

## Effect of Centrifugation on the Stability of Nanoemulsion Base Containing Tween 80, PEG 400, Poloxamer 188, and DMSO

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### ABSTRAK

Nanoemulsi merupakan sistem dispersi dua fase (minyak dan air) dengan ukuran droplet skala nanometer yang memiliki stabilitas fisik lebih baik dibandingkan emulsi konvensional serta banyak dimanfaatkan dalam bidang farmasi dan kosmetik. Stabilitas kinetik nanoemulsi sangat dipengaruhi oleh komposisi surfaktan, kosurfaktan, dan komponen pendukung lainnya. Penelitian ini bertujuan untuk mengevaluasi pengaruh proses sentrifugasi terhadap stabilitas fisik basis nanoemulsi berbahan dasar minyak zaitun dengan variasi konsentrasi Tween 80 dan PEG 400, yang didukung oleh Poloxamer 188 dan DMSO. Penelitian eksperimental laboratorium ini menggunakan metode titrasi air dalam pembuatan nanoemulsi, dilanjutkan dengan ultrasonikasi selama 60 menit. Uji stabilitas dipercepat dilakukan melalui sentrifugasi pada kecepatan 2.000, 4.000, 6.000, dan 8.000 rpm selama 30 menit. Evaluasi fisik meliputi uji organoleptik, pH, viskositas, dan tipe emulsi menggunakan metode pewarna metilen biru. Hasil penelitian menunjukkan bahwa seluruh formulasi stabil pada 2.000–4.000 rpm. Pada 6.000 rpm, F1 dan F2 mulai menunjukkan creaming parsial, dan pada 8.000 rpm terjadi pemisahan fase yang signifikan pada F1 dan F2, sedangkan F3 dan F4 tetap jernih dan homogen. Nilai pH seluruh formulasi berada pada rentang 6,8–7,3 ( $7,03 \pm 0,22$ ), menunjukkan stabilitas kimia yang baik. Viskositas berkisar antara 103–132 cPs ( $111,5 \pm 13,77$ ), masih dalam rentang yang dapat diterima untuk nanoemulsi. Uji tipe emulsi menunjukkan distribusi warna biru homogen, mengonfirmasi bahwa seluruh formulasi merupakan tipe oil-in-water (O/W). Disimpulkan bahwa rasio Tween 80 dan PEG 400 berperan penting dalam meningkatkan stabilitas kinetik nanoemulsi berbasis minyak zaitun. Formulasi F3 dan F4 menunjukkan stabilitas fisik paling optimal dan berpotensi dikembangkan lebih lanjut untuk aplikasi farmasi dan kosmetik.

**Kata Kunci:** Nanoemulsi; Sentrifugasi; Stabilitas fisik; Tween 80; PEG 400; Poloxamer 188

**Diterima:**

11-01-2026

**Disetujui:**

10-03-2026

**Online:**

10-03-2026

### ABSTRACT

Nanoemulsions are biphasic dispersion systems (oil and water) with nanometer-scale droplet sizes that exhibit better physical stability than conventional emulsions and are widely utilized in pharmaceutical and cosmetic applications. The kinetic stability of nanoemulsions is strongly influenced by the composition of surfactants, co-surfactants, and other supporting components. This study aimed to evaluate the effect of centrifugation on the physical stability of an olive oil-based nanoemulsion with varying concentrations of Tween 80 and PEG 400, supported by Poloxamer 188 and DMSO. This laboratory-based experimental study employed the aqueous titration method for nanoemulsion preparation, followed by ultrasonication for 60 minutes. Accelerated stability testing was conducted through centrifugation at speeds of 2,000, 4,000, 6,000, and 8,000 rpm for 30 minutes. Physical evaluations included organoleptic testing, pH measurement, viscosity determination, and emulsion type identification using the methylene blue dye method. The results showed that all formulations remained stable at 2,000–4,000 rpm. At 6,000 rpm, formulations F1 and F2 began to exhibit partial

creaming, and at 8,000 rpm significant phase separation was observed in F1 and F2, whereas F3 and F4 remained clear and homogeneous. The pH values of all formulations ranged from 6.8 to 7.3 ( $7.03 \pm 0.22$ ), indicating good chemical stability. Viscosity values ranged from 103 to 132 cPs ( $111.5 \pm 13.77$ ), which fall within the acceptable range for nanoemulsion systems. The emulsion type test showed a homogeneous blue color distribution, confirming that all formulations were oil-in-water (O/W) systems. In conclusion, the ratio of Tween 80 to PEG 400 plays a crucial role in enhancing the kinetic stability of olive oil-based nanoemulsions. Formulations F3 and F4 demonstrated the most optimal physical stability and have strong potential for further development in pharmaceutical and cosmetic applications.

