



## Nanoemulsion Optimization of Dayak Onion (*Eleutherine bulbosa* (Mill.) Urb.) Tuber Ethanol Extract Using Varying Concentration of VCO, Tween 80, and PEG 400

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### ARTICLE INFO

#### Article history:

Received 04 June 2025

Revised 28 October 2025

Accepted 13 November 2025

Published online 31 December 2025

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**Citation:** Putri RA, Syamsul ES, Warnida H. Nanoemulsion Optimization of Dayak Onion (*Eleutherine bulbosa* (Mill.) Urb.) Tuber Ethanol Extract Using Varying Concentration of VCO, Tween 80, and PEG 400. *Jurnal Kefarmasian Indonesia*. 2025;15(2):197-207.

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### ABSTRACT

Indonesia hosts various medicinal plants, including Dayak onion (*Eleutherine bulbosa* (Mill.) Urb), which contains isoliquiritigenin, a flavonoid with potential anticancer activity. However, its low solubility limits bioavailability and therapeutic effectiveness. To improve drug delivery, nanoscale formulations such as nanoemulsions can enhance membrane penetration and target reach. This study aimed to optimize a nanoemulsion formulation of Dayak onion ethanol extract using the Self-Nanoemulsifying Drug Delivery System (SNEDDS) method with variations of VCO, Tween 80, and PEG 400. The nanoemulsion's characteristics and stability were evaluated experimentally and analyzed statistically using the Independent T-Test, comparing results from Design Expert 12 and laboratory data. The optimized formulation produced a clear pink, stable nanoemulsion for one month, with a pH of  $3.94 \pm 0.22$ , transmittance of  $58.45 \pm 6.01\%$ , particle size of  $319.07 \pm 1.05$  nm, PDI of  $0.44 \pm 0.06$ , zeta potential of  $-31.5 \pm 0.26$  mV, and a creaming index of 0.

**Keywords:** *Eleutherine bulbosa*; Optimization; Nanoemulsion; VCO; Surfactant

### INTRODUCTION

The Dayak onion (*Eleutherine bulbosa* (Mill.) Urb) is a traditional medicinal plant with notable pharmacological potential, especially in its tuber, which is rich in bioactive constituents such as flavonoids, alkaloids, tannins, saponins, phenolics, steroids, and triterpenoids<sup>1</sup>. Isoliquiritigenin, a principal bioactive constituent of *Eleutherine bulbosa* (Dayak onion), possesses significant antioxidant and anticancer properties. Nevertheless, its clinical potential is hindered by poor aqueous solubility and limited bioavailability.<sup>2,3</sup>

Bioavailability can be enhanced through nanotechnology-based approaches, such as the Self-Nanoemulsifying Drug Delivery System

(SNEDDS), which improves the solubility and absorption of active compounds by formulating them into nano-sized particles. Among the various SNEDDS dosage forms, nanoemulsions represent a stable delivery system composed of oil, surfactant, and cosurfactant components.<sup>4</sup>

Nanoemulsions are clear and translucent emulsion systems comprising oil-in-water dispersions stabilized by surfactant molecules, with droplet sizes typically ranging from 50 to 500 nm. These systems offer several advantages, including enhanced absorption rate and consistency, protection of active compounds from oxidative and hydrolytic degradation, and improved bioavailability. Furthermore, nanoemulsions enable controlled drug release through the

modulation of formulation characteristics.<sup>5,6</sup>

The optimal formulation of a nanoemulsion is critically influenced by the composition and concentration of its components. Virgin Coconut Oil (VCO) is utilized as the oil phase due to its ability to enhance the stability and clarity of the nanoemulsion system.<sup>7</sup> Tween 80 was selected as a surfactant due to its safety profile for skin and bodily tissues, functioning effectively as a wetting agent and emulsifier. Its inclusion enhances the stability of nanoemulsion formulations by reducing droplet size, thereby improving dispersion and homogeneity.<sup>8,9</sup>

Polyethylene glycol (PEG 400) functions as a cosurfactant that enhances the performance of surfactants due to its long molecular chains, which enable it to fill interfacial gaps and promote the unification of fine particles within nanoemulsions, thereby improving homogeneity and formulation stability. Additionally, PEG 400 can enhance the efficacy of active pharmaceutical ingredients by facilitating improved drug delivery to therapeutic targets.<sup>10</sup>

The formulation optimization process can be efficiently and systematically conducted using software such as Design Expert® 12 to identify the most suitable composition. This study aims to develop and optimize nanoemulsion formulations of ethanol extract of *Eleutherine bulbosa* (Dayak onion) by employing variations in VCO, Tween 80, and PEG 400 concentrations, utilizing Design Expert® 12 for experimental design and analysis.

