



Optimization of the Proportion of Surfactant, Co-Surfactant, and Candlenut Oil for Self-Nanoemulsifying Drug Delivery System (SNEDDS) of Secang Heartwood (*Caesalpinia sappan* L.) Methanolic Extract

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ABSTRACT. This study aimed to determine the optimum proportion of hazelnut oil, surfactants, and cosurfactants for SNEDDS of Secang Heartwood using the simplex lattice design (SLD) method using the Design-Expert software. The SNEDDS formula was prepared using Tween 80 and Croduret 50 ss as surfactants, propylene glycol as cosurfactant, and candlenut oil based on physical stability parameters: formula transmittance (%), separation phase, and emulsification time. The optimum SNEDDS formula was compared with the predictive value [$p > 0.05$] provided by the SLD; then extract the loading dose, accelerated stability test, analysis of particle size, and zeta potential. The optimum proportion of Tween 80-Croduret 50 ss, propylene glycol, and hazelnut oil, based on the SLD, was 62.43%; 22.57%; and 15.0%. The results showed that the transmittance was 93.2%; emulsification time was 74.67 seconds, and; separation phase was 0.89. The SLD's predictive values of the transmittance percentage, emulsification time, and separation phase were 94.98%, 78.97 seconds, 0.84, respectively. The results of the one-sample *t*-test statistical analysis showed no significant difference between the observative and predictive results. SNEDDS was found capable of loading 25.0 mg of secang heartwood methanolic extract in each system, with a particle size of 23.2 nm, a polydispersity index of 0.142, and zeta potential of +20.8 mV.

INTRODUCTION

Secang heartwood (*Caesalpinia sappan* L.) has great potential to develop as traditional medicine. It generally originates from South-East Asia but easily found in Indonesia (BPOM RI, 2008). Studies revealed that secang heartwood has the nature of an antibacterial, anti-inflammatory, hypoglycemic, vasorelaxant, anti-allergic, anti-acne, and antioxidant agent (Nirmal *et al.*, 2015). Nowadays, the current formulation technology development, especially the nanoparticle-based technology, grows rapidly and focuses on increasing the effectiveness of drug delivery systems (Martien *et al.*, 2012).

The formulation of nanoparticles can be designed using the self-nano emulsifying drug delivery system (SNEDDS), which is an isotropic system composed of natural or synthetic oils, surfactants, and cosurfactants. This system will be emulsified with the spontaneous forming phase oil in the water (Mahmoud *et al.*, 2013). In this study, the system employed candlenut oil as an oil phase (*Aleurites moluccana*) as a carrier containing long-chain fatty acids C-14, linoleic acids, and unsaturated fatty acids (Ako *et al.*, 2005), Tween 80 and Croduret 50 ss as surfactants, and propylene glycol as a cosurfactant.

The optimization of the formula was done by the Simplex Lattice Design method using the Design-Expert software version Stat-Ease Dx 9 Trial. Saryanti (2016) in her research performed an optimization of the proportion of surfactant, cosurfactant, and candlenut oil using the Simplex Lattice Design method. Both the upper and the lower limits of each component, namely 1:4:1 and 1:3:1, respectively, were analyzed using the Design-Expert software. Theoretically, the system can produce oil droplets sized 15.5 nm with a zeta potential of 38.9 mV, percentage of transmittance of 92%, emulsification time of 40 seconds, and is capable of accommodating up to extract as much as 120 mg/g. The purpose of this research was to get the optimum proportion of surfactant, cosurfactant, and candlenut oil by adopting the formula suggested by Saryanti (2016) to produce SNEDDS's methanolic extract of secang heartwood with physical testing parameters: percentage of transmittance,

emulsification time, accelerated stability, particle size analyzer, zeta potential, and the ability to load methanolic extracts of secang heartwood.

