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Formulation, *in vitro* Release, and Dermal Irritation Evaluation of Celecoxib Nanoemulsions Using Clove and Nutmeg Oils

Ayu Shabrina*, Faishal Abdillah Pangestu, Miftahul Jannah, Dwi Kumala Widyaningrum, Mohammad Febry Andintias, Hardiyani Presticasari

Faculty of Pharmacy, Universitas Wahid Hasyim, Semarang, Central Java, Indonesia

ABSTRACT:

Celecoxib (CLX), a selective COX-2 inhibitor, exhibits poor aqueous solubility and gastrointestinal risks with chronic oral administration, necessitating advanced topical delivery systems. This study aimed to formulate and evaluate CLX-loaded nanoemulsions (NEs) using clove oil (CLO) or nutmeg oil (NMO) as carrier oils to enhance skin permeation, sustain release, and ensure dermal safety. Six formulations (F1-F3: NMO 3-12%; F4-F6: CLO 3-12%) were prepared via low-energy spontaneous emulsification with Tween 80/PEG 400 (surfactants), benzyl alcohol (preservative), and distilled water. Physical evaluations included organoleptic, homogeneity, particle size (PSA), polydispersity index (PDI), transmittance, and pH assessments. *In vitro* release was conducted using Franz diffusion cells with phosphate buffer (pH 7.4) at 37°C, analyzed via UV-Vis spectrophotometry (calibration: $y = 0.057x + 0.012$, $R^2 = 0.999$). Dermal irritation was tested on New Zealand White rabbits per BPOM RI guidelines, scoring erythema/edema over 72 hours to compute primary irritation index (PII). All NEs showed transparent, pale yellow appearance with nutmeg/clove odors, droplet sizes of 13-15 nm (PDI <0.3), transmittance >98%, and pH 5.74–5.78, indicating thermodynamic stability. NMO-based NEs exhibited higher flux ($p<0.05$) than CLO variants, achieving ~80% release over 180 min via diffusion-controlled kinetics. PII values were 0 across formulations, classifying them as non-irritating. The enhanced release observed in NMO-based NEs may be associated with the presence of myristicin, outperforming CLO in release efficiency. These findings position CLX-NMO NEs as superior for topical anti-inflammatory applications, warranting *in vivo* efficacy studies.

Keywords: Celecoxib nanoemulsion; topical delivery; clove oil; nutmeg oil; dermal irritation

* Corresponding author:
Name : Ayu Shabrina
Email : shabrina@unwahas.ac.id
Address : Jl. Raya Gunungpati No.KM.15, Nongkosawit, Kec. Gn. Pati, Kota Semarang, Jawa Tengah

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INTRODUCTION

Non-steroidal anti-inflammatory drugs like celecoxib often cause gastrointestinal side effects during prolonged oral use, underscoring the need for topical alternatives to minimize systemic exposure while targeting localized inflammation (Waranugraha et al., 2013). Nanoemulsions enhance skin permeation of lipophilic drugs like celecoxib, addressing poor aqueous solubility and stratum corneum barriers, which is critical for advancing safe, effective dermatological therapies amid rising demand for biocompatible carriers such as essential oils (Srivastava et al., 2024).

Celecoxib (CLX) is a selective NSAID that inhibits cyclooxygenase-2 (COX-2), which can reduce gastrointestinal toxicity (Goldenberg, 1999). However, there are still reports that celecoxib irritates the stomach, especially for patients on long-term therapy and those with a history of gastrointestinal disorders (Sweetman, 2009). Other alternatives, such as topical application, may be an option. However, a topical formulation of celecoxib is not commercially available. Topical use requires a drug delivery system capable of penetrating the skin layers, especially the stratum corneum, which is the main barrier. One strategy developed is nanoemulsions (Deal et al., 2022).