## METHODS

### Equipment and materials

The equipment utilized in this study included a mesh 60 sieve, macerator (Pyrex), glass funnel, analytical balance, filter paper, spatula, horn spoon, vacuum filtration apparatus, rotary evaporator, pH meter, standard laboratory glassware, watch glass, porcelain cup, stirring rod, dropper pipette, micropipette (Eppendorf), volumetric flask (Pyrex), magnetic stirrer

(IKA), Falcon tubes (Falcon), ultrasonic homogenizer (Branson), particle size analyzer (PSA) (Malvern Panalytical), zetasizer (Malvern Panalytical), and Design Expert version 12 software.

The materials utilized in this study included Dayak onion (*Eleutherine bulbosa*) bulbs, silica gel, aluminum foil, ethanol 70%, virgin coconut oil (VCO), Tween 80, polyethylene glycol 400 (PEG 400), and distilled water.

### Preparation of *Eleutherine bulbosa* (dayak onion) simplicia

The sample used in this study was the tuber of Dayak onion (*Eleutherine bulbosa* (Mill.) Urb.). Plant identification was carried out at the Laboratory of Ecology and Tropical Forest Biodiversity Conservation, Faculty of Forestry, Mulawarman University number: 84/UN17.7.025.11/LL/2025.

The preparation of *E. bulbosa* tuber simplicia was conducted through a series of steps. Initially, wet sorting was carried out to remove adhering impurities such as soil, leaves, and roots. The tubers were then washed thoroughly under running water and drained. Subsequently, the clean tubers were sliced into pieces approximately 1–2 cm thick and subjected to air drying for approximately five days under ambient conditions. After drying, dry sorting was performed to eliminate residual impurities. The dried tubers were weighed to determine moisture content, ground into a fine powder using a blender, and sieved through a 40-mesh sieve to obtain a uniform particle size suitable for further analysis and formulation.<sup>11</sup>

### Extraction of *Eleutherine bulbosa* (dayak onion) simplicia

A total of 250 g of *E. bulbosa* tuber simplicia powder was extracted using 70% ethanol by maceration for one days at room temperature. The resulting filtrate was separated, and the remaining residue was re-macerated three times using the same solvent to ensure exhaustive extraction. All collected filtrates were combined and concentrated using a rotary evaporator at

60 °C under a pressure of 220 mmHg until a viscous extract was obtained. This thick extract was subsequently dried using a water bath to yield a solid (dry) extract. The final dry extract was stored in a sterile, airtight container at refrigerated conditions to preserve its stability and prevent degradation.<sup>12</sup>

**Preparation of Nanoemulsion**

Twelve nanoemulsion formulations were prepared using various ratios of virgin coconut oil (VCO) as the oil phase, Tween 80 as the surfactant, and PEG 400 as the co-surfactant. The formulation design was optimized using Design Expert version 12 software.

**Table 1.** Formula of Dayak onion nanoemulsion

Formula	Extract (%)	VCO(%)	Tween 80(%)	PEG 400 (%)
1	1.00	6.00	1.00	8.50
2	1.00	6.00	6.00	1.00
3	1.00	1.00	11.00	1.00
4	1.00	11.00	1.00	1.00
5	1.00	2.67	2.67	11.00
6	1.00	1.00	11.00	1.00
7	1.00	11.00	1.00	1.00
8	1.00	4.33	4.33	6.00
9	1.00	1.00	6.00	8.50
10	1.00	1.00	1.00	16.00
11	1.00	7.67	2.67	3.50
12	1.00	2.67	7.67	3.50

**Nanoemulsion preparation procedure**

A stock solution of the *Eleutherine bulbosa* ethanol extract was first prepared to overcome the low solubility of the extract in both the aqueous and oil phases of the nanoemulsion. One gram of the thick extract was dissolved in 10 mL of 70% ethanol to obtain a homogeneous solution, yielding a stock concentration of 100,000 ppm.

