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RESEARCH **Open Access**

Formulation and Physical Characterization of Essential Oil Bangle (*Zingiber cassumunar Roxb.*) Nanoemulsion Gel

Ungsari Rizki Eka Purwanto[1,*], Mar'atus Sholikhah[1] and Siti Munisih[1]

ABSTRACT

Background: Bangle rhizome (*Zingiber cassumunar Roxb*) essential oil as long been used by Indonesian and often used by postpartum women, as a treatment for abdominal obesity. The formulation of bangle essential oil into topical preparations has not been widely reported. So far, bangle essential oil is not available in pharmaceutical dosage form. The users immediately apply essential oil to the abdominal area and previous study showed that the terpinene-4-ol only diffused 0,39% from 2 mg/cm2 of Bangle essential oil through skin membrane. The development of topical bangle essential oil is necessary to increase the effectiveness of the delivery of active substances through the skin and the comfort of the user. In order to increase the penetration of the terpinen-4-ol, the Bangle essential oil was formulated in the form of a nanoemulsion and then the nanoemulsion was dispersed into a gel base to increase user convenience.

Aim: The aim of the present study was to investigate the potential of nanoemulsion formulations for Bangle essential oil and to know the optimum the composition of surfactants and cosurfactants in nanoemulsion system. This study also aims to determine the effect of base gel used in the nanoemulsion gel formulation on the appropriate physical properties.

Method: The pre-emulsion was made beforehand with oil and a mixture of surfactant and cosurfactant. With the help of a Design Expert® ver. 10.0.1 software, component of sufactant and co-surfactant were optimized. The design formula was divided into seven nanoemulsion formulas with a ratio of Polysorbate 80: PEG 400, F1 (1: 8), F2 (8: 1), F3 (6,25: 2,75), F4 (8: 1), F5 (1: 8), F6 (1: 8), F7 (4,5: 4,5). The optimum consentration of Polysorbate 80 as surfactant and PEG 400 as co-surfactants in Bangle essential oil nanoemulsion was analyzed using simplex lattice design methode. The optimal formula was further evaluated for its distribution, droplet size, and zeta potential. Distilled water was used as the aqueous phase in nanoemulsion. The amount of aqueous phase: the amount of pre-emulsion is 9 : 1. The optimum nanoemulsion formula then dispersed in carbophol hydrogel to be nanoemulsion gel. Physical characterization of Bangle nanoemulsion gel like a pH, adhesion power, spreadability, viscosity before and after cycling test had been investigated.

Result: The optimum composition of surfactant Tween 80 and co-surfactan PEG 400 was 7.659: 1.34. The results showed that the optimal formula with 2% Bangle Essential Oil Loaded in Nanoemulsion had the Z-average 95,2 nm with Index Polidispersity 0,176 and Zeta Potensial -0,1 mV. Bangle Nanoemulsion-Gel had a homogenous organoleptic, spreadability in 6,69 + 0.85 cm, adhesion power in 2.14 + 0.29 seconds, viscosity 5969 + 32.03 cps, and pH 6,58 + 0,29.

Conclusion: Bangle Essential Oil Nanoemulsion-Gel formulation has the good physical characteristics and potentially be used as topical dosage forms. A further study is needed to determine the effectiveness of the treatment of abdominal obesity by topical administration of this preparation.

Keywords: nanoemulsion, gel, bangle, terpinene-4-ol

*Correspondence: ungsari.farmasi@gmail.com
[1] Department of Pharmaceutical Technology, Bachelor of Pharmacy, STIFAR Yayasan Pharmacy Semarang, Semarang, Indonesia
Full list of author information is available at the end of the article

BACKGROUD

Zingiber cassumunar Roxb has long been used by Indonesian. The rhizome which called "Bangle" belongs to the *Zingiberaceae* family. One of the best-known benefits of bangle rhizome is that it is often used for the care of postpartum mothers, namely as a stomach tightener[1,2]. They take advantage of the rough impact of the rhizome or its essential oil[3].