MATERIALS AND METHODS

The apparatus used in this study are stopwatch, rotary evaporator (Stuart), water bath (Grant), vortex (Maxi Mix II Thermolyne), sonicator (Branson 1510), hotplates magnetic stirrer (IKA ® C-MAG HS 7), yellow and blue tips (Thermo), refrigerator (Porkka), moisture balance analyzer (OHAUS), UV/Vis spectrophotometer (Genesys™), micropipette (Gilson), analytical balance (MetlerTeledo), Centrifuge (MiniSpin plus), pH meter (Eutech Instruments), pH-indicator strips (Merck), UV-Vis light 254nm-366nm, flacone, and tools (Pyrex glass).

The materials used are secang heartwood powder obtained from CV Herbadream (Grobogan, Central Java), secang heartwood fraction (The plant determination was carried out at the Biology Laboratory of the Faculty of Mathematics and Natural Sciences of Sebelas Maret University with the code 112/UN27.9.6.4/Lab/2017. The results showed that the plant used in this study was *Caesalpinia sappan* L.), silica gel TLC plates GF-254 (Merck), ethyl acetate pro analysis (Merck), n-hexane pro analysis (Merck), and technical methanol (Brataco); oil phase: candlenut oil (Agung Jaya); co-surfactants: propylene glycol (Agung Jaya); surfactants: Croduret® 50 ss (Croda) and Tween 80 (Agung Jaya); artificial gastric fluid (AGF): distilled water (Agung Jaya) and 37% HCl and NaCl (Merck).

Preparation of Methanolic Extracts of Secang Heartwood (*Caesalpinia sappan* L.)

The extraction process of secang heartwood powder was done by a maceration method with methanol as the solvent with a ratio of 1:10 for 24 hours. The maceration process was carried out with the same solvent within 2×24 hours. The results of the maceration were evaporated using a rotary evaporator at 55 °C until yielding a viscous extract to be calculated (Hangoluan, 2011).

Extract Characterization Test

Organoleptic characteristics of secang heartwood extract observation include color, odor, and consistency. The moisture content of the extract was characterized by weighing 1.0 g of it over an aluminum plate into the Moisture Ballance instrument operated at 105 °C.

Detection of Flavonoid Compound of Extract using the TLC Method

Flavonoid analysis from methanolic extract of secang heartwood extract was carried out using the Thin Layer Chromatography method, using the stationary phase of Silica Gel 60 F₂₅₄ and the mobile phase of ethyl acetate-n-hexane (6:4). Observations were performed under UV 254 and UV 366 lights (Warinhomhaun *et al.*, 2016).

Optimization of SNEDDS Formula with the SLD Method

The optimization of the compositions of SNEDDS composed of Tween 80 and Croduret 50 ss, propylene glycol, and candlenut oil was analyzed using the Design-Expert software. The ratios used were 1:3:1 [upper limit] and 1:5:1 [lower limit]. The ratio of surfactants (Tween 80:Croduret 50 ss) was 85%:15%. The Design-Expert software would generate 14 formulas with repetition on a four-point [Table-1]. The physical test of SNEDDS includes measuring the transmittance using a UV spectrophotometer (% of transmittance), emulsification time (seconds), and stability (F = 1). The SNEDDS system used was 4.0 g.

Loading Dose of Secang Heartwood Extract in the SNEDDS

Methanolic extract of secang heartwood can be loaded in the system with the weight series of 25.0 mg, 50.0 mg, and 100.0 mg. Secang heartwood was homogenized with a magnetic stirrer for 15 minutes and a sonicator for 15 minutes, and then incubated in water bath at 40 °C for 15 minutes. Observations from the solubility of the extract were done visually, followed by centrifugation test at 6000 rpm for 10 minutes. Observations were done regarding the solubility, precipitation, and separation.