A total of 1 mL of the stock solution was added to the oil phase, consisting of virgin coconut oil (VCO), and stirred using a magnetic stirrer at 600 rpm for 5 minutes. Subsequently, Tween 80 (surfactant) and PEG 400 (co-surfactant) were added sequentially, each stirred for 5 minutes. Distilled water was then added gradually until the final volume of the formulation was achieved. To reduce droplet size and obtain a nanoemulsion, the mixture was subjected to ultrasonication for 60 minutes.<sup>13</sup>

**Evaluation Nanoemulsion**

**Physical appearance evaluation**

The physical characteristics of the nanoemulsion, including color, clarity, and phase separation, were evaluated through visual inspection.

**pH measurement**

The pH test was conducted to determine the hydrogen ion concentration of the nanoemulsion using a calibrated pH meter. Prior to measurement, the instrument was calibrated with standard buffer solutions at pH 4.0 and 7.0 until stable and accurate readings were obtained. After calibration, the electrode was rinsed with distilled water and gently dried. The measurement was then performed by immersing the electrode into the sample, and the pH value was recorded as displayed on the instrument screen.<sup>13</sup>

**Percent transmittance measurement**

The percent transmittance test was performed to evaluate the clarity and

transparency of the nanoemulsion formulation. A specified volume of the nanoemulsion sample was placed into a clean cuvette and measured using a UV-Vis spectrophotometer at a wavelength of 650 nm. Prior to measurement, the instrument was calibrated using distilled water as a blank reference.<sup>13</sup>

#### Creaming index measurement

The physical stability of the nanoemulsion was evaluated by determining the Creaming Index (CI) at predetermined time intervals. A 10 mL sample of the nanoemulsion was placed in a graduated glass tube and stored under controlled conditions for 30 days. The total height of the emulsion and the height of the cream layer were recorded periodically. The Creaming Index was calculated to assess the extent of phase separation over time, serving as an indicator of emulsion stability.<sup>15</sup>

#### Particle size and polydispersity index (PDI) measurement

The droplet size and polydispersity index (PDI) of the nanoemulsion were determined using a Particle Size Analyzer (PSA). A total of 100  $\mu$ L of the nanoemulsion formulation was diluted with 50 mL of distilled water to ensure appropriate scattering intensity. The diluted sample was then analyzed to determine the average particle size and size distribution, expressed as the polydispersity index (PDI), which indicates the uniformity of the droplet size distribution.<sup>16</sup>

#### Zeta potential measurement

Zeta potential analysis was conducted using a Zetasizer Nano Series instrument (Malvern Instruments, UK) to evaluate the surface charge and stability of the nanoemulsion. One milliliter of the nanoemulsion sample was diluted with 250 mL of distilled water to ensure optimal conductivity and particle dispersion. The diluted sample was transferred into a cuvette and measured at a controlled temperature of 25 °C.<sup>17</sup>

#### Stability testing

The physical stability of the optimum nanoemulsion formulation was evaluated by storing the preparation at room temperature for 30 days. Stability parameters, including pH, percent transmittance, and creaming index, were assessed on day 1 and day 30 to monitor any changes over the storage period.

## RESULTS AND DISCUSSION

#### Extract preparation

*Eleutherine bulbosa* (Dayak onion) samples were sourced from local farmers in Tering Seberang Village, West Kutai Regency, East Kalimantan. The selection criteria included a harvest age of approximately six months and a bulb diameter of 5–7 cm. These bulbs were chosen due to their known content of bioactive compounds—such as alkaloids, flavonoids, and terpenoids—which possess antioxidant potential.

The bulbs were initially cleaned, sliced into 1–2 cm thick sections, and subjected to air drying for approximately five days. Once dried, the samples were sorted to remove residual impurities, weighed to determine moisture content, finely ground, and sieved using a 40-mesh screen to obtain uniform *simplicia* powder.

A total of 250 g of the resulting powder was extracted with 70% ethanol using the maceration method over a period of four days, followed by three successive re-macerations to ensure complete extraction. The combined filtrates were concentrated using a rotary evaporator and further dried using a water bath to yield a thick, dry extract. The extract was then stored in a sterile, airtight container under refrigerated conditions to maintain stability and prevent degradation.<sup>11,12</sup>

#### Processing of *Eleutherine bulbosa* nanoemulsion formulation

A total of twelve nanoemulsion formulations were prepared using varying concentrations of virgin coconut oil (VCO) as the oil phase, Tween 80 as the surfactant, and PEG 400 as the co-surfactant. The

experimental design and optimization were conducted using Design Expert version 12 software.

