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Self-nanoemulsifying drug delivery system (SNEDDS) of *Amomum compactum* essential oil: Design, formulation, and characterization

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ABSTRACT

The main purpose of this study was to formulate and to characterize a self-nanoemulsifying drug delivery systems of cardamom (*Amomum compactum*) essential oil. The optimum formula was analyzed using a D-Optimal mixture designed by varying concentrations of oil component (*Amomum compactum* essential oil and virgin coconut oil), Tween 80, and polyethylene glycol 400 (PEG 400) (v/v) using a Design Expert® Ver. 7.1.5. Emulsification time and transmittance were selected as responses for optimization. The optimum formula was characterized by droplet size, zeta potential, viscosity, thermodynamic stability, and morphology using Transmission Electron Microscopy. SNEDDS of *Amomum compactum* essential oil was successfully formulated to SNEDDS using 10% of *Amomum compactum* essential oil, 10% of virgin coconut oil, 65.71% of Tween 80, and 14.29% of PEG 400. The characterization result showed the percent transmittance 99.37 ± 0.06, emulsification time 46.38 ± 0.61 s, the average droplet size 13.97 ± 0.31 nm with PI 0.06 ± 0.05, zeta potential −28.8 to −45.9 mV, viscosity 187.5 ± 0 mPa·s, passed the thermodynamic stress tests, and indicated spherical shape. The study revealed that the formulation has increased solubility and stability of *Amomum compactum* essential oil.

INTRODUCTION

Colonization of microbes in the gastrointestinal tract has an impact on the performance of broiler chickens (Dibner *et al.*, 2008). Pathogenic microbes produce toxins which damage the physical structure of the small intestine cell wall, which is crucial in the micronutrient absorption process. Infection of bacteria in poultry and livestock production could be prevented with antibiotics (Apata, 2009). However, antibiotics as growth promoters have already restricted in many countries (Verstegen and Williams, 2002).

Essential oil could be used as an antibiotic replacement because of its ability to inhibit the growth of pathogenic bacteria (Akhtar *et al.*, 2013). The major component *Amomum compactum* essential oil is composed of 1.8 cineole (eucalyptol) 59.3%; d-limonene 29%; α-pinene 6.5%; β-pinene 4.8%; and α-terpineol 0.4% (Huang *et al.*, 1999). The main constituent 1,8 cineole is known to have strong antibacterial activity. The 1,8 cineole has been reported to inhibit the growth of enteric bacteria *Escherichia coli* O157:H7, *Salmonella typhimurium, Klebsiella pneumoniae, Enterobacter aerogenes*, and *Methicillin-resistant Staphylococcus aureus* (Nanasombat and Lohasupthawee, 2005; Zengin and Baysal, 2014; Jamil *et al.*, 2016).

Essential oil also enhances the production of digestive secretions, an antioxidant component, and improve the immunity (Zeng *et al.*, 2015). However, their potency as an alternative to replace in-feed antibiotic decrease due to their volatile nature, insoluble in water and unstable (Jamil *et al.*, 2016). Nanotechnology is an attractive technology in functional applications in the interdisciplinary field. Generally, nanotechnology has a size of 10^{-9} m. The size of nanoemulsion ranges 1-100 nm (Neethirajan and Jayas, 2011). Nanotechnology in essential oils has provided the benefits that are the active compounds more easily absorbed and more efficiently transported to the site of infection (Natrajan *et al.*, 2015). Self-

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nanoemulsifying drug delivery systems have been proposed because of their ability to increase solubility and stability of essential oil-based formulations (Pedro *et al.*, 2013).

Amomum compactum essential oil is limited orally application because of its low oral bioavailability. In this investigation, a new self-nanoemulsifying drug delivery system was developed to improve the solubility and stability of *Amomum compactum* essential oil.

MATERIALS AND METHODS

Materials

The main material *Amomum compactum* seeds were obtained from local suppliers in Bantul Regency, Yogyakarta, Indonesia. Chemicals and other materials used were: Tween 80 (Kao Indonesia Chemical, Bekasi, Indonesia), polyethylene glycol 400/PEG 400 (idCHEM Co., Ltd., Kyunggi, South Korea), virgin coconut oil (Healthy Co, Yogyakarta, Indonesia), sunflower oil, corn oil, canola oil, and soybean oil. Artificial gastric fluid (AGF) consisted of distilled water (Brataco, Yogyakarta, Indonesia), hydrochloric acid 37%, and NaCl (Merck, Germany).

