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Research Article

Development microemulsion formulation combination of citronella and red ginger essential oil

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ABSTRACT

Acne vulgaris is a skin health problem. Citronella oil contains citronellal, geraniol, geranial, β-citronellol, and neral, which have antibacterial properties. Meanwhile, red ginger oil contains gingerol, which has anti-inflammatory properties. These two ingredients are suitable for treating acne vulgaris. The aim of this study are to develop microemulsion formulation combination of citronella and red ginger essential oil. In this experimental study, a microemulsion combination of citronella essential oil and red ginger essential oil was made using Tween 80 as a surfactant and Transcutol® as a co-surfactant, with variations of S-mix (surfactant:cosurfactant) of 3:3, 4:2, and 4.5:1.5 ratios. As an oil carrier, isopropyl myristate is used. The microemulsions are formulated using a titration method. The microemulsion was then tested for characteristics and stability. The results show that the most optimal microemulsion formula was obtained with an S-mix ratio of 4:2 with a globule size of 21.64 nm, a Polydispersion Index of 0.15, and a zeta potential of -3.82. Its pH and viscosity meet the required specifications and are stable.

1. Introduction

Acne vulgaris is a chronic skin disease of the pilosebaceous unit and develops due to blockages in the skin's hair follicles, resulting in chronic inflammation. It commonly attacks 80% of the human population aged 11-30 years (Walsh et al., 2016). Several factors are due to acne vulgaris, including genetics, environmental variables (temperature, pollution, humidity, sun exposure, mineral oils/halogenated hydrocarbons), nutrition, hormonal state, stress, smoking, comedogenic medicines such as androgens, halogens, corticosteroids, bacteria, and cosmetics (Cui et al., 2022)

Treatment of Acne vulgaris to control and prevent inflammation and improve appearance. However, using antibiotics to treat Acne vulgaris is considered less effective because it can cause bacterial resistance. Therefore, herbal products with anti-acne vulgaris properties are an alternative(Dewi & Hanifa, 2021). Citronella oil is an essential oil obtained from the leaves of *Cymbopogon nardus* via steam distillation. Minimum Inhibitor Concentration of Citronella oil against *Staphylococcus aureus* bacteria is 0.05% (v/v)(Pontes et al., 2019) and 0.125% (v/v) against *Propionibacterium acne* (Luangnarumitchai et al., 2007). Red ginger oil is an essential oil obtained from rhizomes of *Zingiber officinale var. Rubrum*, which has been processed by steam distillation. Red ginger oil has antioxidant, anti-inflammatory, antitumor, and antibacterial activity(Sholikhati et al., 2023). The gingerol compound found in red ginger has been proven to have anti-inflammatory activity. This compound can inhibit cytokines, increasing the number of inflammatory cells (Suciyati et al., 2021). Red ginger oil, formulated into an emulgel preparation with an oil content of 1-4%, has an anti-inflammatory effect (Purnama, 2018).

Microemulsions are monophasic, optically isotropic, thermodynamically stable, and clear dispersions. It is formulated from oil, water, surfactant, and a co-surfactant. Microemulsions possess many benefits, including the ability to enhance drug permeability across the skin, low surface tension, high drug loading, and small droplet size(Ita, 2020). Microemulsion is administered via transdermal, topical, and parenteral routes as a drug delivery system (Chandel & Rajput, 2018).

An appropriate combination of surfactant and cosurfactant is required to make a microemulsion. The surfactants usually used in microemulsion preparations are non-ionic surfactants such as Tween 20, Tween 60, and Tween 80 due to they have good percutaneous tolerance and a lower potential for irritation and toxicity (Hasrawati et al., 2016). The co-surfactants are usually short to medium-chain alcohols (C3-C8), such as Propylene glycol, PEG 400, Glycerin, and Diethylene glycol mono ethyl ether (Transcutol®). Besides reducing interfacial tension, the function of cosurfactants also helps change the curvature of reverse micelles (Vaidya & Ganguli, 2019). It has been revealed that combining Tween 80 and Transcutol® to make primaquine nanoemulsion produces good characteristics(Cui et al., 2022).

