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Formulation, Characterization and Stability of Ibuprofen-Loaded Self-Nano Emulsifying Drug Delivery System (SNEDDS)

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ABSTRACT

Ibuprofen is a poorly water-soluble drug with analgesic, antipyretic and anti-inflammatory effects. Self-Nano Emulsifying Drug Delivery System (SNEDDS) formulation is a solution to improve the solubility and bioavailability of ibuprofen. This research purposed to perform a formulation, characterization, and stability studies of ibuprofen-loaded Self-Nano Emulsifying Drug Delivery System (SNEDDS). Screening of ibuprofen SNEDDS was prepared by ternary diagrams for the chosen co-surfactants, surfactants, and oil. The following was characterizations of droplet size, zeta potential, and clarity. The solubility test for the determination of co-surfactant, surfactant, and oil obtained Propylene glycol monocaprylate (Capryol-90), Polysorbate 20 (Tween 20) and PEG 400. The screening of SNEDDS showed nine formulas (compositions) in the range concentration of Propylene glycol monocaprylate (1-3mL), Polysorbate 20 (4-8mL), and PEG 400 (1-3mL). The composition of Propylene glycol monocaprylate (1-2mL), Polysorbate 20 (5-8mL) and PEG 400 (1-3mL) passed the thermodynamic stability test. The test of robustness to dilution and stability study indicated that the formula with Propylene glycol monocaprylate, Polysorbate 20 and PEG 400 with the ratio of 1: 8: 1 and 1: 7: 2 was more stable. In conclusion, the stable ibuprofen SNEDDS could be prepared with Propylene glycol monocaprylate, Polysorbate 20, and PEG 400.

Keywords: Ibuprofen, SNEDDS, characterization, stability

INTRODUCTION

Well-known as an antipyretic, analgesic, and non-steroidal drug for anti-inflammation, ibuprofen is useful for fever, its symptoms, and rheumatoid arthritis and osteoarthritis signs. Due to its low solubility and high permeability, ibuprofen is categorized as BCS class II (Álvarez et al., 2011; Deng et al., 2018). The solubility and bioavailability of ibuprofen should be increased to improve therapy effectiveness by developing the drug delivery system. Among the approaches to enhance dissolution characteristics of water-insoluble drugs are cyclodextrin complexation, particle-size reduction, crystal modification, and self-emulsification (Syukri *et al.,* 2015). Meanwhile, self-micro emulsifying, self-emulsifying, and liposomes are among the most widely-developed methods to improve solubility and bioavailability of orally-given drugs in lipid-based formulations (Shafiq-un-Nabi *et al*., 2007).

Some common permeability enhancers include lipid-based excipients, such as fatty acids and glycerides as well as ionic and non-ionic surfactants. Such excipients can increase membrane fluidity or open tight junctions (Kuentz, 2012). The entry of some highly lipophilic drugs and long-chain triglycerides (TG) into the portal circulation, however, is reduced depending on their entry into the lymphatic circulation. Hence, lymphatic- rather than portal-transported drugs can avoid the first-pass metabolism by the liver that in turn enhances the concentration of drug in lymph ducts and nodes where therapeutic drug action exists (Yáñez, *et al*., 2011).

Self-Nano Emulsifying Drug Delivery System (SNEDDS) becomes one of these simplified approaches to enhance drug solubility and dissolution. In SNEDDS, a thermodynamically stable oil-in-water emulsion is formed spontaneously when an isotropic mixture of drug, oil, surfactant, and co-surfactant enters the aqueous phase under gentle agitation conditions resembling those to be encountered in the GI tract (Dash, *et al*., 2015a; Sriamornsak, *et al*., 2015).

