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Original Research Article

Characterization of *in vitro* spray-dried self-nanoemulsifying drug delivery systems for oral delivery of Bundung extract

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Abstract

Purpose: *To formulate solid self-nanoemulsifying drug delivery system (S-SNEDDS) employing spray drying method and to enhance solubility and bioavailability of Bundung (Actinoscirpus grossus) plant extract as an antioxidant.*
Methods: *The procedure was delineated into six sequential steps. Bundung extract was obtained from the plant by maceration in ethanol for 3 days. Subsequently, five formulations of L-SNEDDS with varying concentrations of oleic acid were prepared, followed by the characterization of liquid SNEDDS (L-SNEDDS). This characterization encompassed transmittance, emulsification time and determination of droplet size, polydispersity index and zeta potential (ZP). The third step involved preparation of S-SNEDDS through the use of a spray drying technique. The fourth step entailed the characterization of S-SNEDDS, which included visual observation, resistance to dilution, globule size measurement, and Differential Scanning Calorimetry. The fifth step involved an in vitro drug release test. The sixth step involved an antioxidant activity test using DPPH and FRAP.*
Results: *Formulation 1 of L-SNEDDS showed 99.3 % transmittance, had the smallest droplet size and best particle distribution, while formulation 2 emulsified fastest in the gastrointestinal tract. Furthermore, formulations 1, 2, 3 and 5 had optimum ZP values. In converting liquid SNEDDS to solid SNEDDS, formulation 3 had a 100 % yield, while formulation 1 had the smallest globule size and the highest antioxidant activity.*
Conclusion: *Formulation 1 of Bundung extract, with 5 % Oleic Acid concentration, is the most optimized as it meets the characterization requirements of L-SNEDDS and S-SNEDDS, passes the in vitro drug release test and has the highest antioxidant activity.*

Keywords: *Characterization, In vitro, S-SNEEDS, Bundung plant, Antioxidant*

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INTRODUCTION

Poor metabolism leads to toxic effects on the body through the production of free radicals [1,2]. Antioxidants, such as those found in *Actinoscirpus grossus* L. (Bundung), help reduce free radicals [3]. Bundung is a typical swamp plant in South Kalimantan that has been used to treat various ailments such as diarrhea, fever, diuretic, vomiting and allergic reactions [4–6]. Previous studies demonstrated that *A. grossus* L. exhibited moderate antioxidant activity and IC_{50} of 128 ppm [2]. Phytochemical composition of the ethanol extract of Bundung plant revealed the

presence of flavonoids, phenolics, saponins, tannins, glycosides, steroids and terpenoids [2]. However, oral bioavailability of Bundung's flavonoids is limited due to their poor water solubility. To address this, nanotechnology has been employed to enhance solubility and bioavailability [7].

Self-Nanoemulsifying Drug Delivery System (SNEDDS) is a promising approach, offering improved storage life and convenience [8]. Solid SNEDDS (S-SNEDDS) combines the benefits of liquid-lipid formulations with the stability of solid dosage forms [9]. This system is particularly well-suited for plants like Bundung, which have poor solubility and bioavailability. Optimization of the pharmacological benefits of Bundung is possible through utilization of S-SNEDDS, providing a potential solution for various health issues.

EXPERIMENTAL

Collection and extraction

Actinoscirpus grossus plants were identified by Goetgh. & D.A. Simpson, based on the initial description by Linnaeus, files. The identification process involved collecting plant specimens from the field, making morphological and anatomical observations, comparing them with other specimens, and using plant identification keys to determine the plant's scientific name. Plant classification: Kingdom: Plantae, Phylum: Tracheophyta, Class: Liliopsida, Order: Poales, Family: Cyperaceae, Genus: Actinoscirpus, Specific epithet: grossus, Scientific name: Actinoscirpus grossus (L.f.) Goetgh. & D.A. Simpson. Depository herbarium specimen was domiciled at the Royal Botanic Gardens, Kew (voucher specimen no. K002987364).

