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Original Research Article

Combination of N-Butanol Gotu Kola Extract, N-Butanol Lerak Extract, and Neem Seed Oil in a Nanostructured Lipid Carrier Herbal Antimicrobial Spermicide

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ABSTRACT

Introduction. The spermicidal effect of the nonoxynol-9 compound paralyzes sperm by rupturing the cell membrane. Nonoxynol-9 compounds, however, can irritate and itch the vagina. Using a Nanostructured Lipid Carrier (NLC) delivery system, alternative herbal spermicides were created in this research using gotu kola, lerak, and neem. To optimize and formulate of NLC formulation herbal spermicides made from a combination of lipids on Glyceryl Monostearate (GMS) and liquid lipids of olive oil using a response surface full factorial design model (2^2), and analyzing particle size tests, spreadability tests, pH, viscosity, and potential zeta tests. **Method.** A full factorial design model (2^2) was employed in this research to optimize and formulate NLC herbal spermicides using a combination of lipids in Glyceryl Monostearate (GMS) and liquid lipid olive oil. **Results and Analysis.** NLC herbal spermicide particle sizes range from 103.8 ± 0.3 to 178.0 ± 1.2 nm. The spreading power of NLC Herbal Spermicide ranges from 5.8 ± 0.05 to 6.3 ± 0.05 cm. The Zeta Potential of NLC Herbal Spermicide has a range of -17.0 ± 0.8 to -24.8 ± 3.3 mV. Resulting pH range is 5.7 ± 0.2 to 6.5 ± 0.1, resulting viscosity is 564 ± 0.3 to 661 ± 0.5 cps. **Discussion.** The equation model for the power distribution response has a p-value smaller than 0.05 which means it is significant so that the equation model can be used to predict the power response. Different things occur in the zeta potential response and spreadability which have a p-value greater than 0.05, so it can be concluded that the ratio of solid lipids and liquid lipids has no effect on the particle size and zeta potential parameters.

Keywords: Gotu Kola, Lerak, Neem, NLC, Spermicides

INTRODUCTION

Spermicide is one of the pharmaceutical ingredients that is still imported. Nonoxynol-9 (N-9) is contained in spermicide products. Epithelial cells are adversely affected by N-9, which also increases vaginal and cervical infections, causes irritability and ulceration, and spreads HIV (Human Immunodeficiency Virus) (Xu *et al.*, 2022). Due to this, it's important to find new spermicidal ingredients with potent dosages that are secure, non-toxic, and capable of functioning both as spermicides and antimicrobials. There seems to be plenty of medicinal plants in Indonesia, natural spermicides are a feasible option. Centella asiatica, often known as gotu kola or pennywort, contains anti-fungal, anti-bacterial, and anti-spermatogenic effects (Sefrioui *et al.*, 2021). The ethanol extract of centella asiatica decreased spermatogenic cells and the motility of sperm mice (Sukarjati, Pramushinta and Widyaswati, 2021). There are several saponin in lerak, also known as sapindus rarak. Lerak can be used to promptly eliminate all spermatozoa as well as to combat Trichomonas vaginalis-related Sexually Transmitted Disease (Damke *et al.*, 2013). At a concentration of 0.5 mg/ml, the saponins in lerak inactivate sperm and erode the spermatozoa membrane (Lu *et al.*, 2013). Spermicidal activity is discovered in neem (Azadirachta indica). Sperm can be destroyed by neem leaf extract at a concentration of 200 mg/ml (Khan *et al.*, 2013; Sharma and Maldonado, 2020).

The effectiveness of intravaginal drug delivery is increased by the use of nanotechnology-based NLC due to its bio adhesiveness in vaginal mucus, penetration, improved stability, and quicker release of active ingredients (Tamjidi, Shahedi, B, *et al.*, 2013). The development of the NLC spermicide utilized the intravaginal approach (Wong, Dhanawat and Rathbone, 2014). NLC is a non-sticky formulation that can be applied easily and is comfortable to use. Its size ranges from 100-1000 nm (Patel *et al.*, 2013; Rahayu, Rosyida and Nuraini, 2022). The objectives of this research is to optimize and formulate of NLC formulation herbal spermicides made from a combination of lipids on Glyceryl Monostearate (GMS) and liquid lipids of olive oil using a response surface full factorial design model (2^2), and analyzing particle size tests, spreadability tests, pH, viscosity, and potential zeta tests. An innovative new intravaginal spermicide is NLC spermicide, which uses natural ingredients. In order to replace N-9, it is anticipated that the NLC spermicide, which is created from a mixture of n-butanol extracts from Gotu Kola, Lerak, and Neem seed oil, would be used to have spermicidal activity and be safe and non-toxic.

