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Development Liquid and Solid Self Microemulsifying Drug Delivery System (L-SMEDDS and S-SMEDDS) Containing Black Seed Oil (*Nigella sativa* L.)

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Authors' contributions

This work was carried out in collaboration among all authors. Authors SEP and SSM designed the study and performed data analysis for L-SEMDDS and wrote the draft of the manuscript. Author FD performed data analysis for S-SMEDDS. All authors read and approved the final manuscript.

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ABSTRACT

Aims: The aims of this research were to develop and characterize liquid and solid micro emulsifying drug delivery system (L-SMEDDS and S-SMEDDS) containing black seed oil.
Study Design: Experimental Research Design (laboratory).
Place and Duration of Study: The study was conducted at research laboratory of pharmacy department UNISBA, between August 2018- August 2019.
Methodology: The optimization of L-SMEDDS was carried out using various comparison of oil, surfactant, and cosurfactant. All formulations were evaluated for percent transmittance, emulsification time, dispersibility, robustness, and thermodynamic stability. The best formula of L-SMEDSS was evaluated for globule size distribution and converted to S-SMEDDS by spray drying method using aerosil 200 as adsorbent. S-SMEDDS were evaluated for organoleptic, flowability, compressibility, emulsification time, dispersibility, robustness and surface morphology.
Results: The best formula of L-SMEDDS contains tween 80 as a surfactant and PEG 400 as cosurfactant (2:1) with a ratio of oil and Smix (2:8). The L-SMEDDS preparation meets the requirement of percent transmittance (95.77%), emulsification time (37.67 seconds), grade A of dispersibility, stable of robustness and thermodynamics study with the average of globule size was

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231 nm. S-SMEDDS preparation meets the requirement of the moisture content, flowability, emulsification time, and stable on robustness testing with a spherical shape.
Conclusion: L-SMEDDS and S-SMEDDS of black seed oil have been developed and have good physical characteristics and stability.

Keywords: Black seed oil; L-SMEDDS; S-SMEDDS; spray drying.

1. INTRODUCTION

Nigella sativa L known as black cumin and black seed that used medicinally for hundred years and considered as the greatest forms of healing medicine in Islamic literature [1]. Many kinds of research have been conducted to explore the pharmacological activities of the seeds and also the oil. The results showed that black seed oil has anti-inflammatory, anticancer, analgesic, antihypertensive, antimicrobial, antifungal, anthelmintic, hepatoprotective, diuretic, bronchodilator, gastroprotective and antidiabetic activities [2,3].

The black seed oil has a hydrophobic property which causes low oral bioavailability and limited therapeutic effects [4]. One formulation strategy that can enhance the solubility and bioavailability of a hydrophobic drug is a self-microemulsifying drug delivery system (SMEDDS). SMEDDS is an isotropic mixture of oil, surfactant, and cosurfactant which can form fine oil in water emulsion upon mild agitation followed with dilution in aqueous media such as GI (Gastrointestinal) fluids with globule size less than 250 nm [5]. The previous study showed that a self-emulsifying system could increase oral bioavailability (Cmax value/maximum concentration) of zedoary essential oil 2.5 times compared with pure oil. In SMEDDS formulation, the oil will form a very small droplet at gastrointestinal and facilitate the dissolution and absorption process [6].

Solid SMEDDS is a drug delivery system that combines the advantage of L-SMEDDS with solid dosage forms related to the stability problem of liquid form. S-SMEDDS developed by incorporating liquid SMEDDS into solid pharmaceutical excipient (adsorbent). Adsorbents must have good capacity to adsorb liquid with highly porous. The example of adsorbent that commonly used in S-SMEDDS formulation is aerosil 200. S-SMEDDS formation could be carried out by spray drying, freeze-drying, solid carriers, melt extrusion, supercritical fluid, high-pressure homogenization, and melt granulation. The resulting powder can be directly inserted into a hard gelatine capsule or added another excipient to convert into tablets [7,8].

The objectives of this research were to develop and characterize liquid and solid SMEDDS containing black seed oil. S-SMEDDS formulation was carried out by the spray drying method using aerosol 200 as adsorbent. Black seed oil acts as oil phase and also as an active ingredient with various pharmacological activities.

