF (nm))
F13	13	93,13 ± 4,36	106,43 ± 17,64
F34	14	1,14 ± 0,16	50,17 ± 15,52

Tabel 4. Results of the Polydispesity Index (PDI)

Formula	HLB	Average ± SD (SGF)	Average ± SD (SIF)
F13	13	0,10 ± 0,00	0,27 ± 0,21
F34	14	0,11 ± 0,05	0,15 ± 0,06

3. Emulsion Time Test

The data from the emulsification time test in Table 5 aims to determine the SNEDDS preparation formed when peristalsis occurs in the gastrointestinal tract by diluting it with simulated intestinal and gastric fluids. In formulas F13 and F34, homogeneous preparations were included when diluted and stirred for >2 minutes. The best results are shown if the practice shows an emulsion time >2 minutes (Wirnarti *et al.*, 2018).

Tabel 5. Result of Emulsification Time

Formula	HLB	Average ± SD (SGF)	Average ± SD (SIF)
F13	13	20,24 ± 0,04	27,60 ± 1,10
F34	14	17,38 ± 0,94	19,43 ± 0,80

4. pH test

Table 6 states that the pH test results of SNEDDS preparations can penetrate well at pH 6-9, which is the pH of the intestine (Zhao *et al.*, 2015). The formula with a pH of 6-8 nanoemulsion W/A will produce a large negative charge and prevent droplets from approaching each other and aggregating to form a stable nanoemulsion preparation (Komaiko and McClements, 2015).

Tabel 6. Result of pH test

Formula	HLB	Average ± SD
F13	13	9,0±0,1
F34	14	8,3±0,46

5. Viscosity Test

The purpose of the viscosity test is to determine the level of available viscosity of SNEDDS due to the influence of other materials such as surfactants and preparation techniques. The results of the viscosity test are listed in Table 7. The formulas F13 and F34 showed an increase in the viscosity of the formula with an increase in the proportion of surfactant in the formulation to achieve an optimal formulation ranging from 7.0 ± 0.1 to 42.0 ± 0.2 centipoises (Syukri*et al.*, 2019).

Tabel 7. Result of Viscosity Test

Formula	HLB	Average ± SD
F13	13	30,49 ± 1,71
F34	14	28,26 ± 11,47

6. Dilution Test with Various Media

The fluid used is a simulated fluid with pH in the gastrointestinal tract, namely the stomach and intestines and distilled water. The pH values in the intestines ranged from 6-9, and the pH in the stomach was 1.2. The results in Table 8 are stable preparations and provide values according to the pH parameters in each gastrointestinal tract. The physiological environment has a pH range varying from pH 1.2 (pH in the stomach) to 7.4 and greater (pH of blood and intestines) (Syukri *et al.*, 2019). The pH value of the resulting nanoemulsion is safe to use as a drug base because it follows the pH of the small intestine (7-7.24) as the main organ of drug absorption (Jusnita *et al.*, 2019).

Tabel 8. Result of Dilution Test with Various Media

Formula	HLB	Average ± SD (SGF)	Average ± SD (SIF)	Average ± SD (Aquadest)
F13	13	1,23 ± 0,12	7,4 ±1,09	8,67 ± 0,15

7. Thermodynamic Stability Test

This test was carried out with three cycles with one cycle at a temperature of -20° and 25° C with a storage time of 48 hours per cycle. The results showed that in the preparations F13 and F34, there was a separation of the clear phase and the cloudy phase on the upper surface of the preparation.

A freeze-thaw test was carried out with three cycles at -20° and 25° C, with a storage time of 48 hours for each process. The effect of this temperature is to observe the instability of preparations such as cracking, creaming. The results on F13 and F34 preparations were unstable due to physical changes in the practices and cracking in each trial.