Methods

The essential oil extraction

The extraction technique of *Amomum compactum* seed essential oil was prepared with steam distillation method. A kilogram of *Amomum compactum* seeds was loaded into the still distillation tank and eight liters of water were added. The rid secured tightly to steam distillation with the collection of the oils starting after a heating time of 30-50 minutes.

Formulation of SNEDDS

Selection of carrier oil

The solubility of *Amomum compactum* seed essential oil in carrier oil was determined. Virgin coconut oil (VCO), sunflower oil, corn oil, canola oil, and soybean oil were screened. Total 4 ml *Amomum compactum* essential oil was continually added to 10 ml carrier oil with vigorous vortex and continued with visual observation.

SNEDDS preparation

SNEDDS were prepared by mixing various combinations of *Amomum compactum* oil with a carrier oil (virgin coconut oil), Tween 80, and PEG 400. The formulations were subjected to sonication using ultrasonicator (J.P Selecta, Barcelona, Spain) for 10 minutes and water bath (Memmert GmbH & Co.KG, Schwabach, Germany) at 37ºC for 15 minutes (Abouelkassem *et al.*, 2015).

Percent transmittance

The sample was prepared by mixing 0.1 ml of SNEDDS with 5 ml distilled water using vortex for 30 seconds. UV spectrophotometer was used to measure the percent transmittance at 650 nm (Sharma *et al.*, 2012).

Emulsification time

Each formulation was dropped wise added to 500 ml of artificial gastric fluid of pH 2 in separate glass beakers at 37 ± 2ºC and contents were gently stirred using magnetic stirrer at 100 rpm. Depending on visual appearance and time taken for self-emulsification (Khan *et al.*, 2015).

VCO as a carrier oil, surfactant (Tween 80), and co-surfactant (PEG 400) in different ratios, SNEDDS with good emulsification and solubility characterization were selected (Ansari *et al.*, 2014). The transmittance values of formulation above 90% indicate the self-nano emulsification efficiency of the SNEDDS (Narkhede et al., 2014). Ratio 1:4:1 (oil: surfactant: co-surfactant) was chosen for development formulation. When it reaches oil phase, essential oil was added.

Optimization of SNEDDS

The subsequent experimental study was determined made from the three-component system: X_1 the oil phase (a mixture of *Amomum compactum* essential oil and VCO, 1:1 v/v), X_2 the surfactant (Tween 80), and X_3 the co-surfactant (PEG 400). The responses (Y_1 = emulsification time, Y_2 = transmittance) were interpreted by Design Expert® software version 7.1.5. (Stat-Ease, Minneapolis, MN). The results of SNEDDS were reproduced in three replicates for emulsification time and transmittance. The data were analyzed with single sample t-test analysis.

Characterization of SNEDDS

Droplet size measurement

Droplet size and polydispersity index of nanoemulsion were determined using Zetasizer Nano ZS (Horiba Scientific SZ-100, Horiba, Kyoto, Japan). The samples were diluted with a ratio of 1: 100 (v/v) using distilled water and repeated in triplicate (Balakumar *et al.*, 2013).

Zeta potential analysis

Zeta potential of the optimum formulations was determined by dynamic light scattering using particle size analyzer (Horiba Scientific SZ-100, Horiba, Kyoto, Japan). The samples were diluted with a ratio of 1:100 (v/v) with distilled water and repeated in triplicate (Balakumar *et al.*, 2013).

Viscosity measurement

The viscosity of SNEDDS was measured using small sample adapter of Brookfield cone and plate rheometer (Model LV2, Brookfield Engineering Laboratories, Stoughton, MA, USA) 12 rpm at room temperature (25 ± 1ºC), repeated in triplicate (Sakulku *et al.*, 2009).

Thermodynamic stability studies

The optimum formula was subjected to further thermodynamic stability studies.

(1) Heating-cooling cycle: Six cycles between 4ºC and 45ºC at each temperature for not less than 48 hours were studied. The formulations that passed at this temperature without any signs of instability (creaming, cracking) were subjected to centrifugation test.

(2) Centrifugation: The formulations were centrifuged for 30 minutes at 3500 rpm. The formulations that did not show any signs of instability (creaming, cracking) were chosen for the freeze-thaw cycle.