Optimization of SNEDDS of Secang Heartwood Methanolic Extract

The Design-Expert software provided as many as 14 formulas of candlenut oil, surfactant, and cosurfactant in percentages (Table 1). The homogenization process was carried out with a vortex for 60 seconds, sonicated for

5 minutes, and incubated at 45 °C for 15 minutes. The homogenous and clear mixture became the first sign of a successful SNEDDS formula.

Observations on the SNEDDS Physical Stability

The 14 SNEDDS formulas were tested for the percentage of transmittance (%). 100.0 µL of SNEDDS was added with 5 ml of distilled water in a volumetric flask and homogenized with vortex for 60 seconds. The percentage of transmittance was measured by UV-VIS spectrophotometry at a wavelength of 650 nm, blank as distilled water (Patel *et al.*, 2011).

Emulsification time was observed in artificial gastric fluid (AGF). 1.0 mL of each SNEDDS formula was made up to 250.0 mL of artificial gastric fluid without pepsin. Each 1.0 L of medium contained 2.0 g of AGF NaCl and 7.0 mL of 37% HCl with a pH value of 1.2. The medium, namely the artificial gastric liquid without pepsin, was conditioned at 37 °C on the magnetic stirrer hotplate with a speed of 100 rpm. Observations were made on the time required for SNEDDS to form the o/w emulsion until the SNEDDS formula was completely emulsified on the medium.

Observations on the SNEDDS stability were carried out through freeze-thawing, which refers to the pioneering research (Avachat and Patel, 2015 and Yuliani *et al.*, 2016). 1.5 mL of SNEDDS was inserted into the Eppendorf tube and then was stored at 4 °C and 30 °C respectively for 24 hours for six cycles. The next stage was centrifugation at 6000 rpm for 10 minutes.

The data obtained were entered into the Design-Expert software with the distribution criteria in ranges [surfactant, cosurfactant, and candlenut oil]; the maximum percentage of transmittance; and the minimum emulsification time. The optimum formula was obtained with a desirability value close to 1, then compared with the SLD prediction formula with statistical analysis [student *t*-test].

Measurement of the Particle Size and Analysis of the Zeta Potential of the Optimum Formula

100.0 µL of SNEDDS was added with 5.0 mL of distilled water and then carefully reversed. After that, a mixture of 3.0 mL was inserted into the cuvette for analysis using the 100-SZ HORIBA. The measurement outputs were particle size, particle size distribution, zeta potential, and standard deviation values.

Data Analysis

The optimum proportion of the SNEDDS formula was obtained by the Simplex Lattice Design [Mixture Design] method using the Design-Expert software. The observation and prediction data of the SLD was done by statistical analysis: one sample *t*-test using the SPSS software.

RESULTS AND DISCUSSION

Characteristics of Secang Heartwood Methanolic Extract

The maceration method used in the extraction process was chosen because of its simplicity and ease of application with a yield of 6.8%. Methanolic solvent is a polar solvent that can take polar and non-polar compounds from secang heartwood (Hangoluan, 2011). The methanolic extract of secang heartwood obtained was red, had secang heartwood aroma, and had a thick consistency. The moisture content obtained was 1.2%, following the requirements that the moisture content of the extract should be less than 10% to avoid contamination by microorganisms (Ministry of Health, 2009).

Analysis of Flavonoids Contained in Secang Heartwood Methanolic Extract

The thin layer chromatography test (Figure 1) produced fractions on visual observation. There were compounds indicated to be pink, brown, and yellow, which represented the presence of anthocyanins, phenolic acids, and flavonoids, respectively (Divya *et al.*, 2013). The TLC Rf values in the methanolic extract of secang heartwood were 0.06; 0.14; 0.22; 0.31; 0.40; 0.51; 0.69; 0.90. TLC at an Rf value of 0.40 allowed the presence of brazilin and protosappanin A (Warinhomhaun *et al.*, 2016).

