The Effect of Centrifugation Test on the Physical Stability of Nanoemulsion Containing a Combination of Poloxamer 407, Tween 80, PEG 400, and DMSO

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ABSTRAK

Pengembangan sistem penghantaran obat berbasis nanoemulsi terus dilakukan untuk meningkatkan stabilitas, kelarutan, dan efektivitas terapeutik zat aktif. Salah satu pendekatan yang digunakan adalah kombinasi surfaktan, kosurfaktan, dan enhancer penetrasi untuk menghasilkan sistem yang stabil secara kinetik. Penelitian ini bertujuan untuk memformulasikan dan mengevaluasi stabilitas fisik nanoemulsi menggunakan kombinasi Tween 80, PEG 400, Poloxamer 407, dan DMSO, serta menentukan formula terbaik berdasarkan parameter fisikokimia dan uji stabilitas dipercepat. Metode penelitian meliputi pembuatan empat formula nanoemulsi (F1–F4) dengan variasi konsentrasi surfaktan dan kosurfaktan. Evaluasi dilakukan melalui pengamatan organoleptik, penentuan tipe emulsi, pengukuran pH, viskositas, serta uji stabilitas menggunakan metode sentrifugasi hingga 8000 rpm untuk mendeteksi kemungkinan terjadinya pemisahan fase, flokulasi, atau koalesensi. Hasil penelitian menunjukkan bahwa seluruh formula termasuk dalam tipe emulsi minyak dalam air (o/w). Uji sentrifugasi menunjukkan tidak adanya pemisahan fase pada semua formula, yang menandakan stabilitas fisik yang baik. Namun, F1 dan F2 menunjukkan tampilan keruh, sedangkan F3 dan F4 memiliki kejernihan yang lebih baik. Nilai pH berada pada rentang 6,6–7,4 yang masih sesuai untuk sediaan topikal, dan viskositas berkisar antara 405–427 cPs yang mendukung kemudahan aplikasi. Berdasarkan keseluruhan parameter evaluasi, kombinasi Tween 80, PEG 400, Poloxamer 407, dan DMSO mampu menghasilkan sistem nanoemulsi yang stabil secara kinetik. Formula F3 dan F4 menunjukkan karakteristik paling optimal dan berpotensi untuk dikembangkan lebih lanjut dalam formulasi farmasetika berbasis nanoemulsi.

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

Diterima:	Disetujui:	Online:
30-01-2026	27-02-2026	27-02-2026

ABSTRACT

The development of nanoemulsion-based drug delivery systems has gained significant attention due to their ability to enhance drug solubility, stability, and therapeutic effectiveness. Optimizing the combination of surfactants, co-surfactants, and penetration enhancers is essential to produce a kinetically stable nanoemulsion system. This study aimed to formulate and evaluate the physical stability of nanoemulsions prepared using Tween 80, PEG 400, Poloxamer 407, and dimethyl sulfoxide (DMSO), and to determine the optimal formulation based on physicochemical characteristics and accelerated stability testing. Four nanoemulsion formulations (F1–F4) were prepared with varying concentrations of surfactant and co-surfactant. The formulations were evaluated for organoleptic properties, emulsion type, pH, viscosity, and physical stability using a centrifugation test at speeds up to 8000 rpm to detect phase separation, flocculation, or coalescence. The results showed that all formulations were classified as oil-in-water (o/w) nanoemulsions. No phase separation was

observed after centrifugation, indicating good physical stability. However, F1 and F2 appeared turbid, whereas F3 and F4 demonstrated better clarity and overall stability. The pH values ranged from 6.6 to 7.4, which are acceptable for topical application, and viscosity values ranged from 405 to 427 cPs, indicating suitable rheological properties for topical use. In conclusion, the combination of Tween 80, PEG 400, Poloxamer 407, and DMSO successfully produced a kinetically stable nanoemulsion system. Among the tested formulations, F3 and F4 exhibited the most optimal characteristics and show strong potential for further development in pharmaceutical nanoemulsion formulations.