(3) Freeze-thaw cycle: The formulations were placed in temperatures between −21ºC and 25ºC with storage at each temperature for not less than 48 hours. Passed formulations were centrifuged 5 minutes at 3000 rpm (Shafiq *et al.*, 2007; Parmar *et al.*, 2011).

The morphology of SNEDDS

The SNEDDS morphology was observed by Transmission Electron Microscopy Joel JEM-100 CX (Joel, Tokyo, Japan). The SNEDDS samples were diluted with water (1: 1000), a sample drop was stained with 2% phosphotungstic acid solution for 30 s and placed on a copper grid (Zhao *et al.*, 2010).

RESULTS

Formulation of SNEDDS

Selection of carrier oil

The solubility of essential oil in the oil phase was important to keep the active components in the solubilized form and it also avoiding the deposition of the active component of emulsification in the intestinal lumen. The higher of solubility causes the required quantity of oil in the formulation is low and consequently, the amount of surfactant and co-surfactant required for emulsification time is low. It was observed that the solubility of *Amomum compactum* essential oil was higher in VCO in comparison to sunflower oil, corn oil, canola oil, and soybean oil (Table 1). The solubility essential oil in VCO was more clearly than sunflower oil, corn oil, canola oil, and soybean oil. VCO has a much shorter chain of C atoms compare with other vegetable oil, so making good solubility and become more transparent (Tristiana *et al.*, 2014).

Table 1: Solubility study of *Amomum compactum* essential oil.

Carrier oil	Visual observation
VCO	Clearly
Sunflower oil	Cloudy
Corn oil	Cloudy
Canola oil	Cloudy
Soybean oil	Cloudy

SNEDDS preparation

The compatibility of oils, surfactants, and co-surfactants to acquire a higher transmittance was the essential foundation in the fabrication of nanoemulsion. The preliminary ratio was tested to determine the quantity of oil (virgin coconut oil), surfactant (Tween 80), and co-surfactant (PEG 400) for further characterization. The effect of surfactant ratio on transmittance is presented in Table 2. Furthermore, the result (Table 3) could be used as a reference for optimization and treatment 2 was chosen.

Table 2: The effect of surfactant ratio on transmittance.

Oil (ml)	Surfactant (ml)	Co-surfactant (ml)	Transmittance (%)
1	1	1	9.37 ± 5.27
1	2	1	55.00 ± 2.05
1	3	1	70.40 ± 13.36
1	4	1	98.43 ± 0.85
1	5	1	98.73 ± 0.92
1	6	1	99.13 ± 0.67
1	7	1	98.60 ± 0.36

Table 3: The addition of essential oil in the oil phase.

Treatment	VCO (ml)	Essential oil (ml)	Tween 80 (ml)	PEG 400 (ml)	Transmittance (%)	Visual observation	Emulsification time (s)
1	0.75	0.25	4	1	99.57	Transparent	57.9
2	0.5	0.5	4	1	99.4	Transparent	61.7
3	0.25	0.75	4	1	98.63	Cloudy	76.16

Formulation optimization of SNEDDS

The optimization formula has aimed to determine the levels of the variables from which product has the best quality. By means of the response surface methodology the influence of three independent variables (the amount of oil, Tween 80, and PEG 400) in two dependent variables (emulsification time and transmittance). The selected formulation was based on the "trading off" of various response variables, i.e. maximizing the percent of transmittance and minimizing the emulsification time.

The formula 1: 4: 1 was used as the basis for finding the optimal formula. The comparison range of oil component: Tween 80: PEG 400 is 1: 3: 1 and 1: 5: 1 (v/v), respectively. The data were used to determine the lower limit and upper limit as in Table 4. In this optimization, D-optimal mixture design was used to find the optimal formula on various formulas made (Table 5). The response was transmittance and emulsification time. The analysis of variance and lack of fit tests are presented in Table 6.

The value of emulsification time was illustrated by colors that follow the spectrum of light (Wiwiek *et al.*, 2017). The high emulsification time value is indicated by increasingly close to red. Figure 1(a) presents a normal probability plot residuals for emulsification time. The straight line represents normally distributed residuals and there was no evidence to indicate the possibility of outliers. (b) The data is around the 0 line and no one stands out.

Table 4: Ranges of the factors investigated using D-Optimal mixture design.

