Jurnal Farmasi dan Ilmu Kefarmasian Indonesia
Pharmacy and Pharmaceutical Sciences Journal
Published by Faculty of Pharmacy Universitas Airlangga
OPEN ACCESS
E-ISSN 2580-8303
P-ISSN 2406-9388

Jurnal Farmasi dan Ilmu Kefarmasian Indonesia Vol. 11 No. 2 August 2024, 137-146
DOI: 10.20473/jfiki.v11i22024.137-146
Available online at https://e-journal.unair.ac.id/JFIKI/

Application of the Simplex Lattice Design Method to Determine the Optimal Formula of Diclofenac Sodium Nanoemulsion

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Submitted: 18 May 2024
Revised: 27 June 2024
Accepted: 8 July 2024

Abstract

Background*: The success of nanoemulsion preparation, with the aim of producing good characteristic values, is determined by the ratio of each component. The design of experiments (DoE) approach using the Simplex Lattice Design (SLD) method can be used to determine the optimal formula for nanoemulsions, with variable factors consisting of oleic acid, Tween 20:ethanol (4:1), and water. The observed response variables included droplet size, PDI, and pH.* ***Objective****: DoE can help reduce the energy, cost, and time needed to make the optimal formula for diclofenac sodium nanoemulsions.* ***Methods****: Nanoemulsions were prepared using low-energy emulsification. Their characteristics were evaluated and analyzed using Design Expert software.* ***Results****: The optimal nanoemulsion formulation consisted of 4.17% oleic acid, 37.5% emulsifier (Tween 20: ethanol, 4:1), and 58.33% water. The nanoemulsion characteristics were good, with 20.37 a droplet size, 0.42 PDI, of 4.75 pH. The observed values were not significantly different from the predicted values, and the formula could effectively trap 1% diclofenac sodium.* ***Conclusion****: The simplex lattice design method is very useful for pharmaceutical development, such as nanoemulsion optimization.*

Keywords*: diclofenac sodium, nanoemulsion, design of experimental, simplex lattice design, optimizing formula*

How to cite this article:
Nahdhia, N., Rijal, M. A. S., Hendradi, E. & Widodo, R. T. (2024). Application of the Simplex Lattice Design Method to Determine the Optimal Formula of Diclofenac Sodium Nanoemulsion. *Jurnal Farmasi dan Ilmu Kefarmasian Indonesia*, 11(2), 137-146. http://doi.org/10.20473/jfiki.v11i22024.137-146

P-ISSN: 2406-9388
E-ISSN: 2580-8303

INTRODUCTION

Nanoemulsion is a novel drug delivery system consisting of water and oil phases stabilized by an emulsifier, which is a combination of a surfactant and cosurfactant. The aim is to reduce the surface tension to obtain nanoscale droplet sizes (10-100 nm). Because of their small size, nanoemulsions can be thermodynamically stable with transparent, monophasic, and low viscosity characteristics (Donthi et al., 2023; Nastiti et al., 2017). Nanoemulsions have recently become a research topic of great interest owing to their high stability, ease of manufacture, and ability to increase the bioavailability of hydrophobic drugs (Jadhav et al., 2020; Shaker et al., 2019).

The manufacturing method and the ratio of each component greatly influence the success with good characteristic values of nanoemulsions, such as transparency, small droplet size, high droplet homogeneity, and appropriate pH. An experimental design-based approach can help obtain the optimal dosage formula from the nanoemulsion to reduce the costs and time required.

The simplex lattice design (SLD) method can be used to obtain an optimal formula with a proportion of the total number of ingredients of one (100%). The maximum and minimum limits for each factor (Hidayat et al., 2020) in the nanoemulsions were determined from the pseudo-ternary diagram (Duangjit et al., 2014). SLD has succeeded in designing optimal formulas for ketoconazole microemulsions (Duangjit et al., 2014), p-coumaric acid microemulsions (Nasser et al., 2024), andrographolide SNEEDS (Indrati et al., 2020), and furosemide SNEEDS (Fithri et al., 2017). Using this method, we can analyze the influence of each component as a causal factor on the response variable.

