Effect of Vegetable Oil on Self-Nanoemulsifying Drug Delivery System of Dayak Onion [Eleutherine palmifolia (L.) Merr.] Extract using Hydrophilic-lipophilic Balance Approach: Formulation, Characteriza

by Esti Hendradi

RESEARCH ARTICLE

Effect of Vegetable Oil on Self-Nanoemulsifying Drug Delivery System of Dayak Onion [*Eleutherine palmifolia* (L.) Merr.] Extract using Hydrophilic-lipophilic Balance Approach: Formulation, Characterization

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ABSTRACT

Eleutherine palmifolia is a typical plant of Kalimantan that has been empirically used by the Dayak people as a cure for various types of diseases. Self-nanoemulsifying drug delivery system (SNEDDS) is a drug delivery system that can be developed for onion Dayak to improve its absorption profile. Selection of oil phase, surfactant, and cosurfactant have an essential role in SNEDDS of Dayak onion. The aims of this study to determine the effect of the use of vegetable oils on SNEDDS using the HLB approach. Several 40 formulations in each oil phase with HLB ranging between 11 and 15 were screened to acquire stable SNEDDS composition without the presence of phase separation. Formulas optimal obtained F33 (HLB 14) using olive oil at a ratio formula of 1:7:2. F29 (HLB 14), using VCO at a formula ratio of 1:7:2. F14 (HLB 14) uses palm oil at a ratio formula of 2:7:1. The result showed that the optimal formula F33 (olive oil) with 58 nm of the particle size, 84.32 ± 0.00 of the transmittance percentage, 22.00 ± 0,18 of the emulsification time. Formula F29 (VCO) with 19.48 nm of the particle size, 91.78 ± 0.02 of the transmittance percentage, 43.00 ± 0.16 of the emulsification time. Formula F14 (palm oil) with 102 nm of the particle size, 90.93 ± 0.02 of the transmittance percentage, 110 ± 0.34 of the emulsification time. The optimal formula that has good characteristics and stability is the F29 (VCO) formula using tween 20/transcutol as the surfactant, PEG 400, as co-surfactant at a ratio formula of 1:7:2.

Keywords: *Dayak Onion, Eleutherine palmifolia, Formulation,* HLB Approach, *Self-nanoemulsifying, SNEEDS.*

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INTRODUCTION

In the process of discovering new pharmaceutical therapies, the pharmaceutical formulation technology and drug delivery system play an essential role.[1] The discovery of new drugs sourced from synthetic active compounds and natural compounds. Making preparations based on drug delivery systems can be an alternative in making pharmaceutical preparations that contain natural ingredients. One of the medicinal plants that have the potential to be developed as a new drug is a Dayak onion.

Dayak onion is a typical Kalimantan plant. The community has empirically used that as a cure for various types of diseases, such as, cancer, hypertension, diabetes, cholesterol, and preventing stroke.[2] The phytochemical content of Dayak onions includes alkaloids, glycosides, flavonoids, phenolics, steroids, tannins, and quinones.[2,3] One of the marker compounds in Dayak onions is naphthoquinone. Naphthoquinone has bioactivity as an antioxidant and anti-cancer.[4,5] Naphthoquinone is a lipophilic compound with a logP value of 3.933 (Han *et al.*, 2008), which means that the solubility of naphthoquinone in water media will be minimal. Therefore, it is necessary to develop a delivery system to improve the bioavailability of naphthoquinone contained in Dayak onion extract.

SNEDDS is a mixture of isotropic oil, surfactant, cosurfactant, and drugs that form nanoemulsion oil-in-water (O/W), when emulsified in water.[6] SNEDDS has several advantages compared to nanoemulsion preparations that are ready to use. SNEDDS is having higher physical or chemical stability in long-term storage. SNEDDS is having smaller volumes of dosage forms that can be given in the form of soft or hard capsules and improving patient compliance.[7] The solubility of drugs can be increased by changing the form of drugs into droplets.[8]

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The composition of oil in the SNEDDS formula will determine the size of the nanoemulsion formed. The choice of oil type is based on its ability to dissolve the drug. Oil is the basis of medicine in SNEDDS.[9] Many oils are selected as the oil phase in the SNEDDS formulation, which has a high self-emulsifying ability and an extensive drug loading capacity[10]. Meanwhile, olive oil, virgin coconut oil (VCO), and palm oil.