This research optimised the microemulsion system for combining citronella and red ginger oil using Tween 80 as a surfactant and Transcutol® as a co-surfactant. Because citronella oil and red ginger oil evaporate quickly, isopropyl myristate was chosen as the carrier oil based on preliminary test results.

2. Materials and Methods

Materials:

The ingredients used in this research were citronella and red ginger oils obtained from PT Syailendra Bumi Investama, Indonesia; Tween 80, Transcutol®, Isopropyl Myristate, and deionised water obtained from CV Nurra Gemilang, Indonesia.

Instrument:

The instruments used in this research were an analytical balance (ACZET CY224C), a Digital Hotplate Stirrer (RIO), a UV-Vis Spectrophotometer (Shimadzu UVmini-1240), a Particle Size Analyzer/Zetasizer (Malvern Instruments), a Centrifuge (Nuve NF 200 Instrument), an Incubator (Memmert), a Refrigerator (Aqua), a Digital pH Meter (SI Analytics Lab 854), a Brookfield viscometer(LVT), and statistical software (IBM SPSS Statistics 26).

Methods:

Preparation of microemulsion.

Microemulsions were made with varying surfactant-cosurfactant (S-mix) ratios of 3:3 as F1, 4:2 as F2, and 4.5:1.5 as F3. Meanwhile, the oil phase is citronella oil: red ginger oil and isopropyl myristate in a ratio of 1:3:1. Determining the ratio of the citronella oil and red ginger oil is adjusted to their respective antibacterial and anti-inflammatory properties. The formula of microemulsion is seen in Table 1. First, Tween 80 and Transcutol® were mixed at 500 rpm for 5 minutes using a magnetic stirrer. Then, add the citronella oil and red ginger oil and stir at 500 rpm for 5 minutes. While still stirring, drop water until the desired volume is reached. Stirring continued for 15 minutes. Microemulsion preparation was carried out at 25°C (Kushwah et al., 2021). Each formula was made in triplicate.

Table 1. The Formula of microemulsion

Ingredient	Composition (%b/v)		
	F1	**F2**	**F3**
Citronella Oil	4	4	4
Red ginger oil	12	12	12
Isopropyl Myristate	4	4	4
Tween 80	24	32	36
Transcutol®	24	16	12
Deionised water	32	32	32

Evaluation

Stability test

The physical stability test was carried out using the Freeze-thaw Cycle method and Centrifugation. The freeze-thaw method is carried out in 6 cycles, where one cycle is kept sample at a temperature of 4°C ± 2°C for 24 hours and at a temperature of 40°C ± 2°C for 24 hours. The observed were organoleptic, % Transmittance, pH, and microemulsion viscosity (Jufri et al., 2006).

The thermodynamic stability test, which involves running a centrifuge at 10,000 rpm for 30 minutes, aims to determine the microemulsion preparation's resistance to gravitational forces (Fitriani et al., 2016).

Organoleptic Test.

Organoleptic tests are carried out to determine the preparation's characteristics visually, such as shape, colour, and smell (Lestari et al., 2023).

Percentage of transmittance

The transparency of microemulsions was determined by measuring the percentage of transmittance at 650 nm using a UV-Vis Spectrophotometer (UVmini-1240, Shimadzu, Japan) with distilled water as the blank.

pH measurement

The pH values of microemulsions were measured (in triplicate) using a calibrated digital pH meter at ambient temperature with a glass electrode at 25±1°C.

Viscosity measurement

The viscosity of MEs was measured at 25°C with a Brookfield viscometer, using spindle no. 2 and a shear rate of 30 rpm.

Measurement of globule size, zeta potential, and Poly dispersion Index

The average globule size, Poly dispersion Index, and zeta potential of MEs were measured at 25°C by zeta sizer Ver.8.00.4813 (Malvern Instrument Serial Number: MAL1243254).