Table I. Composition of oil, surfactant, and co-surfactant for construction of ternary diagrams

Composition	Oil (mL)	Surfactant (mL)	Co-surfactant (mL)
C1	1	8	1
C2	1	7	2
C3	1	6	3
C4	2	7	1
C5	2	6	2
C6	2	5	3
C7	3	6	1
C8	3	5	2
C9	3	4	3
C10	4	5	1
C11	4	4	2
C12	4	3	3
C13	5	4	1
C14	5	3	2
C15	5	2	3

Studies show that SNEDDS improve the solubility, dissolution, and bioavailability of drugs with poor solubility in water, including lovastatin (Yadava, *et al*., 2015), glipizide (Agrawal, *et al*., 2015), nisoldipine (Nekkanti *et al*., 2016), and anti-cancer genistein (Shehata, *et al*., 2016). The SNEDDS of nystatin was found to be able to improve dissolution as well as oral antifungal efficacy (Kassem *et al*., 2016). Another study revealed that, compared to the plain formulation, the andrographolide isolated from *Andrographis paniculata* plant in the form of SNEDDS formulation provided better bioavailability and dissolution (Syukri *et al*., 2018).

Ibuprofen is currently marketed commercially in tablet and capsule dosage forms. Both forms demonstrate low, erratic oral bioavailability because of their poor solubility and dissolution (Shahba *et al*., 2012). Ibuprofen can be formulated into SNEDDS to enhance absorption as well as avoid the first-pass metabolism. This study aimed to prepare, characterize, and examine the stability of ibuprofen in SNEDDS formulation.

MATERIALS AND METHODS

Materials

Ibuprofen was bought from Cross Chem. Polysorbate 80 (Tween 80), Polysorbate 20 (Tween 20), oleic acid, olive oil, polyethylene glycol (PEG) 400, and propylene glycol were obtained from Brataco Indonesia Ltd. Labrasol, Propylene glycol monocaprylate (Capryol 90), and Labrafil M1944CS were gifted by Gattefose (France), Cremophor RH 40 from BASF (Indonesia), and Myritol 318 from Phapros Indonesia Ltd.

Solubility test to select oil, surfactant, and co-surfactant

The shake-flask method was used to determine ibuprofen solubility in different oil, surfactant, and co-surfactant concentrations. Extra ibuprofen was added into each vehicle and mixed in the vortex (Heidolph Reax Top, Germany) for 10min followed by a 48-h mixture shaking at 37°C in a shaking water bath with thermostatically-controlled condition from Memmert WNE 45, Germany. After reaching stability for 24h, the mixture was put in centrifugation from Hettich Mikro 22R, Germany at 6000 rpm for 10min. The supernatant was collected, and concentration was calculated employing UV-Vis spectrophotometer (Shimadzu UV 1800, Japan) at a wavelength of 223nm.

Construction of ternary diagrams

The selected co-surfactants, surfactants, and oils obtained from the solubility study were plotted in a ternary diagram without incorporation of the drug; one side of the triangle represented each selection for identification of the region of self-nano emulsifying (Kassem *et al.,* 2016). A set of oil, surfactant, and co-surfactant mixtures was provided with composition of 1-5; 2-8; and 1-3mL, respectively. The composition of oil, surfactant, and co-surfactant for ternary phase diagrams (Table I).

The assessment was conducted for the nanoemulsion formed after each formulation (compositions) was given 100-fold dilution in aquabidest. The clarity, zeta potential, and droplet size of resulted dispersions were then measured using particle size analyzer from Horiba SZ 100; Japan and UV-Vis spectrophotometer from Shimadzu UV 1800; Japan at a wavelength of 650nm. Dispersions remained up to standard as long as the droplet size was not more than 200nm. Then, the ternary phase diagrams of co-surfactant, surfactant, and oil were plotted.

Preparation of ibuprofen-loaded SNEDDS

As much as 5mL mixture of oil, surfactant, and co-surfactant was used to dissolve Ibuprofen (200mg) for preparation of SNEDDS formulation. Dissolution was conducted in ultrasonic homogenizer (model 300 V/T, USA) for solubilization to obtain clear solution. The mixture was then stored at ambient temperature for future use.

Ibuprofen-loaded SNEDDS characterization

Percentage of clarity (transmittance) studies

Purified water was used to dilute the ibuprofen-loaded SNEDDS formulations 100 times. The clarity (%) was determined through UV–Vis spectrophotometer from Shimadzu UV 1800, Japan at a wavelength of 650nm (Nagi *et al.,* 2017), and the blank was purified water.