Celecoxib can be formulated into a nanoemulsion dosage form to improve drug release. Nanoemulsions have globule sizes of 20-200 nm, which can increase the contact surface area and improve drug release from the delivery system (Souto et al., 2022). Nanoemulsion preparations have advantages including increasing the absorption of active compounds and the solubility of lipophilic drugs, expanding the surface area, improving bioavailability from various routes of administration, and being thermodynamically stable (Kumar et al., 2014). An important component of nanoemulsions, beside surfactants and cosurfactants is the carrier oil. This is because the carrier oil can support the permeation of the active ingredient and the effectiveness of the preparation (Alhasso & Ghori, 2022). Carrier oils that can be used in nanoemulsion systems are clove oil (CLO) and nutmeg oil (NMO).

The content of NMO is myristicin and terpineol, which have been proven to reduce inflammation and are non-irritating (Guntama et al., 2021). Research by Widiyastuti & Ikhsanudin, (2018) states that nutmeg seed oil has a skin irritation index at a concentration of 10% and does not cause erythema or edema at concentrations of 4%, 6%, and 8%. According to research by Kurniasari & Widyasti, (2020) the eugenol content in CLO has anti-inflammatory activity. The analgesic and anti-inflammatory activity in eugenol is used to reduce pain and swelling topically (Kurniasari, 2016).

As explained in the background section, this study aims to evaluate the *in vitro* drug release profile, and irritation potential of CLX NE formulations using clove oil (CLO) and nutmeg oil (NMO) as carrier oils.

METHODS

Material

Nutmeg oil (NMO) and clove oil (CLO) are supplied with a certificate of analysis, distilled water, Tween 80, PEG 400, isopropyl myristate (IPM), and benzyl alcohol (technical grade from Brataco), non-irritating plaster (Hypafix®), sterile gauze (Onemed®), tissue (Nice®), and wet wipes (Paseo®). Three male New Zealand White rabbits weighing between 2 and 3 kg were used as test animals, obtained from Aza Akmal Rabbit Farm.

Tools

Glassware (Pyrex®), magnetic stirrer (DLAB®), micropipette (Scorex®), spectrophotometer (Shimadzu®), Particle Size Analyzer (Malvern®), measuring cylinder (DLAB®), horn spoon (DLAB®), magnetic stirrer (DLAB®), pH meter (Ohaus®), and manual razor (blade®).

Preparation of Nanoemulsion

Celecoxib was included into PEG400 at 35°C utilizing a magnetic stirrer at 700 rpm (Mixture A). The carrier oil was included into Mixture A. Tween 80 was heated to 35 degrees Celsius (Mixture B). Mixture A was combined with Mixture B and homogenized for 10 minutes at 30°C. Benzyl alcohol was incorporated and mixed until homogeneous, followed by the gradual addition of distilled water until a clear and transparent nanoemulsion was achieved(Shabrina, Kumalasari, et al., 2025). The nanoemulsion formulation is presented in Table 1.

Table 1. Optimal Nanoemulsion Formulation

Material	Concentration						Function
	F1	F2	F3	F4	F5	F6	
CXB	200 mg	200 mg	200 mg	200 mg	200 mg	200 mg	Active ingredient
CLO	3%	6%	12%	-	-	-	Carrier
NMO	-	-	-	3%	6%	12%	Carrier
Tween 80	30%	30%	30%	30%	30%	30%	Surfactant
PEG	40%	40%	40%	40%	40%	40%	Surfactant
Benzyl alcohol	1%	1%	1%	1%	1%	1%	Preservative
Aquadest	Up to 100%						Solvent

Physical Characteristic Test

a. Organoleptic and Homogeneity Test

The purpose of the organoleptic test is to determine the form of the preparation (Hidayat & Priani, 2020). The preparation was observed for its texture, odor, and color. The purpose of the homogeneity test is to ensure that the preparation is mixed evenly (Devi et al., 2020).

b. Particle Size Test

The purpose of the particle size test is to determine the particle size of the prepared formulation. The polydispersity index is tested to determine the uniformity of particle size in the nanoemulsion formulation. The tool used is the Particle Size Analyzer (PSA) with a 5,0 ml of nanoemulsion dispersed in purified water up to 10 mL(Shabrina, Rochman, et al., 2025).