Terpinene-4-ol is one of major compound in Bangle essential oil. A study showed that terpinene-4-ol had potential indicated as an aromatherapy for antiobesity[4] and was known to have good skin penetration because it had molecular weight below 500 dalton. Essential oil was known that it has delivery power to the dermis[5]. A dermal pharmacokinetics study showed that terpinene-4-ol from $2 mg/cm^2$ of *Zingiber cassumunar* plai oil only could diffused 0,39+0,06% through skin membrane.[6] The characteristics that are difficult to dissolve in water can then be modified by formulating them into a drug delivery system, and one of the systems that can be applied is a nanoemulsion. Several studies had reported that nanoemulsions could be used as topical carriers with significant advantages including strong penetration and high drug-loading capacity[7]. The weakness of nanoemulsion is an intermediate product, where nanoemulsion has a liquid dosage form and needs special packaging to facilitate its use. One way to overcome this is the manufacture of gel nanoemulsion system. In the presence of the nanoemulsion-gel preparation, user is expected to stay active comfortably without feeling sticky due to the use of Bangle essential oil.

Nanoemulsion formulation from Bangle essential oil would be carried out. Selection of oil excipients, surfactants and cosurfactants was a critical factor in the formulation of pharmaceutical preparations, so that the solubility test of Bangle essential oil on each carrier of the nanoemulsion system would be carried out, then it was optimization with Design Expert® 10.0.1 software. The optimum formula of Bangle essential oil nanoemulsion would be dispersed into a gel base, into gel nanoemulsion.

The presence of a hydrophilic polymer in a gel nanoemulsion formulation will increase the ability to bind water so that it can hydrate the stratum corneum layer and moisturize it. This hydration state will cause changes in the arrangement of the cells of the stratum corneum, thus the permeability of the skin to drug molecules increases so that drug penetration is also increased. Therefore, it would become a candidate for a good topical drug delivery system.

METHODS

Materials

Bangle Essential Oil (Salad®CV.M&H Farm, Indonesia), virgin coconut oil (Coco Olio®), sunflower oil (Mazola®), olive oil (Delhhaize®), soya oil (Happy Soya Oil®), Chremophor-RH40® (Asian Kimia Semarang). Oleic acid, Polysorbate 80, Polysorbate 20, Polyethylene-glycol (PEG) 400, Carbophol 940®, Trietanolamine, Glycerol were purchased from CV. Multi Kimia Raya Semarang. DMDM Hydantoine and Ethoxydiglycol were purchased from CV. Subur Kimia Jaya Surabaya.

Solubility Test of Bangle Essential Oil in Pre-emulsion System

The solubility test was started by mixing 2 mL of Bangle essential oil in 5 mL of the carrier using a stirrer (Velt *Scientifica*®) at a speed of 200 rpm during 10 minutes. The carriers referred to are components of oil, surfactants and cosurfactants that have potential as components in nanoemulsions**,** namely virgin coconut oil, sunflower oil, olive oil, soya oil, oleic acid, Chremophor-RH 40, Polysorbate 80, Polysorbate. 20.

Preparation of Bangle Essential Oil Nanoemulsion

An emulsion preparation requires three main components, namely the oil phase, the water phase, and the surfactant. In this study, the components of oil, surfactants and cosurfactants were obtained from the solubility test above. Based on the results of solubility studies, Virgin Coconut Oil was used as the oil phase for the development of nanoemulsion. Polysorbate 80 was used as surfactant and Polyethylene Glycol (PEG) 400 as the cosurfactant.

Table 1. Bangle Essential Oil Pre-nanoemulsion Formulation

Formula	Bangle Essential Oil	Virgin Coconut Oil	Polysorbate 80	PEG 400
1	1 mL	1 mL	1	8
2	1 mL	1 mL	8	1
3	1 mL	1 mL	6.25	2.75
4	1 mL	1 mL	8	1
5	1 mL	1 mL	1	8
6	1 mL	1 mL	1	8
7	1 mL	1 mL	4.5	4.5

Smix ratio (surfactant: co-surfactant) in pre-emulsion system was optimization with the help Design Expert 10.0.1 software. The optimum concentration of Polysorbate 80 as surfactant and PEG 400 as co-surfactant in Bangle essential oil nano emulsion was optimized using simplex lattice design method with the help Design Expert Software® 10.0.1. We input the data in design software: concentration of Polysorbate 80 in range 1-8 mL and PEG 400 in range 1-8 mL with number of replications was five. Then, the design software suggests seven formulas that we could see in Table 1.