Zeta potential and droplet size

The zeta potential and droplet size of SNEDDS were measured by particle size analyzer from Horiba SZ 100; Japan followed by dilution of SNEDDS samples in purified water for 100 times.

Thermodynamic stability studies

Centrifugation study

Centrifugation of the formulations was conducted at 5000rpm for 30min followed by visual observation to confirm instability, including cracking, phase separation, drug precipitation, or creaming. The formulations without any signs of weakness were selected for the heating-cooling test.

Heating and cooling cycle

The heating and cooling cycle was done in three repetitions at a temperature range of 4°C-45°C and a minimum of 48-hour storage. The period was conducted in one repetition for 8h at a temperature of 4°C and 8h at a temperature of 45°C. The formulations that survived such condition without signs of creaming and phase separation were selected for the freezing and thawing cycle.

Freezing and thawing cycle

The freeze and thaw test was conducted 3 times between −20°C and +25°C temperature with a minimum of 48 hours storage duration. The period was held in one repetition for 8h at a temperature of 4°C and 8h at a temperature of 45°C. Further analysis was performed for the formulations surviving such thermodynamic stress test (Agrawal *et al.,* 2015; Kassem *et al.,* 2016).

Robustness to dilution

Robustness to dilution significantly affects the phase separation of a spontaneously emulsifying system. A system with spontaneous emulsification attempts to emulate *in vivo* conditions where formulations dilute g radually. Dilution of ibuprofen-loaded SNEDDS in purified water was conducted for 25, 50, 100, and 250 times. The droplet size was then evaluated to select the compositions with consistent droplet size after dilution in different dispersion media to proceed with in-vitro assay (Balakumar, *et al*., 2013; Elnaggar *et al*., 2009). Milky-like composition was let rest while the transparent one was observed to determine the droplet size.

Stability study

To assess the accelerated stability, the optimized ibuprofen-loaded SNEDDS was stored in sealed amber glass vials for four weeks at a high temperature (40°±2°C) and relative humidity (75±5%). The changes over time in the physical characteristics, such as drug droplet size and clarity, were monitored to evaluate the physical stability of the optimized composition. The one-way ANOVA was used for comparing droplet size changes every week.

RESULTS AND DISCUSSION

Solubility test to select oil, surfactant, and co-surfactant

Drug solubility in vehicles is essential to determine formulation stability because it is commonly found that many formulations precipitate before experiencing in situ solubilization. A combination of oil, surfactant, and co-surfactant produce a self-emulsifying mixture. Such mixture should provide a transparent and

Table II. Solubility test of ibuprofen in varied oils, surfactants, and co-surfactants (n=3)

Vehicle	Material	Solubility (mg/mL)
Oil	Propylene glycol monocaprylate	64.53±0.19
	Myriol 318	13.33±0.01
	Oleic acid	60.67±0.09
	Olive oil	9.53±0.01
Surfactant	Labrasol	83.18±0.74
	Labrafil M1944CS	26.18±0.02
	Polysorbate 20	97.71±0.16
	Polysorbate 80	73.10±0.16
	Cremophor RH 40	36.55±0.14
Co-surfactant	PEG 400	35.02±0.08
	Propylene glycol	32.34±0.09

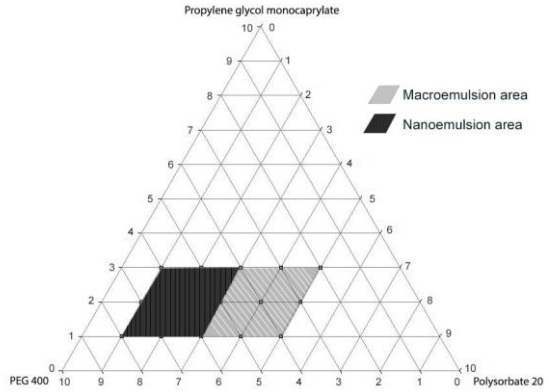

Figure 1. Ternary diagram of ibuprofen showing the region of o/w nanoemulsion in Propylene glycol monocaprylate, Polysorbate 20 and PEG 400 as the oil, surfactant and co-surfactant

isotropic liquid at a room temperature with fine solubility to integrate a dose of drug in a minimum volume of mixture (Kassem *et al*., 2016)