A sample of *Actinoscirpus grossus* L. (Bundung) aerial parts was collected from Banjarmasin City, South Kalimantan. Collected plants were dried in the sun with a black cover and pulverized. Bundung extract was obtained by maceration. A quantity (1 kg) of simplicia powder was soaked in 10 liters of 96 % ethanol for 3 days with intermittent stirring. Thereafter, it was filtered and the filtrate was evaporated using a rotary evaporator [10].

Formulation and characterization of liquid SNEDDS

Liquid self-nanoemulsifying drug delivery system was prepared using the composition of oil, surfactant and cosurfactant (Table 1). The extract (4.5 g) was added to the mixture, sonicated for 30 minutes and conditioned for 10 minutes using a water bath at 40 °C. The mixture was left for 24 h and observed for physical stability at room temperature [11].

The characterization of L-SNEDDS, during the transmittance stage, was evaluated using a UV spectrophotometer at a wavelength of 650 nm. In the emulsification time stage, measurements were taken at 37 °C with stirring at 120 rpm. The particle size distribution, zeta potential (ZP) and polydispersity index were subsequently determined using a particle size analyzer [12].

Formulations of solid SNEDDS

The formula of solid self-nanoemulsifying drug delivery system of Bundung extract is shown in Table 2. A solution of polyvinylpyrrolidone (PVP) or lactose (1 g) was mixed with 100 mL of distilled water and stirred until the solution was homogeneous. Aerosil adsorbent was added until a homogeneous powder with adequate flow properties was obtained. Then, 5 mL SNEDDS dosage form was blended into the hydrophilic solution with stirring at 100 rpm. Thereafter, the solution was subjected to spray drying using a Buchi B-290 spray dryer, with an inlet temperature of 120 °C and an outlet temperature of 80 °C, an aspiration rate of 90 %, a scale pump rate of 25 % and a pressure of 50 mBar [9,10,13].

Table 1: Formula of liquid self-nanoemulsifying drug delivery system Bundung extract

Material	Formulation					Material function
	F1	F2	F3	F4	F5	
Bundung extract (g)	4.5	4.5	4.5	4.5	4.5	Active substance
Oleic acid (%)	5	10	15	20	25	Oil phase
Tween 80 (%)	60	60	60	60	60	Surfactant
Propylene glycol (%)	75	75	75	75	75	Co-surfactant

F1 (Bundung extract Liquid-SNEEDS formula 5% Oleic Acid concentration), F2 (10% Oleic Acid concentration Bundung extract Liquid-SNEEDS formula), F3 (15% Oleic Acid concentration Bundung extract Liquid-SNEEDS formula), F4 (Bundung extract Liquid-SNEEDS formula 20% Oleic Acid concentration), F5 (Bundung extract Liquid-SNEEDS formula 25% Oleic Acid concentration)

Table 2: Formulation of solid self-nanoemulsifying drug delivery system of Bundung extract

Material	Formulation					Material function
	F1	*F2*	*F3*	*F4*	*F5*	
L-SNEEDS (mL)	10	10	10	10	10	Active substance
PVP (g)	2	2	2	2	2	Filling agent
Aerosil (g)	6	6	6	6	6	Adsorbents
Aquadest (mL)	200	200	200	200	200	Solvents

Characterization of solid SNEDDS

To evaluate emulsification characteristics, the prepared nanoemulsion was examined after 24 h for any indications of powder precipitation [13]. In the resistance to dilution test, S-SNEDDS dosage form was diluted (10, 100, 1000 times) with different dissolution media, namely water, 0.1 N HCl and buffered with different pH values (1.2, 4.5, and 6.8) [13]. The globule size was determined with a Malvern Zetasizer SZ-100 [9]. Differential scanning calorimetry and thermal analysis of the sample, PVP, lactose and S-SNEDDS were also carried out [13].