In this study, the active ingredient used is diclofenac sodium (DS), which has low solubility (partition coefficient 13.4). Diclofenac sodium is an NSAID that inhibits prostaglandin synthesis as an inflammatory agent by inhibiting COX-1 and COX-2 enzymes (Hendradi et al., 2021). Diclofenac sodium has disadvantages, such as first-pass metabolism, and long-term use causes ulcers and stomach bleeding (Hendradi et al., 2017; Latifah et al., 2023; Md et al., 2020; Sacha et al., 2019). In this study, an O/W nanoemulsion of diclofenac sodium was formulated to increase its solubility and bioavailability and reduce its side effects using the simplex lattice design method to determine the most optimal formula.

MATERIALS AND METHODS

Materials

Diclofenac sodium was provided by PT Dexa Medica (Indonesia); oleic acid and Tween 20 were purchased from PT Brataco (Indonesia); absolute ethanol was purchased from Merck (Germany); and distilled water. All excipients were of pharmaceutical grade.

Tools

Design-Expert software version 13, a UV-Vis spectrophotometer (Hitachi UH5300, Japan), a particle size analyzer (Delsa^{TM} Nano C, US), and a pH meter (Eutech pH 700, US).

Methods

Preparation of pseudo-ternary phase diagram

An aqueous titration method was adopted to develop a pseudo-ternary phase diagram to draw the nanoemulsion region and define the concentration ratios of the individual components. Tween 20 as a surfactant and ethanol as a co-surfactant, at a ratio of 4:1, were added to oleic acid at different weight ratios. The mixture was then stirred gently for 5 min. The aqueous phase was added dropwise with vigorous stirring. The preparations obtained were observed visually; preparations with a clear appearance and easy-to-flow were categorized as nanoemulsions (Gul et al., 2022).

Determining the optimal formula of nanoemulsion with SLD

The largest area that formed an equilateral triangle was determined from the nanoemulsion area in the pseudoternary diagram. The upper and lower limits of each component were input into Design-Expert software using the SLD method. SLD forms 14 formulas with different component ratios, which are then incorporated into nanoemulsion systems. Each formula was then tested for its characteristics, including droplet size (Y_1), PDI (Y_2), and pH (Y_3). The optimal formula was selected based on the specified acceptance criteria, namely, maximum oil, minimum Smix, minimum droplet size, PDI <0.5, and pH 2-8.

Preparation of diclofenac sodium-loaded nanoemulsion

The optimal blank nanoemulsion formula based on the SLD results was used to trap 1% diclofenac sodium. Diclofenac sodium was added to the mixture of oil and the co-surfactant until it dissolved. The surfactant was then added and the mixture was stirred. Water was then added dropwise (1.000 rpm, 30 min).

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Characterization of nanoemulsion

a) Droplet size and PDI

A nanoemulsion sample diluted with aquadest was placed into a cuvette using a particle analyzer (Delsa^{TM} Nano C, US). The data (output) are the droplet size values calculated from the average fluctuation of the light scattering intensity and PDI, which describes the particle size distribution.

b) pH value

The electrode of the pH meter was submerged in the sample by dipping. The pH result was denoted by the value displayed on the instrument.

c) Percent transmittance

The percent transmittance (%T) of the nanoemulsions was measured using a UV-Vis spectrophotometer at 650 nm with distilled water as a blank.

d) Viscosity

Using an Ostwald viscometer, a 5 mL sample was inserted into the viscometer. Using a filler pipette, the sample fluid was sucked until it was slightly above the top mark on the capillary tube. The time required for the liquid to flow from the top to the bottom of the viscometer was recorded. The viscosity value was calculated using the following formula (Poggio et al., 2015):

$$\eta_{sample} = \frac{\eta_{water} \times \rho_{sample} \times t_{sample}}{\rho_{water} \times t_{water}}$$