Each formulation was evaluated for pH, percent transmittance, and creaming index to assess its physical characteristics

and stability. The resulting data were analyzed using the Design Expert software to generate an optimal formulation model for *E. bulbosa* nanoemulsion, based on the desired physicochemical parameters.

**Table 2.** Evaluation Results of the 12 Nanoemulsion Formulations

Formula	Extract (%)	pH	% Transmittance	Creaming Index
1	1.00	5.07	0.27	0.5
2	1.00	5.15	0.08	0.25
3	1.00	5.17	0.79	0
4	1.00	5.16	0.25	0.75
5	1.00	4.91	87.78	0
6	1.00	5.04	99.04	0
7	1.00	5.25	1.91	1.5
8	1.00	5.16	19.93	1.00
9	1.00	5.06	74.72	0
10	1.00	5.06	93.76	0.1
11	1.00	5.29	17.16	2.00
12	1.00	5.47	40.09	3.00

The pH measurements of the twelve *Eleutherine bulbosa* ethanol extract nanoemulsion formulations showed a pH range of 4.91 to 5.47. These values fall within the acceptable pH range for skin (4.5–6.5) and oral cavity (5–7) applications. Variations in pH among the formulations were primarily influenced by differences in the composition of the nanoemulsion, particularly the concentration of Tween 80. Higher concentrations of Tween 80 resulted in higher pH values. This is attributable to the inherent pH of Tween 80, which ranges from 6 to 8, and thus contributes to an increase in the overall pH of the nanoemulsion when used in greater amounts.<sup>18</sup>

Based on the percent transmittance evaluation of the twelve nanoemulsion formulations, several formulas exhibited suboptimal clarity. However, formulations 5, 6, and 10 demonstrated satisfactory percent transmittance values, meeting the acceptable range. Specifically, formulation 5 showed a transmittance of 87.78%, formulation 6 achieved 99.04%, and formulation 10 recorded 93.76%. A high-quality nanoemulsion typically exhibits a

percent transmittance above 80%, as higher transmittance values indicate that the droplet size is within the nanometer range and that the formulation has a clear and transparent appearance.<sup>14</sup>

The creaming index test of the nanoemulsion was conducted to observe and quantify the occurrence of phase separation or sedimentation in the formulation. Creaming may occur due to gravitational forces, differences in density, and the viscosity of the continuous phase. A lower creaming index indicates better formulation stability.<sup>15</sup>

In this study, out of the twelve formulations tested, formulas 3, 5, 6, and 9 demonstrated good physical stability, with a creaming index value of 0, indicating no visible phase separation. In contrast, formulations 1, 2, 4, 7, 8, 10, 11, and 12 exhibited varying degrees of phase separation, with creaming layers ranging from 0.5 to 3 mL. The evaluation was performed using Falcon tubes, each containing 10 mL of nanoemulsion formulation.

**Optimum nanoemulsion formula**

The optimum nanoemulsion formula was determined after the evaluation data from all twelve formulations were processed using Design Expert software. The results of the optimization are presented in (Table 3) and illustrated in (Figure 1).

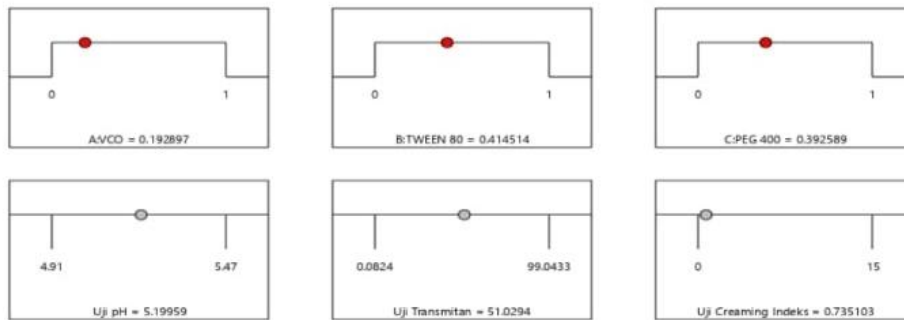
**Optimization of *Eleutherine bulbosa* Nanoemulsion**