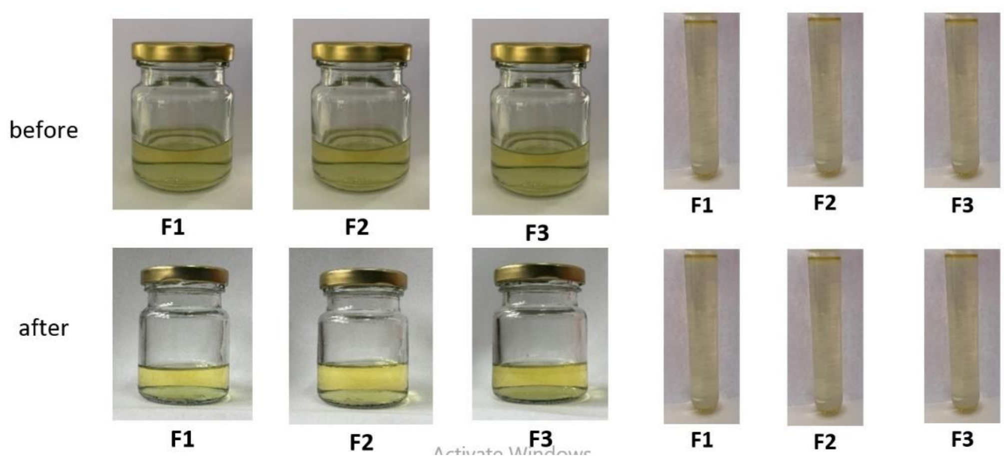
Data analysis

Quantitative data in this study were analysed using the ANOVA test at a confidence level of 95% using IBM SPSS Statistics 26 software.

3. Results and Discussions

Organoleptic

Organoleptic observations were carried out in fresh microemulsion, after stability tests using the freeze-thaw method, and after thermodynamic stability tests. Before the stability test, F1, F2, and F3 were clear, homogeneous, yellow, and aromatic liquids. After testing the stability of the freeze-thaw and thermodynamic methods, it was found that F1 and F2 remained transparent, homogeneous, and aromatic liquids, but F3 was a thick and separated liquid (Figure 1). The thermodynamic stability test at 10,000 rpm for 30 minutes predicts the preparation's physical stability over the next year due to gravitational forces. The test results show that F1 and F2 will remain stable for the next year, while F3 will be unstable (Fitriani et al., 2016). The F3 is separated due to the proportion of surfactant and co-surfactant not being good, which is less than the proportion of co-surfactant. Co-surfactants raise the fluidity of the interface due to the presence of fluidizing groups like unsaturated bonds, then demolish liquid crystalline or gel structure and alter the HLB value in such a way as to cause the spontaneous formation of microemulsion (Kale et al., 2017).



(a) (b)

Figure 1. The microemulsion of a combination of citronella oil and red ginger oil with an S-mix ratio of 3:3 (F1), 4:2 (F2), and 4.5:1.5 (F3) at **(a)** before and after the Freeze-Thaw Cycling Stability test; **(b)** before and after the thermodynamic stability test.

The result of pH evaluating

pH checks were carried out on fresh microemulsion and after stability testing using the freeze-thaw method. The results are shown in **Figure 2**. Before the stability test, the pH value of F1 was 6.37 ± 0.02, F2 was

6.40 ± 0.02, and F3 was 6.43 ± 0.06. The three formulas have a pH that is not significantly different (p=0.267 >0.05). Meanwhile, after checking the pH after carrying out the stability test, the results showed that the pH of F1 was 5.85 ± 0.10, the pH of F2 was 6.24 ± 0.03, and the pH of F3 was 6.41 ± 0.04, which shows the pH value of F1 is lower than F2 and F3, while F2 is not significantly different from F3 (p=0.052 > 0.05). In each formula, when compared before and after the stability test, it was found that the pH of F1 and F2 had decreased, while the pH of F3 was stable.