2. MATERIALS AND METHODS

2.1 Materials

Black seed oil was gifted by PT Lantabura International Indonesia. Tween 80, PEG 400, ethanol were purchased from PT. Bratachem, Indonesia. Vortex (Thermo Scientific), sonicator bath (Bransonic CPX2800H-E), electronic balance (Mettler Toledo AL 204), spectrophotometer UV-Vis (Shimadzu-UV mini-1240), dissolution tester (Vanguard), moisture analytical balance (Mettler Toledo MJ33), spray dryer (Buchi 190 Mini Spray Dryer), Particle Size Analyzer (PSA) (Beckman Coulter), and Scanning Electron Microscopy (SEM) were used in this study.

2.2 Formulation L-SMEDDS Black Seed Oil

L-SMEDDS was prepared by various comparison of surfactant and cosurfactant, and comparison of oil and Smix (surfactant+cosurfactant) (Table 1). L-SMEDDS were prepared by mixing oil, surfactant and cosurfactant, heated at 40^{o}C, then homogenized using vortex mixer. As the initial screening, percent transmittance of each preparation was determined using spectrophotometer UV/Vis [9,10].

2.3 Physical evaluation of L-SMEDDS

2.3.1 Percent transmittance

1 ml of L-SMEDDS were dissolved in 100 mL of distilled water and then percent transmittance

values were determined by spectrophotometer UV at 650 nm using distilled water as a blank [11].

2.3.2 Dispersibility and emulsification time

1 mL of SMEDDS was added into 250 ml of distilled water in the type II dissolution apparatus (37 ± 0.5°C, 60 rpm). The emulsification time and the appearance of emulsion formed were observed visually. The in vitro emulsification performance of SMEDDS were evaluated using the following grading system [12].

Grade A: Rapidly forming emulsion having a clear or bluish appearance
Grade B: Rapidly forming, slightly less clear emulsion, translucent bluish appearance
Grade C: Fine milky emulsion forming within 2 minutes
Grade D: Slow forming (>2 minutes), grayish-white emulsion, having a slightly oily appearance
Grade E: Exhibiting poor emulsification, with an oily appearance.

2.3.3 Robustness to dilution

1 mL of the formula was diluted (100 times) in three different media, distilled water, HCl 0.1 N and phosphate buffer pH 6.8. The mixture was stirred at 100 rpm (37 ± 0.5°C). The stability of the emulsion formed was observed after 24 hours of storage, related to coalescence, precipitation and phase separation [13].

2.3.4 Determination of globule size and distribution of SMEDDS after dilution

100 µL of the SMEDDS formula was diluted with 50 mL distilled water and stirred until homogeny. Globule size and distribution were determined using Particle Size Analyzer (PSA) [13].

2.3.5 Thermodynamic stability testing

This test was carried out in three-stage (centrifugation, heating-cooling cycle, and freeze-thaw cycle. Centrifuge: The SMEDDS formula was centrifuged at 3,500 rpm for 30 minutes. Heating cooling cycle: Three cycles between refrigerator temperature of 4°C and 45°C with storage for each temperature not less than 48 hours. Freeze-thaw cycle: Three cycle between -21°C and 25°C 48 hours with storage for each temperature not less than 48 hours was done for SMEDDS. Observations were made of the sedimentation and phase separation for each stage [13,14].

2.4 Formulation of S-SMEDDS Black Seed

The optimum formula of L-SMEDDS was converted to S-SMEDDS. The solidification process was carried out using a spray drying method with the addition of a solid carrier (aerosil 200). 5 grams of SMEDDS were added to the aerosol suspension (2.5 grams in 250 mL ethanol) and stirred for 15 minutes. The suspension formed then spray using inlet temperature 60°C and outlet temperature 40°C with a feeding rate of 4mL / min [15]

Table 1. Optimization of SMEDDS formula

Formula	Surfactant : Cosurfactant	Oil : Smix (surfactant+cosurfactant)
F1	1:1	1:9
F2		2:8
F3		3:7
F4		4:6
F5		5:5
F6	3:2	1:9
F7		2:8
F8		3:7
F9		4:6
F10		5:5
F11	2:1	1:9
F12		2:8
F13		3:7
F14		4:6
F15		5:5

2.5 Physical Evaluation of Black Seed Oil S-SMEDDS

2.5.1 Flow properties of black seed oil S-SMEDDS

Flow properties of S-SMEDDS including angle of repose, bulk density, percent compressibility index, and hausner ratio were determined [16].