1 mL of Bangle essential oil was got into a centrifuge conical tube with 1 mL of Virgin Coconut oil and mixed with the help of a vortex mixture for 5 minutes. Then, Polysorbate 80 and Polyethylene Glycol 400 mixed together with the oil phase the help of a vortex (Faithful®) mixture for 5 minutes, sonicated with ultrasonic (Branson 1800®) for 10 minutes, and incubated for 5 minutes in a water bath at 40°C. This was done in three consecutive cycles. Distilled water was used as the aqueous phase. The aqueous phase was added slowly. The amount of aqueous phase: the amount of pre-emulsion is 9: 1. Respon result of all running formulas was analyzed by ANOVA with the help Design Expert® version 10.0.1.

Evaluation of Bangle Essential Oil Nanoemulsion

Measurement of The Transmittance Value

The transmittance of nanoemulsions was measured using spectrophotometry (Shimadzu Bio-Spec Mini®*)* at a wavelength of 650 nm with distilled water to determine the level of clarity[8].

pH

The pH measurement of nanoemulsion preparations was carried out using a pH-meter (Trans instrument HP 9000®). First, the electrodes are calibrated with standard buffer solutions of pH 4 and pH 7. Then the electrodes are immersed in the preparation. The pH value that appears on the screen is then recorded[9].

Measurement of Globule Size Distribution

The size of the nanoemulsion globules was measured using a particle size analyzer (HORIBA Scientific SZ-100®). The nanoemulsion sample of 1 gram was dissolved in 100 grams of ultrapure water in a beaker glass or measuring flask. A total of 10 mL of the solution was taken and put into the cuvette.

Zeta Potential

Zeta potential measurements were carried out using a zetasizer (HORIBA *Scientific* SZ-100®). The nanoemulsion was placed in zeta cells and the results were recorded.

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Preparation of Bangle Essential Oil Nanoemulsion Gel

Table 2. Gel Base Formulation

Materials	Concentration
Carbophol	1%
Triethanolamine	1%
Glycerine	15%
DMDM Hydantoine	0,03%
Ethoxydiglycol	2%

Carbopol 940® was dispersed in aquadest. The comparison of Carbopol 940® and aquadest was 1:10. Carbopol 940® was milled with triethanolamine until the gel mass was formed. Then added DMDM Hydantoine, ethoxydiglycol and glycerin. It was stirred until homogeneous. 10 mL prepared nanoemulsion was introduced into the gel base ad 20 gram and stirred until homogeneous. The nanoemulsion gel was made in five replications.

Physical characterization of Bangle Essential Oil Nanoemulsion-Gel

Organoleptic Test

Organoleptic testing was carried out by observing changes in consistency, color, odor and homogeneity of the gel preparation.

pH Test

The pH test was done by measuring the pH value using a pH-meter (Trans instrument HP 9000®). The pH value appears on the pH meter and then recorded.

Adhesion Test

A total of 500 mg of the preparation was placed on a slide covered with a slide another, then given a load of 1.0 kg for 5 minutes. After that, the slide was attached to the test equipment and measuring the time of adhesion starting when the load on the test equipment was carried out removed until the second slide was removed.

Spreadability Test

The spreadability test was carried out by placing 0.5 grams on a glass cylinder and leaving it for 1 minute. Then the spread was measured on 4 sides with using a ruler. 200 g is added to the load until the weight is constant.

Viscosity Test

Viscosity measurement was done by placing the sample in a Brookfield viscometer to ubmerged spindle. The spindle was set to a speed of 50 rpm.

Cycling Test

This cycling test was carried out in 3 cycles. Gel preparations are stored at cold temperatures 4 ± 2°C for 24 hours then removed and placed at a temperature of 25 ± 2°C, this process was calculated 1 cycle. Observations were made whether there was instability in the gel preparation after treatment for 3 cycles. The physical conditions during the test were compared with the previous conditions.

Mechanical testing (centrifugation)

Samples were inserted into centrifuge tubes and underwent centrifugation at 3,800 rpm for 5 hours and they were observed for phase separation and syneresis.