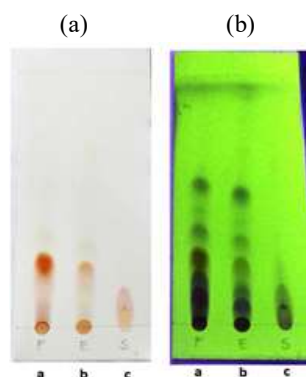


Figure 1. TLC analysis with the mobile phase of ethyl acetate: n-hexane (6: 4) with the stationary phase of Silica Gel 60 GF 254. Observations on visible light (a) and UV 254 light (b) of fraction of secang heartwood extract [a], fraction of secang heartwood methanolic extract [b], and fraction of the optimum formula of SNEDDS of secang heartwood methanolic extract [c].

Optimization using SLD SNEDDS Formulas

The upper and lower limits specified to be input in the Design-Expert software for oil:surfactant:cosurfactants were 1:3:1 and 1:5:1, respectively. The Simplex Lattice Design obtained 14 formulas which were further analyzed for their physical stability (Table 1). The combination of Tween 80-Croduret 50 ss surfactants was applied at a ratio of 85%:15%, which could be less than 20 nm (Saryanti, 2016). The yield of secang heartwood methanolic extract could contain 25.0 mg/g, which in the SNEDDS system showed the optimum stability and the appropriate emulsion transmittance percentage and time required. Propylene glycol is a cosurfactant that safe to use orally. The use of cosurfactants can reduce surface tension flexibility (Senapati *et al.*, 2016).

Table 1. The results of the analysis of 14 formulas with the SLD method using the DX software and the parameters of the physical stability responses of SNEDDS of secang heartwood methanolic extract.

Run	Percentage of Oil [A], Surfactant [B], and Cosurfactant [C] Based on SLD				Physical Stability of SNEDDS of Secang Heartwood Methanolic Extract		
	Oil (%)	Surfactant (%)	Cosurfactant (%)	Extract (g)	Transmittance (%)	Emulsification time (sec)	Separation phase (F -value=1)
1	15.0	60.0	25.0	0.1	76.3	49	0.88
2	16.7	61.7	21.7	0.1	95.2	133	0.87
3	16.7	66.7	16.7	0.1	98.4	129	1.00
4	15.0	65.0	20.0	0.1	98.9	82	0.86
5	20.0	65.0	15.0	0.1	100.2	147	0.92
6	15.0	70.0	15.0	0.1	98.5	165	1.00
7	25.0	60.0	15.0	0.1	81.5	94	0.57
8	25.0	60.0	15.0	0.1	88.6	58	0.50
9	20.0	60.0	20.0	0.1	70.6	69	0.64
10	21.7	61.7	16.7	0.1	88.9	113	0.67
11	20.0	65.0	15.0	0.1	94.9	90	0.64
12	18.3	63.3	18.3	0.1	96.2	83	0.69
13	15.0	70.0	15.0	0.1	98.3	96	1.00
14	15.0	60.0	25.0	0.1	85.6	44	0.67

*SNEDDS systems: 4 g

The physical analysis parameters include transmittance value; a high transmittance value indicates a small particle size, which when dispersed in water makes the solution visually clear because of the very small size of the oil droplets (Ahmad *et al.*, 2014). Emulsification time describes the duration of the SNEDDS formula from the early drop until emulsified to form a homogeneous mixture on medium with light agitation (Puspita *et al.*, 2016; Prihapsara *et al.*, 2017). According to Sakthi *et al.* (2013), emulsions have various emulsification times, namely less than 30 seconds, less than 1 minute, less than 2 minutes, and between 4 – 5 minutes. The centrifugation test aims to see the separation of the oil phase by destroying the emulgator/surfactant layer that is absorbed around the grain. The freeze and thaw method was used to determine the physical stability of the SNEDDS formula at different

temperature treatment periods in a relatively short time (Yuliani *et al.*, 2016). A formula that has not undergone deposition or is stable has a phase separation value close to 1, $(F) = 1$.