Independent variables (factors)	Range	
	Low	High
X_1 = Quantity of oil	14.29	20
X_2 = Quantity of Tween 80	60	71.43
X_3 = Quantity of PEG 400	14.29	20

The model (Figure 2) showed the significant ($p < 0.05$) relationship between the quantity (oil, Tween 80, PEG 400) and

the response (emulsification time). The lack of fit analysis (Table 6) showed no significant ($p > 0.05$) means there had a high match between predicted value and actual data.

Table 5: Formulation design (Design Expert® Ver. 7.1.5.).

Run	Oil component (%)	Tween 80 (%)	PEG 400 (%)	Transmittance (%)	Emulsification time (s)
1	17.737	67.973	14.290	99.6	53.48
2	14.607	66.947	18.446	99.7	51.36
3	14.293	71.417	14.290	99.9	42.43
4	20.000	60.005	19.995	99.8	74.40
5	20.000	60.005	19.995	99.1	75.17
6	14.293	71.417	14.290	99.1	49.00
7	16.764	66.028	17.208	99.8	42.89
8	20.000	65.220	14.780	99.8	65.00
9	17.493	62.507	20.000	99.6	70.94
10	17.454	64.168	18.378	99.8	43.17
11	14.986	65.014	20.000	99.6	48.03
12	14.449	68.774	16.777	99.9	53.74
13	14.986	65.014	20.000	99.5	49.33
14	20.000	62.616	17.384	99.6	61.64
15	17.737	67.973	14.290	99.8	55.64
16	20.000	65.220	14.780	99.5	57.80

Table 6: Analysis of the Quadratic Model.

Response	*F* value	Probability > *F*
Y_1 = Emulsification time		
Model	7.94	0.0034 significant
Lack of fit	0.85	0.5496 nonsignificant
Y_2 = Transmittance		
Model	2.82	0.0959 nonsignificant
Lack of fit	0.87	0.5907 nonsignificant

Emulsification time was known as a great importance parameter for describe the stability of the system and prepare emulsification in gastric fluid of SNEDDS self-emulsifying characteristics (Singh *et al.*, 2011). Tween 80 as a non-ionic surfactant were found to have good solubility and better emulsification ability, that allowed rapid dispersion when in contact with biological fluids (Sanka *et al.*, 2016). As shown in Figure 2, the time required for emulsification decreases with the increased concentration of Tween 80. PEG 400 commonly use in nanoemulsion formulation to increase solubility and bioavailability (Nekkanti *et al.*, 2011).

Percent transmittance

Percent of transmittance was used to observe the self-emulsification process by measuring the transmittance of the solution during dissolution as the emulsification process happened (Villar *et al.*, 2012).

The value of the transmittance was illustrated by colors that follow the spectrum of light (Wiwiek *et al.*, 2017). The higher transmittance value indicated more approach to red. Figure 3(a) presented a normal probability plot residuals for transmittance. The straight line showed normally distributed residuals and there was no evidence to indicate the possibility of outliers. (b) The data is around the 0 line and no one stands out.

The special cubic model (Figure 4) showed that there was no significant ($p > 0.05$) relationship between the quantity (oil, Tween 80, PEG 400) and the response (transmittance). The lack of fit analysis (Table 6) resulted not significant ($p > 0.05$) means there was a high match between predicted value and actual data.

Based on Figure 5, the recommended optimum formula was 20% oil, 65.71% Tween 80, and 14.29% PEG 400 with desirability 0.790.

The result of the optimum formula was verified with single sample t-test with OpenStat® (Table 7). The p-value of emulsification time was higher than 0.05 which implied that there was no significant difference between predicted value and actual data (Winarti *et al.*, 2017).

Table 7. Verification of optimum formula with single sample t-test.

Response	Predicted value	Actual data ± SD	p-value
Emulsification time	45.049	46.38 ± 0.61	0.065
Transmittance	99.151	99.37 ± 0.06	0.023

Characterization of SNEDDS

Droplet size

The mean droplet size and polydispersity-index (PI) were calculated from volume, intensity, and bimodal distribution assuming spherical particles. PI was a measure of particle homogeneity (Patel *et al.*, 2010). The particle size distribution of the selected formulation was found to be 13.97 ± 0.31 nm, which was highly desirable. The polydispersity-index (PI) was low (0.06 ± 0.05), indicating that the system had narrow size distribution. The droplet size was an important factor in SNEDDS formulation, as this determines the rate and extent of drug release as well as absorption and improve bioavailability (Parmar *et al.*, 2011). The oil phase positively influenced the formation of droplet

size (Shanmugam *et al.*, 2011). The addition of surfactants to the nanoemulsion systems caused the interfacial film to stabilize and condense (Villar *et al.*, 2012).