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**Keywords:** Nanoemulsion; Centrifugation; Physical stability; Tween 80; PEG 400; Poloxamer 188

**Received:**  
2026-01-11

**Accepted:**  
2026-03-10

**Online:**  
2026-03-10

## 1. Introduction

Nanoemulsions are biphasic dispersion systems (oil and water) composed of two immiscible liquids, in which one phase is dispersed as fine droplets within a continuous phase and stabilized by emulsifying agents. Depending on the continuous phase, nanoemulsions can be classified as oil-in-water (O/W) or water-in-oil (W/O) systems [1]. A key characteristic of nanoemulsions is their nanometer-scale droplet size, typically around 20–200 nm, which contributes to a clearer appearance than conventional emulsions due to reduced light scattering [2].

In the pharmaceutical and cosmetic fields, nanoemulsions are widely used as delivery systems because their physicochemical properties can enhance the performance of active compounds, particularly those with limited solubility. Nanoemulsion systems facilitate a more uniform distribution of active ingredients within the formulation matrix, thereby increasing the likelihood of achieving the desired therapeutic or cosmetic effect, including in topical preparations. Moreover, nanoemulsions are often considered superior to conventional emulsions due to their relatively improved physical stability and transparent or translucent appearance, especially when the droplet size is very small [3].

To anticipate instability within a shorter time frame, accelerated stability testing is required. One commonly applied method is centrifugation testing, as it simulates increased gravitational force, thereby accelerating phase separation and enabling earlier detection of instability phenomena [1]. In nanoemulsion development, centrifugation is frequently used as a preliminary indicator to assess resistance to external forces and to predict the tendency for phase separation during storage [4].

However, although centrifugation-based evaluation has been widely employed, some studies tend to emphasize the relationship between surfactant type and particle size without comprehensively addressing the contribution of combining surfactants with co-solvents to the kinetic stability of the system [5][6][7]. In addition, the use of olive oil as the oil phase remains an interesting topic for further investigation in terms of its resistance to centrifugal forces, considering that olive oil has been utilized in certain cosmetic formulations and holds relevant application value.

Based on these considerations, this study aims to investigate the effect of centrifugation on the physical stability of a nanoemulsion formulated using Tween 80 as the surfactant, PEG 400 as a supporting component (co-surfactant), Poloxamer 188 as a stabilizer, and DMSO as a co-solvent, according to the formulation design. The evaluation will be conducted at various centrifugation speeds to assess the system's resistance to artificial gravitational forces and its tendency to undergo phase separation

[2]. The findings are expected to provide insight into the relationship between formulation composition and the intrinsic stability of nanoemulsions, and to serve as a reference for developing more stable and effective nanoemulsion formulations for pharmaceutical and cosmetic applications.

## 2. Methods

### Design Study

This laboratory-based experimental study was conducted to evaluate the effect of the centrifugation process on the physical stability of a nanoemulsion base composed of olive oil, Tween 80, PEG 400, Poloxamer 188, and DMSO.

### Materials

The equipment used in this study included an analytical balance (Mettler Toledo), beakers (Pyrex®), graduated cylinders (Pyrex®), a dropper pipette, a glass stirring rod, a burette (Pyrex®), a magnetic stirrer (IKA® C-MAG HS 7), an ultrasonic bath (Elmasonic S 30H), a centrifuge (Hettich), and a spatula. The materials used in this study consisted of olive oil (Smart Organik), Poloxamer 188 (Sigma-Aldrich), Tween 80 (Sigma-Aldrich), PEG 400 (Sigma-Aldrich), dimethyl sulfoxide (Supelco), 95% ethanol (Onemed), and distilled water (Onelab Waterone).