The O-mix, S-mix, and water ratios are the same in all microemulsion formulas. The decrease in pH in F1 and F2 after the stability test may have been caused by the sample being taken out of the Climate Chamber at 40°C. As temperature rises, molecular vibrations increase, resulting in water's ability to ionize and form more hydrogen ions (H+). The more H+ ions contained in a solution, the more acidic the solution will be and can affect the pH value that is read due to temperature changes. Thus, pH decreases with increasing temperature (Atlas Scientific, 2023). The reduced pH is also caused by Tween 80 undergoing hydrolysis, which releases sorbitan monoleic fatty acid. In F3, there was no decrease because the concentration of Tween 80 was high (Dwivedi et al., 2020). However, in general, the pH of F1, F2, and F3 before and after the stability test still meets the pH requirements for topical preparations, namely in the skin pH range of 4.5-6.5 (Ali et al., 2013).

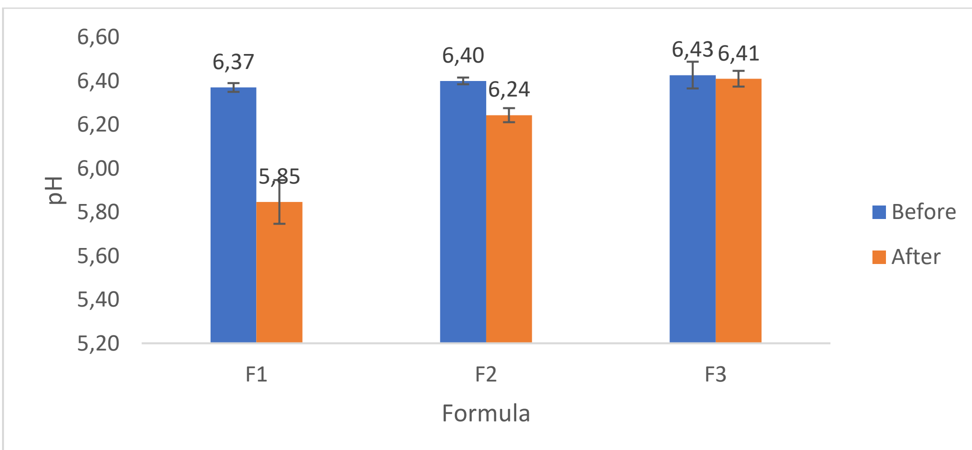


Figure 2. pH of Microemulsion combination of citronella oil and red ginger oil with Smix ratios of 3:3 (F1), 4:2 (F2), and 4.5:1.5 (F3) before and after freeze-thaw cycling stability test.

Viscosity

The viscosity of the microemulsion was determined using a Brooke field viscometer, and the spindle used was number 62 with a speed of 30 rpm. Before the stability test, the viscosity of F1 was 83 ± 10mPa.s, F2 was 108 ± 8 mPa.s, and F3 was 272 ± 10 mPa.s. The viscosity of F3 was more than F2, and the viscosity of F2 was more than F1. After stability testing, the viscosity of F1 was 92 ± 8mPa.s, F2 was 122 ± 8mPa.s, and F3 was 288 ± 15mPa.s. Figure 3 shows the viscosity of each formula before and after the stability test, in which the viscosity of F1 and F2 were reduced, but F3 was not significantly different (p=0.063 > 0.05). In the microemulsion formula, the content of Tween 80 as a surfactant in F3 is higher than F2, and F2 is higher than F1 and vice versa for the Transcutol® content. The viscosity of Tween 80 is 425 mPa.s (Rowe et al., 2009) while Transcutol is 4.8 mPa.s (Gattefossé, 2020), so the higher the level of Tween 80 in the formula, the viscosity of the microemulsion increases.