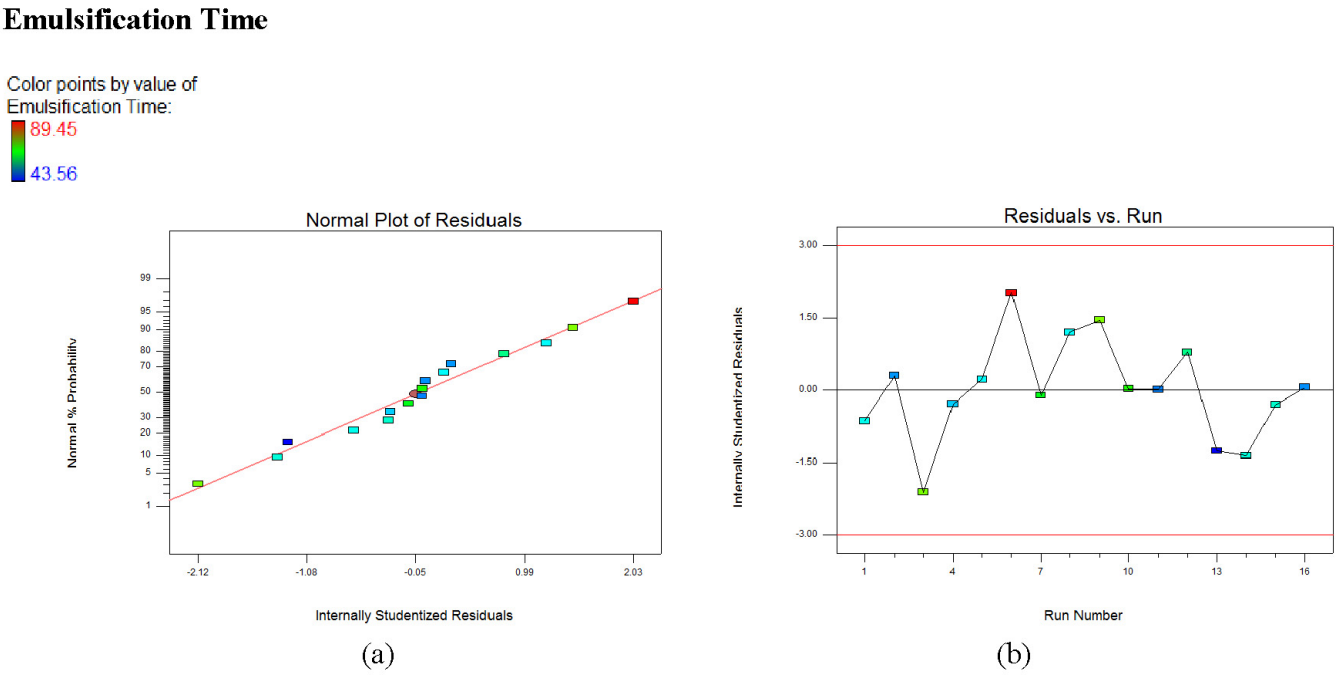

Fig. 1: Graph of a residual parameter of emulsification time (Design Expert® Ver. 7.1.5.).

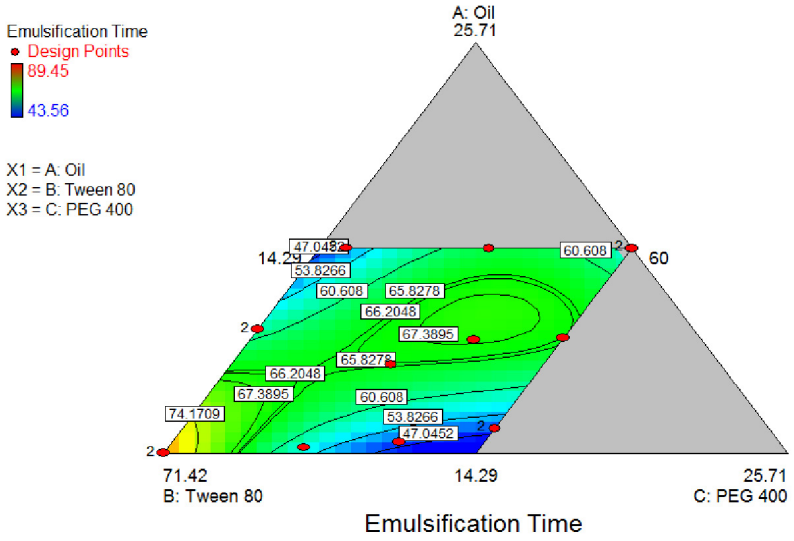

Fig. 2: Special model cubic of emulsification time graphic values (Design Expert® Ver. 7.1.5.).