The Optimum Formula of the SNEDDS of Secang Heartwood Methanolic Extract

Experimental designs are often used in research to provide maximum information with only a few experiments. In this research, Simplex Lattice Design was used to optimize component proportions. Candlenut oil (A), Tween 80-Croduret 50 ss (B), and propylene glycol (C) were selected as independent factors. The ANOVA statistical analysis explained that the response model with the transmittant value was quadratic, while the emulsification time and stability showed a linear model. The effect of the model proportion of oil, surfactant, and cosurfactant of each formula must have a significant difference. The lack of fit value could explain the closeness of observation to software's prediction. It must show no significant difference between the results of observational research and the prediction of SLD (Bolton, 2002). Table 2 shows that there is no significant effect on the mixture of oil, surfactant, and co-surfactant on the parameters emulsion response time and SNEDDS stability. The response of the transmittance value shows that the surfactant and cosurfactant components in the mixture have the greatest effect, which can increase the percent value of the transmittance coefficient by +0.51.

The profile of the mixture composition was determined by Simplex Lattice Design based on the equation: $Y = \alpha_1(A) + \alpha_2(B) + \alpha_3(C) + \alpha_{12}(A)(B) + \alpha_{13}(A)(C) + \alpha_{23}(B)(C) + \alpha_{123}(A)(B)(C)$, in which Y is the response, ABC is the component proportion, and α is the coefficient. The profile properties of the mixture is determined by Simplex Lattice Design based on the equation: $Y = \alpha_1(A) + \alpha_2(B) + \alpha_3(C) + \alpha_{12}(A)(B) + \alpha_{13}(A)(C) + \alpha_{23}(B)(C) + \alpha_{123}(A)(B)(C)$. Where Y is the response, ABC is the proportion of components, and α is the coefficient.

Table 2. Analysis of the physical stability parameters of SNEDDS of secang heartwood methanolic extract using Software Design Expert based on mathematical model and statistical analysis [ANOVA].

Physical response of SNEDDS Formula	Mathematic Equations	Mathematic Model	<i>p</i> -value [ANOVA] $p > 0.005$
Transmittance (%)	$Y = -5.97(A) - 4.12(B) - 19.91(C) + 0.29(A)(B) - 0.310(A)(C) + 0.51(B)(C)$	<i>quadratic</i>	0.01
Emulsification time (second)	$Y = -1.66A + 3.28B + 4.46C$	<i>Linear</i>	0.04
Separation Phase (<i>F</i> -value)	$Y = -0.03(A) + 0.02(B) - 2.52(C)$	<i>Linear</i>	0.0004

The numbers in the triangle show the proportion of the oil, surfactant, and cosurfactant in the modeling. The highest response is shown in the red area; the yellow area shows lower response, and; the green and blue areas show even lower response (Figure 3). The formula was chosen based on the greatest desirability value, which was around 0.663 on the superimpose diagram, which meant that the formula would produce the most optimal formula according to the desired target characteristics. The optimum proportion of candlenut oil, surfactants, and cosurfactants was 15%, 62.43%, 22.57%, respectively.