2.5.2 Reconstitution properties of black seed oil S-SMEDDS

Emulsification time, dispersibility, and robustness of dilution tests were conducted to S-SMEDDS with similar procedure with L-SMEDDS [16].

2.5.3 Surface morphology of black seed oil S-SMEDDS

Surface morphology of S-SMEDDS particle was observed using Scanning Electron Microscopy (SEM) [16].

3. RESULTS AND DISCUSSION

SMEDDS was prepared using surfactant Tween 80 and PEG 400 as cosurfactant based on our previous study. Tween 80 and PEG 400 have good miscibility properties with black seed oil compare with others surfactant and cosurfactant. It will improve the efficiency of SMEDDS formation. The L-SMEDDS formula was optimized by variation of surfactant and cosurfactant concentration. For initial screening percent transmittance of all formula were determined. Percent transmittance value (>90%) and the transparency of the formed emulsion were indicate that globule size in the nanometer range [17]. The result of SMEDDS formulation showed in Table 2. The result showed that comparisons oil and Smix that could produce a transparent emulsion system were 1:9 and 2:8. Another comparison (3:7, 4:6, 5:5) could not produce a fine emulsion. At that comparison surfactant concentration not sufficient to stabilize the interfacial area in the microemulsion system. The same condition also happens at comparison surfactant and cosurfactant 1:1. Based on that result, further evaluation just performed to 4 formula, there are F6, F7, F11, F12.

Based on Table 3, the optimum formula of L-SMEDDS is F12. Formula F12 meets all physical characteristic requirements of SMEDDS. The preparation could be dispersed in water to produce a clear and stabile emulsion system based on dispersibility, robustness, and thermodynamic stability studies. Globule size determination of diluted SMEDDS F12 was determined using dynamic light scattering method. The result showed that the optimum formula has an average globule size of 231 nm with PDI (polydispersity index) 0.48 after diluted (Fig. 1). SMEDDS formulation must have a globule size <250 nm and formula F12 meets that requirement [5].

The optimum formula of L-SMEDDS (F12) was converted to S-SMEDDS using a spray drying method. This method was selected due to the fast process, can be used for heat-sensitive substances, and could resulting good characteristics of S-SMEDDS [15]. Another study showed that the spray drying method could produce better powder flow properties compared to the freeze-drying method [18]. The solid carrier used to form S-SMEDDS is aerosil 200 which has inherent properties. The evaluation result of the S-SMEDDS showed in Table 4.

The S-SMEDDS evaluations show that the resulting powder (S-SMEDDS) has good flow property based on angle repose value. Flow property could useful for tablet manufacturing or capsule filling. The S-SMEDDS can form a clear and stable emulsion system after dilution with grade B of dispersibility. The result showed that S-SMEDDS potential to form microemulsion spontaneously in the GI tract. SNEDDS and SMEDDS must have grade A or B of dispersibility [19].

Table 2. Percent transmittance of SMEDDS formulation

Form	% Transmittance	Form	% Transmittance	Form	% Transmittance
F1	95.20 ± 0.20*	F6	97.77 ± 0.06	F11	98.03 ± 0.12
F2	48.27 ± 0.31*	F7	93.90 ± 0.10	F12	95.77 ± 0.15
F3	<20.00	F8	<20.00	F13	<20.00
F4	<20.00	F9	<20.00	F14	<20.00
F5	<20.00	F10	<20.00	F15	<20.00

(*) show phase separation after 15 minutes after storage

Morphological surface of S-SMEDDS was assessed by SEM. The result showed that S-SMEDDS particle has spherical shape with smooth and little porous on its surface (Fig 2). That condition will provide the advantages for dispersion process of S-SMEDDS to form microemulsion in GIT [18,20]. Particle size of S-SMEDDS containing black seed oil in the range 1-10 µm.