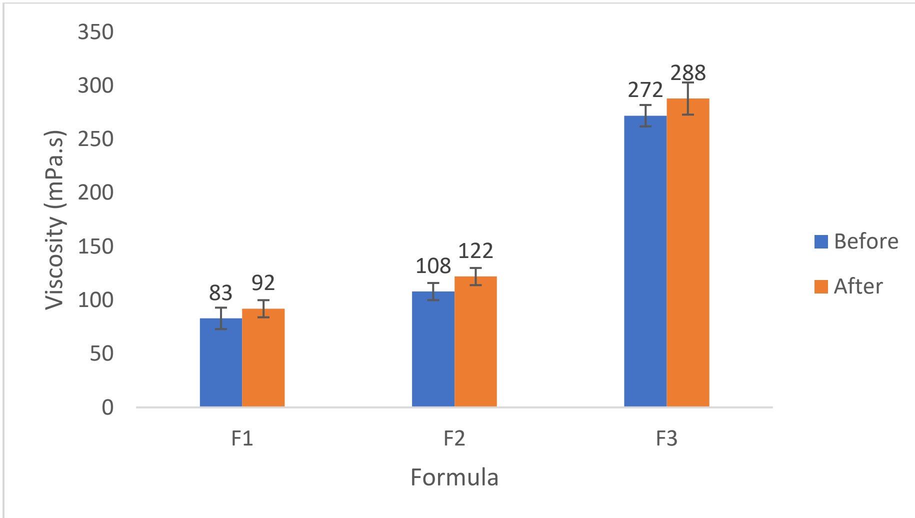


Figure 3. The viscosity of the microemulsion combination of citronella oil and red ginger oil with Smix ratios of 3:3 (F1), 4:2 (F2), and 4.5:1.5 (F3) before and after the freeze-thaw cycling stability test.

Transmittance percentage

Transmittance percentage is used to measure the clarity of a solution or dispersed system quantitatively. A high transmittance percentage value means the globule size is getting smaller (Abdassah, 2017). If the transmittance produced is >79%, it can be declared clear (Rosano et al., 1987). Figure 4 shows that before the stability test, the percentage of transmittance F1 was 94.3 ± 1.6, F2 was 99.9 ± 1.4, and F3 was 31.8 ± 2.2. Meanwhile, after carrying out the stability test, the percentage of transmittance F1 was 95.4 ± 0.8, F2 was 100.5 ± 0.4, and F3 was 60.1 ± 5.2. F1 and F2 remained clear after the stability test, while F3 was cloudy. The F3 has the highest concentration of Tween 80 and less Transcutol®. The mixing process is carried out at ambient temperature to prevent evaporation of the essential oils. The high viscosity of Tween 80 makes the mixture less homogeneous, so the appearance of F3 becomes cloudy and then separates.

Globule size, polydispersity index and zeta potential

Table 2 shows the results of examining the microemulsion's globule size, polydispersity index, and zeta potential. The globule size of F1 is 41.48±0.66nm, F2 is 21.64±0.28nm, and F3 is 20.25±0.12nm. This data shows that the higher the surfactant content, the smaller the globule size. Even though the three are different, they all still have a globule size range of 20-200 nm, so they meet the globule size requirements for microemulsion preparations (Chandel et al., 2018). The S-mix ratio using a more significant amount of surfactant will produce a smaller particle size than with the amount of surfactant made the same. Ideally, the amount of surfactant used should be more significant than the cosurfactant. Surfactants have the function of reducing surface tension, while cosurfactants function to help surfactants prevent phase separation (Priani et al., 2020).