Based on the background above, we formulated SNEDDS of Dayak onion extract by comparing the oil phase (olive oil, VCO, and palm oil) and a mixture of surfactant to obtain HLB range 11 to 15. Combinations of both surfactants were designed to have mixed HLB > 10 to form O/W system, which is easy to become emulsion spontaneously in aqueous media. Co-surfactant in this SNEDDS [polyethene glycol (PEG) 400]. The formula produced based on the comparison characteristics between olive oil, VCO, and palm oil. Currently, there has not been a report exploring the influence of HLB value on SNEDDS as an extract template. Hence, the present study developed SNEDDS containing extract to establish a SNEDDS system for Dayak onion using HLB approach. Afterward, the formulation was subsequently subjected to the physicochemical characterization for oral delivery of Dayak onion.

MATERIALS AND METHODS

Materials

Dayak onion extract, olive oil (Sasso, Italia), VCO (Herba Bagoes, Indonesia), palm oil (Ikan Dorang, Indonesia), tween 80 (Merck, Germany), tween 20, span 20 (Bratachem, Indonesia), and Transcutol (Gattefose, France).

Surfactants Selection and Preparation SNEDDS

Two hydrophilic surfactants (tween 20, tween 80) were mixed with two hydrophobic surfactants (span 20 and transcutol) to formulate four binary surfactant combinations with HLB ranging from 11 to 15 (Table 1). HLBmix of each surfactant was calculated by using the following equation: HLBmix = fAHLBA + fBHLBB

In SNEDDS formulation, the HLB method can be used as a starting point to acquire excellent emulsification characteristics. More than one surfactant can be blended to get desirable HLB. Selected surfactants should have good miscibility with other components in SNEDDS formula to produce a stable and homogenous system. Other criteria have relatively low toxicity for oral administration.

SNEDDS formula selection is made by using HLB. The formula made is 20 grams/formula with the ratio of oil:surfactant:co-surfactant (1:7:2 and 2:7:1). The success of mixtures is characterized by the formulation of clear, transparent solutions, and no phase completion is obtained. Formulas that show good results will begin the manufacturing and characterization of Dayak onion-loaded SNEDDS. The oil phase used in this study is olive oil (A), VCO (B), palm oil (C). The draft formula and the amount of the surfactant mixture are presented in Table 1.

Preparation Dayak Onion-Loaded SNEDDS

The SNEDDS preparation was made using Dayak onion extract. 50 mg extract added to 20 g of SNEDDS that had been formed while continuing to stir for 15 minutes using a stirrer with a speed of 400 rpm at 25°C ± 2°C for further characterization.

Characterization of Dayak Onion-loaded SNEDDS

Transmittance Test

Observation of the clarity of the emulsion formed in the previous stage was carried out using an ultraviolet-visible spectrophotometer by measuring absorption at a wavelength of 650 nm. If the results of the sample transmittance percentage are close to the percentage of distilled water, which is 100%, then it can be assumed that the size of the nanoemulsion droplets has been nano-sized.[11]

Emulsification Time

Emulsification time was calculated for Dayak onion SNEDDS in two mediums. Namely, artificial gastric fluid (AGF) without pepsin, and artificial intestinal fluid (AIF) without pancreatin. Self emulsification time is the time required by the pre-

Table 1: Preparation formula SNEDDS and mixed surfactant ratio at various HLB

Rasio HLB mix	*Oil phase*	*Tween 20/transcutol*	*Tween 20/span 20*	*Tween 80/transcutol*	*Tween 80/span 20*	*PEG 400*
Ratio Formula 2:7:1						
11	2	43.52/36.48 (F1)	30/50 (F2)	23.7/53.6 (F3)	50.37/29.63 (F4)	1
12	2	49.92/30.8 (F5)	42.5/37.5 (F6)	33.58/46.42 (F7)	57.77/22.23 (F8)	1
13	2	56.32/30.8 (F9)	55/25 (F10)	43.46/36.54 (F11)	65.2/14.8 (F12)	1
14	2	62.72/17.8 (F13)	67.50/12.50 (F14)	53.3/26.7 (F15)	72.6/7.1 (F16)	1
15	2	69.19/10.88 (F17)	80 (F18)	63.21/16.79 (F19)	80 (F20)	1
Ratio Formula 1:7:2						
11	1	43.52/36.48 (F21)	30/5 (F22)	23.7/53.6 (F23)	50.37/29.63 (F24)	2
12	1	49.92/30.80 (F25)	42.5/37.5 (F26)	33.58/46.42 (F27)	57.77/22.23 (F28)	2
13	1	56.32/30.8 (F29)	55/25 (F30)	43.46/36.54 (F31)	65.2/14.8 (F32)	2
14	1	62.72/17.8 (F33)	67.50/12.50 (F34)	53.3/26.7 (F35)	72.6/7.1 (F36)	2
15	1	69.19/10.88 (F37)	80 (F38)	63.21/16.79 (F39)	80 (F40)	2