### Preparation of Nanoemulsion Base

**Table 1.** Composition Of The Nanoemulsion Base Formulation

Materials	Concentration (%)			
	F1	F2	F3	F4
Olive Oil	5	5	5	5
PEG 400	22,5	25	27,5	30
Tween 80	20	22,5	25	27,5
Poloxamer 188	2	2	2	2
DMSO	2	2	2	2
Aquadest	Ad 50 mL			

The nanoemulsion base was prepared using the aqueous titration method. The procedure began by weighing Poloxamer 188 and dissolving it in 95% ethanol. Tween 80 and PEG 400 were then measured according to the formulation, combined in a beaker, and stirred with a magnetic stirrer for approximately 10 minutes until a homogeneous mixture was obtained. Subsequently, olive oil was added to the Tween 80-PEG 400 mixture, and stirring was continued for another 10 minutes to produce a uniform oil-surfactant phase.

Next, the aqueous phase was added dropwise from a burette into the oil phase while maintaining continuous stirring with the magnetic stirrer. Water addition was continued until one-third of the total aqueous volume had been incorporated, after which Poloxamer 188 was introduced gradually into the system. Once the aqueous volume reached two-thirds, DMSO was added stepwise using a micropipette. Stirring was maintained until a homogeneous nanoemulsion system formed.

After the nanoemulsion base was obtained, ultrasonication was performed using a sonicator for 60 minutes. This step was intended to remove foam generated during mixing and to reduce and homogenize the droplet size.

### **Centrifugation Stability Test**

Samples from each formulation were transferred into centrifuge tubes and centrifuged at 2,000, 4,000, 6,000, and 8,000 rpm for 30 minutes at room temperature. After centrifugation, the samples were visually evaluated to assess homogeneity, clarity, and the presence or absence of phase separation.

### **Physical Evaluation**

Physical evaluation was carried out to assess and determine the physical stability of each nanoemulsion base formulation that had been prepared. The observed parameters included:

#### **Organoleptic Test**

The organoleptic test was performed by observing color using the sense of sight, odor using the sense of smell, homogeneity (whether phase separation occurred) through visual observation, and the overall consistency of the sample or test product. The organoleptic parameters evaluated were aroma, color, homogeneity, and the consistency of the nanoemulsion preparation [8].

#### **pH Test**

The pH test was conducted using a pH meter that was previously calibrated with standard buffer solutions of pH 4.00 and 7.00. After calibration, the electrode was immersed into the sample at room temperature and storage temperature, and the pH value was recorded once the reading stabilized [9].

The pH of a nanoemulsion is crucial to ensure compatibility with the skin or biological membranes, particularly when the product is intended for pharmaceutical or cosmetic applications. pH stability during storage is also an indicator of the chemical stability of the formulation and may affect the stability of active ingredients and surfactant components. Changes in pH may indicate the occurrence of hydrolysis, oxidation, or degradation of formulation components. Periodic monitoring of pH during stability studies provides essential information regarding the integrity of the formulation [10].

#### **Viscosity Test**

Viscosity is a critical parameter in determining the flow properties and application characteristics of nanoemulsions. It influences emulsion stability, as formulations with higher viscosity tend to resist flow and movement but are generally more stable against phase separation. Conversely, emulsions with lower viscosity are easier to apply but may be less stable, particularly over long-term storage. The appropriate selection of viscosity also affects user comfort, especially for topical applications [11].

Viscosity was measured using a Brookfield viscometer by placing the preparation into a beaker, turning on the instrument, and adjusting the rotational speed accordingly. Changes in viscosity during storage may indicate structural alterations or system destabilization [12].

#### **Emulsion Type Test**

Determination of the emulsion type (oil-in-water or water-in-oil) is a fundamental characterization that defines the properties and application of a nanoemulsion. Simple identification methods include the dilution test, electrical conductivity test, and dye solubility test using water-soluble or oil-soluble dyes [10].

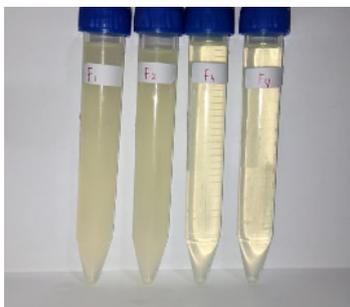
The nanoemulsion type test was performed by mixing the nanoemulsion preparation with methylene blue on a watch glass, followed by stirring and visual observation. Methylene blue was used as a dye because it is water-soluble and

produces a uniform color distribution. These characteristics are suitable for identifying oil-in-water (O/W) nanoemulsions [13].