METHOD AND ANALYSIS

In this research, the full factorial design model is employed. In this design, two variables are assessed to find the best formula. Glyceryl Monostearate (GMS) (A) and liquid lipid olive oil (B) concentrations are optimized and formulated in this research design; for an explanation, see Table 1. This formula's optimization seeks to produce the best outcomes for the independent variable (X), which include the particle size (X_1), zeta

potential (X_2), and spreadability (X_3). The NLC formulation of Gotu Kola n-butanol extract, Lerak n-butanol extract, and neem seed oil was conducted using the full factorial design model.

Table 1. NLC Formula Design Using Full Factorial Design Model 2^2 for Gotu Kola n-Butanol Extract, Lerak n-Butanol Extract, and Neem Seed Oil

Independent Variables	% (b/v) Concentration		Coded Values	
	Low	High	Low	High
A = Glyceryl Monostearate Solid Lipid Concentration	9	12	-1	+1
B = Liquid Lipid Concentration of Olive Oil	6	8	-1	+1

Table 2. Indicator NLC Neem Seed Oil, Gotu Kola n-Butanol Extract, and Lerak n-Butanol Extract with Full Factorial Design Model 2^2

Component	Formula (mg)			
	I	II	III	IV
Lerak n-Butanol Extract	2,5	2,5	2,5	2,5
Gotu Kola n-Butanol Extract	6,5	6,5	6,5	6,5
Neem Seed Oil	0,5	0,5	0,5	0,5
Gliseril Monostearat	10	10	15	15
Olive oil	9	7	7	9
Tween 80	15	15	15	15
Phosphate Buffer pH 7.4	ad 100	ad 100	ad 100	ad 100

The Equipments and Materials

The instruments and equipments used in this research were the Shimadzu V-Vis Spectrophotometer, Ultra Turrax Homogenizer, Ohaus Analytical Balance, Malvern Zetasier, Spreadability Tester, L-AQUA pH Meter, Brookfield CAP 1000 Type Viscometer.

Meanwhile, the materials used in this research were Gotu Kola n-Butanol Extract, Lerak n-Butanol Extract, Neem Seed Oil, glyceryl monostearate (Sinopharm Chemical), olive oil (Sinopharm Chemical), Tween 80 (Solvay Chemicals International), and KH2PO4 (Merck) phosphate buffer with pharmaceutical grade purity.

Research Procedures

NLC Formulation of Gotu Kola n-Butanol Extract, Lerak n-Butanol Extract, and Neem Seed Oil

On a heated plate, solid lipids and liquid lipids were melted at 50° ± 5°C to create the NLC formulation of gotu kola n-

butanol extract, lerak n-butanol extract, and neem seed oil. Using an Ultra-turrax homogenizer, the lipid mixture was homogenized at 6000 rpm for 2 minutes at 50° ± 5°C. The lipid phase was supplemented with gotu kola n-butanol extract, lerak n-butanol extract, and neem seed oil, which were all thoroughly dissolved after being stirred at an accuracy of 6000 rpm for two minutes at 50° ± 5°C. Tween 80 and phosphate buffer were heated to 50° ± 5°C, added to the oil phase, and homogenized at a speed of 6000 rpm for 15 minutes. After that, the preparations were agitated at a speed of 1500 rpm for 30 minutes until it reached room temperature (Sukarjati, Kusuma and Rahayu, 2022).

Physicochemical Characteristics of NLC
The Size of NLC Particles

Malvern Zetasier was used to assess zeta potential, particle size, and particle size distribution. In a beaker glass, up to 1 gram of the formulation is mixed with 10 ml of CO_2-free water before being transferred to a 1.5 mL cuvette. The test was conducted at a temperature of 25°C and a 165° angle (Anderson *et al.*, 2013).