η = viscosity (mPa.s)
ρ = density (g/mL)
t = The time for the liquid to flow from the top to the bottom mark (s)

RESULTS AND DISCUSSION

Preparation of pseudo-ternary diagram

In the oil:Smix ratio from 1:1 to 1:7 until the addition of 100% distilled water, a cloudy and thickened preparation was formed (Table 1). This is due to the lack of Smix, which reduces the surface tension between oil and water. In oil:Smix 1:8, a visual change occurred after the continuous addition of distilled water (up to 100%) from cloudy to translucent with a blue glint (Figure 1 F8). However, we did not categorize this preparation as a nanoemulsion because according to Jintapattanakit (2018), colloidal dispersions with this appearance have a droplet size of >100 nm and a transmittance of <90%. The ratio of oil to mix used was 1:9 (Table 2).

Table 1. The appearance of preparation with ratio of oil:Smix 1:1 until 1:9

Formula	Oil (g)	Smix (g)	Smix (surf : co-surf)	Appearance	Transmittance
F1	1	1		Cloudy	
F2	1	2		Cloudy	
F3	1	3		Cloudy	
F4	1	4		Cloudy	<5 %
F5	1	5	4 : 1	Cloudy	
F6	1	6		Cloudy	
F7	1	7		Cloudy	
F8	1	8		Translucent with blue glint	73.40 ± 0.26 %
F9	1	9		Transparent	99.23 ± 0.21 %

Figure 1. The appearance of preparation with ratio of oil:Smix 1:1 until 1:9

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Table 2. The formula of nanoemulsion which can produce a nanoemulsion region

Oil (g)	Smix (g)	Water (g)
1	9	14 - 41
1	10	14 - 56
1	11	16 - 71
1	12	16 - 101
1	13	16
1	14	18

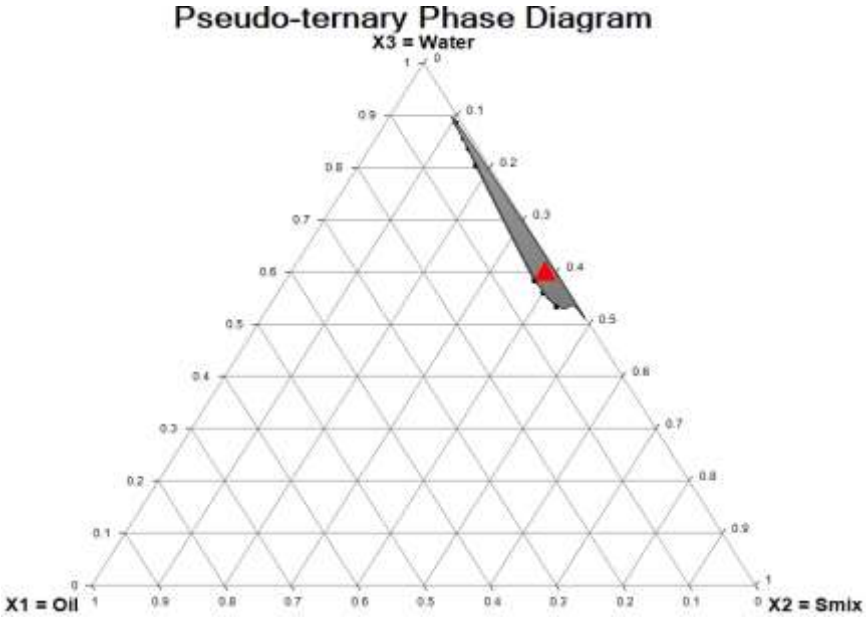

Figure 2. The pseudo-ternary phase diagram of oil (oleic acid), Smix (Tween 20-Ethanol 4:1), and water