1. Introduction

A nanoemulsion is a dispersion system consisting of oil and water phases, which can exist either as oil-in-water (O/W) or water-in-oil (W/O) types, with droplet sizes ranging from approximately 20 to 200 nm and stabilized by a combination of surfactants and co-surfactants (1). In the pharmaceutical and cosmetic fields, this system is utilized to enhance the solubility, bioavailability, and penetration ability of active compounds through the skin or biological membranes (2). Moreover, nanoemulsions as drug delivery systems offer advantages in terms of physical stability and visual clarity compared to conventional emulsions (3).

The stability of a nanoemulsion is influenced by several key factors, including droplet size, the type of surfactant used, the ratio between the oil and water phases, and storage conditions (4). Physical instabilities such as creaming, flocculation, and coalescence can lead to phase separation, which ultimately reduces the effectiveness of the formulation (5). To prevent such occurrences, stability testing is required to identify potential instabilities within a short period. One commonly applied method is centrifugation testing, as this technique simulates the effect of gravitational acceleration to accelerate phase separation in emulsion systems (6,7).

Several previous studies have investigated the stability of nanoemulsions using the centrifugation method; however, most have only focused on the relationship between surfactant type and particle size without thoroughly discussing the effect of combining surfactants with co-solvents on kinetic stability (8,9). Furthermore, the use of olive oil as the oil phase in nanoemulsion systems has rarely been evaluated in terms of its resistance to centrifugal force, despite its high pharmacological and cosmetic value due to its oleic acid content and antioxidant compounds (10).

This study aims to address the limitations of previous research by investigating the effect of the centrifugation process on the physical stability of nanoemulsions formulated using a combination of Tween 80 as a surfactant, PEG 400 as a co-surfactant, Poloxamer 407 as a stabilizer, and DMSO as a co-solvent. The testing was carried out at various centrifugation speeds to evaluate the system's resistance to artificial gravitational force. It is expected that the results of this study will provide insights into the influence of formulation composition on the kinetic stability of nanoemulsions and serve as a reference for developing more stable and effective formulations for pharmaceutical and cosmetic applications.

2. Methods

Study Design

This study employed a true experimental design with a comparative post-test-only approach, aimed at evaluating the effect of variations in formulation composition and centrifugation speed on the physical stability of the nanoemulsion.

Instruments and Materials

The instruments used in this study included a measuring cylinder (Pyrex), a dropper pipette, an analytical balance (Mettler Toledo), a hot plate, a magnetic stirrer (IKA C-MAG HS 7), a centrifuge (Hettich), a glass stirring rod, and an ultrasonic bath (Elmasonic S 30H).

The materials used in this study included Olive oil (Smart Organik), Tween 80 (Sigma-Aldrich), PEG 400 (Sigma-Aldrich), Poloxamer 407 (Sigma-Aldrich), Dimethyl Sulfoxide (Chemical Bull), Methylen Blue and distilled water as the aqueous phase.

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	32.5	32.5	37.5	37.5
Tween 80	30	30	35	35
Poloxamer 407	2	2	2	2
DMSO	0.5	1	1	2
Aquadest	Ad 50 mL			

The nanoemulsion base was prepared using the aqueous titration method. The process began with weighing Poloxamer 407, which was then dissolved in 95% ethanol. Next, Tween 80 and PEG 400 were measured according to the formulation composition, mixed in a beaker, and stirred using a magnetic stirrer for approximately 10 minutes until a homogeneous mixture was obtained. Olive oil was then added to the Tween 80 and PEG 400 mixture and stirred for another 10 minutes to produce a uniform oil–surfactant phase mixture (11). Can be seen in table 1.

