




Tocotrienol-Rich Fraction Nanoemulsion: A Novel Approach for Ocular Drug Administration

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Abstract: Tocotrienol-rich fraction (TRF), a substance extracted from palm oil, contains tocotrienol, which was shown to delay cataract development and progression in an experimental cataract model. Other than that, TRF also reduced retinal neurodegenerative changes in diabetic retinopathy animal models. However, TRF is an oily substance, which makes it difficult to apply topically to the eye, which is the most favorable route of administration for ocular tissue. Topical ocular drug delivery is less invasive and more targeted, thus producing fewer systemic adverse effects. Nanoemulsion is one of the promising colloidal drug delivery systems for topical ocular use. In this study, we aimed to investigate the optimum ratio of surfactant, oil, and water needed to develop a TRF nanoemulsion formulation that was suitable for ocular use. The solubility of TRF in different types of surfactants was also investigated. Ternary phase diagrams (TPDs) were constructed using three different surfactant systems (Poloxamer 188, Tween 80, and a combination of Tween 80 and Span 80). The result showed 1 % w/w TRF was soluble in Tween 80 and a combination of Tween 80 and Span 80 solution, but not in Poloxamer 188. Observations on isotropic, turbid, or multilayer formulations were plotted on TPD. Among the TPD constructions, the TPD consisting of Miglyol 812 with TRF (oil phase)/Tween 80/ Water system (aqueous phase) was selected due to the large isotropic region. Five formulations (TRF 1, TRF 2, TRF 3, TRF 4, and TRF 5) were chosen based on the TPD selected, and the formulations were prepared by the low-energy emulsification method. The physicochemical characterization of their size, polydispersity index (PDI), zeta potential, and pH of these formulations was evaluated. Among the formulations prepared, TRF 5 was the most stable formulation with droplet size, PDI, zeta potential, and pH values of 11.44 nm, 0.062, -7.75 mV, and 6.57, respectively. Further studies are needed to determine the ocular toxicity, penetration, and pharmacokinetics of this formulation.

Keywords: tocotrienol-rich fraction; ocular delivery; low-energy emulsification method; nanoemulsion.

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1. Introduction

Palm oil tocotrienol-rich fraction (TRF) consists of around 80% tocotrienol and 20% tocopherol. Both tocotrienol and tocopherol possess superior antioxidant properties [1], making

TRF a potent antioxidant. They neutralize free radicals at the cellular membrane by donating their phenolic hydrogen to the lipid-free radicals [2]. TRF also possesses other biological properties, including neuroprotective, anti-inflammatory, and anti-angiogenic effects, which are beneficial for several ocular diseases, such as cataract, retinopathy, and glaucoma [3]. This statement was proven by demonstrating the protective effect of tocotrienol against cataract in galactose- and diabetes-induced rat model [4,5]. Other than that, TRF was shown to protect retinal neurodegenerative changes in diabetic retinopathy animal models [6].

However, being an oily, lipophilic compound, it needs to be formulated into a specialized drug delivery system if applied topically. Topical instillation of drug application is the most preferred method of drug delivery for the treatment of ocular diseases [7]. This route of administration gives drugs the most direct access to ocular tissue and is the least invasive. Despite the mentioned advantages, delivering drugs topically generally results in poor uptake in ocular tissues, largely due to the eye's natural anatomical and physiological defenses. Less than 5% of the drug reaches intraocular tissue following topical application of a conventional drug formulation [8]. Therefore, topical eye formulations should be designed to improve drug availability in the eye. This can be achieved by increasing how long the drug stays on the cornea and by helping it pass through the eye's natural barriers.

Colloidal drug delivery systems offer the advantage of providing sustained, controlled drug release to the targeted tissue. They can also overcome ocular barriers, which will improve ocular bioavailability. One of the examples of colloidal drug delivery systems is a nanoemulsion. Nanoemulsion is a drug delivery system that offers solubilization for an oily compound such as TRF in a water-based formulation (oil-in-water nanoemulsion). Nanoemulsion is composed of two immiscible liquids that are stabilized by using a suitable surfactant to form a single phase [9]. It is thermodynamically unstable but kinetically stable, which helps resist phase separation, flocculation, coalescence, Ostwald ripening, and creaming/sedimentation [10]. Nanoemulsions adopt the characteristic of being transparent, translucent, and having a low viscosity. It also has a uniform droplet size (less than 200 nm) compared to emulsion and microemulsion. The small size of nanoemulsions causes them to have a high surface area, which is an important characteristic for an emulsion [6]. Nanoemulsion in drug delivery has excellent penetration, high bioavailability, prolonged retention time, and reduces the wastage of drugs as it uses lower drug dosage [11]. Thus, nanoemulsion was a suitable delivery system to be used to deliver TRF to study its efficacy for ocular delivery.