The optimum nanoemulsion formula generated by Design Expert was replicated three times to compare the actual experimental results with the predicted values from the software. analysis was performed using an independent t-test to determine whether there were significant differences between

the mean values of the two sample groups. The results of this analysis are presented in (Table 4). The optimum formula was subjected to three stability tests, including pH measurement, percent transmittance evaluation, and creaming index assessment. Additionally, the nanoemulsion formulation underwent three physicochemical characterizations: droplet size analysis, polydispersity index (PDI) measurement, and zeta potential analysis. pH testing was carried out using a calibrated pH meter with standard buffer solutions of pH 4 and 7. The electrode was immersed into the formulation, and measurements were performed in triplicate. The results were 3.69, 4.03, and 4.15, with a mean value of  $3.94 \pm 0.22$  SD,

**Table 3.** Percentage Composition of the Optimum Nanoemulsion Formula

Recommendations	VCO (%)	Tween 80 (%)	PEG 400 (%)	Aquades (%)
1	2.93	5.15	6.89	80.04



**Figure 1.** Recommended Formula Output from Design Expert SoftwareEvaluasi formula

**Table 4.** Results of the Statistical Evaluation of the Optimum Nanoemulsion

Response	Replication 1	Replication 2	Replication 3	Mean ± SD
Ph	3.69	4.03	4.15	3.94±0.22
Transmittance (%)	51.51	61.67	62.15	58.45±6.01
Creaming Indexs	0	0	0	0
Droplet Size (nm)	318.0	319.1	320.1	319.07±1.05
Index Polydispersity	0.477	0.376	0.472	0.44±0.057
Index (PDI)				
Zeta Potential (mV)	-31.2	-31.6	-31.7	-31.5±0.26

which is close to the acceptable pH range for oral nanoemulsion formulations.<sup>13</sup>

The percent transmittance test was conducted using a UV-Vis spectrophotometer at a wavelength of 650

nm, following calibration with distilled water as the blank. The results from three replicates showed transmittance values of 51.51%, 61.67%, and 62.15%, with a mean of  $58.45 \pm 6.01$  SD. These values fall below the

clarity standard for nanoemulsions, which ideally should exceed 80%.<sup>14</sup>

The creaming index test was performed to evaluate the stability and homogeneity of the nanoemulsion formulation. The test utilized a 10 mL Falcon tube filled with the nanoemulsion sample, which was observed for 10–20 minutes to detect any phase separation. All three replicates showed a creaming index value of 0, indicating no visible separation, thus confirming the physical stability of the optimum formula.<sup>15</sup>

Particle size and polydispersity index (PDI) tests were conducted to assess the droplet size distribution and uniformity of the nanoemulsion system. Measurements were carried out using a Particle Size Analyzer following the dilution of 100  $\mu$ L of the sample in 50 mL of distilled water.

The average results from three replicates indicated a droplet size of  $319.07 \pm 1.05$  nm and a PDI of  $0.44 \pm 0.06$ , both of which fall within the optimal range for nanoemulsions (100–500 nm for size and  $<0.5$  for PDI), suggesting that the formulation is homogeneous and physically stable.<sup>16,19</sup> Zeta potential analysis was conducted to evaluate the long-term stability of the nanoemulsion by measuring the electrostatic repulsion between particles. Optimal zeta potential values are generally considered to be greater than +30 mV or less than -30 mV. The results from three replicates of the optimum formula showed an average zeta potential of  $-31.5 \pm 0.26$  mV, indicating compliance with the stability criteria for colloidal systems.<sup>19</sup>