Table 3. The characterization of nanoemulsions in determined formulas by SLD

Formula	X_1 Oil (%)	X_2 Smix (%)	X_3 Water (%)	Y_1 Droplet Size (nm)	Y_2 PDI	Y_3 pH
1	1.00	37.50	61.50	19.90	0.40	5.12
2	2.59	39.09	58.33	11.20	0.05	4.81
3	3.11	38.03	58.86	20.10	0.34	4.87
4	1.00	40.67	58.33	11.40	0.09	5.19
5	4.17	37.50	58.33	17.60	0.46	4.78
6	1.00	39.09	59.92	10.40	0.08	5.05
7	1.53	39.61	58.86	16.50	0.17	5.02
8	2.06	38.56	59.39	14.80	0.13	4.90
9	1.00	37.50	61.50	19.60	0.22	5.06
10	4.17	37.50	58.33	18.80	0.43	4.88
11	1.53	38.03	60.44	16.70	0.37	4.92
12	1.00	40.67	58.33	8.90	0.04	5.20
13	2.59	37.50	59.92	18.30	0.49	4.84
14	2.59	39.09	58.33	18.30	0.30	4.82

P-ISSN: 2406-9388
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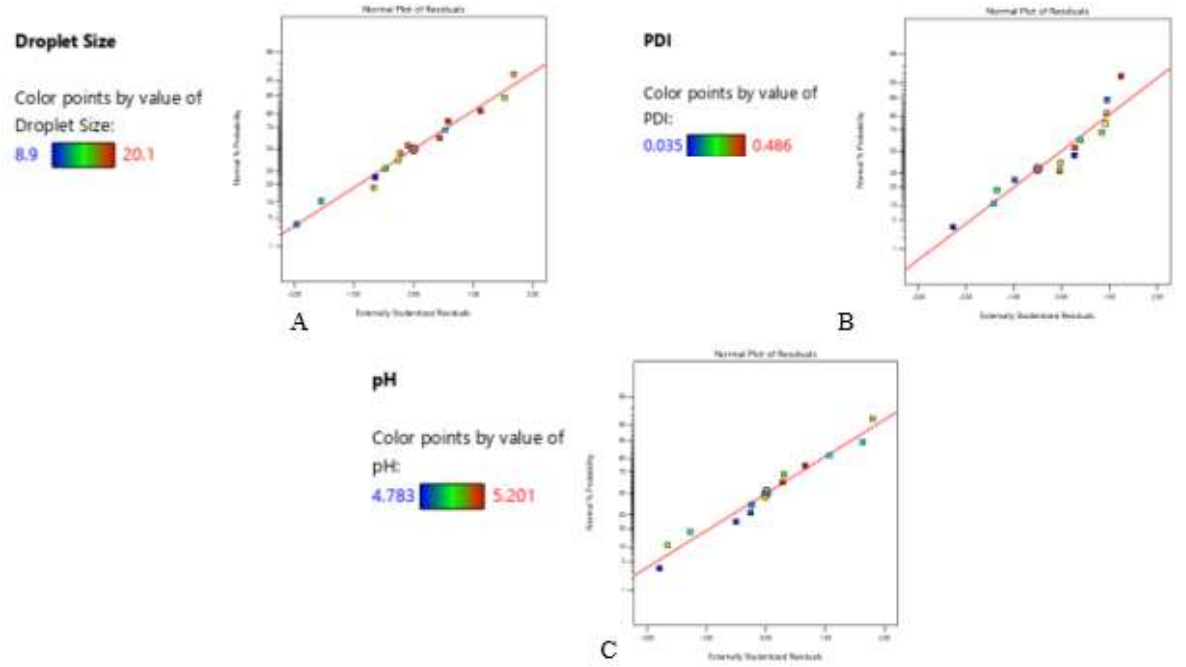

Figure 3. Normal plot of residuals of responses: (A) droplet size, (B) PDI, and (C) pH