The objective of this study was to investigate the optimum ratio of surfactant, oil, and water needed to develop a TRF nanoemulsion formulation for ocular use. Other than that, the solubility of TRF in different types of surfactants was studied. This work aims to establish TRF nanoemulsion as a potential novel approach for ocular drug administration.

2. Materials and Methods

The tocotrienol-rich fraction was provided by ExcelVite Sdn. Bhd. Malaysia and Miglyol 812 were provided by IOI Oleochemical GmbH (Germany) as a gift. Poloxamer 188, Tween 80, and Span 80 were purchased from Sigma-Aldrich (Germany). The deionized water was filtered in a laboratory using Milli-Q, Millipore, Billerica, MA.

2.1. Solubility study.

TRF (0.03 g, 1% w/w) was weighed (Mettler Toledo, USA) and poured into a screw cap test tube containing 3.00 g of Poloxamer 188. The percentage of TRF was chosen according to the research reported by Yap, W. [12]. The mixture was homogenized using a vortex mixer (VM-300, Gemmy Industrial CORP-Taiwan) and then centrifuged at 4000 rpm for 15 min. The phase separation of the mixture was observed by the naked eye. These steps were repeated using Miglyol 812 oil, Tween 80, Span 80, and water. The surfactants were selected based on their ability to solubilize TRF, safety, and biocompatibility for ocular use (with preference for non-ionic surfactants) and their capacity to form a stable and homogeneous system as observed in the solubility test.

2.2. Construction of the ternary phase diagram.

TRF (0.15 g, 1.00% w/w) was added to Miglyol 812 oil with a total weight of 15.00 g. The mixture was stirred until homogeneous using a stirrer for 30 min at room temperature (25.0 ± 0.5°C). The oil phase mixture of (Miglyol 812 oil and TRF) and poloxamer 188 (as a surfactant) was weighed at various weight ratios ranging from 0:100 to 100:0 with a total of 11 test tubes separately. The mixture with a total weight of 0.50 g was vortexed using a vortex mixer (VM-300, Gemmy Industrial CORP-Taiwan). Water (5.00% w/w) was then added to the mixture and vortexed until it was homogenized. The mixture was then centrifuged again at 4000 rpm for 15 min, and any phase separation was observed. Water was added at 5% w/w increments until 90% w/w of water. Ternary phase diagrams were constructed using Chemix School v3.50 software (Arne Standnes, Norway). The experiment was repeated using different surfactants (Tween 80 alone and a mixture of Tween 80/Span 80, ratio 1:1). It should be noted that all ternary phase diagrams were constructed using the same component ratios for comparison purposes; however, only the system containing the largest isotropic region was selected for further formulation development.

2.3. Selection and preparation of nanoemulsion formulation.

Five formulations were chosen based on the ternary phase diagram selected for nanoemulsion formulation (Table 1). Nanoemulsion was prepared by the spontaneous emulsification method. In preparation for TRF 1, the oil phase which consists of miglyol 812 oil (0.99% w/w), tocotrienol (0.01% w/w), and Tween 80 (19.00% w/w) with a total weight of 0.50 g were mixed using an overhead stirrer (IKA RW16 Digital, Nara, Japan) 300 rpm at room temperature 25 °C for 4 h. Water (80.00% w/w) was added dropwise into the mixture and was continuously homogenized. The nanoemulsion was stored in a vial covered with aluminum foil and kept in the dark for further studies. The steps were repeated for TRF 2, 3, 4, and 5.

Table 1. Composition of nanoemulsion formulation

| Formulation | Composition (%w/w) | | | |
|-------------|--------------------|--------------------------|------------------|-----------------|
| | Tween 80 | Miglyol 812 ^a | TRF ^b | Deionized water |
| TRF1 | 19.00 | 0.99 | 0.01 | 80.00 |
| TRF2 | 23.00 | 1.98 | 0.02 | 75.00 |
| TRF3 | 29.50 | 2.48 | 0.03 | 68.00 |
| TRF4 | 34.00 | 1.98 | 0.02 | 64.00 |
| TRF5 | 37.00 | 2.97 | 0.03 | 60.00 |

Note: a+b = 1% w/w of oil phase; Abbreviation: TRF, Tocotrienol-Rich Fraction.