Centrifugation test on SNEDDS F13 and F34 preparations to determine the presence of deposits after screening at a certain speed and time, namely at a speed of 3500 rpm for 30 minutes (Syukri*et al.*, 2018). The results that appear after screening are preparations that occur separation of the clear yellowish phase and the dark red phase. The practice was then placed at a temperature of -20° C and 25° C and allowed to stand for 24 hours. The results were observed and showed that both formulas froze and indicated that the preparation was unstable.

The instability of the preparation is due to the surfactant being unable to reduce the interfacial free energy and providing a mechanical barrier for coalescence to occur, resulting in a less spontaneous thermodynamic dispersion (Pratiwi, 2018).

Conclusion

The SNEDDS formula using the ratio of palm oil, surfactant, and co-surfactant used in this study was able to form SNEDDS, but after the addition of the active ingredient dayak onion extract as the active ingredient showed less stable results on the stability of the physical preparation of SNEDDS with marked cracking and creaming in practice. When testing the characteristics of the SNEDDS preparation.

References

Annisa, Rahmi., EstiHendradi., dan DewiMelani. 2016. Pengembangan Sistem Nanostructured Lipid Carriers (NLC) Meloxicam Dengan Lipid Monostearin Dan Miglyol 808 Menggunakan Metode Emulsifikasi. *J. Trop. Pharm. Chem.* Vol 3. No. 3.

Astuti, IkaYuni, Marchaban, Ronny Martien, dan Agung Endro Nugroho. 2018. Physical Characterization and Dissolution Study of Pentagamavunon-0 Loaded Self Nano-Emulsifying Drug Delivery System. *Indonesian J. Pharm*. 29(2), 6.

Basalious., Emad B., Nevine S., dan Shaimaa M. Badr-Eldin. 2010. SNEDDS Containing Bioenhanchers for Improvement of Dissolution and Oral Absorption of Lacidipine. I: Development and Optimization. *International Journal of Pharmaceutics*. No. 391, Hal: 203-211.

Date, A.A., Desai, N., Dixit, R., dan Nagarsenker, M. 2010. Selfnanoemulsifyingdrug delivery systems: formulation insights, applications, and advances. *Nanomedicine.* 5: 1595–1616.

Debnath, S., Satayanarayana, dan Kumar, G.V. 2011. Nanoemulsion-A Method to Improve The Solubility of Lipophilic Drugs. *Int. J. Adv. Pharm. Sci*., 2: 72–83.

Huda, Nurul dan iisWahyuningsih., 2016. Karakterisasi Self-Nanoemulsifying Drug Delivery System (SNEDDS) MinyakBuah Merah (Pandanus conoideus Lam.). *JurnalFarmasi dan IlmuKefarmasian Indonesia*. Vol. 3(2).

Jusnita , Nina, dan KhairunnisaNasution. 2019. FormulasiNanoemulsiEkstrakDaunKelor (Moringa oleifera Lamk). *JurnalTeknologi dan Manajemen Agroindustri*. Volume 8 Nomor 3: 165-170.

Komaiko, J., dan McClements, D.J. 2015. Food-grade nanoemulsion filled hydrogels formed by spontaneous emulsification and gelation: optical properties, rheology, and stability, Food Hydrocolloid., 46, 67–75.

Marpaung YG. 2014. FormulasiNanoemulsiMinyakSawitdengan High PressureHomogenizer. [Skripsi]. Bogor (ID): InstitutPertanian Bogor.

Martien, Ronny,. Adhyatmika,. Iramie D. K. Irianto,. Verda Farida,. Dian Purwita Sari. 2012. PerkembanganTeknologiNanopartikelSebagaiSistemPenghantaranObat. *MajalahFarmaseutik.* Vol. 8 (1).

Nasr, A., Gardouh, A., &Ghorab, M. 2016. Novel Solid Self-Nanoemulsifying Drug Delivery System(S-SNEDDS) for Oral Delivery of Olmesartan Medoxomil: Design, Formulation, Pharmacokinetic and Bioavailability Evaluation. MDPI.*Pharmaceutics Journal*. 8(20):1-29.