In the next stage, the aqueous phase was slowly added dropwise from a burette into the oil phase mixture while continuously stirring with a magnetic stirrer. Water was added until one-third of the total volume was reached, after which Poloxamer 407 was gradually incorporated into the mixture. When the water volume reached about two-thirds of the total, DMSO was added gradually using a micropipette. The stirring process was continued until a homogeneous and stable nanoemulsion system was formed (12).

The following step involved ultrasonication of the obtained nanoemulsion base using a sonicator for 60 minutes. This process aimed to remove bubbles formed during mixing and to reduce and homogenize droplet size. After sonication, the mixture was

centrifuged at 8000 rpm for 30 minutes to separate any non-homogeneous components and ensure the physical stability of the resulting nanoemulsion system (13).

Centrifugation Stability Test

Samples from each formulation were placed into centrifuge tubes and centrifuged at speeds of 2000, 4000, 6000, and 8000 rpm for 30 minutes at room temperature. After centrifugation, the samples were visually observed for homogeneity, clarity, and any signs of phase separation (14).

Organoleptic Test

The organoleptic test was carried out by observing color using the sense of sight, odor using the sense of smell, the presence or absence of phase separation (homogeneity) through visual observation, and the consistency of the sample or test product. The organoleptic parameters evaluated included the aroma, color, homogeneity, and consistency of the nanoemulsion formulation (15,16).

pH Test

The pH test is an important parameter that must be adjusted to ensure both drug stability and user comfort. For example, in topical formulations, the pH should be adjusted to match the physiological pH of the skin (approximately 4.5–6.5) to prevent irritation. Meanwhile, for oral formulations, an appropriate pH is required to maintain the stability of the active substance within the gastrointestinal environment (1).

Viscosity Test

The viscosity evaluation was conducted to determine the thickness of the resulting nanoemulsion. Viscosity describes a fluid's resistance to flow; the greater the resistance, the higher the viscosity (11,17).

Emulsiom Type Test

The emulsion type test was conducted to determine whether the formed emulsion was oil-in-water (o/w) or water-in-oil (w/o). The test was performed using a staining method by adding a water-soluble dye (methylene blue) to the formulation (18).

## 3. Results and Discussion

Centrifugation Stability Test

The centrifugation test was conducted to evaluate the physical stability of the nanoemulsion using an accelerated method that applies centrifugal force to simulate the effect of gravitational acceleration. This technique serves to accelerate the occurrence of potential instabilities such as creaming, flocculation, or coalescence in a shorter time compared to conventional storage stability testing. The basic principle involves applying a centrifugal force greater than gravity, causing droplets in the dispersion system to separate more quickly if the formulation is unstable. Therefore, centrifugation testing can be used to assess the kinetic stability of a nanoemulsion, which refers to the system's ability to maintain homogeneity and clarity even when exposed to external forces. If no phase separation or visible change occurs after centrifugation, it can be concluded that the nanoemulsion possesses good physical stability and has the potential to remain stable during long-term storage (1).
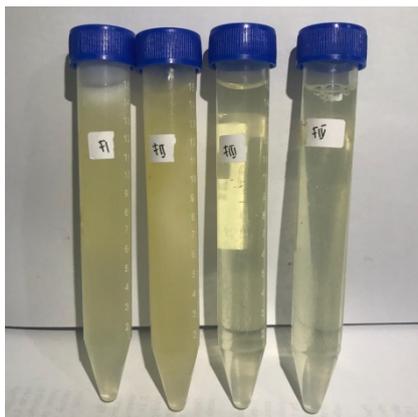
Figure 1. Centrifugation Test Results at 2000 rpm

At a speed of 2000 rpm, the resulting centrifugal force was relatively low and therefore insufficient to affect the interfacial tension between the oil and water phases in the nanoemulsion system. All formulations (F1–F4) exhibited good physical stability without significant phase separation. However, differences in clarity among the formulations were clearly observed. Formula F1 showed a thin white layer at the top, indicating minor phase separation between the oil and water phases. This phenomenon is an early sign of creaming, in which oil droplets migrate to the surface due to density differences between the dispersed and continuous phases, suggesting that the physical stability of F1 was relatively lower. Formula F2 appeared slightly turbid, while F3 and F4 demonstrated higher transparency. This was attributed to the different surfactant-to-cosurfactant ratios, where F3 and F4 contained higher concentrations of Tween 80 and PEG 400, which reduced the interfacial tension between oil and water, produced smaller droplet sizes, and enhanced the clarity of the system (19). Can be seen in figure 1.