2.4. Physicochemical characterization of nanoemulsion formulation.

2.4.1. Particle size and polydispersity index (PDI) measurement.

The particle size and PDI of the nanoemulsions were determined using a Zetasizer Nano ZS (Malvern Instruments, Malvern, UK) based on dynamic light scattering at 173 ° and 25°C. The software (DTS Nano v5.03, Malvern Instruments Ltd.) calculated the mean hydrodynamic diameter (z-average) from the autocorrelation of the scattered light intensity. Prior to analysis, all samples were diluted with deionized water. A PDI below 0.2 is considered desirable, as it reflects a narrow particle size distribution.

2.4.2. Zeta potential measurement.

Dynamic light scattering was used to measure the zeta potential of the nanoemulsions by using Malvern Nano ZS90, Malvern, UK. The measurement was carried out at a scattering angle of 173° at 25°C. The nanoemulsions were first diluted with deionized water to the appropriate concentration and then loaded into the sample cell. The electrophoretic mobility of the particles under an applied electric field was measured, and the zeta potential values were obtained from the average of these readings.

2.4.3. pH measurement.

The pH values of the samples were measured by immersing the pH electrode into 20 mL of the sample using a pH meter (model HI 8417, Hanna Instruments Inc., Woonsocket, USA) at room temperature.

2.4.4. Stability study.

The freshly prepared formulations were centrifuged for 15 min at 4000 rpm and then observed for phase separation. The samples with no phase separation were then stored in the laboratory at room temperature ($25.0 \pm 0.5^\circ\text{C}$) and were observed visually for the presence of separation within 30 days.

3. Results and Discussion

3.1. Solubility analysis.

Based on Figure 1, 1% w/w of TRF was soluble in Miglyol 812 oil and insoluble in water. This is due to the properties of TRF itself, which act as lipid-soluble [13]. The presence of a hydroxyl (-OH) group on the aromatic chromanol ring increased TRF's phospholipid solubility, resulting in less surfactant availability at the water interface [14]. Thus, a hydrophilic surfactant was needed to stabilize the interface. In this study, Tween 80: Span 80 with an HLB value of 9.65 is considered a lipophilic surfactant that was not able to solubilize the TRF. Besides, this mixture of surfactants also creates a large droplet size, which is more than 200 nm [15]. This showed that Tween 80: Span 80 is not suitable for the preparation of nanoemulsion formulations. Next, even though both Poloxamer 188 and Tween 80 have high HLB values (hydrophilic surfactant), which are suitable for producing O/W nanoemulsion, Poloxamer 188 is not able to solubilize TRF. The solubility of surfactant plays an important role in the preparation of nanoemulsions. This is due to the drug's high solubility in the oil

phase, indicating a high carrying capacity in the nanoemulsion solubilized form [16]. As TRF is soluble in Tween 80, and it was used in the preparation of nanoemulsion formulation.