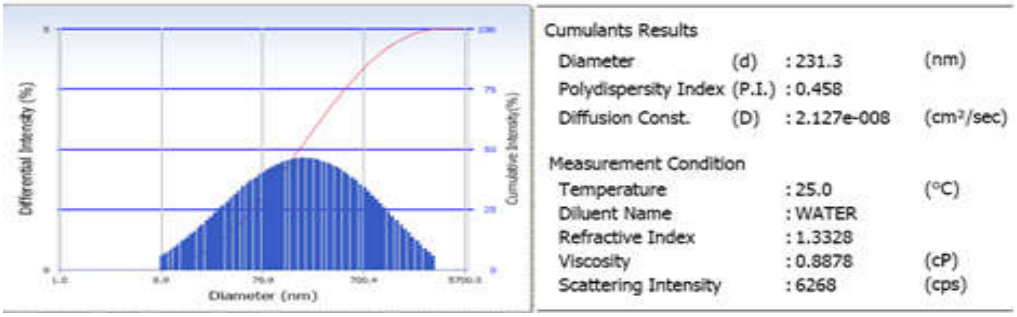

Fig. 1. Result of globule size and distribution test

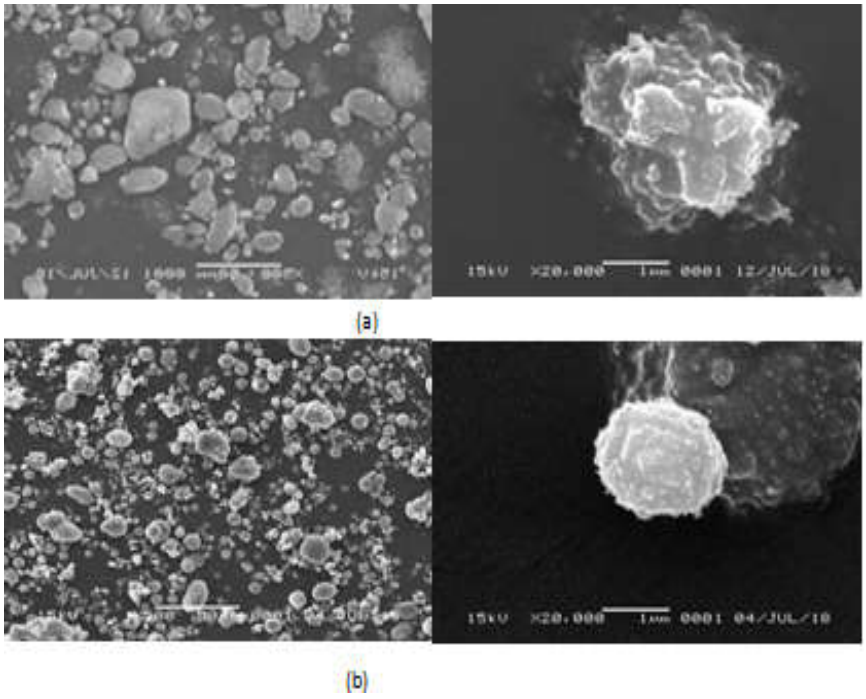

Fig. 2. SEM of (a) Aeorosil 200 (b) S-SMEDDS

Table 3. Physical evaluation result of selected formula of L-SMEDDS

Evaluation		F6	F7	F11	F12
Emulsification Time (s)		305± 0.6	41.3 ± 3.1	218 ±0.2	37.7 ± 2.1
Dispersibility Grade		D	A	D	A
Robustness	Distilled water	Stable	Stable	Stable	Stable
	HCl	Stable	Stable	Stable	Stable
	Phosphate buffer	Stable	Stable	Stable	Stable
Thermo	Centrifugation	Stable	Unstable	Stable	Stable
dynamic	Heating cooling	Stable	Unstable	Stabile	Stable
stability test	Freeze thaw	Stable	Unstable	Stable	Stable

Table 4. Result of S-SMEDDS evaluation (F12)

Parameter		Result
Powder properties	Water content	1.75%
	Angle of repose	27.65 ^{o}
	Bulk density	0.379 g/mL
	Tapped density	0.482 g/mL
	% compressibility	23.24
	Hausner Ratio	1.3
Dispersibility	Dispersibility time	35.01 s
	Emulsification grade	B
Robustness to dilution	Distilled water	Stable
	HCL	Stable
	Phosphate Buffer	Stable

4. CONCLUSION

The best formula of L-SMEDDS contains tween 80 as surfactant and PEG 400 as cosurfactant (2:1) with ratio of oil and Smix 2:8. L-SMEDDS preparation meets the requirement of percent transmittance (95.77%), emulsification time (37.67 second), grade A of dispersibility, stable of robustness and thermodynamics study with the average of globule size was 231 nm. S-SMEDDS preparation meets the requirement of the moisture content, flowability, emulsification time, and stable on robustness testing with a spherical shape.

DISCLAIMER

The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

CONSENT

It is no applicable.

ETHICAL APPROVAL

It is no applicable

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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