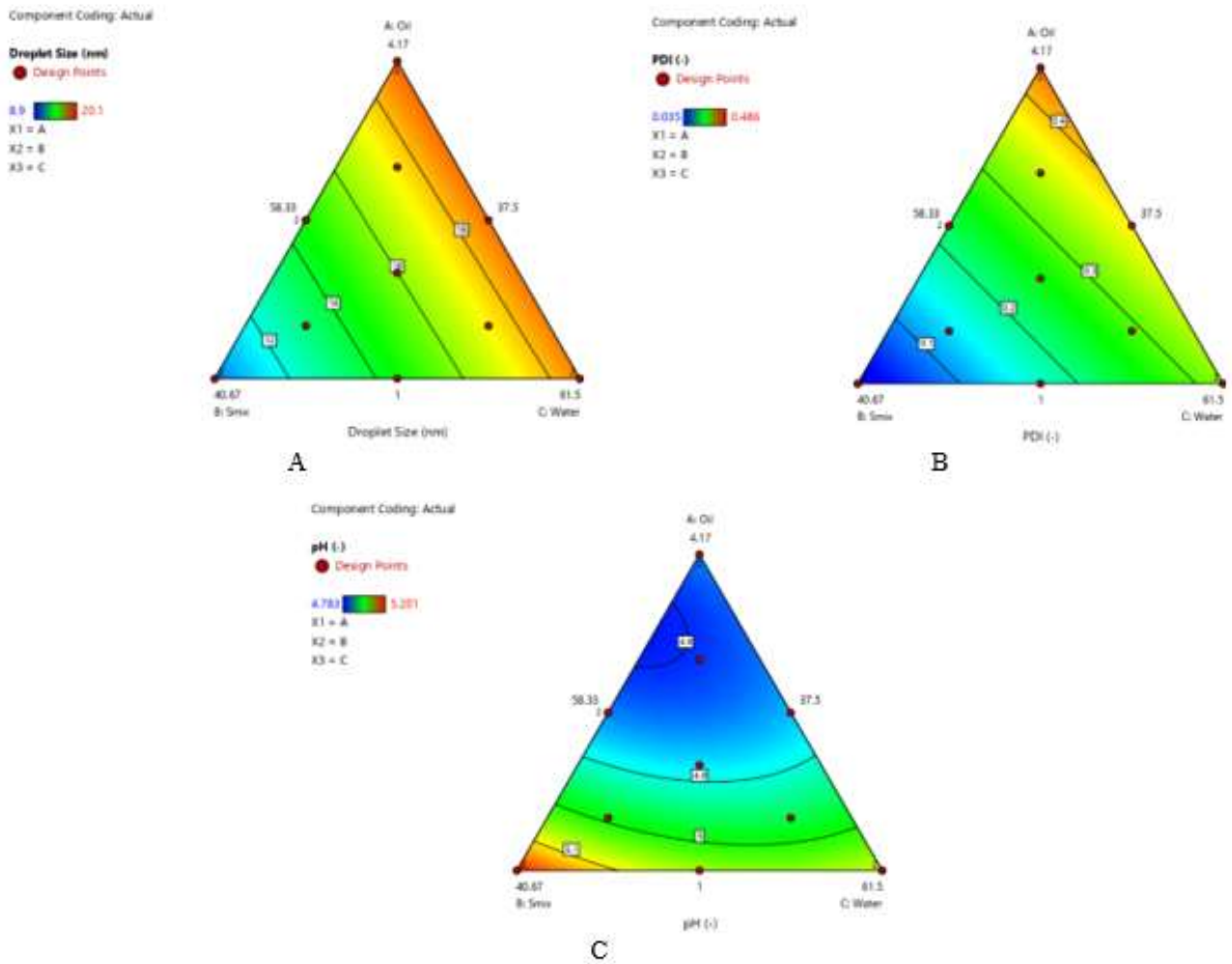

Figure 4. Model graph of nanoemulsion characteristics: (A) droplet size, (B) PDI, and (C) pH