In vitro drug release testing

Formulations (L-SNEDDS and S-SNEDDS) were filled into size 0 capsules. *In vitro* drug release studies were conducted using dissolution testing in simulated gastrointestinal fluids at pH values 1.2 and 6.8 at 37 °C. Samples were collected at predetermined time points (5, 10, 20, 30, 45, 60, 90 and 120 min). The samples were subsequently filtered and analyzed by high-performance liquid chromatography. The mean dissolution time (MDT) and dissolution efficiency were calculated to compare the dissolution enhancement rates of L-SNEDDS and S-SNEDDS [9].

Determination of antioxidant levels

In the 2, 2-diphenyl-1-picrylhydrazyl (DPPH) method, a DPPH solution of 0.4 and 0.2 mM dissolved in ethanol was prepared and the maximum wavelength of DPPH was determined. Then, determination of operating time and IC_{50} value of quercetin with an initial concentration of 1000 ppm was carried out by diluting it to several lower concentrations of 1, 2, 3, 4, 5, and 6 ppm. Absorbance was read at the maximum wavelength obtained (516 nm). Finally, the IC_{50} value of the sample was determined. The solution was allowed to stand for 30 minutes and the absorbance was read [2].

In antioxidant testing using the Ferric Reducing Antioxidant Power (FRAP), 1 mL of sample solution at different concentrations of oleic acid (F1, F2, F3, F4 and F5) or vitamin C (standard solution) was pipetted into a tube. Thereafter, 1 mL each of phosphate buffer solution and $K_3Fe(CN)_6$ was added and incubated at 50 °C for 20 min. Then, trichloroacetic acid (1 mL) was added and centrifuged at 3000 rpm for 10 min. The top layer was separated, followed by the addition of 1 mL of distilled water and 0.5 mL ferric chloride (0.05 %). Absorbance of sample solution, determined at a wavelength of 720 nm with 3 replicates, was used to calculate the percentage reducing power (%RP). A linear regression equation was obtained to calculate the IC_{50} value [14].

Statistical analysis

Data are presented as mean ± standard deviation (SD) of triplicate samples. Significance values were obtained using one-way analysis of variance (ANOVA) test and Kruskal-Wallis H test for analysis of statistically significant differences among multiple groups. Values of $p < 0.05$ were considered statistically significant.

RESULTS

Yield of Bundung extract

The yield obtained from *Actinoscirpus grossus* (Bundung) extraction process is 4.55 %, and the color of extract is dark green and has the characteristic odour of Bundung extract

Transmittance value of L-SNEDDS

Analysis of transmittance value measurements on Liquid-SNEDDS of Bundung extract shows the optimum average value in formulation 1, which is 99.3% (Table 3).

Emulsification time

Bundung extract L-SNEDDS preparation was dissolved into 3 media, namely distilled water, AGF (Artificial Gastric Fluid) and AIF (Artificial Intestinal Fluid), then emulsification time data was obtained. Formulation 2 obtained the fastest emulsification time in all three media compared to other formulations (Table 4).

Table 3: Transmittance value of liquid-SNEDDS of Bundung extract

Formulation	Appearance	Mean ± SD (%)	*P*-value
F1	Clear	99.30±0.17	
F2	Clear	97.80±0.30	
F3	Clear	96.40±0,057	0.008[a]
F4	Clear	94.80±0.00	
F5	Slightly cloudy	89.9±0.34	

[a]Kruskal-Wallis H test

Table 4: Emulsification time observation results

Media	Formulation	Mean±SD (Seconds)	*P*-value
Aquadest	F1	22.96±0.58	0.012[b]
	F2	12.82±1.82	
	F3	63.87±4.3	
	F4	55.17±3.97	
	F5	26.84±17.9	
AGF	F1	44.84±10	0.012[b]
	F2	11.71±0.56	
	F3	88.20±1.59	
	F4	50.72±6.99	
	F5	250.2±3.75	
AIF	F1	16.45±6.42	0.001[a]
	F2	10.98±2.95	
	F3	46.11±11.11	
	F4	28.27±2.63	
	F5	33.60±7.22	

[a] *One-way ANOVA test;* [b] *Kruskal-Wallis H test*

Droplet size

Formulations 1, 2, 3 and 5 produce particles in nanometer size range of 20 - 200 nm (Table 5).