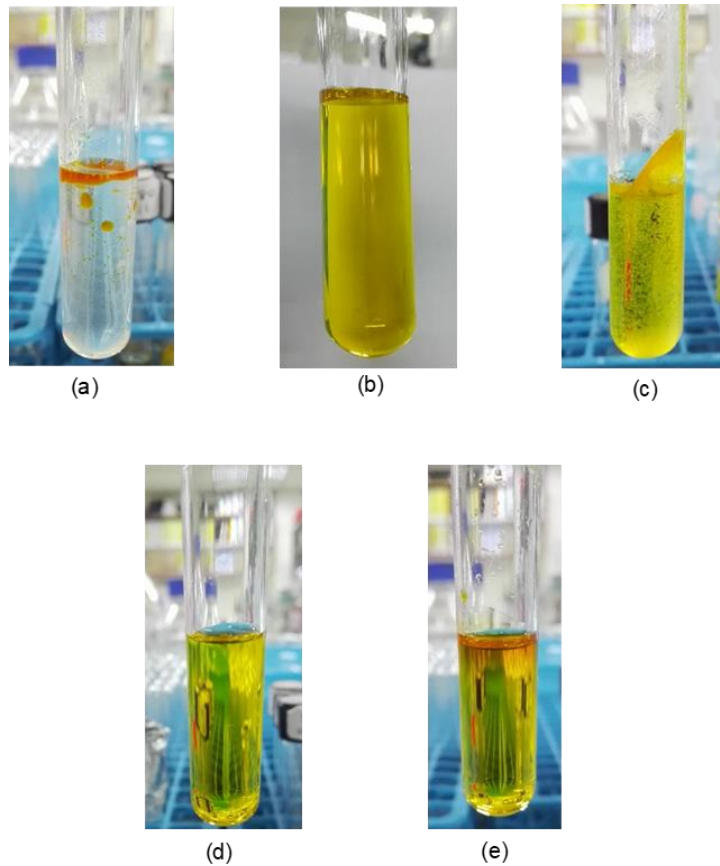


Figure 1. Sample appearance 1% w/w of TRF in 3.0 g of (a) Distilled water; (b) Miglyol 812 oil; (c) Poloxamer 188; (d) Tween 80; (e) Tween 80: Span 80.

3.2. Phase behavior analysis.

3.2.1. Ternary phase diagram of Miglyol 812 + TRF/Poloxamer 188/water system.

Figure 2 shows a ternary phase diagram with a small isotropic region in the water-rich apex of this diagram. The isotropic region started to form after the increment of 35% until 90% of water.

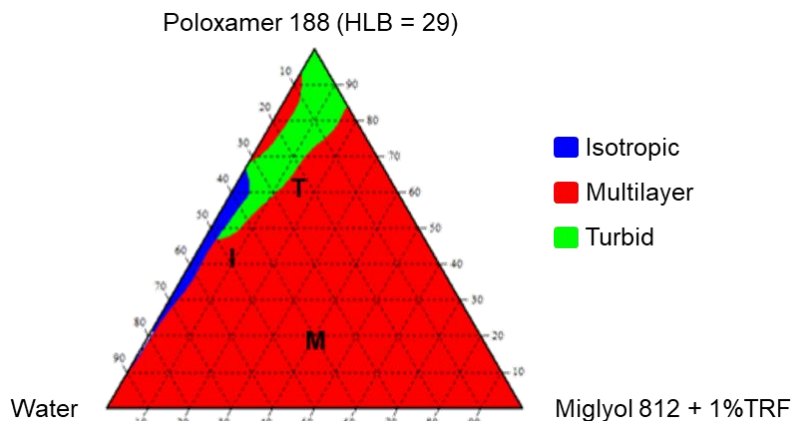


Figure 2. Ternary phase diagram of Miglyol 812+TRF/Poloxamer 188/Water system.

This isotropic (clear appearance) indicates the formation of a nanoemulsion [17]. Other than that, Poloxamer 188 has an HLB value of 29, which is suitable for the cataract treatment

as it protects lipids from peroxidation [18]. Besides, Poloxamer P188 was also considered a copolymer with a high HLB value. However, Almeida *et al.* [19] stated that copolymers that have a good capability to encapsulate drugs were the ones with lower HLB values. The solubility study of Poloxamer P188 yielded an unstable ternary phase diagram (Figure 2), with a large multilayer region covering the system, followed by a turbid, isotropic region.

3.2.2. Ternary phase diagram of Miglyol 812 + TRF/Tween 80: span 80/water system.

Figure 3 shows that the isotropic region favored the surfactant-rich apex and oil-rich apex of the diagram. This figure has a higher isotropic region than Figure 2. This is due to a combination of the surfactants used, which could enhance the stability of the nanoemulsion by reducing the interfacial tension between the oil and aqueous phases [20]. However, the isotropic region of Figure 3 also does not cover the water-based region. This is due to the HLB value of the mixture of Tween 80 and Span 80 with a ratio of 1:1, which is 9.65. Surfactants with greater than 10 HLB values can stabilize oil-in-water nanoemulsions compared to surfactants with low HLB values [21]. Hence, Tween 80: Span 80 was not a suitable surfactant for the formulation of nanoemulsion.