RESULTS

The five biggest peak area from thirty peak which indicated five major components in Bangle essential oil.

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The major component from Bangle essential oil were marked with letter a, b, c, d and e. They were α-pinene, β-pinene, sabinene, β-cymene and terpinen-4-ol (Figure 1).

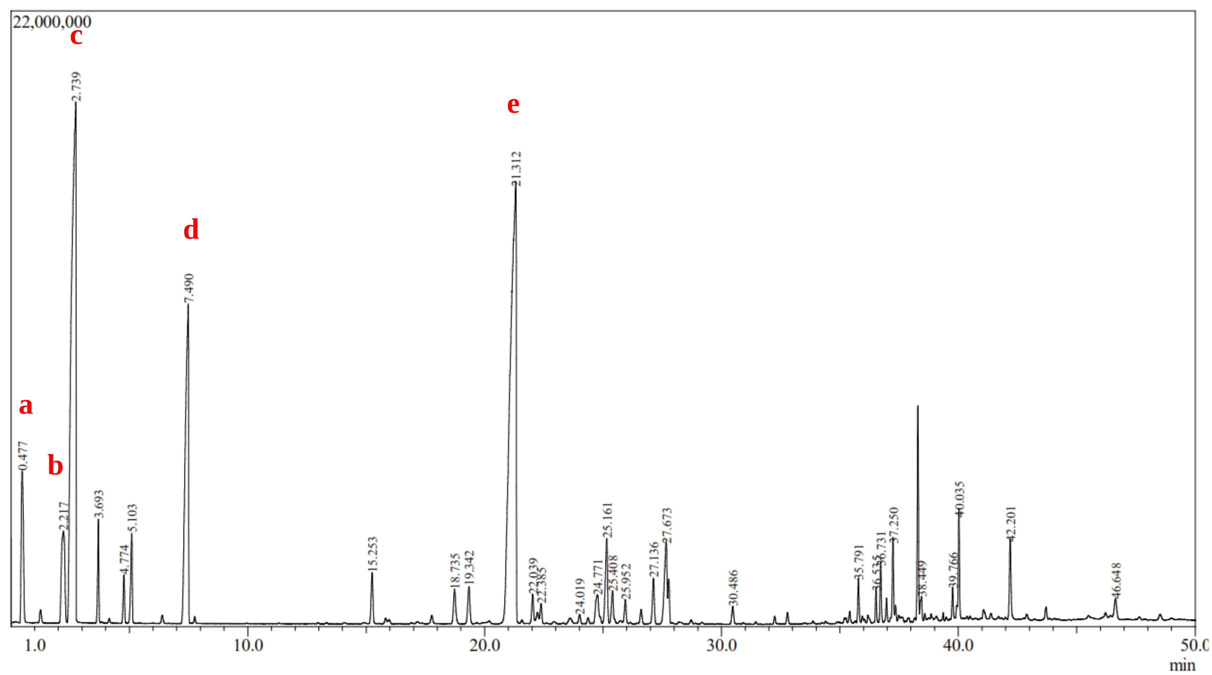

Figure 1. Gas Chromatogram of Bangle Essential Oil (a) α-pinene (b) β-pinene (c) sabinene (d) β-cymene (e) terpinen-4-ol

Table 2. Solubility Test Result of Bangle Essential Oil in Several Oils, Surfactans and Co-Surfactans

Solvent	Result
Virgin coconut oil	Soluble, cloudy
Sunflower oil	Sediment, cloudy
Oilve oil	Soluble, cloudy and milky
Soya oil	Sediment, clear
Oleic acid	Sediment, cloudy and milky
Chremophor RH40	Soluble, clear
Polysorbate 80	Soluble, clear
Polysorbate 20	Soluble, clear

In this study, we had done screening excipient before formulation. Five commonly used oils such as virgin coconut oil, sunflower oil, olive oil, soya oil, and oleic acid, were screened for their properties to dissolve bangle essential oil compounds maximally. We also screened the surfactant and co-surfactant for the best excipient compound for nano emulsion of Bangle essential oil. Results of the solubility of Bangle essential oil in various essential oils, surfactants and co-surfactants were presented in Table 2.