### **3. Results and Discussion**

#### **Centrifugation Results**

The centrifugation test is used as an accelerated stability method to evaluate the physical stability of nanoemulsions by applying centrifugal force that mimics increased gravitational acceleration. This technique speeds up the occurrence of potential instabilities such as creaming, flocculation, and coalescence, allowing signs of phase separation to be detected more rapidly than under normal storage conditions. In principle, a centrifugal force greater than gravity will promote droplet separation if the dispersion system is insufficiently stable[14]. Therefore, centrifugation provides an early indication of the nanoemulsion's kinetic stability, particularly its ability to maintain homogeneity and clarity under external stress. If no phase separation or visible changes are observed after centrifugation, the nanoemulsion can be considered physically stable and likely to remain stable during long-term storage.



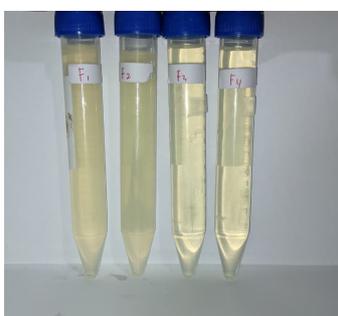
**Figure 1.** Centrifugation Test Result at 2000 rpm

At 2,000 rpm, the generated centrifugal force was relatively low and therefore insufficient to disrupt the interfacial equilibrium of the system. All formulations remained homogeneous with no apparent phase separation, although their clarity differed. This difference is associated with the ability of Tween 80 and PEG 400 to form a flexible and stable interfacial layer around the oil droplets. Poloxamer 188 acts as a steric stabilizer by creating a physical barrier surrounding the droplets, thereby preventing aggregation. In addition, olive oil as the oil phase contributes to increasing the viscosity of the continuous phase, which in turn reduces droplet mobility and slows the creaming process. These results are consistent with Rachman et al. (2023), who reported that olive oil-based nanoemulsions remain stable under low centrifugal stress. DMSO, as a co-solvent, also plays an important role by enhancing oil-phase solubility and reducing interfacial tension, thereby strengthening the system's initial kinetic stability [7].



**Figure 2.** Centrifugation Test Result at 4000 rpm

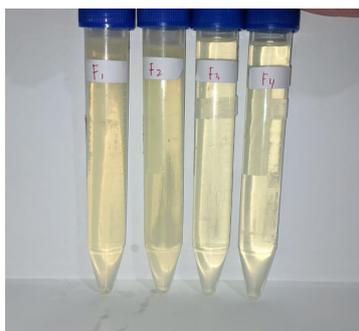
When the centrifugation speed was increased to 4,000 rpm, the generated centrifugal force was higher; however, all formulations were still able to maintain homogeneity without observable creaming or flocculation. The white layer in F1 became thicker and more distinct, indicating a greater degree of phase separation due to accelerated droplet migration, which led to an increased concentration of the oil phase at the top. F1 and F2 remained turbid, likely because larger and/or aggregated droplets caused stronger light scattering. These findings suggest that the steric repulsion provided by Poloxamer 188, together with the Tween 80-PEG 400 ratio, was sufficient to withstand the artificial gravitational acceleration. The formation of a multilayer surfactant/co-surfactant interfacial film also helped suppress droplet movement and coalescence. In addition, ultrasonication prior to centrifugation produced a more uniform droplet-size distribution, thereby reducing the likelihood of Ostwald ripening [15]. This result is consistent with studies on olive oil nanoemulsions formulated with Tween 80 and PEG 400, which reported high stability at an optimal surfactant-to-co-surfactant ratio [16].



**Figure 3.** Centrifugation Test Result at 6000 rpm

When the centrifugation speed was increased to 6,000 rpm, the centrifugal force acting on the system rose markedly. Under these conditions, formulation F1 began to show early signs of instability, indicated by the formation of a white layer at the top, suggesting partial creaming. This phenomenon implies that the surfactant-to-co-surfactant ratio in F1 was not optimal to effectively cover the entire droplet surface, causing the droplets to migrate upward due to density differences. In contrast, formulations F2, F3, and F4 remained stable, highlighting the important role of Poloxamer 188 in forming structures with a hydrophobic core and a hydrophilic corona that enhance steric repulsion between droplets (Pratap-Singh et al., 2021). In addition, the unsaturated fatty acid content of olive oil may promote partial coalescence in systems with weaker interfacial protection [17]

This stability indicates that the interfacial forces between the oil and water phases were sufficiently strong to withstand the applied artificial gravitational acceleration. The combination of Tween 80 and PEG 400 reduced the interfacial tension, thereby lowering the system's free energy and enhancing its resistance to centrifugation [18][19]. In addition, DMSO as a co-solvent helped improve the solubility of the oil phase in the aqueous phase and prevented droplets from readily merging (coalescence) during centrifugation [20]. Therefore, the stability maintained up to 6,000 rpm supports the assumption that the nanoemulsion system exhibits good kinetic stability.