concentrate for homogeneous mixture up on dilution where the disappearance of SNEDDS is observed visually. 100 µL of each formulation was added dropwise to the 200 mL medium with a magnetic stirrer speed of 100 rpm at 37 ± 0.5°C. The time required for the disappearance of the SNEDDS was recorded.[12]

pH Measurement

The pH measurement of each formula is done using a pH meter. 10 mL of Dayak onion SNEDDS, then electrodes were inserted into SNEDDS Dayak onion, and then the number indicated by the pH meter.[13]

Viscosity

Viscosity testing was carried out using a cone and plate viscometer (Brookfield, USA). Stationary plates were filled with 0.5 to 20 mL Dayak onion SNEDDS. SNEDDS samples are placed in the sample cup; the sample is ensured to be bubble-free and spread evenly on the surface of the cup. Furthermore, the sample cup reassembled on viscometer, and the viscometer is turned on, then left for a while until the reading is stable.[13]

Particle Size Analysis

This test was analyzed using dynamic light scattering on a particle size analyzer (Nanowave II Microtech, USA). 1 gram of Dayak onion SNEDDS extract was dissolved with 10 mL water (1:10) at 25°C, then put in a cuvette and measured the particle size distribution in the sample.

Thermodynamic Stability Studies

Heating-Cooling Cycle

Heating-cooling cycles were performed three times at temperatures between 4 ± 2°C and 45 ± 2°C each stored for a minimum of 48 hours. The formulations surviving these temperatures without any cracking, creaming, phase separation, coalescence, or phase inversion were selected for the freeze-thaw stress test. All formulations were diluted with double distilled water (1:25), and resulting nanoemulsion was observed for instability problems.[14,15]

Freeze-Thaw Cycle

The freeze-thaw test included three cycles in a temperature range of −20 ± 2°C and 25 ± 2°C stored for at least 48 hours. All formulation was diluted with double distilled water (1:25), and resulting nanoemulsion was observed for instability problems.[16]

RESULTS AND DISCUSSION

The SNEDDS formula in this study uses three types of oil, namely olive oil, VCO, and palm oil. Vegetable oil in the SNEDDS formula for its characteristics. VCO was chosen as the oil phase in the formulation because VCO contains fatty acids. Fanconi anemia (FA), which are containing 43 to 53% fatty acids so that VCO is more easily emulsified and can produce preparations with nanometer-size.[10] Olive oil contains oleic acid, which has a high emulsion ability and an extensive drug dissolving capacity. The development of olive oil into a stable form, such as, nanoemulsion becomes very potential if it is related to the number of properties possessed. Oleic acid is commonly used as an emulsifying agent and improving the low solubility profile in the water. It can also be used as an additive for oral SNEDDS formulations. The use of palm oil in Indonesia is mainly for food (98.36%), and the level of consumption has increased from year to year.[18] Long-chain fatty acid palm oil (LCT). In the formation of SNEDDS, LCT oils are more easily formed, but nanoemulsion can produce SNEDDS that are less stable.

Surfactants Selection and Formulation SNEDDS

The screening was intended to discover the harmonious combination of surfactant and co-surfactant with olive oil. They accumulate the synergy effect of both substances to reduce the surface tension between oil and water to facilitate clear and homogenous nanoemulsion. The results could be seen in Table 2.