Oils, surfactants, and co-surfactants for SNEDDS formulations are selected according to the highest solubility of ibuprofen in each of them. Besides, the selection is also based on the ability of the mixtures to form nanoemulsion when diluted 100 times with aquabidest. The results of ibuprofen solubility test in different sets of oil, surfactant, and co-surfactant (Table II).

Table II indicates that the oil phase, Propylene glycol monocaprylate, had the best solubilizing capacity (64.53±0.19), and for the same reason Polysorbate 20 (97.71±0.16) and PEG 400 (35.02±0.08) were chosen as the best surfactant and co-surfactant.

Construction of ternary diagrams

The self-nano emulsifying area is determined using a ternary phase diagram, which is also utilized to assess oil, surfactant, and co-surfactant concentrations for stable SNEDDS. Figure 1 illustrated the ternary phase diagram of formulations with a carrier consisting of Propylene glycol monocaprylate, Polysorbate 20, and PEG 400.

The shaded/dark area marks the regions of nanoemulsion and macroemulsion. The formulation with 1-3mL of Propylene glycol monocaprylate (oil), 4-8mL of Polysorbate 20 (surfactant), and 1-3mL of PEG 400 (co-surfactant) has produced transparent nanoemulsion without sedimentation. In such region, spontaneous self-emulsification results in dispersion that is thermodynamically stable. Meanwhile, the composition having 4-5mL Propylene glycol monocaprylate produces milky-like or crude macroemulsion (Kassem *et al.,* 2016; Parmar *et al*., 2011) in which no self-emulsification occurs.

Preparation of ibuprofen-loaded SNEDDS

The inexistence of precipitation and phase separation for 48h indicates that ibuprofen

Table III. Droplet size, zeta potential, clarity, and description of ibuprofen-loaded SNEDDS as an effect of various oil, surfactant and co-surfactant concentrations (n=3)

Composi-tion	Droplet size (nm)	Zeta potential (mV)	Clarity (%)	Description
C1	12.63±1.68	-24.37±0.29	99.98±0.01	Transparent
C2	12.00± 2.60	-37.37±0.64	99.83±0.01	Transparent
C3	15.20±1.70	-24.55±0.29	99.48±0.04	Transparent
C4	15.00±0.10	-31.00±0.52	99.98±0.01	Transparent
C5	20.97±1.72	-41.53±0.58	99.86±0.01	Transparent
C6	15.76±1.58	-34.83±0.68	100.00±0.00	Transparent
C7	70.53±3.43	-22.03±0.55	100.00±0.00	Transparent
C8	41.33±3.23	-18.73±0.51	99.71±0.02	Transparent
C9	47.60±1.73	-37.90±0.61	99.41±0.01	Transparent
C10	321.67±12.00	-17.40±0.36	33.16±0.02	Cloudy
C11	NA	-30.40±0.17	33.67±0.01	Cloudy
C12	NA	-36.10±0.00	26.77±0.02	Cloudy
C13	498.70±19.41	-46.97±0.29	13.12±0.00	Cloudy
C14	NA	-63.33±0.40	20.29 ±0.01	Cloudy
C15	NA	-27.20±0.35	16.77±0.11	Cloudy

NA: Not Available (Droplet size was undetected

dissolves in SNEDDS. In this study, ibuprofen was stable in the SNEDDS formulation with 200mg/5mL drug loading. The results of the characterization by calculating the droplet size, clarity, and zeta potential (Table III).