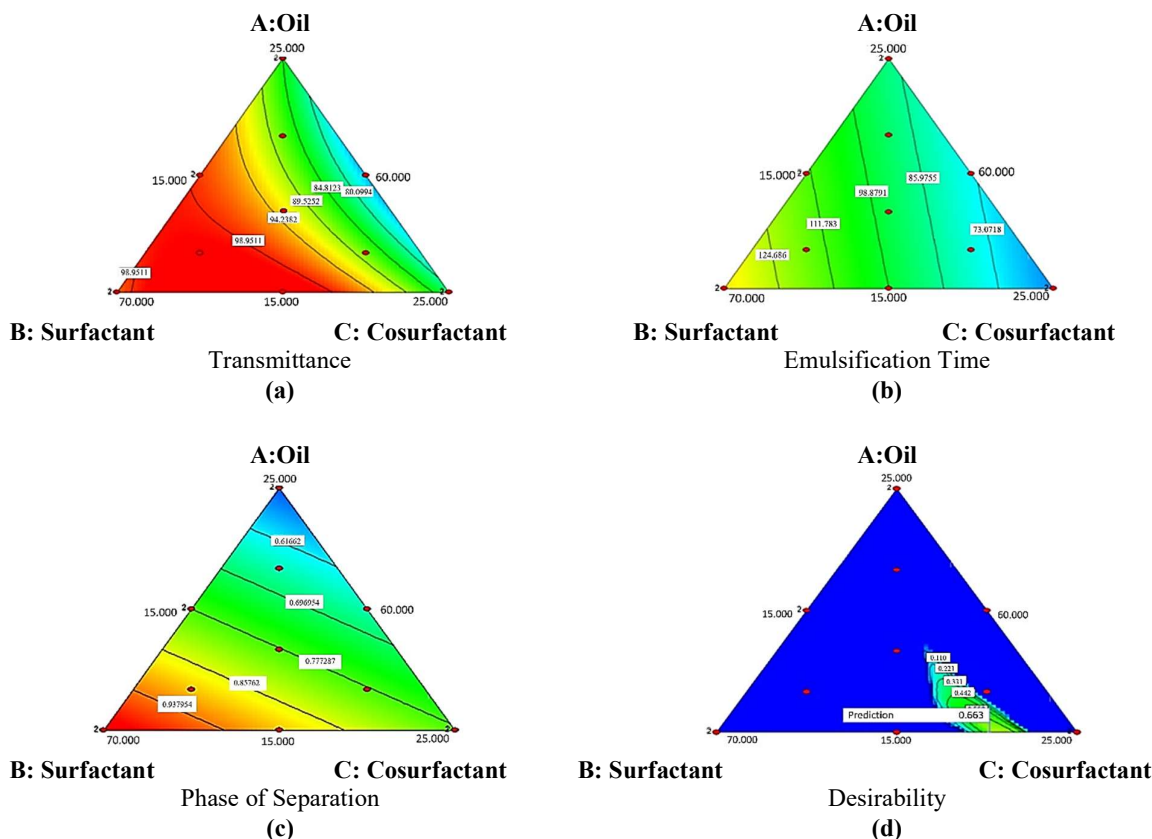


Figure 3. The counterplot diagram of the SNEDDS stability response parameters: transmittance (a), emulsification time (b), and phase of separation (c). The superimpose diagram shows the optimum area of candlenut oil :surfactant:cosurfactant (d).

The values of the prediction obtained by the Simplex Lattice Design method showed the predictive value of the software against the observative value given by the optimum formula. Based on the test results as presented in Table 3, the percentage of transmittance (clarity), emulsification time, and phase separation (stability) show that the results of the observation on the optimum formula were not significantly different compared to the prediction of Design-Expert software (p -value $0.05 >$]

Table 3. Results of verification of SLD predictive values compared to the observative values of the Optimum Formula of SNEDDS of secang heartwood methanolic extract.

The response of physical stability	SLD Prediction	Observation	Sig-value [$p > 0.05$]
Transmittance (%)	94.98	94.32±SE 0.924	0.56
Emulsification time (second)	78.97	74.67±SE 0.882	0.10
Phase separation (F)	0.84	0.89±SE 0.019	0.11

Measurement of PSA and the Zeta Potential of the SNEDDS Optimum Formula

The size of the droplet of SNEDDS of secang heartwood methanolic extract was 23.2 nm with a polydispersity index of 0.142 (Figure 4). The low polydispersity index shows a small particle size distribution of the average particle size in SNEDDS (Avachat and Patel, 2014). The uniformity of particle size can increase bioavailability because the drug will absorb more quickly at the same rate (Balakumar *et al.*, 2013). The zeta potential value obtained from SNEDDS of secang heartwood methanolic extract was + 20.8 mV (Figure 5). A high zeta potential value will result in a relatively stable material. A positive zeta potential value indicates that the system has a positive SNEDDS charge and is sufficient to ward off repulsiveness so that it will produce a stable formula (Dash *et al.*, 2015).