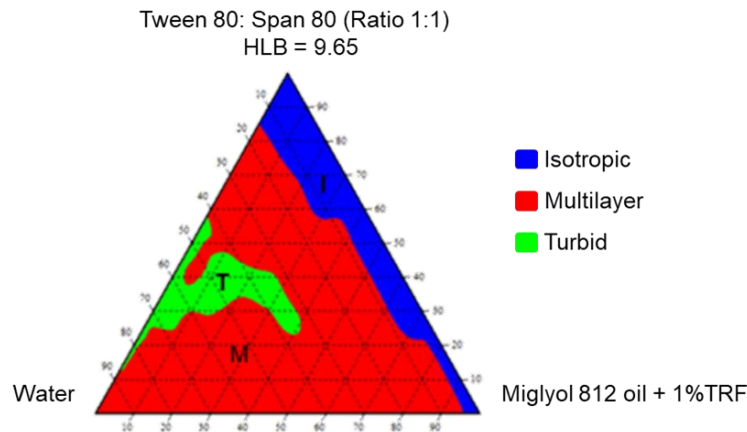


Figure 3. Ternary phase diagram of Miglyol 812 + TRF/Tween 80: Span 80/Water system.

3.2.3. Ternary phase diagram of Miglyol 812 + TRF/Tween 80/water system.

The ternary phase diagram system of Miglyol 812 + TRF/Tween 80/Water is shown in Figure 4. Tween 80 (HLB = 15) contained isotropic, turbid, and multilayer regions. Results show that 90% of water is able to be solubilized by using 10% of Tween 80.

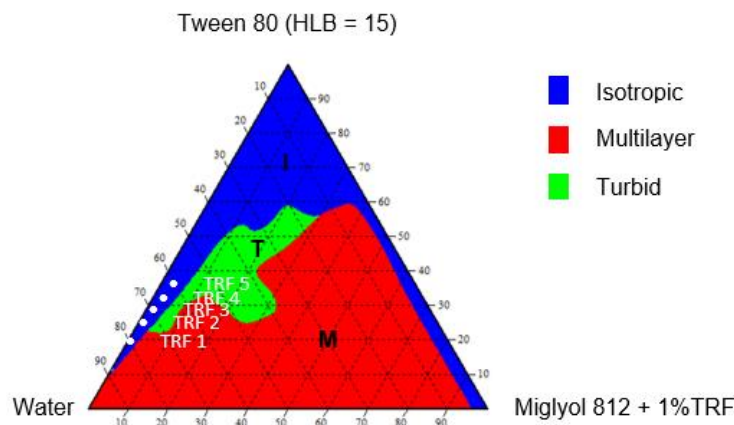


Figure 4. Ternary phase diagram of Miglyol 812 + TRF/Tween 80/Water system.

After a 3% increase in water, the multilayer region began to form, whereas the turbid region began to form at 15% water addition. As the sample was turbid, it showed the formation of a coarse emulsion [22]. Apart from that, Farahin *et al.* [23] reported that higher HLB values of non-ionic surfactants tend to produce large isotropic and homogenous regions in ternary phase diagrams. This is due to the surfactant (Tween 80) itself, which can reduce the interfacial tension between the aqueous and oil phases. Moreover, non-ionic surfactants also have low toxicity and irritancy, making them suitable for drug delivery purposes. As a result, the system containing surfactant Tween 80 alone was selected as the surfactant for the preparation of nanoemulsion formulation, due to its ability to form a system with the largest isotropic region in the ternary phase diagram, indicating a higher potential for stable and clear formulations.

3.3. Preparation of nanoemulsion formulation.

Based on the selected ternary phase diagram (Figure 4), five formulations were selected for nanoemulsion development, all of which fall within the isotropic region. Figure 5 illustrates the physical appearance of these formulations after centrifugation for 15 min. Among them, TRF 1, TRF 4, and TRF 5 remained stable, appearing as transparent (isotropic) solutions. In contrast, TRF 2 and TRF 3 were unstable, forming cloudy dispersions after centrifugation. This is due to the poor water solubility of the oil phase. Additionally, unfavorable electrostatic repulsions and steric hindrance resulting from an inadequate surfactant composition may have contributed to phase separation [24]. Surfactants play a critical role in nanoemulsion stability by reducing interfacial tension and forming a steric or electrostatic barrier that prevents droplet coalescence [25]. An optimized surfactant concentration is therefore essential to stabilize the oil-water interface and maintain the homogeneity of the formulation.

