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INTRODUCTION Cod liver oil (CLO) is a food supplement extracted from the cod liver. Cod liver oil has long been used as medicine or as a functional food. Cod liver oil is a potential source of vitamin D, vitamin A, and omega fatty acids (eicosapentaenoic acid/EPA and docosahexaenoic acid/DHA)1. Cod liver oil can prevent heart disease by increasing the elasticity of blood vessels, lowering blood pressure, reducing lipid level, and increasing the HDL level2-4.

Cod liver oil can support the treatment of type II diabetes mellitus (T2DM) by increasing insulin sensitivity5. Other studies have shown that CLO has cytotoxic, neuroprotective, hepatoprotective, anti-ulcer, and anti-inflammatory activities. Cod liver oil can also help brain development for children's growth6,7. In oral use, CLO is generally developed as an Emulsion-based delivery system. In the oil in a water emulsion system, CLO is in a dispersed form that is coated or protected by water8,9. The emulsion form of CLO is further modified into a nanoemulsion form10,11. The advantage of the nanoemulsion system is has a small globule size (nano-scale) and increasing its absorption and bioavailability12.

However, the study that develops cod liver oil into another form of nanoemulsion system: The self-nanoemulsifying drug delivery system (SNEDDS), has not been carried out. In this study, CLO was developed in SNEDDS. The SNEDDS is a preconcentrated or anhydrous form of nanoemulsion, a mixture of oils, surfactants, and cosurfactants13. This system is expected to self-emulsify quickly in the aqueous stomach system and produces nano globules with a size of 20-200 nm. The advantages of SNEDDS over nanoemulsion are enhancing the physical and chemical stability of the formulation and the ability to fill them into unit dosage forms, such as soft/hard capsules, which improves their commercial viability and patient compliance14.

Several studies have been carried out to develop SNEDDS for lipophilic active compounds. The results show that SNEDDS can increase the absorption and bioavailability of active compounds in oral delivery15,16. This study aimed to develop SNEDDS of CLO for oral delivery. Physical and stability evaluations were carried out to the preparations. MATERIALS AND METHODS Materials The materials used in this study were COD (Lancida Hebar Technology), Cremophor® RH-40 (BASF), polyethylene glycol (PEG) 400 (Bratachem), and monopotassium phosphate/KH2PO4 (Merck).

The main instruments used in this study were gas chromatography-mass spectrometry/GC-MS (Shimadzu GCMS-QP2010 Ultra), magnetic stirrer (Thermolyne S131120-33Q), particle size analyzer/PSA (Beckman Coulter), spectrophotometer UV-Vis (Shimadzu UV mini-1240), sonicator (Branson), analytical balance (Mettler Toledo AL204), dan vortex mixer (Thermo Scientific). Methods The research was carried out in

several stages of the method as shown in Figure 1. / Figure 1. Research flow chart Miscibility study of oil and surfactant/co-surfactant The test was carried out by the miscibility study between CLO and surfactant/cosurfactant.

The surfactants used were Cremophor® RH-40 and Tween 80; the cosurfactant used was propylene glycol, Transcutol®, and PEG 400. Miscibility studies were performed by preparing 1 mL of the CLO in a test tube then added with surfactant/cosurfactant until a clear mixture was obtained. Stirring and observation were provided every time addition of 1 mL of surfactant/cosurfactant17. Optimization of surfactant and cosurfactant ratio for CLO-SNEDDS At this stage, the SNEDDS formula was optimized by varying the concentration of surfactants and cosurfactants at a ratio of oil and Smix (surfactant + cosurfactant) was 1 : 9.

Comparison of surfactant and cosurfactant used was 3 : 1; 2 : 1; and 3 : 2. The SNEDDS prepared by mixing oil, surfactant, and co-surfactant at a temperature of 40°C, then stirred until homogeneous. The CLO-SNEDDS preparations were characterized by the percent transmittance test18. Physical evaluation of CLO-SNEDDS Percent transmittance – As much as 1 mL of each SNEDDS preparation was diluted up to 100 mL using distilled water. Measurement was carried out at a wavelength of 650 nm using a UV-Vis spectrophotometer. Distilled water was used as blank19. Dispersibility test – A dispersibility test was performed using a type II dissolution apparatus.