Droplet size

Range of droplet size of C1 to C9 is between 12.00±2.60nm and 70.53±3.43nm. C1 to C9 are defined as nanoemulsion because they form a clear dispersion, and since C10 to C15 have a milky/cloudy appearance, they are categorized as macroemulsion (Table III). Macroemulsion (C10 to C15) with the larger droplet size was not detected the droplet size using particle size analyzer (Horiba SZ 100) because the equipment only covers the droplet size less than 1000nm. Nanoemulsion size has a droplet size of less than 200nm (Balakumar, *et al.,* 2013). Oil phase in high concentration will produce a large droplet size.

Meanwhile, a large number of cases indicate that increasing surfactant concentration will decrease droplet size because surfactant molecule localization on the interface of oil-water will stabilize oil droplets. High surfactant concentration will improve the penetration of water into oil droplets that lead to the breakdown of oil droplets and formation of larger droplets (Balakumar, *et al.,* 2013). Small co-surfactant molecules will enhance surfactant function in emulsification as they penetrate the film of surfactant on the interface of oil-water, and small droplet size will reduce interfacial tension and improve the spontaneous process of emulsification. Since the free energy required to produce tiny droplet size in a system with self-emulsification is lacking, oil nanoemulsion will be spontaneously formed in water (Heshmati*, et al.,* 2018).

Clarity

Nanoemulsion is a water-oil-surfactant system, which forms a complete mixture that is optically isotropic and a solution that is thermodynamically stable. Clarity is measured in a clarity test to maintain the isotropic range. In such an analysis, the dispersion-system transparent level will be obtained from water-solution dispersion absorbance at 650nm wavelength. Table 3 showed Composition 1 (C1) to 9 (C9) have clear dispersion with almost 100% clarity, indicating fulfilment of the nanoemulsion requirement.

On the other hand, C10 to C15 produced a milky-like solution with a clarity value of less than 34%. Compositions with less clarity have a more significant droplet size and result in milky-like macroemulsion. The data showed that aqueous dispersion having low transparency is usually cloudy, and globules of oil have larger dispersion. Nanoemulsion clarity indicates self-emulsification efficacy by identifying dispersion stability in a reproducible or short period.

Table IV. Thermodynamic stability studies of ibuprofen-loaded SNEDDS as an effect of various oil, surfactant, and co-surfactant concentrations (n=3)

Composition	Centrifugation	Heating and cooling cycle	Freezing and thawing cycle
C1	Allowed	Allowed	Allowed
C2	Allowed	Allowed	Allowed
C3	Allowed	Allowed	Allowed
C4	Allowed	Allowed	Allowed
C5	Allowed	Allowed	Allowed
C6	Allowed	Allowed	Allowed
C7	Not Allowed	Not Allowed	Not Allowed
C8	Not Allowed	Not Allowed	Not Allowed
C9	Not Allowed	Not Allowed	Not Allowed

Table V. Robustness to dilution studies of ibuprofen-loaded SNEDDS (n=3)

Composition	Droplet size (nm)			
	1:25	1:50	1:100	1:250
C1	11.30±0.17	11.00±0.62	12.63±1.68	10,50±0.40
C2	11.43±0.21	13.43±2.06	12.00±2.60	10.47±1.16
C3	11.60 ±0.27	12.13±0.84	15.20±1.70	23.93±1.72
C4	251.93±5.85	310.80±8.25	15.00±0.10	65.17±2.21
C5	332.10±6.07	268.13±5.79	20.97±1.72	53.43±1.10
C6	NA	NA	15.76±1.58	46.50±5.60

NA: Not Available (Droplet size was undetected)

Zeta potential

A high value of zeta potential has better stability since there is resistance to aggregation of the formulation. Zeta potential of less than -30mV and more than +30mV is generally appropriate for the stability of a system (Dash, *et al.,* 2015b). The nanoemulsion area of C1, C3, C7 and C8 produces a zeta potential of more than -30mV (-24.37±0.2, -24.55±0.29, -22.03±0.55, and -18.73±0.51mV, correspondingly), whereas the others result in lower than -30mV zeta potential (Table III). It means C1, C3, C7 and C8 fail to meet the criteria of zeta potential value for a system stability. A negative value of zeta potential indicates the existence of free fatty acid, surfactant, and co-surfactant in the formulation. It also shows the considerable force of repulsion between droplets to prevent aggregation (Syukri *et al.,* 2018).