The Viscidity

The CAP 1000 Brookfield type viscometer cone and plate instrument was used to determine viscidity. After putting the NLC formulation in the cup, spindle No. 40 of the tool is turned on at a speed of 10 rpm. On the digital display, the viscidity value will automatically appear (Al-Khdheeawi and Mahdi, 2019).

Spreadability Test

The formulation is weighed at 50 mg, and then tested for dispersion for 1-2 minutes on a glass plate. Using a ruler with replication 3 times to measure the distribution's diameter (Salamah, Sulistiawati and Aktawan, 2018).

pH Test

pH measurements were conducted using a L-AQUA pH Meter to determine any changes in the pH of the NLC formulations during storage time.

Data Analysis

A Full Factorial Design of Experiment (DOE) was used for the statistical analysis, and Minitab 16.0 was used. The concentration of glyceryl monostearate (GMS) (A) and liquid lipids of olive oil (B) served as the research's independent variables. Particle size (X^1), zeta potential (X^2), and scattering power (X^3) are the dependent variables. The dependent variable, X', is predicted using the multiple linear regression approach by considering the impact of the independent variables, A and B. You can use the Least Square Method to calculate b0, b1, and b2, which results in the equation shown below (Zaman, 2021):

$$b0 + b1 \sum A + b2 \sum B = \sum X$$

Description:
b0 = Independent Variable Coefficient Values
b1 = Coefficient Value of A
b2 = Coefficient Value of B

RESULTS

Four formulations were developed to maximize the GMS solid lipid concentrations and the liquid lipid concentrations of olive oil in the NLC preparations. The formula includes the active ingredients n-Butanol Gotu Kola Extract, n-Butanol Lerak Extract, and

Neem Seed Oil. Glyceryl monostearate (GMS) is the solid lipid utilized. GMS was chosen because it is a stable polymorph with a negligible tendency to transform into other polymorphs. Liquid and solid lipids will combine. Olive oil is the liquid lipid that is combined with the NLC lipid matrix. The rate of release of active substances and entrapment effectiveness in NLC systems are significantly influenced by the utilization of olive oil as a liquid lipid, which also has a significant role in minimizing crystallization.

Table 3. The Results of Physicochemical Characteristics of NLC Extract n-Butanol Gotu Kola, n-Butanol Lerak Extract and Neem Seed Oil

Formula	The Size of Particles ± SD (nm)	Polydispersity Index ± SD (PDI)	Zeta Potential ± SD (mV)	The Viscidity ± SD (cps)	Spreadability ± SD (cm)	pH ± SD
F I	113,7 ± 13,3	0,320 ± 0,05	-24,8 ± 3,3	564 ± 0,3	5,8 ± 0,05	5,7 ± 0,2
F II	178,0 ± 1,3	0,425 ± 0,05	-24,6 ± 0,9	633 ± 0,5	6,2 ± 0,05	6,5 ± 0,1
F III	103,8± 0,3	0,382 ± 0,05	-17,0 ± 0,8	661 ± 0,5	6,3 ± 0,05	5,9 ± 0,1
F IV	104,5 ± 1,1	0,326 ± 0,04	-21,2 ± 2,4	589 ± 0,7	5,8 ± 0,05	6,1 ± 0,1

According to Table 3, the NLC particle sizes of Neem Seed Oil, Lerak n-Butanol Extract, and Gotu Kola n-Butanol Extract ranged from 103.8 ± 0.3 to 178.0 ± 1.3 nm. Based on Figure 1 (Contour plot of particle size) it can be seen that A and B do not have a significant effect on particle size with a p value of 0.260 ($p > 0.05$). The linear regression equation using the full factorial design method is represented in equation 1.

X1 (nm) = 356 – 8.34A + 15.9B ..... (1)

Based on statistical analysis, it can be concluded that the ratio of liquid lipids and solid lipids does not affect the particle size parameter. NLC has a particle size range of 10-600 nm. The addition of liquid lipids to the formula has a role in reducing the size; the NLC particle size reduces as the liquid lipid concentration rises. Furthermore, it has been shown that the addition of liquid lipids to solid lipids tends to promote the creation of tiny particles, which may be because the lipid phase matrix has become more mobility.