Table 5: Particle (droplet) size of L-SNEDDS

Formulation	Mean±SD (nm)	*P*-value
F1	136.4±1.53	0.009[a]
F2	153.2±1.77	
F3	160.9±1.40	
F4	356.4±33.60	
F5	179.5±2.40	

[a] *Kruskal-Wallis H test*

Polydispersity index

Particle distribution is indicated by polydispersity index (PI). The polydispersity index value obtained for each formulation is less than 1, indicating that the globules formed have a relatively uniform size (Table 6).

Zeta potential of L-SNEDDS formulations

The results of determining the ZP value show that formulations 1, 2, 3 and 5 have ZP values that are not less than -30 mV and not more than +30 mV (Table 7).

Table 6: Polydispersity index of L-SNEDDS formulations

Formulation	Mean±SD	*P*-value
F1	0.165±0.06	0.001[a]
F2	0.341±0.004	
F3	0.255±0.037	
F4	0.535±0.10	
F5	0.254±0.016	

[a]*ANOVA test*

Table 7: Zeta potential of L-SNEDDS formulations

Formulation	Mean±SD (mV)	*P*-value
F1	-20.6±0.80	0.012[a]
F2	-20.7±1.13	
F3	-22.8±0.63	
F4	-38.3±11.78	
F5	-12.2±1.25	

[a]*Kruskal-Wallis H test*

Yield and organoleptic properties of S-SNEDDS of Bundung extract

The yield of solid self-nanoemulsifying drug delivery system of Bundung extract is shown in Table 8. They were all light green. Despite the difference in oil phase concentration, all formulations were transparent, stable and showed no phase separation after 24 hours.

Table 8: S-SNEDDS yield of Bundung extract

Formulation	Weight (g)	Yield (%)
F1	10.67	82.08
F2	10.12	77.85
F3	13.20	100
F4	9.53	73.31
F5	11.08	85.23

Resistance to dilution

The results showed that the aqueous nanoemulsions were unstable at 10x dilution because phase separation or precipitation occurred after 24 h. However, the aqueous SNEDDS did not show precipitation or phase separation at 100x and 1000x dilutions on different dilution media.

Globule size determination

Measurement of the size distribution of globules with a size of less than 100 nm formed in formulas 1, 2, 3, and 5 (Table 9).

Table 9: Globule size

Formulation	Mean±SD (nm)	*P*-value
F1	48.34±9.84	
F2	63.92±4.06	
F3	60.40±6.2	0.000[a]
F4	170.9±7.2	
F5	63.09±1.39	

[a] *One-Way ANOVA test*

Polydispersity index (particle distribution)

A polydispersity index value of <0.5 in formulations 1 and 3 indicates that the globules formed are uniformly sized (Table 10).

Table 10: Results of the polydispersity index

Formulation	Mean±SD	*P*-value
F1	0.445±0.021	
F2	0.562±0.052	
F3	0.446±7.64	0.012[a]
F4	0.841±0.025	
F5	0.921±0.018	

[a] *Kruskal-Wallis H test*

Zeta potential value of S-NEDDS

Zeta potential determination data to understand the physical stability of nanoemulsions are listed in Table 11.

Table 11: Results of Zeta potential of S-NEDDS

Formulation	Mean±SD (mV)	*P*-value
F1	20.79±1.34	
F2	4.68±1.22	
F3	21.24±1.51	0.000[a]
F4	-9.13±0.50	
F5	16.34±0.67	

[a] One-Way *ANOVA test*

Differential scanning calorimetry

The DSC analysis confirmed the presence of an endothermic peak for L-SNEDDS at 125.67°C and for PVP at 147.33 °C. At temperatures between 130 and 137 °C, the endothermic melting point of S-SNEDDS was indicated, which is the prominent melting endothermic peak showing the characteristics of observed S-SNEEDS (F1) at 132.33 °C, S-SNEEDS (F2) at 130.67 °C, S-SNEEDS (F3) at 130.17 °C, S-SNEEDS (F4) at 137.67 °C, and S-SNEEDS (F5) at 130.67 °C. All formulations show similar DSC thermogram patterns, but were distinguished by their enthalpy values (Figure 1).