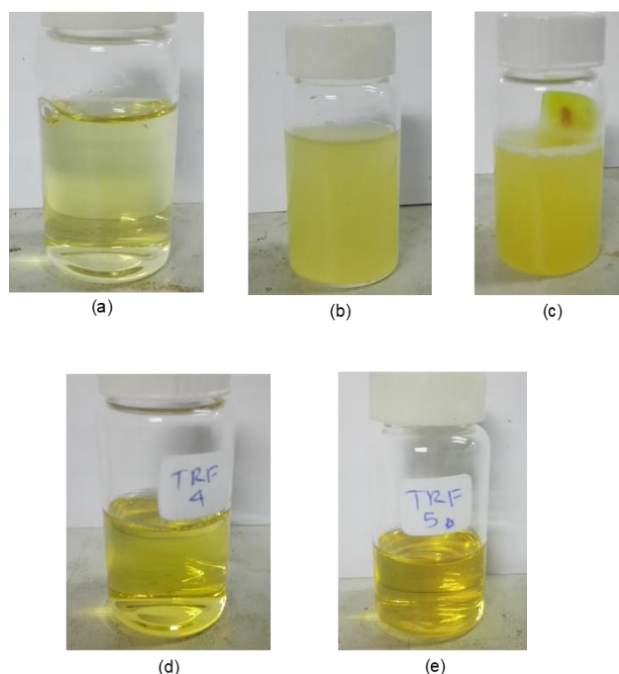


Figure 5. The appearance of the formulation of (a) TRF 1; (b) TRF 2; (c) TRF 3; (d) TRF 4; (e) TRF 5.

3.4. Physicochemical characterization of nanoemulsion.

Based on Table 2, the droplet sizes of TRF 1, TRF 4, and TRF 5 were smaller compared to TRF 2 and TRF 3. These results showed that the formulation with the smaller size has an isotropic sample appearance, whereas the cloudy formulations have a larger size. The

differences in size might be due to the stability of the formulation itself. The smaller the size, the larger the surface area, which is good for long-term stability and improved drug encapsulation efficiency [9].

In the context of ocular delivery, smaller droplets also facilitate better drug penetration into ocular tissues, which is crucial for therapeutic effectiveness [26]. Additionally, the high water content (>60%) in these formulations contributed to their low viscosity, making them suitable for ocular application as eye drops. This ensures ease of administration, improved spreading on the eye surface, and greater patient comfort.

A high concentration of Tween 80 will increase the number of emulsifier molecules migrating from the oil phase to the aqueous phase of the nanoemulsion. A low concentration of Tween 80 in the oil-water interfacial layer was insufficient to cover the surface of oil droplets. Thus, coalescence and flocculation of droplets occur, resulting in larger droplet size [27]. TRF 2 and TRF 3 should be smaller than TRF 1 due to their higher Tween 80 concentration, but the higher oil concentration in both TRF 2 and TRF 3 might also increase droplet size.

The size of the nanoemulsion and its distribution were characterized by polydispersity index (PDI) and zeta potential. A PDI value higher than 0.3 is considered polydisperse, which refers to a broad distribution, whereas a PDI lower than 0.3 is considered monodispersed, which refers to a narrow distribution [26]. Based on Table 2, TRF 1 and 5 are categorized as monodispersed. Furthermore, the result also showed that the smaller the size, the smaller the PDI value.

For the zeta potential of nanoemulsion, it should be higher than ± 30 mV [28]. Table 2 shows that only TRF 3 met the criteria of nanoemulsion for zeta potential value. Zeta potential values above 30 mV or below -30 mV tend to result in stronger particle repulsion, which can help prevent coalescence and flocculation and lead to better nanoemulsion stability [29]. Although Figure 5 shows that TRF 1, 4, and 5 appear stable by visual observation, their zeta potential values suggest they may not be physically stable over time.

Table 2. Particle size, polydispersity index (PDI), zeta potential, and pH of the TRF nanoemulsions.

| Formulation | Composition (% w/w) | | | | Size (nm) | PDI | Zeta Potential (mV) | pH |
|-------------|---------------------|-----------------|------|-------|-----------|-------|---------------------|------|
| | Tween 80 | Miglyol 812 oil | TRF | Water | | | | |
| TRF 1 | 19.00 | 0.99 | 0.01 | 80.00 | 13.85 | 0.257 | -10.71 | 6.39 |
| TRF 2 | 23.00 | 1.98 | 0.02 | 75.00 | 270.40 | 0.488 | -26.75 | 6.50 |
| TRF 3 | 29.50 | 2.48 | 0.03 | 68.00 | 1090.50 | 0.877 | -32.05 | 6.46 |
| TRF 4 | 34.00 | 1.98 | 0.02 | 64.00 | 14.92 | 0.341 | -16.50 | 6.48 |
| TRF 5 | 37.00 | 2.97 | 0.03 | 60.00 | 11.44 | 0.062 | -7.75 | 6.57 |

Abbreviations: TRF, Tocotrienol-Rich Fraction; PDI, Polydispersity Index.