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E-ISSN: 2580-8303

Table 4. Analysis of variance and lack of fit tests of the model for the responses

Responses	Range	Model	Regression equation	*p*-value		Lack of fit (*p*-value)	
Y_1 (droplet size)	8.9 – 20.1 nm	Linear	Y = 19.01A + 10.27B + 18.68C	0.00	Significant	0.63	Not significant
Y_2 (PDI)	0.035 – 0.486	Linear	Y = 0.4346A + 0.0132B + 0.3232C	0.00	Significant	0.72	Not significant
Y_3 (pH)	4.78 – 5.20	Quadratic	Y = 4.84A + 5.19B + 5.08C – 0.72AB – 0.40AC – 0.31BC	0.00	Significant	0.36	Not significant

Table 5. Summary of the regression analysis of the responses

Responses	R^2	Adjusted R^2	Predicted R^2	The different between adjusted R^2 and predicted R^2 (must be <0.2)
Y1 (droplet size)	0.6412	0.5759	0.4894	0.0865
Y2 (PDI)	0.7043	0.6505	0.5534	0.0971
Y3 (pH)	0.9362	0.8963	0.8058	0.0865

The ratios of each component were plotted in a pseudo-ternary phase diagram using ProSim Ternary software. The gray areas represent the nanoemulsion regions. From this area, an equilateral triangular area (red area) (Fig.2) was selected as the upper and lower boundaries of each component, which was used as the ratio of the independent variable in the SLD method, and the following equation was obtained:

$1 \leq X_1 \leq 4.17$

$37.5 \leq X_2 \leq 40.67$

$58.33 \leq X_3 \leq 61.33$

$X_1 + X_2 + X_3 = 100\%$

Characterizations of nanoemulsion

The normal curve plot of the residual analysis (Fig.3) showed that the data for the three response variables were normally distributed because the data were spread around the diagonal line and followed the direction of the diagonal line; therefore, it was continued with ANOVA analysis (Annisa, 2021). The characterization data showed a good relationship between factors and response variables, marked by the *p*-value of the model, which was significant ($p<0.05$), and the lack of fit was not significant ($p>0.05$) for all responses (Table.4), especially for the pH response, which has a value of R^2 approaching 1 (Table.5).

(a) Droplet size

The droplet size of nanoemulsions ranges from 10-100 nm (Nastiti et al., 2017). In the nanoemulsion formula, the droplet size was 8.9 – 20.1 nm (Table.4). Based on the regression equation (Table.4), oleic acid was the most dominant factor affecting the droplet size. Oleic acid induced an increase in particle size, whereas Smix induced a decrease in particle size (Fig.4 A)**.** When the proportion of oil increases, the droplet size also increases owing to the expansion of nanoemulsion droplets; therefore, the proportion of Smix decreases. With increasing Smix, the nanoemulsion droplet size decreases because Smix can reduce the surface tension between oil and water and produce smaller droplet sizes (Ahmed et al., 2022; Bashir et al., 2021).

(b) PDI

The PDI value of a good preparation was <0.5 (Bashir et al., 2021). The nanoemulsions produced PDI values between 0.035 and 0.486. Based on the regression equation (Table.4), the oil factor influences the PDI value more than the Smix and water factors. Large amounts of oil reduce the proportion of Smix so that its ability to reduce surface tension is reduced, and fewer homogeneous droplets are produced (Bashir et al., 2021). A low PDI occurred when the number of Smix increased (Fig.4 B).