In vitro drug release

In vitro drug release was conducted using the High-Performance Liquid Chromatography method. Qualitative analysis was carried out by observing the retention time, while quantitative analysis was conducted by determining the area or concentration, which was then calculated to obtain the quercetin content in the Bundung extract S-SNEEDS sample.

Antioxidant properties

The results of DPPH-radical scavenging antioxidant activity on the samples and quercetin are presented in Table 12. Of the five formulations, the highest antioxidant activity was exhibited by F1, as evidenced by the smallest IC_{50} value of 141.17.

Antioxidant result using FRAP

Antioxidant data from FRAP are listed in Table 13. The results show that F1 has the greatest antioxidant activity.

DISCUSSION

Optimized Bundung liquid self-nanoemulsifying drug delivery system (L-SNEDDS) formulation was achieved by using oleic acid as the oil phase, which increases bioavailability of water-soluble active substances and acts as an emulsifying agent, hence expected to bind Bundung extract effectively [15]. Non-ionic surfactants, such as Tween 80, are used in SNEDDS formulations as they are safer, biocompatible, and unaffected by pH compared to ionic surfactants [13]. Short-chain molecules or co-surfactants assist in reducing interfacial tension, thereby shrinking the particle size of nanoemulsions. Propylene glycol as a co-surfactant functions to enhance drug loading, accelerate self-emulsification time and regulate droplet size in nanoemulsions [16]. A transmittance approaching 100 % within the visible light spectrum indicates a high degree of transparency. The established requirement for optimal L-SNEDDS formula is > 90 % transmittance. The L-SNEDDS formulations that meet the requisite are F1 with 5 % oil phase, F2 with 10 % oil phase, F3 with 15 % oil phase, and F4 with 20 % oil phase. This indicates that SNEDDS formula has a globule size within the 20 - 200 nanometer range.