**Figure 4.** Centrifugation Test Result at 8000 rpm

At the highest speed of 8,000 rpm, differences in stability among the formulations became more pronounced. Formulation F1 exhibited significant phase separation, characterized by the formation of a dense white layer at the top, whereas formulations F3 and F4 remained clear and homogeneous. This condition confirms that the Tween 80-PEG 400 ratios in F3 and F4 were optimal for maintaining the integrity of the interfacial layer under extreme centrifugal stress. The synergy between PEG 400, which increases interfacial flexibility, and Poloxamer 188, which enhances steric stabilization, enabled the droplets to withstand high shear forces. These findings are consistent with reports showing that specific surfactant-co-surfactant combinations can produce nanoemulsion systems that remain stable without creaming during centrifugation tests [18]

According to Syukri (2019), a nanoemulsion system that remains homogeneous after high-speed centrifugation indicates its ability to maintain low interfacial tension and a narrow droplet size distribution [21]. This suggests that the small droplets remain well dispersed, without aggregation or sedimentation during the test. These findings also indicate that the surfactant-co-surfactant proportion and the addition of DMSO play important roles in strengthening kinetic stability, particularly by reducing the overall free energy of the system[22].

Thus, the results of centrifugation testing up to 8,000 rpm demonstrate that formulations F3 and F4 possess excellent physical resistance to centrifugal forces. These findings further indicate that the nanoemulsion systems have strong potential for application in pharmaceutical and cosmetic formulations that require high stability during storage and use.

## Physical Evaluation Results

### Organoleptic Test

**Table 2.** The Organoleptic Test Results of the Nanoemulsion Base

Formula	Parameter		
	Color	Odor	Homogeneity
F1	Turbid	Characteristic odor of olive oil	Not Homogeneous
F2	Turbid	Characteristic odor of olive oil	Not Homogeneous
F3	Clear	Characteristic odor of olive oil	Homogeneous
F4	Clear	Characteristic odor of olive oil	Homogeneous

The organoleptic evaluation showed that the nanoemulsion-based formulations F1 and F2 appeared turbid, non-homogeneous, and exhibited phase separation during the observation period. In contrast, F3 and F4 appeared clear, homogeneous, and did not show any phase separation throughout the observation period. Clarity, homogeneity, and the absence of phase separation indicate that the formulations possess good visual stability. Oil-in-water (O/W) nanoemulsions based on olive oil with small droplet sizes and a narrow size distribution generally exhibit a transparent and visually stable appearance, which serves as an initial indicator of successful emulsification [23]. Visual parameters such as color, odor, and degree of homogeneity can be used as preliminary indicators in assessing the physical stability of pharmaceutical or cosmetic formulations[24].

### pH Test

**Table 3.** The pH Test Results Of The Nanoemulsion Base

Formulations	pH
F1	6,9
F2	6,8
F3	7,1
F4	7,3
Mean ± SD	7.03 ± 0,22

Based on the test results, all selected formulations exhibited pH values within the range of 6.8–7.3. This range reflects neutral to slightly alkaline conditions and indicates that the formed nanoemulsion systems possess good chemical stability. Nanoemulsions with a near-neutral pH generally demonstrate higher dispersion stability because excessive ionization, which could disrupt the interfacial layer of the droplets, does not occur [25].

The uniformity of pH values across all formulations suggests that variations in the concentrations of Tween 80 and PEG 400 did not significantly affect the acidity of the system. This is because Tween 80 and PEG 400 are nonionic surfactant and cosurfactant, respectively, which do not ionize in aqueous media and therefore do not directly influence the concentration of hydrogen ions [26].