Despite the oil, the surfactant is an essential component of SNEDDS.[19] The properties of surfactant, such as HLB value in oil, viscosity, and affinity for oil, strongly affect the process of nanoemulsification and the size of nanoemulsion droplet.[20] The mixture of hydrophilic and hydrophobic surfactants can be used to form nanoemulsion with desired characteristics. HLB of Surfactant with < 10 is hydrophobic and can produce W/O emulsion, whereas, over > 10 is hydrophilic and can form O/W emulsion. Surfactant concentration plays a role in the formation of droplets in nanometric size.[21] The bigger the ratio between hydrophilic and hydrophobic surfactants, the higher the HLB. The proper mixture of surfactants with lower and higher HLB may produce nanoemulsion that is stable even diluted with water. The proper mixture may also lower the interfacial tension to facilitate dispersion process by forming a flexible film that can readily deform around droplet.[22]

One hundred twenty formulas of SNEDDS with HLB between 11 to 15 using different ratios of oil, surfactant and co-surfactant (Table 1) were evaluated for their stability after 24 hours of storage at room temperature. The most stable formula, which did not show phase separation, was selected as a template for Dayak onion SNEDDS formulation.

Fourteen stable formulas were obtained after 24 hours of storage (Table 3). Higher HLB values indicate higher hydrophilicity, which affects a reduction in the curvature at the oil interface, resulting in smaller droplets. Therefore, in this study, the stable SNEDDS formula with the highest HLB value was chosen. Besides, the selection of the best formula is also based on higher oil concentrations to obtain a protective effect against drugs, but produces nanoemulsions with small droplets.[23] The selection of surfactants with the lowest possible concentration can reduce the risk of toxicity and irritation[24]. Based on the analysis of 14 stable formulas obtained F33 (HLB 14) using olive oil at a formula ratio of 1:7:2. F29 (HLB 14) uses VCO at a formula ratio of 1:7:2. F14 (HLB 14) uses palm oil at a formula ratio of 2:7:1. The formulas were chosen because they have the highest HLB, which makes the emulsification process more comfortable, the highest concentration of the oil component, and the lowest surfactant concentration.

Table 2: Result organoleptic surfactants selection and formulation SNEDDS

Formula	*Olive oil (A)*	*VCO (B)*	*Palm oil (C)*	*Formula*	*Olive oil (A)*	*VCO (B)*	*Palm oil (C)*
F1	Coalescence	Coalescence	Coalescence	F21	Coalescence	Coalescence	Coalescence
F2	Coalescence	Coalescence	Coalescence	F22	Coalescence	Coalescence	Coalescence
F3	Coalescence	Coalescence	Coalescence	F23	Coalescence	Coalescence	Coalescence
F4	Coalescence	Coalescence	Coalescence	F24	Coalescence	Coalescence	Coalescence
F5	Coalescence	Coalescence	Coalescence	F25	Coalescence	Coalescence	Coalescence
F6	Coalescence	Coalescence	Coalescence	F26	Coalescence	Coalescence	Coalescence
F7	Homogeneous	Homogeneous	Coalescence	F27	Coalescence	Coalescence	Coalescence
F8	Homogeneous	Coalescence	Coalescence	F28	Coalescence	Coalescence	Coalescence
F9	Coalescence	Coalescence	Coalescence	F29	Homogeneous	Homogeneous	Coalescence
F10	Coalescence	Coalescence	Coalescence	F30	Coalescence	Coalescence	Coalescence
F11	Coalescence	Coalescence	Coalescence	F31	Coalescence	Coalescence	Coalescence
F12	Homogeneous	Coalescence	Coalescence	F32	Homogeneous	Coalescence	Coalescence
F13	Homogeneous	Coalescence	Homogeneous	F33	Homogeneous	Coalescence	Coalescence
F14	Coalescence	Coalescence	Homogeneous	F34	Coalescence	Coalescence	Coalescence
F15	Coalescence	Coalescence	Coalescence	F35	Coalescence	Coalescence	Coalescence
F16	Coalescence	Homogeneous	Coalescence	F36	Coalescence	Coalescence	Coalescence
F17	Coalescence	Coalescence	Coalescence	F37	Coalescence	Coalescence	Coalescence
F18	Coalescence	Homogeneous	Coalescence	F38	Coalescence	Coalescence	Coalescence
F19	Coalescence	Homogeneous	Coalescence	F39	Coalescence	Coalescence	Coalescence
F20	Homogeneous	Coalescence	Coalescence	F40	Coalescence	Coalescence	Coalescence