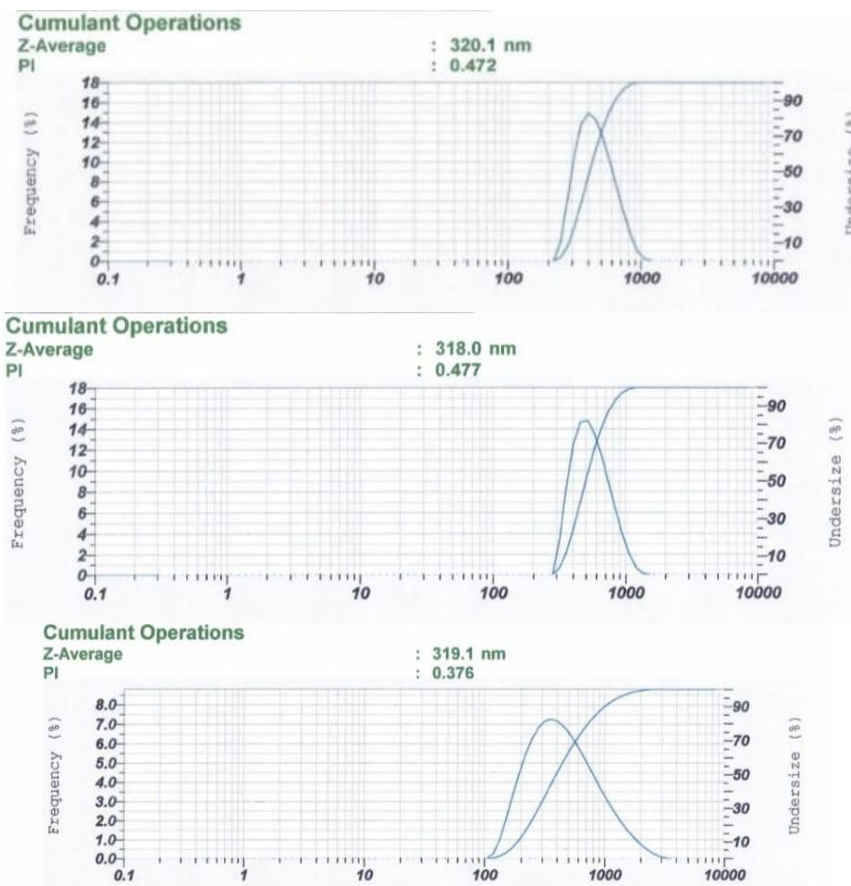


Figure 2. Particle size and polydispersity index (PDI) measurement results

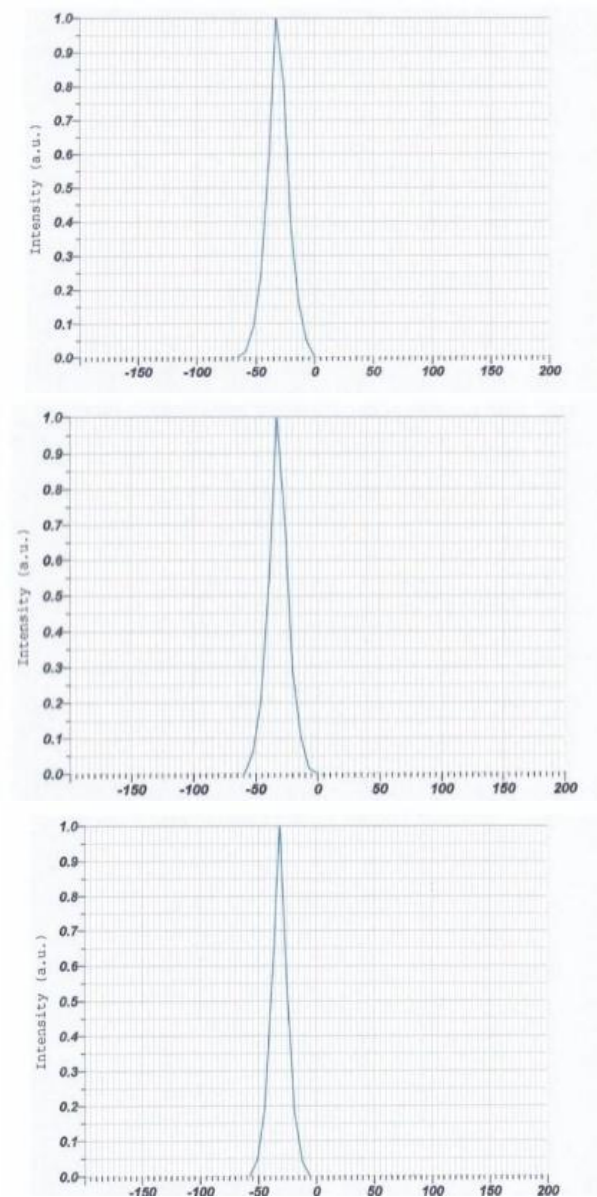


Figure 3. Zeta potential measurement results

**Stability of the Optimum Nanoemulsion Formula**

Stability testing of the nanoemulsion was conducted by storing the formulation at room temperature (20–25°C) for 30 days. Evaluations were performed on days 1 and 30 using pH measurement, percent transmittance analysis, and creaming index assessment.