### Viscosity Test

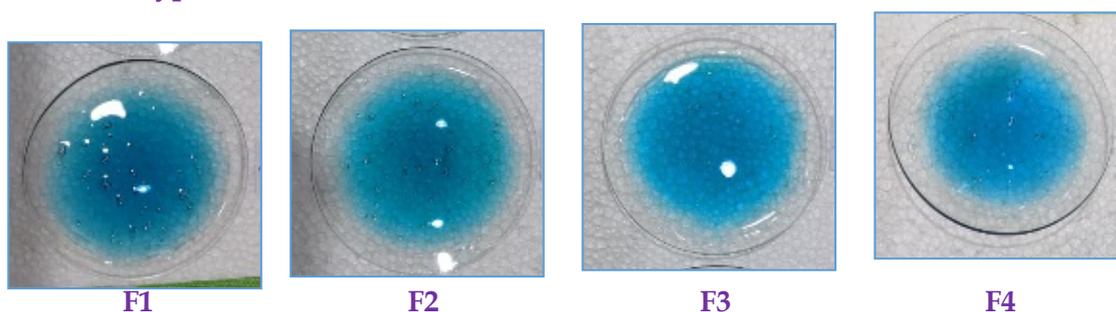
**Table 4.** The viscosity test results of the nanoemulsion base

Formulations	Viscosity (cPs)
F1	103
F2	104
F3	107
F4	132
Mean ± SD	111,5 ± 13,77

The viscosity measurement results demonstrated differences among the formulations, showing a tendency for viscosity to increase with higher concentrations of surfactant and cosurfactant in the formulation. This increase in viscosity is associated with stronger intermolecular interactions within the nanoemulsion system. The interactions among Tween 80, PEG 400, and Poloxamer 188 contribute to the formation of a network structure that enhances resistance to flow within the system [27]. Furthermore, higher viscosity can reduce the mobility of oil droplets, thereby inhibiting coalescence and creaming during storage [26].

The acceptable viscosity range for nanoemulsion preparations generally falls between 10–2000 cPs, encompassing low- to medium-viscosity systems[13]. Viscosity values within this range are expected to provide adequate physical stability while maintaining good flowability, ensuring ease of application and user comfort, particularly for topical or oral formulations[28].

### Emulsion Type Test



**Figure 5.** The Emulsion Type Test Results Of The Nanoemulsion Base

The results of the emulsion type test using methylene blue showed that the nanoemulsion base produced a blue color that was homogeneously distributed throughout the system. This uniform color distribution indicates that the continuous phase of the system is the aqueous phase, confirming that the nanoemulsion base belongs to the oil-in-water (O/W) type. Methylene blue is a water-soluble dye; therefore, in O/W emulsions, the dye disperses evenly because it associates with the continuous aqueous phase. In contrast, in water-in-oil (W/O) emulsions, the color would not be uniformly distributed since the aqueous phase exists only as the dispersed phase within the oil [13].

Determination of the emulsion type is an essential characterization parameter because it is closely related to the physical properties, stability, and intended application of the formulation. O/W emulsions are generally more stable and more suitable for pharmaceutical and topical cosmetic applications, as they provide a non-greasy feel, are easily washed off with water, and exhibit good compatibility with biological environments that are predominantly aqueous. Therefore, the homogeneous blue coloration observed in the methylene blue test confirms that the formulated

nanoemulsion system successfully formed an O/W type emulsion with characteristics appropriate for the development of a stable and user-friendly preparation[29].

#### 4. Conclusion

The results of this study demonstrate that the formulation composition, particularly the ratio of Tween 80 to PEG 400 supported by Poloxamer 188 and DMSO, plays a crucial role in determining the physical stability of olive oil-based nanoemulsions under centrifugal stress. All formulations remained stable at 2,000–4,000 rpm; however, at 6,000 rpm F1 began to show partial creaming, and at 8,000 rpm it exhibited significant phase separation, whereas F3 and F4 remained clear and homogeneous, indicating superior resistance to artificial gravitational forces and better kinetic stability. Physical evaluations supported these findings, as F3 and F4 showed clear and homogeneous organoleptic characteristics, all formulations had pH values within the neutral range (6.8–7.3) indicating chemical stability and suitability for pharmaceutical or cosmetic use, and viscosity values (103–132 cP) were within the acceptable range for nanoemulsions, with higher surfactant concentrations contributing to improved resistance against droplet movement and phase separation. Furthermore, the homogeneous blue coloration in the methylene blue test confirmed that all formulations were oil-in-water (O/W) nanoemulsions, with F3 and F4 demonstrating the most optimal overall stability and strong potential for further pharmaceutical and cosmetic applications.

#### Acknowledgments

The author would like to express gratitude to the Laboratory of Pharmaceutical Dosage Form Technology, State University of Gorontalo, for the support, facilities, and guidance provided during the implementation of this research.

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