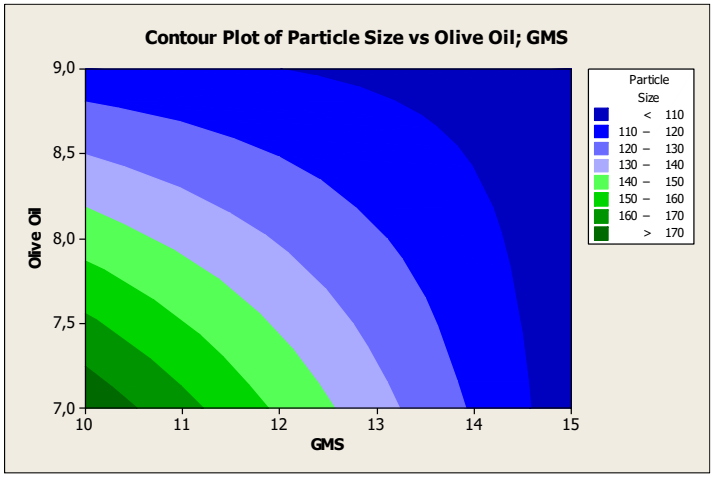

Figure 1. Contour Plot of Particle Size NLC of Gotu Kola n-Butanol Extract, Lerak n-Butanol Extract, and Neem Seed Oil

The spreadability of the NLC of Gotu Kola n-Butanol Extract, Lerak n-Butanol Extract and Neem Seed Oil had a range of 5.8 ± 0.05 to 6.3 ± 0.05 cm as described in table 3. Based on figure 2 (Contour plot of spreadability) it can be seen that A and B have a significant effect on the spreadability with a p value of 0.02 ($p < 0.05$). The linear regression equation using the full factorial design method is represented in equation 2.

X2 (cm) = 7.70 + 0.0100 A – 0.225 B ..... (2)

According to statistical analysis, the ratio of polymer to surfactant significantly affects the dispersion value. The spreadability test's objective is to determine how evenly the gel covers the skin. 5-7 cm is a suitable gel dispersion. It will be difficult for the formulation to spread when applied to the skin if the diffusibility is too low (Pratasik, Yamlean and Wiyono, 2019).

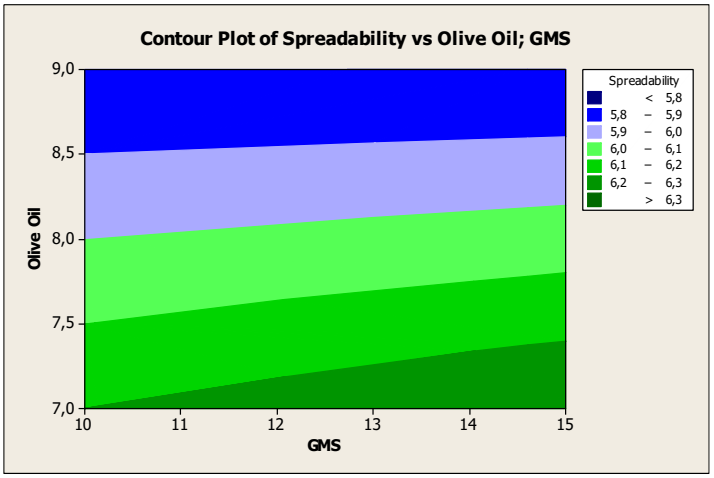

Figure 2. Contour Plot of Spreadability NLC of Gotu Kola n-Butanol Extract, Lerak n-Butanol Extract, and Neem Seed Oil

Zeta Potential of NLC Gotu Kola n-Butanol Extract, Lerak n-Butanol Extract and Neem Seed Oil has a range of -17.0 ± 0.8 to -24.8 ± 3.3 mV as presented in table 3. Based on Figure 3 (Contour plot of Potential Zeta) indicates that A and B have no significant effect on Zeta Potential with a p value of 0.214 ($p > 0.05$). The linear regression equation using the full factorial design method is represented in equation 3.