Tabel 3: Result characterization of dayak onion extract-loaded SNEDDS (n = 3)

Selected SNEDDS formula	*Percentage of transmittance (%) ± SD*	*Emulsification time (second)*		*pH ± SD*	*Viscosity (cps) ± SD*	*Droplet Size (nm)*
		AIF ± SD	*AGF ± SD*			
Olive oil						
F7	86.17 ± 0.01	87 ± 0.15	34.16 ± 0.02	5.16	34.55 ± 1.02	30.9
F8	92.52 ± 0.01	64 ± 0.22	49 ± 0.02	5.02	43.12 ± 0.24	11.39
F13	93.07 ± 0.01	91 ± 0.09	106 ± 0.02	5.02	35.55 ± 0.3	11.93
F20	96.6	95 ± 0.12	106 ± 0.02	5.04	24.99 ± 0.5	20.97
F29	95.59	67 ± 0.24	61 ± 0.02	5.09	14.55 ± 0.1	10.32
F32	94.32	38 ± 0.18	31 ± 0.11	5.25	28.85 ± 0.1	11.2
F33	84.32	22 ± 0.18	20 ± 0.11	5.25	44.05 ± 1.1	58
Virgin coconut oil (VCO)						
F7	93.57 ± 0.02	56 ± 0.22	66 ± 0.02	5.02	48 ± 0.1	32.3
F16	96.52 ± 0.01	31 ± 0.12	30 ± 0.02	5.06	34.87 ± 0.45	26
F18	98.39 ± 0.01	35 ± 0.16	36 ±0.02	5.06	41.99 ± 0.4	11.03
F19	99.74 ± 0.03	95 ± 0.02	82 ± 0.02	5.07	45.23 ± 1.2	10.27
F29	91.78 ± 0.02	43 ± 0.16	48 ± 0.02	5.22	34.54 ± 1.05	19.48
Palm oil						
F13	94.36 ± 0.02	100 ± 0.12	51 ± 0.02	5.22	54.72 ± 0.2	104
F14	90.93 ± 0.02	110 ± 0.34	100 ± 0.02	5.51	80.55 ± 0.55	102

The combination of surfactant F33 (HLB 14) in the SNEDDS formula with olive oil and F29 (HLB 13) in the SNEDDS formula with VCO uses a combination of tween 20/ transcutol. The combination of surfactant in the formula F14 with palm oil uses tween 80/ transcutol on HLB 14. The use of this combination has good results because the surfactant tween 20, tween 80, and transcutol can cover the oil phase. The presence of polyoxyethylene chains from tween can be a steric obstacle to joining droplets.[25]

There are two mechanisms of nanoemulsion formation by surfactants, *viz.*, by reducing the surface tension of one liquid, and preventing the incorporation of other liquid droplets. Liquid substances with smaller surface tension will quickly spread and become a continuous phase. At the same time, surfactant molecules will collect at the liquid interface boundary to prevent the reassembly of the dispersed phase. Nonionic surfactants help to improve emulsion stability by forming an interface layer that has a high enough elasticity so as not to allow the joining of droplets, as a result of movement between droplets.[11]

Characterization of Dayak Onion Extract-Loaded SNEDDS

Transmittance Test

Optimum clarity is achieved if the value of the transmittance is the highest possible or closer to 100%.[27] It is well accepted that transmittance values higher than 80% are considered as sufficient to be recognized as emulsions with nano-sized for the droplets of O/W.[28] The size of the dispersed phase dramatically influences the appearance of nanoemulsions. If the nanoemulsion system has a minimal globule size through which light is passed. The beam of light will be forwarded so that the color of the solution looks transparent, and the resulting transmittance is even higher. Aquadest is used as a comparison because it does not have particles that hold the transmission of light, so that it will continue the light passing through it without the effect of scattering light, so that it has a transmittance value of 100%.[29]

In the selection of Dayak onion SNEDDS formula in terms of the value of transmittance percentage formula, which has the highest HLB values , including F33 (olive oil), F29 (VCO), and F14 (palm oil). The formula produces a transmittance value > 80%. The use of surfactants in SNEDDS formulations must be as minimal as possible to minimize the risk of unwanted effects due to excessive use of surfactants.