Table 3. Pysichal Characteristic of Several Optimization Surfactan and Co-Surfactan on Bangle Essential Oil Nanoemulsion Formula

Formula	Tween 80	PEG 400	Transmittance (%)	pH	phase separation
1	1	8	97.6	6.98	0
2	8	1	98.3	7.44	0
3	6.25	2.75	96.9	6.91	0.94
4	8	1	98,3	7.36	0
5	1	8	96.5	7.3	0
6	1	8	97.7	7.35	0
7	4.5	4.5	94.7	7.32	0

In the preliminary study, we had tried the several combinations of Polysorbate 80 and PEG 400 for nanoemulsion system. The upper limit selected for Polysorbate 80 and PEG 400 were 8 mL and the lower limit for Polysorbate 80 and PEG 400 were 1 mL. The combination of tween 80 (8 mL) and PEG 400 (1 mL) can provide a high percentage of transmittance in nanoemulsion. This research made 7 runs or experiment sequences as shown in Table 3. Component of tween 80 and PEG 400 became independent variable in this research.

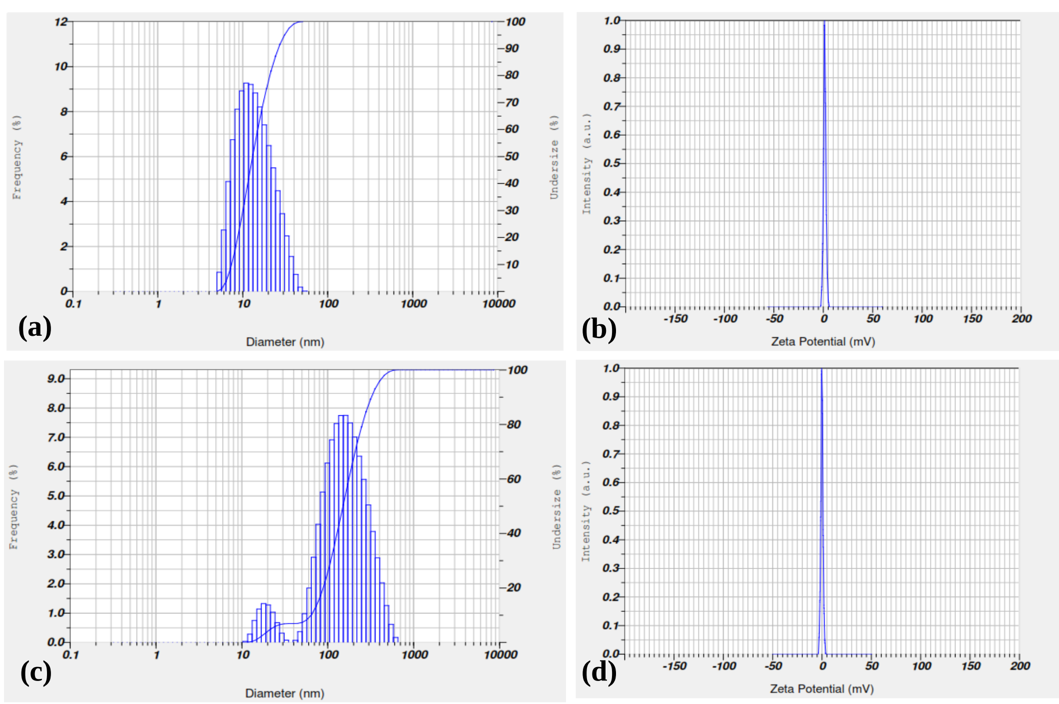

Figure 2. The Measurements Result of The Optimum Nanoemulsion Globule Average Size, Polydispersity Index and Zeta Potential (a) 1% Bangle Essential Oil Loaded in Nanoemulsion : Z-average 12, 8 nm with Polidispersity Index 0,176 and (b) Zeta Potensial 1,4 mV (c) 2 % Bangle Essential Oil Loaded in Nanoemulsion : Z-average : 95,2 nm with Index Polidispersity : 0,176 and (d) Zeta Potensial -0,1 mV

The result of transmittance, pH and phase separation are displayed in Table 3. The criteria response selected by a goal in range to obtain which maximum value of transmittance, minimum value of pH and phase separation. The difference in the test data was analyzed statistically (ANOVA) with the help of the Design-Expert® 10.0.1 software. The result were displayed in Table 4. In Design Expert 10.0.1 software, each result response will be analyzed to obtain a polynomial equation with a suitable orde.