The pH values of all formulations were below the neutral pH of the eyedrop (7.11 ± 0.01) based on Table 2. The slightly low pH of these formulations might be due to the aggregation of particles. The pH of these formulations was critical because it could affect the drug's bioavailability [30]. In this case, TRF 5 has a good pH value (Table 2) compared to the other four formulations, due to its pH being the closest to the control pH (neutral). Other than that, the pH of tears was 7.4 with a buffering capacity (ability to resist changes in pH) that could tolerate the pH range 4.0-8.0. However, the stimulation of blinking and tearing might affect the pH values out of this range. As a result, the bioavailability of the drug might be reduced [31].

3.5. Stability study.

Table 3 showed that TRF 4 and 5 were stable for up to 30 days. This might be due to the smaller size, which gave a large surface area that led to good stability of the nanoemulsions [32]. Thus, it could prevent sedimentation and coalescence for a certain period [33]. This is because the rate of diffusion is higher than the rate of sedimentation, which is induced by the gravitational force [34]. Next, for TRF 2 and 3, neither was stable from day 1 to day 30. They formed cloudy nanoemulsions first before starting to have a phase separation on day 3 (TRF 2) and day 2 (TRF 3). This might be due to the formation of coalescence, where the droplets start to merge and become large droplets [35]. Apart from that, TRF 1 was stable until day 5. This might be because the Ostwald ripening phenomenon occurred, where the small size became larger due to longer storage time. However, this effect could be prevented by the addition of polymeric surfactant on the interface, which can increase the elasticity of droplets [36].

Table 3. Stability observation for formulations over time.

| Formulation | Time (Day) | | | | | | | |
|-------------|------------|---|---|---|---|----|----|----|
| | 1 | 2 | 3 | 4 | 5 | 10 | 20 | 30 |
| TRF 1 | ✓ | ✓ | ✓ | ✓ | ✓ | x | x | x |
| TRF 2 | x | x | x | x | x | x | x | x |
| TRF 3 | x | x | x | x | x | x | x | x |
| TRF 4 | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| TRF 5 | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |

Notes: ✓ = Stable with no phase separation; x = Not stable.

4. Conclusions

Nanoemulsions are delivery systems widely used in pharmaceutical applications, and their use in cataract treatment has been reported for years. However, the nanoemulsion containing TRF for protective effects against cataracts remains unclear. In this study, the physicochemical stability of a nanoemulsion containing TRF was compared among different surfactants. Results proved that Tween 80 was a suitable surfactant compared to the other surfactants, as it was able to create a large isotropic region in the ternary phase diagram. These findings suggest that TRF combined with Tween 80 has strong potential to yield a stable nanoemulsion suitable for ocular drug administration. Nevertheless, the concentration of surfactants in ocular formulations must be carefully optimized, as excessive levels may cause irritation and compromise ocular safety. Further investigations are needed to evaluate the ocular toxicity, penetration, and pharmacokinetics of this formulation.

Author Contributions

Conceptualization, N.S. and N.A.A.N.; methodology, N.S.; validation, N.Se., S.A.A., N.S., and N.A.A.N.; formal analysis, N.Se.; investigation, N. Se. and S.A.A.; resources, N.A.A.N. and S.S.; data curation, N.Se. and S.A.A.; writing—original draft preparation, S.A.A. and N.S.; writing—review and editing, S.A.A., N.S. and N.A.A.N.; visualization, S.A.A., N.S. and N.A.A.N.; supervision, N.S. and N.A.A.N.; project administration, N.A.A.N.; funding acquisition, N.A.A.N., and S.S.. All authors have read and agreed to the published version of the manuscript.

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Informed Consent Statement

Not applicable.

Data Availability Statement

Data supporting the findings of this study are available upon reasonable request from the corresponding author.

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Conflicts of Interest

The author reports no conflicts of interest in this work.

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