(c) pH

The nanoemulsion formula produced a pH between 4.78 and 5.20 with normally distributed data (Fig.3). The regression equation for the pH response model is quadratic (Table.4). This implies that the response is not only influenced by each factor, but also by the presence of a mixed interaction between the two factors. The dominant factor affecting the pH value was Smix, as indicated by the regression equation. In addition, pH is influenced by the interaction between two factors: oleic acid – Smix (A–B) (sig. 0.0014). The pH response is not influenced by the interaction between oleic acid – water (A–C) (sig. 0,0589), or Smix – water (B–C) (sig. 0.1251). The pH value of the nanoemulsion can be increased by Smix, whereas it can be decreased by oleic acid (Fig.4 C).This is based on the materials' pH, where oleic

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E-ISSN: 2580-8303

acid has a pH of 4.32 ± 0.16, Tween 20 7.39 ± 0.03 (Rowe et al., 2012), and ethanol 7.32 ± 0.12. A low oleic acid pH can reduce the pH value when oleic acid levels are high.

Determination of the optimal formula

SLD determined the optimal formula of nanoemulsion based on pre-arranged acceptance criteria, namely the maximum amount of oil (to increase the ability to dissolve diclofenac sodium), minimum Smix (reduces irritation), water within range, minimum droplet size, PDI <0.5, and the pH in the range (because it corresponds to the stable pH of diclofenac sodium, namely 2-8 (Manjunatha et al., 2007)). The predicted optimal formula was 4.17% oil, 37.5% Smix (4:1), and 58.33% water with a high desirability value of 0.965 (Table.6). A high desirability value (close to 1) indicates that the formula can satisfy the desired criteria for all responses with a high level of compliance.

Verify the optimal formula

The verification results of the optimal formula showed no significant difference (P > 0.05) between the predicted and observed values (Table.7). These results indicate the validity of the proposed model (Annisa, 2021).

The characterizations of diclofenac sodium-loaded nanoemulsion

(a) Organoleptic

The nanoemulsion formed in the blank and DS-loaded nanoemulsion produced a transparent, non-separation, liquid (easily flowing), with a slightly bright yellow color (Tab.8). This characteristic indicates that the nanoemulsion has small droplets with high stability because of the working mechanism of surfactants and co-surfactants, which prevents destabilization mechanisms, including flocculation, coalescence, Ostwald ripening, and creaming (Donthi et al., 2023; Nastiti et al., 2017).

(b) Droplet size

The small droplet size (nanoscale) increases the surface area to release a higher drug content at the target location. The manufacturing process and components of each nanoemulsion can influence the droplet size. In this study, the method for preparing nanoemulsions was low-energy. According to Santana et al. (2013), the low-energy emulsification method has advantages over high-energy emulsification, because it can produce smaller droplet sizes and higher stability. High levels of surfactant and co-surfactant also influence the droplet size with a working mechanism, namely, providing a mechanical barrier and reducing the surface tension between the adsorbing oil-water interface, thus preventing coalescence. The selection of nanoemulsion components is also an essential factor. Tween 20 (HLB 16.7) was chosen because it has an HLB close to that of oleic acid (HLB 17) (Rao et al., 2015). When the HLB in the emulsification system approaches the value of the HLB of oil, the surfactant molecules are arranged more tightly in the oil-water interfacial film, resulting in greater interfacial film strength and increased electrical repulsion between droplets (Rao et al., 2015). Moreover, the droplet size can be smaller when the surfactant HLB is high (Fadhel & Rajab, 2022).

(c) PDI

The PDI value provides information on the physical stability of the dispersed system. The particle size distribution became more uniform at low PDI values (<0.5). This indicates a more stable system in the long term, as it can prevent flocculation, coalescence, and creaming by reducing the Ostwald ripening rate (Bashir et al., 2021; Nastiti et al., 2017).

(d) pH

The pH of the nanoemulsion formed was at a pH where diclofenac sodium was stable (2-8). The independent t-test showed a significant difference between the blank nanoemulsion and DS-loaded nanoemulsion (Table.8). The pH of the DS-loaded nanoemulsions increased. Diclofenac sodium dissociates in the solution to produce diclofenac and sodium ions (Na^+). Diclofenac ions can bind H^+ ions from the solution, reducing acidity and increasing the pH.