Another factor influencing the system's clarity was the presence of DMSO as a co-solvent. At low concentrations, DMSO can enhance the solubility of olive oil in the aqueous phase and reduce the energy required for droplet formation . Therefore, the increased DMSO content in F3 and F4 contributed positively to system stability and resulted in a clearer nanoemulsion appearance.
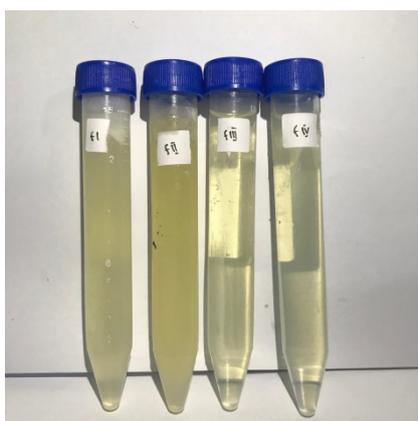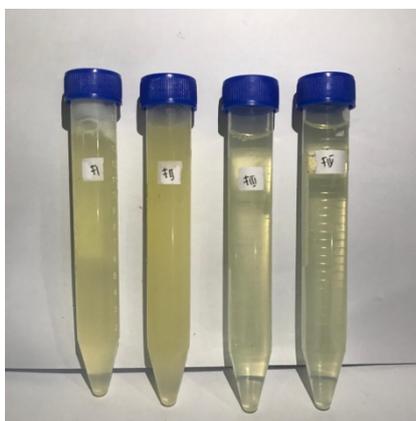

Figure 2. Centrifugation Test Results at 4000 rpm

At a speed of 4000 rpm, the resulting centrifugal force increased; however, all formulations remained stable without any signs of creaming or flocculation. This condition indicated that all four formulations possessed sufficient kinetic stability to

withstand external forces. The stability was likely attributed to the formation of an interfacial layer composed of Tween 80 and Poloxamer 407, which effectively coated the droplets and prevented coalescence between particles (20). Can be seen in figure 2.

The white layer in Formula F1 became thicker and more distinct, indicating an increased degree of phase separation. This occurred because the centrifugal force accelerated droplet migration along the density gradient, causing the oil phase to concentrate more at the top. Formulas F1 and F2 also remained slightly turbid, possibly due to the presence of larger droplets that caused greater light scattering. Meanwhile, Formulas F3 and F4 appeared clear and homogeneous, suggesting that a higher surfactant–cosurfactant ratio and increased DMSO concentration strengthened the inter-droplet protective layer and maintained system stability against centrifugal force (21,22).

These findings are consistent with reported that nanoemulsion systems with an optimal surfactant ratio can maintain stability under centrifugal force up to a certain limit without experiencing physical instability (23). Therefore, centrifugation at 2000 and 4000 rpm can be considered an initial stage that demonstrates the high physical stability of all four formulations (5,6)
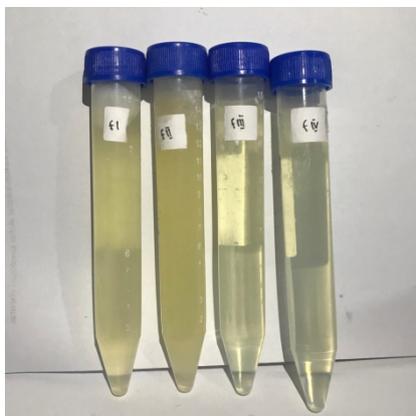