Thermodynamic stability test

Kinetic stability is crucial for differentiating nanoemulsion from the emulsion, showing the systems' thermodynamic stability. Nanoemulsion system of SNEDDS is formed following in situ solubilization, and creaming, cracking, or precipitation can be avoided when stability is achieved (Senapati, *et al.,* 2016). For formulations C1 to C9, the study of thermodynamic stability performed include heating and cooling cycle; centrifugation; and freezing and thawing cycle, and then the results (Table IV).

C1 to C6 have no signs of phase separation, turbidity, or drug precipitation (Table IV). Therefore, they are eligible for robustness to dilution test. C7, C8 and C9 did not show a good thermodynamically stability test because these formulae contain a larger of oil compositions. Usually, a larger of the oil composition the droplet size the larger. These conditions tend to cause to the instability system.

Robustness to dilution

To emulate an in vivo state, SNEDDS compositions are diluted for 25, 50, 100, and 250 times in media. After the dilution process, emulsion uniformity in SNEDDS compositions should remain (Elnaggar et al., 2009). Robustness to dilution test guarantees SNEDDS emulsion uniformity in various frequencies of dilution (Table V). Ibuprofen-loaded SNEDDS dilution is conducted 25-, 50-, 100-, and 250-fold using aquabidest, and droplet size is evaluated.

Table VI. The stability studies optimized ibuprofen-loading SNEDDS formulation (n = 3)

Week to	C1		C2	
	Droplet size	Clarity	Droplet size	Clarity
0	12.63±1.68	99.98±0.01	12.00±2.60	99.83±0.01
1	12.70±1.45	97.87±0.00	12.67±1.33	99.04±0.01
2	14.63±0.31	97.84±0.00	14.67±1.53	99.01±0.02
3	14.47±1.89	99.93±0.00	13.57±2.02	99.47±0.02
4	13.63±1.41	99.89±0.01	13.23±0.40	99.73±0.00

C1 and C2 with Propylene glycol monocaprylate, Polysorbate 20, and PEG 400 at a ratio of 1: 8: 1 and 1: 7: 2, correspondingly, become the most stable compositions since, after dilution, they have a steady droplet size and are then eligible for accelerated stability test (Table V). A regular droplet size after dilutions shows the possible uniformity of *in vivo* drug release. Thus, the preparations might have the capability of anticipating gradual dilution in the GI tract (Syukri *et al.,* 2018).

Stability study

The results of stability studies to optimize ibuprofen-loaded SNEDDS formulations C1 and C2 (Table VI). One-way ANOVA showed that no significant difference ($p<0.05$) the droplet size during storage for 4-week. Both preparations are physically stable, and there are no apparent changes in physical appearance, including the droplet size and clarity, during the 4-week storage at a higher temperature (40°C±2°C) and relative humidity (75±5%). It is then clear that stable preparations are found in the ibuprofen-loaded SNEDDS formulations with Propylene glycol monocaprylate, Polysorbate 20 and PEG 400 as the oil, surfactant and co-surfactant at a ratio of 1: 8: 1 (C1) and 1: 7: 2 (C2).

CONCLUSION

Ibuprofen was prepared in SNEDDS formulation with Propylene glycol monocaprylate, Polysorbate 20, and PEG 400 as the oil, surfactant, and co-surfactant, respectively. Nine compositions with the concentration of Propylene glycol monocaprylate (1-3mL), Polysorbate 20 (4-8mL), and PEG 400 (1-3mL) were the optimal formulation to form a nanoemulsion. The formulation with the ratio of 1: 8: 1 and 1: 7: 2 of Propylene glycol monocaprylate, Polysorbate 20 and PEG 400 were selected compositions after the study of thermodynamic stability, robustness to dilution, and accelerated stability. These evaluations showed the droplet size between 10.50±0.40-13.43±2.06nm after dilution and 12.00±2.60-19.67±1.53nm after accelerated stability studies.

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