As much as 1 mL of CLO-SNEDDS was added to the 250 mL of distilled water and stirred at 37±0.5ºC at 50 RPM. Visual observation was carried out according to the emulsification grade, as shown in Table I17,20. Table I. Grade of dispersibility Grade _Specification _ _A _Rapidly forming emulsion, with a clear or bluish appearance _ _B _Rapidly forming with slightly less clear emulsion, with a bluish-white appearance _ _C _Fine milky emulsion _ _D _Slow to emulsify, dull, greyish white emulsion having a slightly oily appearance _ _E _Poor or minimal emulsification with large oil droplets on the surface _ _ Robustness to dilution test – Robustness tests were carried out by diluting 1 mL of each CLO-SNEDDS with 100 mL of distilled water, 0.1 N HCl, and phosphate buffer pH 6.8. The mixtures were stirred using a magnetic stirrer and then stored for 24 hours to observe any physical change of system, including phase separation and precipitation21,22.

Determination of droplet size and polydispersity index – Droplet size and polydispersity index were determined using a PSA. The test was carried out on the diluted CLO-SNEDDS. A total of 100 µL of CLO-SNEDDS was diluted with 50 mL of distilled water23. Thermodynamic stability study – The stability was evaluated by centrifugation, a heating-cooling cycle, and a freeze-thaw cycle. Centrifugation tests were carried out at

3,500 RPM for 30 minutes. At heating cooling tests, CLO-SNEDDS were stored at two different temperatures (45 and 4ºC). The tests were carried out in three cycles with storage at each temperature for not less than 48 hours.

The freeze-thaw tests were carried out at two different temperatures: -21 and 25ºC, conducted for three cycles with storage at each temperature for not less than 48 hours24. RESULTS AND DISCUSSION The SNEDDS was known to be one of the nano-based drug delivery systems suitable for the delivery of hydrophilic or lipophilic compounds. The CLO delivery in SNEDDS was expected to increase its dissolution, absorption, and bioavailability. The SNEDDS was prepared by mixing oil, surfactants, and cosurfactants without adding water, so SNEDDS was also known as a preconcentrated or anhydrous form of nanoemulsion13.

The SNEDDS would form a nanoemulsion system spontaneously by gastrointestinal (GI) peristaltic. Miscibility of oil with surfactants and cosurfactants was important for the effectiveness of SNEDDS formation. The result showed that CLO has good miscibility property with Cremophor®RH-40 and PEG 400. Surfactants and cosurfactants in the nanoemulsion were used to form a good and flexible interfacial film and decrease surface tension value to almost zero and support the spontaneous formation of nano globules25, as shown in Table II. Table II.

Result of CLO miscibility study Type _Substance _Ratio Miscibility _ _Surfactant _Tween 80 _1 : 6 _ _ _Cremophor®RH-40 _1 : 5 _ _Cosurfactant _PEG 400 _1 : 4 _ _ _Propylene glycol _1 : 6 _ _ _Trancutol _1 : 7 _ _ The first step of the optimization formula was to determine the optimum ratio of the surfactant and the cosurfactant. Surfactants and cosurfactants used were Cremophor®RH-40 and PEG 400. The percent transmittance test was used as the initial screening method to select the optimum ratio of surfactants and cosurfactants. The result showed that formula F2 (2 : 1) had a percent transmittance value closest to 100%, as shown in Table III.

Therefore, the 2 : 1 ratio of surfactant and cosurfactant was used for the following research step. Table III. Optimization result of ratio surfactant and cosurfactant Formula _Oil : Smix _S : CoS _%transmittance _ _F1 _1 : 9 _3 : 1 _98.00±0.01 _ _F2 _1 : 9 _2 : 1 _99.60±0.06 _ _F3 _1 : 9 _3 : 2 _98.70±0.26 _ _ The next step was carried out to determine the optimum ratio of oil and smix using the percent transmittance test as an initial screening. The result showed that F2A, F2B, F2C, F2D, and F2E meet the percent transmittance requirement for SNEDDS (>90%), as shown in Table IV26. Therefore, the five formulas of CLO-SNEDDS were continued for further evaluation. Table IV.