Figure 3. Centrifugation Test Results at 6000 rpm

At a speed of 6000 rpm, the centrifugal force increased approximately threefold compared to that at 2000 rpm. Under these conditions, Formula F1 exhibited more noticeable phase separation, characterized by a thicker white layer, although no color change was observed in the lower portion. This indicated that the interfacial layer of Formula F1 was relatively weak and that the droplet size was comparatively larger, thereby increasing the likelihood of coalescence. Formula F2 appeared slightly turbid but remained homogeneous, while Formulas F3 and F4 maintained their clarity, demonstrating superior physical stability in these two formulations. Can be seen in figure 3.

This stability indicates that the interfacial forces between the oil and water phases were sufficiently strong to withstand the effects of artificial gravity. The combination of Tween 80 and PEG 400 effectively reduced interfacial tension, thereby lowering the system's free energy and enhancing the nanoemulsion's resistance to centrifugal stress (19). In addition, the presence of DMSO as a co-solvent helped improve the solubility of the oil phase in the aqueous phase and maintained proper droplet dispersion, thus preventing coalescence during the centrifugation process (24).

Moreover, Poloxamer 407 plays an essential role as a stabilizer since this polymer can increase the viscosity of the continuous phase and form a protective layer around the droplet surface. This layer acts as a steric barrier that prevents droplet

collisions, which could otherwise lead to phase separation. Therefore, the maintained stability of the system at speeds up to 6000 rpm indicates that the nanoemulsion possesses good kinetic stability (20).

Figure 4. Centrifugation Test Results at 8000 rpm

At this stage, the test was carried out at the highest speed, namely 8000 rpm, equivalent to a gravitational acceleration of approximately 7000–8000 g. The observations showed that formulas F3 and F4 remained clear, while F1 exhibited the most apparent phase separation, forming a dense white layer on the top. This condition indicates that formula F1 was unable to maintain its stability under high centrifugal force due to a suboptimal surfactant–co-surfactant ratio. Larger droplets in this formula experienced an increased buoyant force, causing them to concentrate on the upper layer. Formula F2 appeared slightly turbid but remained stable. The absence of significant physical changes at high speeds demonstrates that the nanoemulsion system has achieved optimal kinetic stability. Can be seen in figure 4.

Nanoemulsions that remain homogeneous after high-speed centrifugation exhibit an ability to maintain low interfacial tension and possess a narrow droplet size distribution (22). This condition indicates that the small droplets within the system did not undergo aggregation or sedimentation during the testing period. These findings also reinforce that a balanced surfactant–co-surfactant ratio and the addition of DMSO contribute significantly to enhancing the system's kinetic stability by reducing its total free energy (23).

Thus, the results of the test at 8000 rpm show that formulas F3 and F4 exhibit excellent physical stability against centrifugal forces. This strongly indicates that the formulated nanoemulsion system has promising potential for pharmaceutical and cosmetic formulations that require high stability during storage and application.

Organoleptic Test

Table 2. Results of the Organoleptic Evaluation of the Nanoemulsion Base

Formula	Parameter		
	Physical Appearance	**Odor**	**Homogeneity**
F1	Turbid	Characteristic olive oil odor	Homogeneous
F2	Turbid	Characteristic olive oil odor	Homogeneous
F3	Clear	Characteristic olive oil odor	Homogeneous
F4	Clear	Characteristic olive oil odor	Homogeneous

The organoleptic evaluation included observations of color, odor, homogeneity, and consistency. Based on Table 2, the four nanoemulsion base formulations showed physical appearances ranging from turbid to clear, had a characteristic olive oil odor, and were homogeneous. These visual differences are associated with droplet size and polydispersity, where smaller and more uniformly distributed droplets (low PDI) produce clearer systems, while larger or more polydisperse droplets result in a turbid appearance (2). Can be seen in table 2.