Nurdianti, L & Rahmiyanti, I. 2016. Uji AktivitasAntioksidanKrimEkstrakDaun Mangga (Mangifera indica L) Terhadap DPPH (1,1-diphenyl-2- picrylhydrazil). Jurnal Kesehatan Bakti Tunas Husada. 16 (1).

Nurdianti, L & Rahmiyanti, I. 2016. Uji AktivitasAntioksidanKrimEkstrakDaun Mangga (Mangifera indica L) Terhadap DPPH (1,1-diphenyl-2- picrylhydrazil). Jurnal Kesehatan Bakti Tunas Husada. 16

Pratiwi, Liza dkk. 2018. Uji StabilitasFisik dan Kimia Sediaan SNEDDS (*Self-nanoemulsifying Drug Delivery System*) dan NanoemulsiFraksiEtilAsetatKulit Manggis (*Garcinia mangostana* L.). *Traditional Medicine Journal*. Vol. 23(2).

Ren, F., Qiufang, J., Jingbin, C., Jianming, C., Yongjia, S. 2009. Self-Nanoemulsifying Drug Delivery System (SNEDDS) of Anethole Trithione by Combined Use of Surfactants *Journal of Dispersion Science and Technology*. Vol. 30, Hal: 580-586.

Sahumena, M. H. (2014). *PengembanganNanopartikel Ketoprofen dengan Teknik SNEDDS dan Uji AktifitasAntiinflamasi. Tesis Program PascaSarjana*; Universitas Gadjah Mada, Yogyakarta.

Sapra, K., Sapra, A., Singh, S.K., dan Kakkar, S. 2012. Self emulsifying drug delivery system: A tool in solubility enhancement of poorly soluble drugs. *Indo global journal of pharmaceutical science.*, 2: 313–332.

Shafiq-un-Nabi, S., Shakeel, F., Talegaonkar, S., Ali, J., Baboota, S., Ahuja, A., dkk. 2007. Formulation development and optimization using nanoemulsion technique: a technical note. *AAPS pharmscitech.* 8: E12–E17.

Syukri Y., HannieFitriani., HeriantoPandapotan., dan bambangHernawan Nugroho. 2019. Formulation, Characterization, and Stability of Ibuprofen-Loaded Self-Nano Emulsifying Drug Delivery System(SNEDDS). *Indonesian Journal of Pharmacy*. Vol. 30 (2) 2019: 105 – 113.

Syukri Y., Martien R., Lukitaningsih E. and Nugroho A. E. 2018. Novel Self-Nano Emulsifying Drug Delivery System (SNEDDS) of andrographolide isolated from Andrographis paniculataNees: Characterization, in-vitro and in-vivo assessment. Journal of Drug Delivery Science and Technology, 47, 514–520.

Syukri, Y., Agung, E.N., Ronny, M., dan Endang, L. 2016. ValidasiPenetapan Kadar IsolatAndrografoliddariTanamanSambiloto (*Andrographis paniculataNees*) Menggunakan HPLC. *J. SainsFarmasi dan Klinis*.Vol. 2, No.4, Hal: 8-14.

Winarti, Lina., Suwaldi, Ronny Martien, dan Lukman Hakim. 2016. Formulation Of Self-Nanoemulsifying Drug Delivery System Of Bovine Serum Albumin Using Hlb (Hydrophilic-Lypophilic Balance) Approach. *Indonesian J. Pharm.* Vol. 27. No. 3 : 117 – 127.

Wirnarti, Suwaldi, Matin, Hakim. 2018. Formulation of Insulin Self Nanoemulsifying Drug Delivery System and Its In Vitro-In Vivo Study. *Indonesian J. Pharm*. Vol. 29, No. 3, Hal: 158-166.

Zhao, T., Maniglio, D., Chen, J., Chen, B., Motta, A., Migliaresi, C. 2015. Design and optimization of Self-NanoemulsifyingFormulations for Lipophilic Drugs. *Nanotechnology*. No. 26, Hal:125-130.