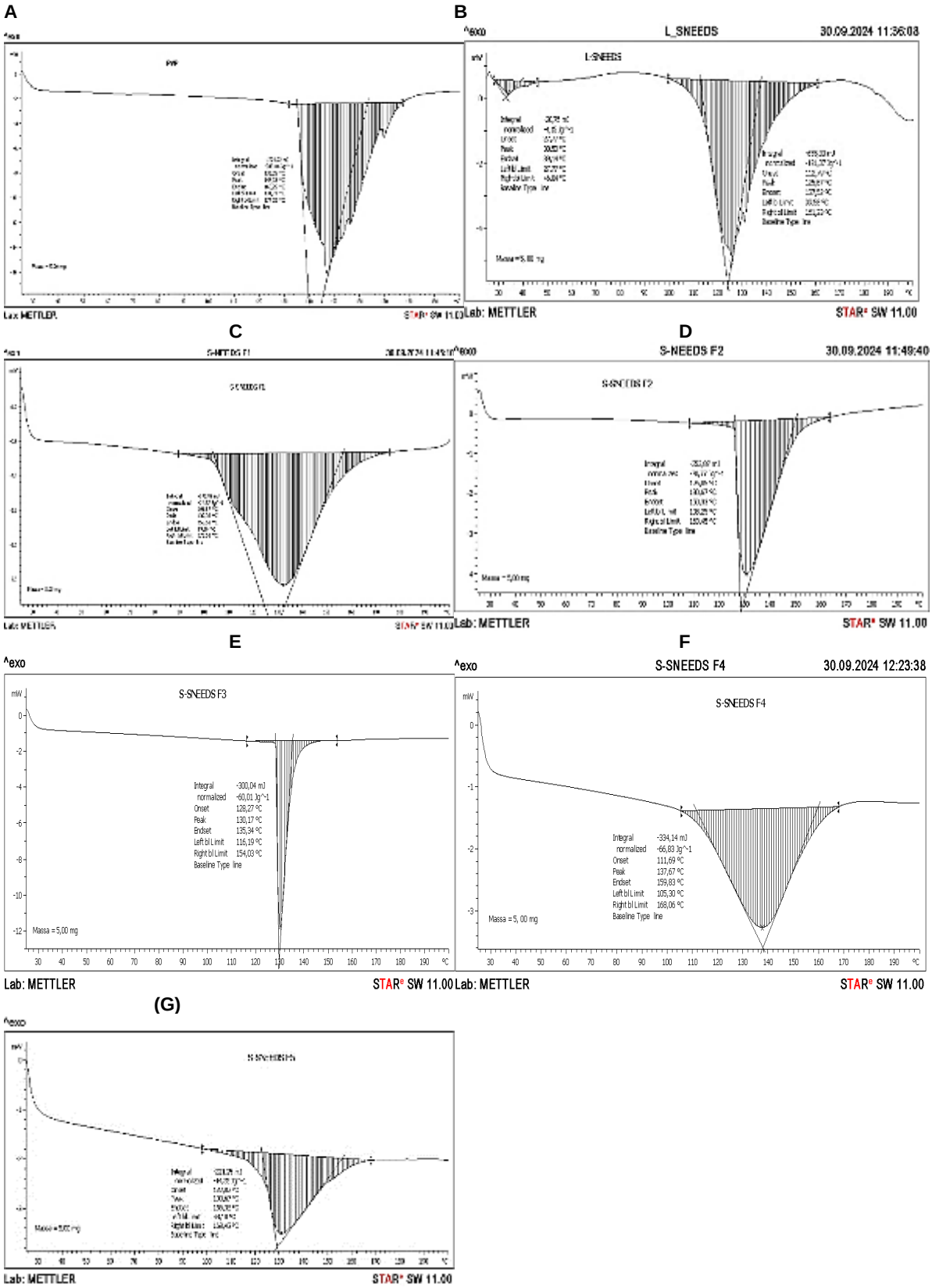

Figure 1: Differential scanning calorimetry results on (A) PVP, (B) L-SNEEDS, (C) S-SNEEDS Formulation 1, (D) S-SNEEDS Formulation 2, (E) S-SNEEDS Formulation 3, (F) S-SNEEDS Formulation 4, (G) S-SNEEDS Formulation 5

Table 12: Results of percentage inhibition and IC_{50} of S-SNEEDS on DPPH

Sample	Concentration (ppm)	Mean absorbance	Mean % inhibition	IC_{50} (µg/mL)	Category
Quercetin (Comparison Solution)	1	0.712	15.44	3.08	Very strong
	2	0.549	34.80		
	3	0.405	51.90		
	4	0.268	68.17		
	5	0.170	79.81		
	6	0.117	86.10		
Linear regression equation: y = 14.4171x+5.5767					
S-SNEEDS Formulation 1	100	0.462	45.13	141.17	Medium
	150	0.397	52.85		
	200	0.395	53.09		
	250	0.381	54.75		
	300	0.374	55.46		
	350	0.315	62.59		
Linear regression equation: y = 0.06x+41.5339					
S-SNEEDS Formulation 2	100	0.529	37.17	224.29	Very weak
	150	0.462	45.13		
	200	0.411	51.19		
	250	0.397	52.85		
	300	0.396	52.97		
	350	0.378	55.11		
Linear regression equation: y = 0.07x+34.2997					
S-SNEEDS Formulation 3	100	0.603	28.38	273.88	Very weak
	150	0.446	47.03		
	200	0.442	47.51		
	250	0.412	51.07		
	300	0.400	52.49		
	350	0.394	53.21		
Linear regression equation: y = 0.08x+28.0891					
S-SNEEDS Formulation 4	100	0.526	37.53	293.22	Very weak
	150	0.474	43.71		
	200	0.441	47.62		
	250	0.439	47.86		
	300	0.418	50.36		
	350	0.417	50.48		
Linear regression equation: y = 0.05x+35.3391					
S-SNEEDS Formulation 5	100	0.551	34.56	350.47	Very weak
	150	0.522	38.00		
	200	0.493	41.45		
	250	0.443	47.39		
	300	0.438	47.98		
	350	0.426	49.41		
Linear regression equation: y = 0.06x+28.9720					