Emulsion Type Test

The emulsion type test was conducted to determine whether the formulation was oil-in-water (o/w) or water-in-oil (w/o). The test was performed using a staining method by adding a water-soluble dye (methylene blue) to the formulation. In an oil-in-water (o/w) emulsion, oil droplets are dispersed in the aqueous phase. The external water phase interacts with the water-soluble dye, resulting in a uniformly colored and homogeneous appearance (18). Can be seen in figure 5.

| **F1** | **F2** | **F3** | **F4** |
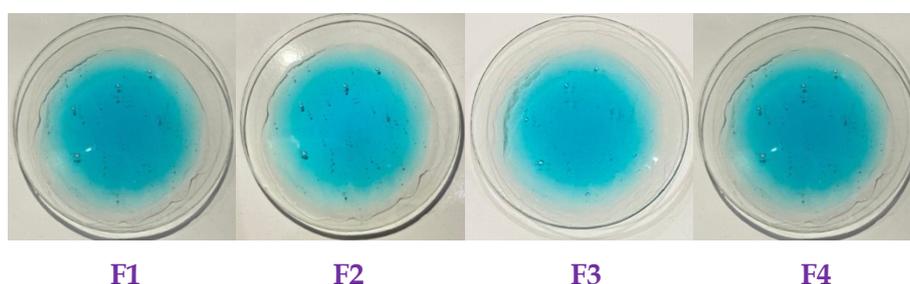
Figure 5. Emulsion Type Test

The results of the emulsion type test using methylene blue showed that all nanoemulsion base formulations were oil-in-water (o/w) systems, in which oil acted as the dispersed phase and water as the continuous medium. In this type of emulsion, oil droplets are surrounded by the aqueous phase. The external water phase interacts with

the water-soluble dye, producing a uniform and homogeneous color throughout the sample (18).

pH Test
Table 3. pH Test Results

Formula	pH
F1	7.3
F2	7.4
F3	6.6
F4	6.8
Mean ± SD	7.03 ± 0.39

The pH measurement was performed using a pH meter. This test was conducted to ensure the chemical stability of the formulation as well as its safety in use, particularly for topical applications. The pH evaluation aimed to determine the acidity level of the nanoemulsion base and to assess its compatibility with the physiological pH range of the skin. The normal pH of human skin ranges from 4.5 to 6.5; therefore, an ideal topical formulation should fall within this range to minimize the risk of irritation and to maintain the skin barrier function (1). Can be seen in table 3.
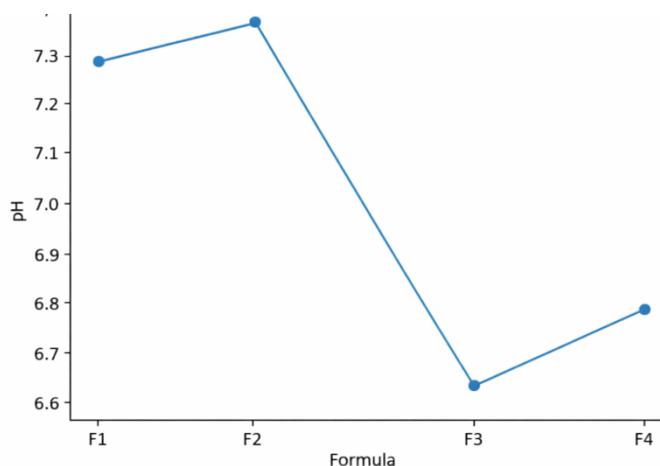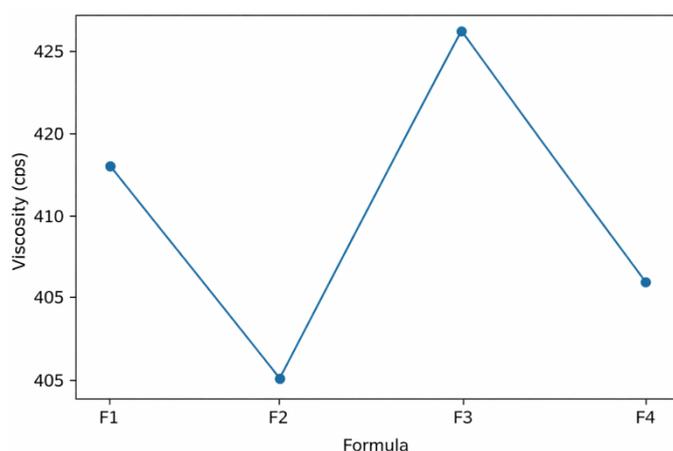