Optimization result of ratio oil and smix Formula _Oil : Smix _S : CoS _%transmittance _

_F2A _1 : 9 _2 : 1 _99.60±0.06 _ _F2B _1 : 8 _2 : 1 _98.80±0.05 _ _F2C _1 : 7 _2 : 1 _97.53±0.32 _ _F2D _1 : 6 _2 : 1 _97.90±0.85 _ _F2E _1 : 5 _2 : 1 _95.76±0.25 _ _F2F _1 : 4 _2 : 1 _39.00±3.21 _ _ Dispersibility tests, robustness tests, and thermodynamic stability tests were carried out on F2A, F2B, F2C, F2D, and F2E, as shown in Table V. The objective of dispersibility tests was to determine the ability of SNEDDS to disperse entirely and quickly when subjected to dilution under mild agitation.

The test was carried out by visual observation, and then the grade was determined according to Table I. The SNEDDS preparations must exhibit grade A and B characteristics on the dispersibility test. The CLO-SNEDDS (F2A-F2E) could quickly produce a clear emulsion (nanoemulsion) system when diluted in water so that it was categorized as grade A in the dispersibility test. The ability of SNEDDS to form nanoemulsion spontaneously when diluted in water occurs due to the presence of surfactants and cosurfactants that were capable of forming an interfacial layer in the nano globules system27.

The purpose of the robustness test was to determine the system's stability after the SNEDDS preparation is diluted in three types of solvents with different pH values, like in the digestive tract conditions. The solvents used were distilled water medium, HCl 0.1 N (stomach condition), and a phosphate buffer pH 6.8 (small intestine condition). The results showed that CLO-SNEDDS was able to form a stable system after dilution, using the three types of solvents, characterized by the absence of phase separation and precipitation28.

The subsequent study was the thermodynamic stability test, carried out by three types of tests (centrifugation, heating cooling, and freeze-thaw). The results showed that CLO-SNEDDS (F2A, F2B, F2C, and F2D) had good stability marked by not occurring phase separation and sedimentation. This indicates that the CLO-SNEDDS (F2A, F2B, F2C, and F2D) had good kinetic and thermodynamic stability. The F2E formula shows instability in thermodynamic testing, which could occur because the number of surfactants and cosurfactants was insufficient to form a stable nanoemulsion system29.

Based on the dispersibility, robustness, and thermodynamic test, it could be concluded that CLO-SNEDDS (F2A, F2B, F2C, and F2D) had good physical characteristics. Formula F2D with a ratio of oil and smix 1 : 6 was chosen as the final formula (Figure 2). The formula was chosen because it still produces SNEDDS with good physical characteristics, with the least amount of smix. This was expected can minimize the risk of negative effects of surfactants and cosurfactants for oral administration.

Table V. Dispersibility, robustness, and thermodynamic stability tests results Evaluation _F2A _F2B _F2C _F2D _F2E _ _Dispersibility _Emulsification time (s) _35.30±0.55 _33.83±0.32 _34.30±0.61 _35.86±2.52 _43.73±0.38 _ _ _Appearance _Clear _Clear _Clear _Clear _Clear _ _ _Grade _A _A _A _A _A _ _Robustness _Distilled water _Stable _Stable _Stable _Stable _Stable _ _ _HCl 0.1 N _Stable _Stable _Stable _Stable _Stable _ _ _Phosphate buffer pH 6.8

_Stable _Stable _Stable _Stable _Stable _ _Thermodynamic _Centrifugation _Stable _Stable _Stable _Stable _Stable _ _ _Heating cooling _Stable _Stable _Stable _Stable _Stable _ _ _Freeze-thaw _Stable _Stable _Stable _Stable _Unstable _ _Conclusion _Qualify _Qualify _Qualify _Qualify _Unqualify _ _

The F2D formula was further evaluated by determining an average of globules size and polydispersity index (PDI) of the nanoemulsion system. The results of globule size analysis using a particle size analyzer showed that CLO-SNEDDS (F2D) was able to form a nanoemulsion system after dilution with a globule size of 125 nm and a PDI value of 0.515.

These results followed the globule size requirements for SNEDDS (20-200 nm) and PDI of <0.730. / Figure 2. The CLO-SNEDDS Formula F2D CONCLUSION The CLO-SNEDDS preparation with the ratio of a surfactant and cosurfactant (2 : 1) and a ratio of oil and smix (1 : 6) had good physical characteristics based on %transmittance, dispersibility, robustness, and thermodynamic stability studies. The CLO-SNEDDS (F2D) preparation was able to produce a nanoemulsion system after dilution with a globule size of 125 nm and a PDI of 0.515.

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