The results showed a decrease in pH from  $3.94 \pm 0.22$  to  $3.66 \pm 0.42$  and in transmittance from  $58.45 \pm 6.01\%$  to  $54.13 \pm 4.34\%$ , while the creaming index remained at 0. The reduction in pH and transmittance suggests potential chemical changes and droplet size variation during storage. However, the physical stability of the formulation was maintained, as no phase separation was observed.<sup>14,20</sup>

**Table 5.** Stability test results

Test Parameter	Replicate	Day 1	Day 30
pH	1	3.69	3.27
	2	4.03	3.60
	3	4.15	4.11
% Transmittance	1	51.51	51.42
	2	61.67	59.13
	3	62.15	51.83
Creaming Index	1	0	0
	2	0	0
	3	0	0

**Table 6.** Comparison of nanoemulsion stability parameters

Response	Day 1	Day 3
pH	3.94±0.22	3.66±0.42
% Transmittance	58.45±6.01	54.13±4.34
Creaming Index	0	0

**Data Analysis**

**Normality test and independent t-test for the optimum formula**

The Shapiro–Wilk normality test showed that the pH data ( $p = 0.485$ ) and percent transmittance data ( $p = 0.077$ ) were normally distributed ( $p > 0.05$ ), indicating that they met the assumption of normality. The creaming index data could not be analyzed statistically, as all observed values were zero and thus could not be processed by the statistical software.

An independent sample t-test was conducted to compare the predicted values generated by the Design Expert software with the experimental data. The results revealed a significant difference in the pH parameter between the predicted value (5.19) and the experimental value ( $3.94 \pm 0.22$ ), with a significance level of 0.012 ( $p < 0.05$ ). In contrast, the percent transmittance did not show a statistically significant difference between the predicted value (51.03%) and the experimental value ( $58.45 \pm 6.01\%$ ), with a significance level of 0.166 ( $p > 0.05$ ). The creaming index could not be statistically analyzed, as all experimental values were zero, rendering the data ineligible for statistical testing.

**Normality test and independent t-test for nanoemulsion stability**

The normality test was performed using the Shapiro–Wilk method. The results indicated that the pH and percent transmittance data on Day 1 and Day 30 were normally distributed, with significance values greater than 0.05 (pH: 0.485 and 0.765; transmittance: 0.077 and 0.089). The creaming index data were not analyzed statistically because all recorded values were zero, making them unreadable by the statistical software.

Subsequently, an independent t-test was conducted to evaluate the stability of the nanoemulsion formulation. The results showed no significant differences between Day 1 ( $3.94 \pm 0.22$ ) and Day 30 ( $3.66 \pm 0.42$ ) pH values, with a significance value of 0.350 ( $p > 0.05$ ), as well as between percent transmittance on Day 1 ( $58.45 \pm 6.01\%$ ) and Day 30 ( $54.13 \pm 4.34\%$ ), with a significance value of 0.370 ( $p > 0.05$ ). The creaming index remained at zero throughout the storage period, indicating that no phase separation occurred.

## CONCLUSION

The optimum nanoemulsion formula of Dayak onion ethanol extract, composed of VCO (2.92%), Tween 80 (5.14%), and PEG 400 (6.88%) as determined by Design Expert 12, exhibited a clear pink appearance and demonstrated good physical stability over one month of storage, with no creaming observed (creaming index = 0). The average percent transmittance was  $58.45 \pm 6.01\%$ , and the pH was  $3.94 \pm 0.22$ . The average droplet size was  $319.07 \pm 1.05$  nm with a polydispersity index of  $0.45 \pm 0.06$ , and the zeta potential was  $-31.5 \pm 0.26$  mV, indicating a stable colloidal system.

## Conflict of Interest

The authors declare no conflict of interest.

## Authors' Declaration

The authors hereby declare that the work presented in this article is original and that any liability for claims relating to the content of this article will be borne by them.

## Acknowledgments

The author would like to express gratitude to the Ministry of Education, Culture, Research, and Technology under DRTPM DIKTI Contract number 113/E5/PG.02.00.PL/20242, dated June 11, 2024, and LLDIKTI XI Kalimantan under Contract number 92/LL11/KM/20244, dated June 19, 2024 for their funding this research.

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