Figure 6. pH Test Results

All formulations showed pH values ranging from 6.6 to 7.3, indicating that the preparations were neutral to slightly alkaline. The pH of formulation F11 (the lowest, 6.6) was slightly above the normal skin pH range but still close enough to be considered safe for topical use. In general, many topical formulations also exhibit near-neutral to slightly alkaline pH with good stability, typically within the range of 6 to 8. These results are consistent with previous studies recommending formulations with pH close to the skin pH (approximately 5–7) to optimize stability and user comfort (2). Can be seen in figure 6.

Viscosity Test

Table 3. Viscosity Test Results

Formula	Viscosity (cPs)
F1	420
F2	405
F3	427
F4	410
Mean ± SD	415.5 ± 9.5

Viscosity measurements were performed using a Brookfield viscometer with spindle No. 03 at 100 rpm, using 50 mL of sample. The viscosity test was conducted to evaluate the flow resistance of the nanoemulsion under shear conditions. Viscosity is strongly influenced by surfactant and cosurfactant composition, oil content, phase ratio, and the internal structure of the nanoemulsion. In emulsion systems, viscosity generally increases with higher dispersed phase volume and surfactant concentration. In addition, poloxamers such as P407 are known as hydrophilic polymers that form micellar network structures, which can significantly enhance viscosity [1]. Can be seen in table 3.

Figure 7. Viscosity Test Results

The viscosity of the nanoemulsion formulations is presented in Figure 7, showing variations among the four formulations. For formulations F1 to F4, the viscosity values were 420 cPs for F1 and 405 cPs for F2, which fall within the low to moderate viscosity range. These results indicate that increasing the concentrations of PEG 400 and Tween 80 enhances the micellar structure in the continuous phase, thereby increasing viscosity. PEG is a hydrophilic polymer that promotes intermolecular interactions through hydrogen bonding, while Tween 80, a nonionic surfactant, contributes to viscosity enhancement by forming more compact micellar aggregates [1,2]. Can be seen in figure 7. Formulations F3 and F4 showed viscosity values of 427 cPs and 410 cPs, respectively. The decrease in viscosity observed in these formulations reflects the effect of increased DMSO concentration, which enhances the fluidity of the continuous phase [5].

4. Conclusion

Based on the results of the centrifugation stability test and physicochemical evaluation, all nanoemulsion formulations (F1–F4) demonstrated good physical stability without phase separation under accelerated conditions. However, F1 and F2 appeared turbid, while F3 and F4 showed better clarity and overall stability. This difference was influenced by the higher surfactant–co-surfactant ratio and the presence of DMSO in F3 and F4. All formulations were classified as oil-in-water (o/w) systems, with pH values ranging from 6.6–7.4 and viscosity between 405–427 cPs, indicating suitability for topical application. Overall, the combination of Tween 80, PEG 400, Poloxamer 407, and DMSO successfully produced a stable nanoemulsion system, with F3 and F4 showing the most optimal characteristics for further pharmaceutical development. Notably, comprehensive nanoemulsion characterization parameters (e.g., droplet size distribution, polydispersity index, and zeta potential) have been reported in a separate published article; therefore, the present work specifically strengthens the evidence for physical stability under mechanical stress as a key screening step in nanoemulsion base development.

Acknowledgments

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