Emulsification Time

Determination of emulsification time to obtain pictures of the ease with which SNEDDS form an emulsion, while in the body. Little emulsification time is mediated by the action of surfactants and cosurfactants, which can immediately form the interface layer of oil and water. Cosurfactants play a role in emulsification time rather than reducing the size of the droplet. Co-surfactant will slip and form a space between surfactants so that the structure is more swollen, but has high fluidity and can form nanoemulsion faster.[29] The results of determining the emulsification time can be seen in Table 3.

Observation of nanoemulsion formation refers to the standard test of dispersibility. Observations were made on the chosen formula. As Table 3 shows, the ratio formula 2:7:1 is less able to help surfactants in reducing the surface tension of SNEDDS-onions pounded on Dayak onions in the base of palm oil. Observations on formulas F33 (olive oil) and F 29 (VCO) meet the emulsification period of < 1-minute. The formula that gives good results is a formula with a ratio of 1:7:2 with a higher amount of co-surfactant. The co-surfactant type, PEG 400, has a higher HLB. A higher HLB value means a higher level of hydrophilicity, resulting in a faster emulsification time.[30]

pH and Viscosity

The measurement results of the pH formula produce pH in the range of 5.02-5.51. Viscosity measurements are carried out using a viscosimeter. Viscosity shows the characteristics of a liquid. Viscosity is the resistance of a liquid to flow. The higher the viscosity of preparation, the higher the resistance. Profile the results of pH and viscosity in Table 3.

Particle Size Analysis

Particle size analyzer is a critical factor in self-emulsification because it determines the speed and ease of the drug to be optimally absorbed and the stability of the emulsion formed. Particle size testing results are presented in Table 3.

The droplet size is a critical parameter of SNEDDS evaluation. The smaller the droplets, the larger the area of absorption and the faster the drug release. The small droplets may provide a larger surface area that enables pancreatic lipase to hydrolyze and promotes more drug release[31]. All SNEDDS formulas using three different oil phases have particle sizes between 10 to 200 nm. This is following the literature, if the success of SNEDDS is seen from the SNEDDS particle size value of 10 to 200 nm. F33 (olive oil) ratio of 1:7:2 has a droplet size of 58 nm. F29 (VCO) 1:7:2 ratio has a droplet size of 10.32 nm. F14 (palm oil) ratio of 2:7:1 has a droplet size of 102 nm. The previous test that the transmittance percentage affected the SNEDDS droplet size. Transmittance percentage, which is getting closer to 100% has apparent characteristics and smaller particle size. This is appropriate for formulas using olive oil and VCO. However, in the formula F14 (palm oil), a high transmittance percentage does not show a small droplet size. This is because palm oil is LCT oils, which are more easily formed. However, nanoemulsion can produce SNEDDS that are less stable.

Thermodynamic Stability Studies

The formula continued in this stability test is F33 (HLB 14) using olive oil at a ratio formula of 1:7:2. F29 (HLB 14) using VCO at a formula ratio of 1:7:2. F14 (HLB 14) uses palm oil at a ratio formula of 2:7:1.

Heating-Cooling Cycle

The tests showed that the formula F29 remained stable after being stored at the temperature of 4 ± 2°C and 45 ± 2°C. Formulas F33 and F14 show unstable results after stability testing.

Freeze-Thaw Cycle

The tests showed that the formula F29 remained stable after being stored at the temperature of –20 ± 2°C and 25 ± 2°C. Formulas F33 and F14 show unstable results after stability testing.

Nanoemulsion is a system that is thermodynamically stable and is produced on the presence of oil, surfactants, and co-surfactants without phase separation, creaming, or cracking.

This differentiates nanoemulsion from macroemulsion, which is kinetically unstable and may result in phase separation.[32]

The absence of precipitate after centrifugation showed that protein was dissolved in the oil phase aided by surfactants. Moreover, the amount of extract dissolved in oil can be calculated.

CONCLUSION

The optimal formula that has excellent characteristics and stability is the F29 (VCO) formula using tween 20/transcutol surfactant, and PEG 400 co-surfactant at a ratio of 1:7:2 formula. Formula F29 (VCO) with 19.48 nm of the particle size, 91.78 ± 0.02 of the transmittance, and 43 ± 0.16 of the emulsification time.

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