X3 (mV) = -27,1 + 1,12 A - 1,10 B …… (3)

The ratio of polymer to surfactant does not significantly affect the Zeta Potential value, as according statistical investigation.

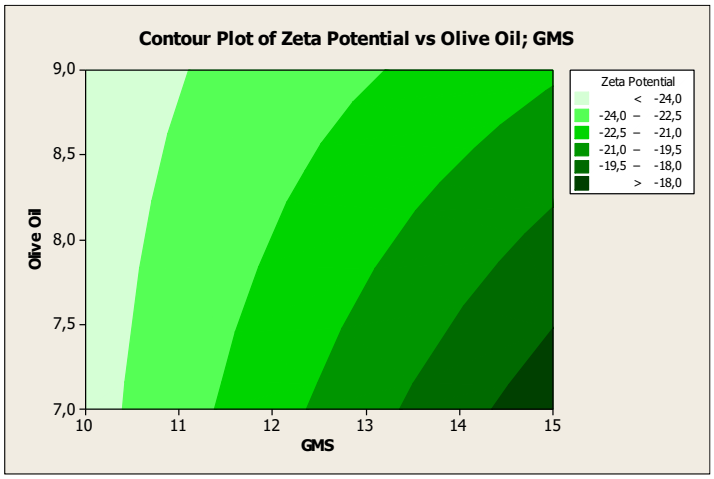

Figure 3. Contour Plot of Zeta Potential NLC of Gotu Kola n-Butanol Extract, Lerak n-Butanol Extract, and Neem Seed Oil

The distribution of molecular masses in a sample is measured by the Polydispersity Index (PDI). This figure represents the calculation's outcome, which is the average molecular weight divided by the total number of average molecular weights. The size distribution should be as near to zero as possible; a number in the range of 0.1-0.25 indicates a narrow size distribution; and a value greater than 0.5 indicates a large size distribution. The four formulas have good PDI results since the size distribution is greater than 0.5, as evidenced by the average polydispersity index values for F1 (0.320 ± 0.05), F2 (0.425 ± 0.05), F3 (0.382 ± 0.05), and F4 (0.326 ± 0.04) obtained from measurement of the particle size distribution (Tamjidi, Shahedi, Varshosaz, *et al.*, 2013).

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DISCUSSION

According to the results of the regression analysis, the coefficient A (GMS concentration) has a coefficient of 6.3. Among a coefficient of 3.8, this indicates that variable A has a bigger impact on the possible Zeta value than variable B. Table 3 indicates that the NLC formulations of gotu kola n-butanol extract, lerak n-butanol extract, and neem seed oil exhibit good stability with zeta potential values greater than -30 mV in each formula. If the preparation is unstable,

as indicated by a Zeta Potential value of less than 10mV, the particles will coalesce into one due to an attraction force between them.

Moreover, The objective of measuring pH is to determine how acidic and alkaline of formulation, especially one that will be applied topically. The ideal pH for topical formulations is 4.5-7, which is the range for skin. Skin irritation results from overly acidic and dry, itchy effects from overly alkaline formulations (Simon and Djajadisastra, 2012; Rahayu, Sari and Ebtavanny, 2019). Based on the findings of pH testing, a pH range of 5.7 to 6.5 was discovered. Table 3 presents the viscidity measurement findings, which range from 564 0.3 to 661 0.5 cps. The NLC viscidity rises with the amount of solid lipids included in the formula (Iqbal *et al.*, 2012)

CONCLUSION

Using a full factorial design model, the Gotu Kola n-Butanol Extract, Lerak n-Butanol Extract and Neem Seed Oil were successfully combined with glyceryl monostearate, a solid lipid, olive oil, and liquid lipid. Particle size was significantly impacted by the ratio of solid to liquid lipid concentrations, but not dispersive power or zeta potential. The findings of the NLC research of the Gotu Kola n-Butanol Extract, Lerak n-Butanol Extract and Neem Seed Oil are anticipated to serve as a foundation for additional NLC analyses of the Gotu Kola n-Butanol Extract, Lerak n-Butanol Extract and Neem Seed Oil, including testing of their physicochemical properties, stability, and NLC activity.

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