Table 13: Percentage reducing power and antioxidant activity of S-SNEEDS in FRAP

Formulation	Average absorbance	Antioxidant activity (mgAAE/g extract)	Category
F1	0.650	21.53	Very Strong
F2	0.935	59.19	Strong
F3	0.903	55.17	Strong
F4	0.898	54.52	Strong
F5	0.910	56.08	Strong

An emulsion is considered good when the emulsification occurs rapidly in less than 1 minute with clear or transparent appearance [12]. An increase in the amount of oleic acid affects the emulsification time and function of other SNEDDS components. Oleic acid acts as a carrier of active substances. Oleic acid is capable of self-emulsifying and has a high drug-dissolving ability [15]. Globule sizes produced by Formulations 1, 2, 3, and 5 meet the nanometer range of 20 - 200 nm. Small particle size is influenced by the surfactants and cosurfactants used. Surfactants and cosurfactants reduce the free energy of the system so that it will prevent thermodynamic instability at changes in pH and volume [11]. Polydispersity index is a parameter that describes the extent of molecular mass distribution in a given sample. The acceptable polydispersity index value range is 0 – 0.5 [15]. Therefore, of the five formulations, F1 has the best particle distribution, with the smallest polydispersity index value of 0.165. The objective of ZP measurement is to assess the colloidal stability or physical stability of nanoemulsions. A ZP value of the system is deemed stable if it is less than -30 mV or greater than +30 mV [16]. Formulations 1, 2, 3 and 5 have ZP values that are not less than -30 mV and not more than +30 mV. The factor that affects the ZP value is the type of surfactant. The surfactant used is Tween 80, a non-ionic surfactant that tends to reduce ZP value [13].

Preparation of Solid-SNEDDS of Bundung extract was carried out using aerosol adsorbent composed of oil to form a powder that is free flowing, has hydrophobic properties, and easily releases active substances [13]. In addition, the use of lactose prevents electrostatic interaction of the resulting powder with the texturizing spray drying to increase its yield. The results obtained from this technique have yielded percentages ranging from 73.31 to 100 %. A small amount of weight loss occurred during the aerosil-making process, which is very lightweight, resulting in some masses flying in the air that could not be controlled. In developing Liquid-SNEDDS into Solid-SNEDDS, the most optimal formulation was identified as the third formulation, which yielded 100 %.

The appearance of solid self-nanoemulsifying drug delivery systems was categorized as clear (transparent or clear with a greenish tinge), unclear (cloudy), stable (no settling after 24 hours), and unstable (showing settling within 24 hours). Despite the difference in oil phase concentration, all formulations were transparent, stable and showed no phase separation after 24 h. The resistance to dilution results showed that the aqueous nanoemulsions were unstable at 10x dilution because phase separation or precipitation occurred after 24 h. However, the aqueous SNEDDS did not show precipitation or phase separation at 100x and 1000x dilutions on different dilution media. The observation results for each of the five formulations showed varying globule sizes. Compared to the particle size of Liquid-SNEEDS, there was a reduction in particle size after the Solid-SNEEDS dosage form was formed. This study reveals that solid-SNEEDS preparations are more stable than liquid-SNEEDS or nanoemulsion dosage. The evaluation results show that the higher the amount of antioxidant active substance incorporated into the oil phase, the bigger the globules formed.