Table 4. ANOVA for Quadratic Mixture Model of Optimization Surfactants and Co-Surfactants in Bangle Essential Oil Nano emulsion Formula with Design Expert 10.0.1

Response	**Model**	**Lack of Fit**	**Final Equation***
Transmittan	Significant	Not significant	y = 11, 14473 A+ 10, 97361 B -0,21219 AB
pH	Not significant	Not significant	y = 0,83098A + 0,81291B – 0,014086 AB
Phase separation	Not significant	Not significant	y = -0,014151A – 0,032939B + 0,031719 AB

A was coefficient for Polysorbate 80,
B was coefficient for PEG 400, and
AB was coefficient for combination of Polysorbate 80 and PEG 400

Based on the analysis result from Design Expert, the optimum composition of surfactant Tween 80 and co-surfactant PEG 400 in Bangle essential oil nanoemulsion was 7,659: 1.34. We also tried adding Bangle essential oil loading in the nanoemulsion system. Figure 2 shows the optimum formula containing 1% Bangle has an average globule of 12.8 nm and when the optimal formula for nanoemulsion containing 2% Bangle is made, the globule avergae was up to 95.2 nm.

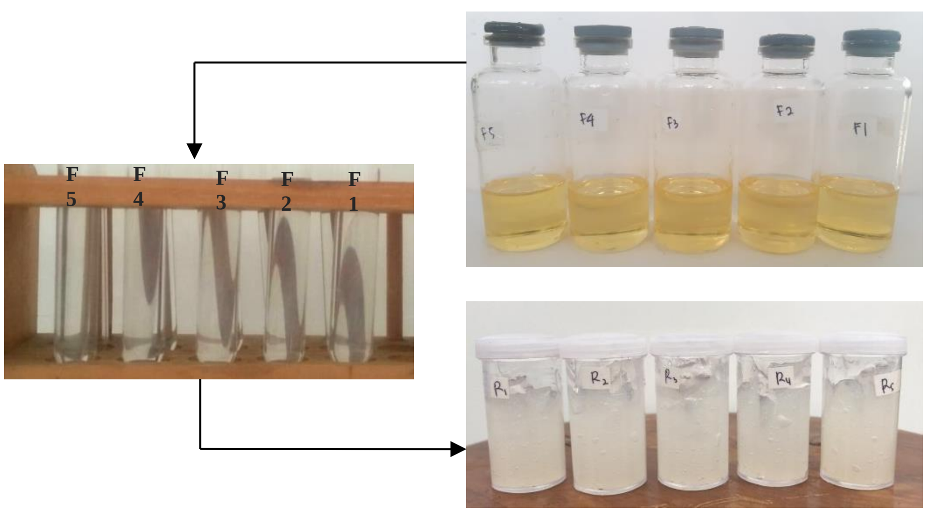

Figure 3. (a) Bangle Essential Oil Pre-emulsion (b) Bangle Essential Oil Nanoemulsion (c) Bangle Essential Oil Nanoemulsion Gel

In Figure 3 showed that the stages of the Bangle essential oil pre-emulsion product then it becomes a nanoemulsion and the last one was dispersed into a gel base. The physical characteristics of bangle essential oil nanoemulsion gel were displayed in table 4.