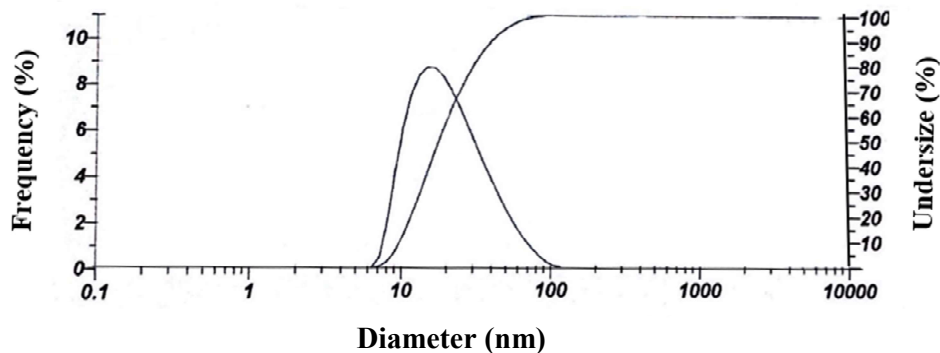


Figure 4. Particle size measurement output.

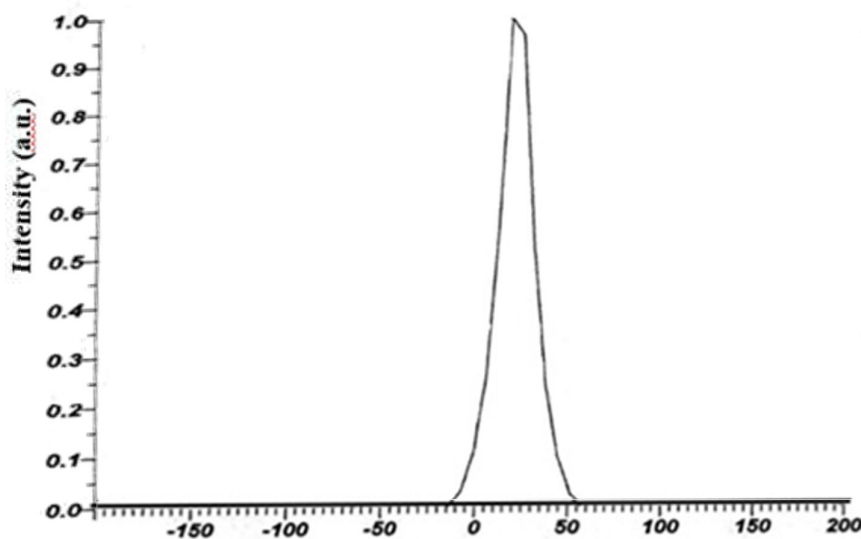


Figure 5. Zeta potential measurement output.

CONCLUSION

The optimum proportion of Tween 80-Croduret 50 ss, propylene glycol, and candlenut oil, based on the physical stability of SLD, was 62.43%:22.57%:15.0%. The results of observations showed a transmittance percentage of 94.32%; emulsification time of 74.67 seconds; and separation phase of 0.89. Meanwhile, the SLD's predictive results got a transmittance value of 94.98%, emulsification time of 79 seconds; and separation phase of 0.84. The results of the one-sample *t*-test statistical analysis showed that there was no significant difference between the observation and prediction systems of SLD. SNEDDS could load 25.0 mg of secang heartwood methanolic extract in each SNEDDS system, with a particle size of 23.2 nm, a polydispersity index of 0.142, and zeta potential of +20.8 mV.

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