The acceptable range of polydispersity index values is 0 to 0.5 [9]. Thus, formulations 1 and 3 are the formulations that form clear and transparent nanoemulsions with a size of less than 100 nm and a polydispersity index of less than 0.5. Therefore, these formulations will be developed further. Based on the range of polydispersity index, formulations 1 - 3 values ranged between 0.08 - 0.7, meaning that these formulations have the best operating distribution algorithm. A high positive or negative ZP is indicative of excellent physical stability, attributable to electrostatic repulsion between particles. Zeta potential values ranging from +30 to -30 mV are generally considered adequate to maintain good physical stability through electrostatic repulsion. Conversely, low ZP values result in particle aggregation and flocculation due to the predominance of van der Waals forces, leading to physical instability.

All formulations showed similar Differential Scanning Colorimetry thermogram patterns but could be distinguished by their enthalpy values. The higher the SNEDDS charge, the lower the enthalpy obtained. The distinction is seen in the amount of weight loss, where the higher the SNEDDS charge, the greater the weight loss. Additionally, there was no crystallization of PVP during the solidification process due to the disappearance of the PVP endothermic peak. The heating process in DSC also causes amorphization of the Bundung extract, thus increasing the water solubility of S-SNEDDS. In the amorphous form, the active substance induces a dissolution rate, improves physical stability, and exhibits higher water solubility. The S-SNEDDS produced is also endothermic or heat-absorbing, indicating that the S-SNEDDS enhance the solubility of the main compound in water, accelerate the dissolution rate, and improve the dosage form of physical stability [9].

In vitro drug release used quercetin as the positive control. Quercetin is a flavonoid that has antioxidant properties. The results of injecting a standard quercetin solution at a wavelength of 372 nm gave a retention time of 1.602 min. The highest quercetin level was found in the third formulation of S-SNEEDS capsules at the 60th minute in simulated intestinal fluid pH 6.8, which amounted to 0.008737 mg/mL. This indicates that quercetin levels in all samples were determined in the simulated intestinal fluid because the samples reached retention times similar to the retention time of quercetin standard solution and contain flavonoid compounds that have antioxidant properties. In an antioxidant test using DPPH (2,2-diphenyl-1-picrylhydrazyl), the percentage inhibition of Bundung extract S-SNEDDS shows that the higher the sample concentration, the higher the % inhibition, which implies that the higher the concentration, the higher the antioxidant content in S-SNEDDS of Bundung extract that reduces the activity of DPPH free radicals [14].

Antioxidant test using FRAP (Ferric Reducing Antioxidant Power) shows that S-SNEEDS of *Actinoscirpus grossus* extract formulation 1 has moderate antioxidant activity in the DPPH and strong activity in FRAP. This study shows that IC_{50} of S-SNEEDS gave disparate outcomes when subjected to disparate measurement methodologies. Nevertheless, both methods have a very high correlation, suggesting that they exert a mutual influence and replace each other [14].

CONCLUSION

This study indicates that Solid-SNEEDS are more stable than Liquid-SNEEDS or nanoemulsion dosage forms. The S-SNEDDS have favorable thermodynamic physical stability. The characterization shows that F1 of L-SNEEDS and S-SNEEDS of Bundung extract with 5 % oleic acid is the optimal formulation because it has the optimal percent transmittance, emulsification time, particle size, polydispersity value, and ZP value. Formulation 1 also met the criteria on appearance and passed the dilution resistance test, as well as having the highest antioxidant activity in both the DPPH and FRAP. Solid-SNEEDS capsule could be stable in simulated gastric and intestinal fluids, with an antioxidant activity of IC_{50} of S-SNEEDS, yielding disparate results with different methods of measurement.

DECLARATIONS

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Ethical approval

Ethical approval was obtained from the Ethics Committee of Sari Mulia University (approval No.175/KEP-UNISM/VI/2024).

Use of Artificial intelligence/Large language models

We also declare that we did not use Generative artificial intelligence (AI) and AI-assisted technologies in writing the manuscript.

Availability of data and materials

Datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Conflict of interest

No conflict of interest is associated with this work.

Contribution of authors

We declare that this work was done by the author(s) named in this article, and all liabilities pertaining to claims relating to the content of this article will be borne by the authors.

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