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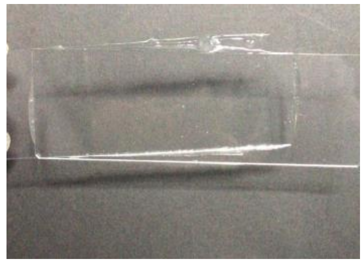
Table 4. Physical Characteristics of Bangle Essential Oil Nanoemulsion Gel

Physical Testing	**Result**
Homogenity	 all resulting gels were homogeneous
Spreadability	6.79 ± 0.85 cm
Adhesion	2.14 ± 0.29 seconds
Viscosity	5969 ± 32.03 cps
pH	6,58 ± 0,29

DISCUSSION

The essential oil of Bangle that we used in this reseach obtained was clear yellow and possessed an aromatic odor. The gas chromatogram of Bangle essential oil showed that there were 30 peaks where it indicated that there were 30 compounds from Bangle essential oil. The highest component of it is terpinen-4-ol (28,42%) and the other major component are α-pinene (3,58%), β-pinene (3,37%), sabinene (25,30%), β-cymene (11,17%) out of 30 compounds identified (Figure 1). Based on the data published so far, our results appear to be somewhat different from previously reported data on the chemical composition of other Bangle essential oil.

The chemical composition of the essential oils of different Bangle essential oil in previous study had investigated. Analysis of the oils from Northeast India by GC and GC/MS revealed that the rhizome oil contained terpinen-4-ol (50.5%), (E)-l-(3,4-dimethoxyphenyl)buta-1,3-diene (19.1%), (E)-1-(3,4-dimethoxyphenyl)but-1-ene (6.0%) and β-sesquiphellandrene (5.9%) as major constituents out of 21 compounds identified[10]. The results of GC-MS analysis of the essential oil of *Zingiber cassumunar* Roxb. from Purwakarta, Indonesia showed that the main components were 4-terpineol (42.5%), β-pinene (23.41%), γ-terpinene (6.28%) and β-sesquiphellandrene (5.92%)[11].

Before we formulated the essential oil to nanoemulsion. We had done a solubility test for Bangle essential oil ini several oils, surfactans and co-surfactans (Table 2). Based on the results of solubility studies, Virgin Coconut Oil (VCO) was used as the oil phase for the development of nanoemulsion. Polysorbate 80 was used as surfactant and Polyethylene Glycol 400 as the cosurfactant. We chose VCO as the oil phase because when the Bangle essential oil diluted with VCO, there was no sedimentation. When the VCO mixed with chremophor RH40, the mixture could not vortex well, maybe this wass due to high viscosity of chremophor, so polysorbate 80 was chosen as a surfactant and it was more complete when we added polyetilen-glycol (PEG) 400 as a co-surfactant.

The production of the nanoemulsion system required a oil, and correct combination of surfactant (tween 80) and co-surfactant (PEG 400). The process needed to optimize the combination in order to gain each portion of components which would produce an optimum formula with good potency. Simplex lattice design mixture using Design Expert® ver. 10.0.1 were used to determine the optimum formula of the nanoemulsion system.

In the ANOVA results from Design Expert® 10.0.1, the significantly different results in the models showed that the different combinations of components (Poysorbate 80 and PEG 40) for each run result different respons or it mean that there was an effect of each component on the response. As we could see in the transmittance response in Table 4, the most significant model was the transmittance response. This showed that the transmittance response was strongly influenced by the proportion of the combination of surfactant and cosurfactant components in nanoemulsion.

The mathematical equation obtained from the analysis of Design Expert® 10.0.1 for the transmittance response was the quadratic mixture equation as seen in the equation : y = 11, 14473 A+ 10, 97361 B -0,21219 AB. Polysorbate 80 component played a more dominant role in increasing the value of transmittance, which was indicated by the highest coefficient was 11.14473. Selection of a surfactant such as Polysorbate 80 based on the hydrophilic-lipophilic balance (HLB) value was important to determine the quality of the nanoemulsion. Polysorbate 80 had an HLB value of 15 which means it had a more hydrophilic part and was capable of producing oil-in-water emulsions. The surfactants work by a mechanism that reduced the interface tension between the oil phase and the water phase after the pre-emulsion had been dispersed in the dispersing aqueous medium. The type and amount of surfactant would affect the size of the oil droplets in the water phase. Which surfactant to choose had the ability to interact with molecules capable of dispersing oil and oil in water to produce nanoemulsion.[12]

Furthermore, when PEG 400 in higest proportion, it also resulted the high of transmittance. This was because PEG was suitable for dissolving bangle essential oil into emulsion droplet. In some literature it is also stated that PEG 400 has the ability to dissolve substances and reduce interface tension.For example, in the research of Vidyasagar and Naik, 2012[13] which used PEG 400 as a size controlling agent for the manufacture of ZnO nanoparticles. In Chen YS et.al, 2018[14] research which made SNEDDS butylidenephthalide, it was shown that the emulsion with surfactant K-HS15 failed to form when used without PEG 400.