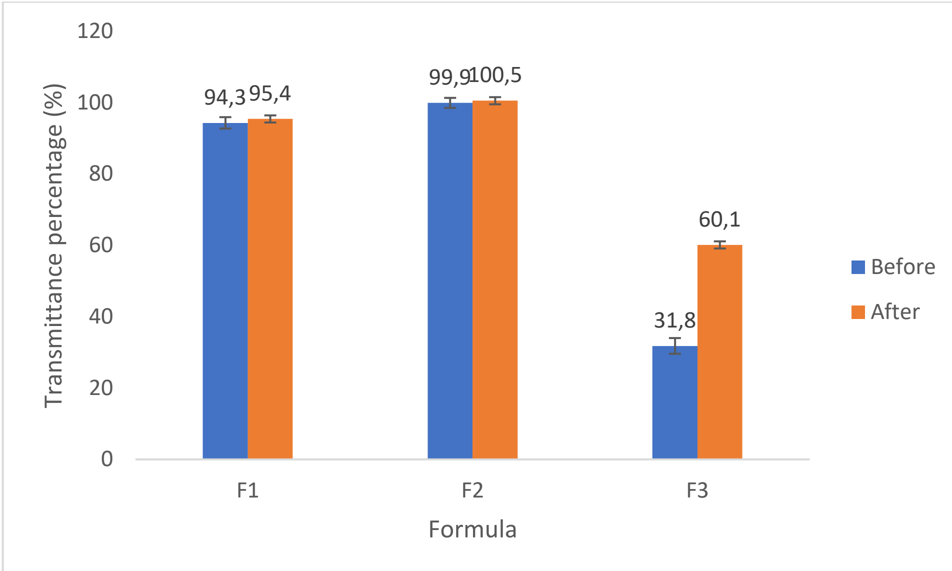


Figure 4. Transmittance percentage of the microemulsion combination of citronella oil and red ginger oil with Smix ratios of 3:3 (F1), 4:2 (F2), and 4.5:1.5 (F3) before and after freeze-thaw cycling stability test.

Besides the composition of the S-mix, other factors that influence globule size are the speed and duration of stirring—stirring aims to provide kinetic energy, which causes the dispersed phase to become small globules (Hasrawati et al., 2016). The longer the stirring time, the smaller the particle size obtained. The stirring time and speed required to make a microemulsion are short and low because the microemulsion forms spontaneously. The resulting microemulsion will contain many air bubbles if the stirring speed is too high. Meanwhile, if the stirring speed is too low, the resulting microemulsion will not be homogeneous (Karimah et al., 2021).

Table 2. The characteristic of microemulsion

Parameter	**Formula**		
	F1	**F2**	**F3**
Globule size (nm)	41.48 ± 0.66 [a]	21.64 ± 0.28 [b]	20.25 ± 0.12 [c]
Polydispersity Index	0.258 ± 0,010 [a]	0.150 ± 0.015 [b]	0.091 ± 0.002 [c]
Zeta Potensial (mV)	-5.55 ± 0,92 [a]	-3.82 ± 1.12 [a]	-4,85 ± 3.59 [a]

[a,b,c)] Different notations indicate there are significant differences (One Way ANOVA; p<0.5)

The polydispersity index of F1 is 0.258 ± 0.010, F2 is 0.150 ± 0.015, and F3 is 0.091 ± 0.002. As the surfactant content increases in each microemulsion formulation, the Polydispersity Index value will decrease. The three formulas have Polydispersity Index values that comply with the requirements, namely in the range of 0.01-0.7. A small Polydispersity Index value (<0.7) indicates that the sample is monodisperse and more stable in the long term. A polydispersity index value close to zero indicates that the distribution of particles in the component is uniform in the same size. The smaller the Polydispersity Index value or closer to zero, the more uniform and homogeneous the particle size is (Karimah et al., 2021).

Zeta potential is commonly used to characterise the surface charge properties of microemulsions and is related to the electrostatic interactions of microemulsions. Zeta potential values < -30 mV and > + 30 mV produce excellent and acceptable physical stability formulations. A high zeta potential describes the repulsive force between particles, so the higher the value, the smaller the chance of flocculation occurring (Firmansyah et al., 2022). Table 2 shows that the zeta potential value of microemulsion F1 is -5.55 ± 0.92mV, F2 is -3.82 ± 1.12mV, and F3 is -4.85 ± 3.59mV. The zeta potential values of F1, F2, and F3 are not significantly different. The three microemulsion formulas have a zeta potential value close to zero because the surfactant used is Tween 80, which is a nonionic surfactant. Tween 80 has no charge on its hydrophobic groups, so the oil droplets' surface is surrounded by Tween 80, which tends to have no charge. The low zeta potential results prove this, but the resulting microemulsion preparation is good because there is no phase separation (Zubaidah et al., 2023).

4. Conclusions

The microemulsion formula combining citronella essential oil (*Cymbopogon nardus*) and red ginger essential oil (*Zingiber officinale var. Rubrum*) using Tween 80 as a surfactant and Trancutol® as a cosurfactant in a ratio of 4:2 is the most optimal because it has a small globule size, low polydispersity index, and good stability.

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