(e) Transmittance

Both the blank and loaded nanoemulsions produced high transmittance, that is, >95% (Table.8), which also aligns with the nanoscale droplet size. The transparency of the system is caused by the dispersed phase droplets being no greater than ¼ of the wavelength of visible light (Sintov & Shapiro, 2004); therefore, the nanoemulsion reflects little light and appears transparent.

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E-ISSN: 2580-8303

Table 6. The optimal formula of nanoemulsion and predicted value selected by SLD

Number	Component (%)			Predicted Value			Desirability	
	Oil	Smix	Water	Droplet Size	PDI	pH		
1	4.17	37.5	58.33	19.01	0.43	4.84	0.965	Selected

Table 7. Comparison of predicted and observed values of optimal formula of nanoemulsion

Responses	Predicted value	Observed value*	*p*-value	
Droplet size (nm)	19.01	20.37 ± 3.80	0.600	Not significant
PDI	0.43	0.42 ± 0.02	0.137	Not significant
pH	4.84	4.75 ± 0.16	0.412	Not significant

*Mean ± SD (n=3)

Table 8. The characterization of blank nanoemulsion and DS-loaded nanoemulsion from optimal formula

Characterization	Blank nanoemulsion	DS-loaded nanoemulsion	*p*-value	
Organoleptic	Transparent, liquid (easy to flow), no separation, light yellow	Transparent, liquid (easy to flow), no separation, light yellow		
Droplet size (nm)	20.37 ± 3.80	16.77 ± 0.84	0.18	Not significant
PDI	0.42 ± 0.02	0.25 ± 0.09	0.04	Significant
pH	4.75 ± 0.16	6.03 ± 0.02	<0.00	Significant
Transmittance (%)	99.20 ± 0.44	98.60 ± 0.69	0.273	Not significant
Viscosity (mPa.s)	76.98 ± 1.60	145.84 ± 3.55	<0.00	Significant

(f) Viscosity

Nanoemulsions are characterized by their low viscosity and easy flow. Low viscosity can accelerate the drug release process at the target site (Bashir et al., 2021), and viscosity is greatly influenced by the components that make up the nanoemulsion. The viscosity test results showed a significant increase in the viscosity of the loaded nanoemulsion compared to the blank because of the presence of diclofenac sodium adsorbed in the core (Tabke.8). However, the DS-loaded nanoemulsion was still a liquid preparation with a viscosity of 145.84 mPa.s and a good droplet size, PDI, and transmittance.

CONCLUSION

This study showed that the blank nanoemulsion was successfully optimized using the simplex lattice design method. The optimal nanoemulsion formula comprised 4.17% oleic acid, 37.50% Smix (Tween 20:ethanol 4:1), and 58.33% water. There was no significant difference between the predicted and observed values, resulting in good characteristic results. This formula has also been successful in loading 1% diclofenac sodium, with good results. This indicates that the simplex lattice design method is advantageous for optimizing nanoemulsion formulations.

ACKNOWLEDGMENT

The authors express their gratitude to the Project Management Unit (PMU) of Maulana Malik Ibrahim State Islamic University for funding this research, which allowed it to be successfully completed.

AUTHOR CONTRIBUTIONS

Conceptualization, N.N., M.A.S.R., E.H.; Methodology, N.N., M.A.S.R., E.H.; Software, N.N.; Validation, N.N., M.A.S.R., E.H.; Formal Analysis, N.N.; Investigation, N.N., E.H.; Resources, N.N., M.A.S.R., E.H; Data Curration; N.N.; Writing - Original Draft, N.N.; Writing - Review & Editing, M.A.S.R., E.H.; Visualization, N.N., M.A.S.R., E.H.; Supervision, M.A.S.R., E.H.; Project Administration, E.H.; Funding Acquisition, N.N., E.H.

CONFLICT OF INTEREST

The authors declared no conflict of interest.

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