In contrast to the transmittance response, for pH and phase separation responses, the ANOVA results showed no significant difference between models. This means that the combination of Polysorbate 80 and PEG 400 components when used in a nanoemulsion system did not affect the pH of the preparation later. Of course this was to be expected in a formulator where the excipient used did not affect the stability of the active substance with changes in pH.

In addition, there was value of “lack of it” in the result of ANOVA. The three of responses resulted no significant differences in value of “lack of it”. The lack of fit parameter was needed because of replication or repeated observations. The lack of fit parameter implies the deviation or inaccuracy of replication in an equation. These parameters are used to detect whether the equation model accurately describes the experimental design. If the lack of fit parameter is not significantly different, then the equation model describes experimental data, whereas if the lack of fit parameter has a significantly different value, then the equation model is not appropriate and cannot describe the experimental data.

The optimum formula of Bangle essential oil nanoemulsion consists of polysorbate 80 : PEG 400 7,659 : 1,341 with desirability 0,638. The prediction results of the optimal formula from the composition of each ingredient in the bangle essential oil nanoemulsion were then used as the basis for the manufacture of gel nanoemulsion. The size of the nanoemulsion particles produced was an important factor because it would affect the speed of release of the drug to be absorbed. The size distribution of nanoemulsion particles were analyzed using a Particel Size Analyzer (Figure 2). The average globul size of Bangle essential oil nanoemulsion at loading dose 1% was 12,8 nm. With an increase in the essential oil loading in nanoemulsion preparations, the resulting average particle size also increased. The average globul size of Bangle essential oil nanoemulsion at loading dose 1% was 95,2 nm.

The test results show that the polydipersity index value is 0.176. The polydipersity index value states the homogenity of the nanoemulsion particle diameter to describe the nanoemulsion particle size distribution. If the polydispersity index value gets closer to zero, the particles formed will be more homogeneous[15].

The zeta nanoemulsion potential was measured to determine the properties of the nanoemulsion surface charge related to the electrostatic interactions of the nanoparticles. The zeta potential is influenced by the composition of the particles and the medium in which the particles are dispersed. The zeta potential value describes the optimization between repulsion or attraction between particles[16]. A good zeta potential value for nanoemulsion preparations is more than +30mV[16]. However, the results of zeta potential measurements of nanoemulsion preparations showed a value of -0.4 mV. This may be influenced by the surfactant used in the nanoemulsion formula, namely Polysorbate 80 because Polysorbate 80 is a non-ionic surfactant.

After the cycling test, the nanoemulsion gel the viscosity had increased in 4,26% so spreadability had

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decreased in 0,38%; adhesion power had increased 43,81% The centrifuged tests revealed that nanoemulsion and nanoemulsion base gel were remained homogenous without any phase separation throughout the test indicates good physical stability of both preparations.

As a research limitation, this study was only used as an initial discourse of the formulation of Bangle essential oil topical products. From this research, it was hoped that there would be a product description that could provide information for further formulation development. Of course in the future it would be carried out with further research in order to continue to complement the product data for therapeutic development with herbal bangle essential oils topically.

CONCLUSION

A newly nanoemulsion gel formulation containing Bangle essential oil is successfully developed. The optimum formulation selection depends on the physicochemical properties of each compound. The nanoemulsion gel formulation had good physical characteristic. A further study is needed to determine the effectiveness of the treatment of abdominal obesity by topical administration of this preparation. Clinical evaluation involving animal and human subjects will be conducted.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

AUTHORS' CONTRIBUTION

UREP and MS contributed by running the laboratory work, analysis of the data and drafting the paper. SM to critical reading of the manuscript. All the authors have read the final manuscript and approved the submission.

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AUTHOR DETAILS

[1]Department of Pharmaceutical Technology, Bachelor of Pharmacy, STIFAR Yayasan Pharmacy Semarang, Semarang, Indonesia

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