Zeta potential

Zeta potential values of the selected formulation were found in the range of −28.8 to −45.9 mV. The high negative charge was probably due to the presence of free fatty acids present in the formulation (Balakumar *et al.*, 2013). Zeta potential values which were less −30 mV or greater than 30 mV indicated a stable nanoemulsion (Yang and Benita, 2000). Therefore, the results of zeta potential measurement indicated stable SNEDDS formulation.

Viscosity measurement

The viscosity of the selected formulation was found to be 187.5 ± 0 mPa.s. The viscosity of Tween 80 was high (425 mPa.s) so the inclusion of PEG 400 could improve the self-emulsification (Rowe *et al.*, 2009). The lower viscosity of SNEDDS mainly due to the smaller droplet size (Shakeel *et al.*, 2013).

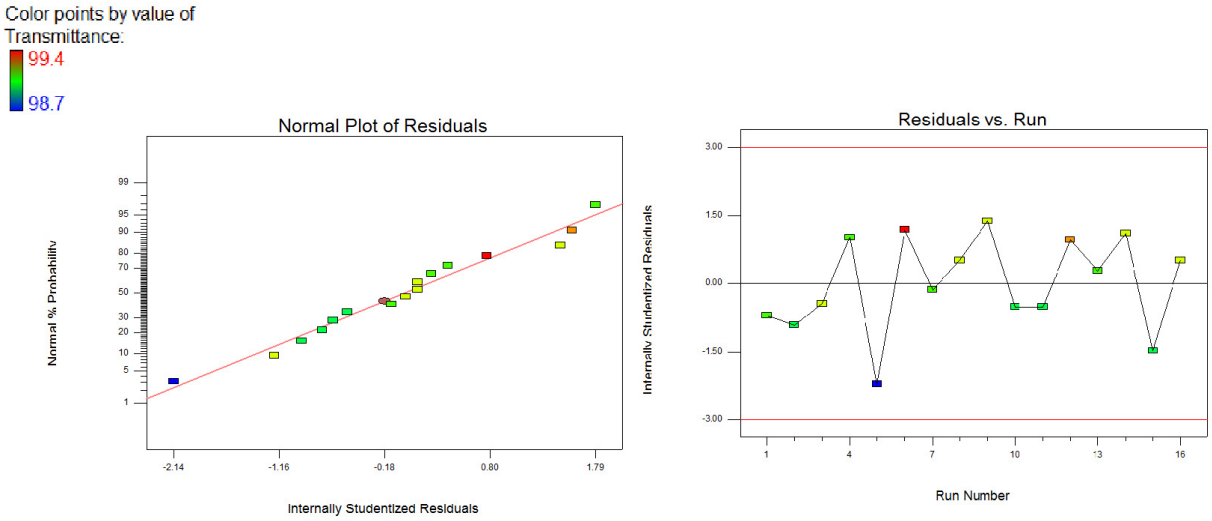

Fig. 3: Graph of a residual parameter of transmittance (Design Expert® Ver. 7.1.5.).

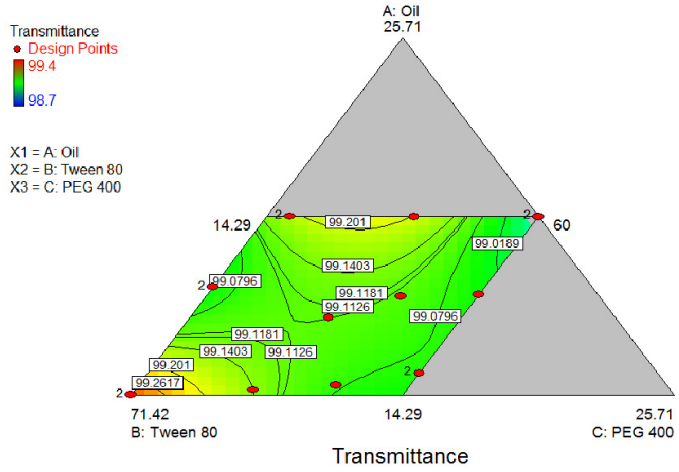

Fig. 4: Special model cubic of transmittance graphic values (Design Expert® Ver. 7.1.5.).

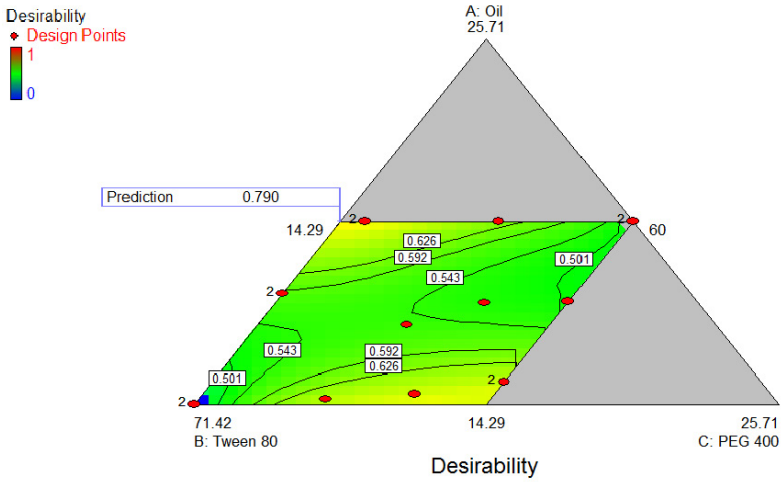

Fig. 5: Superimposed of special model cubic emulsification time and transmittance.

Thermodynamic stability

It was observed that the optimum formulation passed the thermodynamic stress tests (Table 8). The optimum formulation did not show any signs of instability indicated stability of the system. The system of SNEDDS should be spontaneous emulsification in the intestinal tract to form a nanoemulsion. The SNEDDS system must have sufficient quality to withstand stability in order to restrain creaming, cracking, or precipitating. The selected formulation was subjected to heating-cooling cycle, centrifugation, and freeze-thaw cycle exposure (Bandyopadhyay *et al.*, 2012).

Table 8: Thermodynamic stability test.

Stability test	Replication 1	Replication 2	Replication 3
Heating-cooling cycle	√	√	√
Centrifugation	√	√	√
Freeze-thaw cycle	√	√	√

Transmission electron microscopy (TEM)

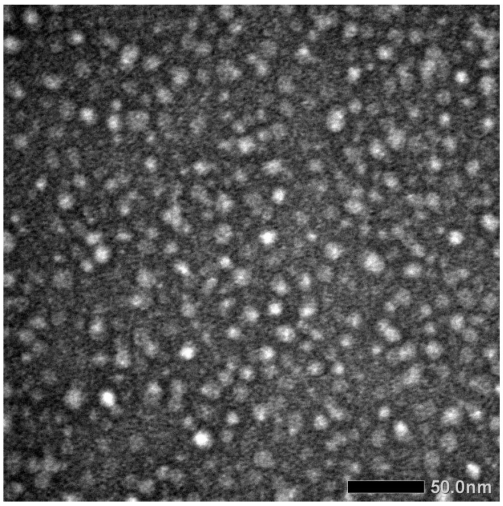

Fig. 6: Transmission electron micrograph of SNEDDS with magnification 80 K.

The nanoemulsion appeared a bright spot on a dark background with a spherical shape which homogenous droplet size (Figure 6). Different and non-aggregated nanoemulsion droplets indicated physically stable nanoemulsion (Badran *et al.*, 2014).

CONCLUSION

SNEDDS of *Amomum compactum* essential oil could be formulated with ratio 10% of *Amomum compactum* essential oil, 10% of virgin coconut oil, 65.71% of Tween 80, and 14.29% of PEG 400. The formulation had a high percent transmittance 99.37 ± 0.06, low emulsification time 46.38 ± 0.61 s, small droplet size 13.97 ± 0.31 nm with PI 0.06 ± 0.05, stable zeta potential −28.8 to −45.9 mV, low viscosity 187.5 ± 0 mPa.s, passed the thermodynamic stability tests, and spherical shape. The study revealed that the formulation could improve the water solubility and stability of *Amomum compactum* essential oil. Optimizing this formula may permit its use as an antibacterial and potentially be used as an alternative to the antibiotic in poultry production.

CONFLICT OF INTEREST

All contributing authors report no conflict of interest.

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