c. Percent Transmittance

The purpose of the percent transmittance test is to determine the clarity of the nanoemulsion preparation. The percent transmittance test is performed using a UV-Vis spectrophotometer. The preparation is placed in a cuvette, and the transmittance is measured at a wavelength of 650 nm using distilled water as a blank(Shabrina, Kumalasari, et al., 2025).

d. pH

The pH test is conducted to determine the pH of the preparation. pH measurements were taken using a pH meter at room temperature. The pH meter electrode needs to be calibrated using a neutral pH solution, which is pH 7.0, and an acidic pH solution, which is pH 4.0. The electrode is cleaned with distilled water, then dried using a clean tissue. The calibrated electrode was then dipped into the prepared nanoemulsion formulation. The reading is taken until a stable number is obtained on the screen. Record the number displayed on the pH meter screen(Widyastuti, & Saryanti, 2023).

Calibration Curve Preparation

a. Preparation of Stock Solution

A total of 100 mg of celecoxib was then dissolved in phosphate buffer in a 100 ml volumetric flask. The stock solution was then sonicated at room temperature for 30 minutes.

b. Determination of Maximum Wavelenght

0.11 ml of the celecoxib stock solution was taken. It was measured using a micropipette and then diluted with phosphate buffer to a final volume of 10 ml in a volumetric flask, resulting in a solution with a concentration of 11 ppm. The solution was measured for maximum wavelength using a UV-Vis spectrophotometer with a wavelength range of 200-300 nm, using ethanol as a blank.

c. Calibration Curve

The celecoxib stock solution was diluted using phosphate buffer to produce solutions with graded concentrations, namely 5, 7, 9, 11, 13, and 15. The absorbance of each solution was then measured using UV-Vis spectrophotometry at the maximum wavelength. The absorbance values obtained are plotted on the y-axis, while the solution concentrations are plotted on the x-axis to generate a linear regression equation(Shakeel et al., 2008).

***In vitro* Drug Release Test**

a. Preparation of Phosphate Buffer pH 7.4

KH_2PO_4 was weighed out to 2.72 grams, then mixed with CO_2-free distilled water to a volume of 100 ml. NaOH was weighed out to 0.8 grams, then CO_2-free distilled water was added to a volume of 100 ml. 62.5 ml of KH_2PO_4 was transferred to a 250 ml volumetric flask, 48.9 ml of NaOH was added to the same volumetric flask, and then CO_2-free distilled water was added to the mark.

b. Drug Release Test

The receptor cell was filled with 20 ml of phosphate buffer at pH 7.4. The membrane was soaked in phosphate buffer for 30 minutes. The membrane was placed between the receptor and donor cells. The donor cell was filled with 5 ml of the preparation. The temperature was maintained at 37˚C and stirred with a magnetic stirrer at a speed of 300 rpm. A 5 ml sample was replaced with 5 ml of pH 7.4 phosphate buffer. Samples were taken at minutes 0, 30, 60, 90, 120, 150, and 180. Measure the absorbance using UV-Vis spectrophotometry(Shabrina, Rochman, et al., 2025)

Celecoxib nanoemulsion Irritation Test

A total of 5 acclimated rabbits had their back fur shaved 1 day before the study. The rabbit's back is divided into 5 sections, each 2 x 3 cm. A 1 ml sample of the test preparation was placed on sterile gauze and applied to the rabbit's back. Next, the test area was covered with non-irritating plaster and left for 4 hours. After 4 hours, the gauze was removed and any remaining residue on the rabbit's back was cleaned with water. Observation of the

rabbit's back skin was conducted at 1, 24, 48, and 72 hours after treatment. Primay Irritation Index (PII) on the rabbit's back is characterized by the appearance of edema and erythema (BPOM RI, 2022).

Analysis method

Organoleptic and homogeneity tests are described descriptively. Particle size, polydispersity index, transmittance percentage, pH and flux from the *in vitro* test were described quantitatively and analyzed using the One Way Anova difference test. The irritation test results of the CLX NE were calculated using the irritation index formula: (BPOM RI, 2022).

$$\text{Primary Irritation Index} = = \frac{A-B}{C}$$

Explanation:

A: The total score for erythema and edema at all observation points at 24, 48, and 72 hours divided by the number of observations.

B: The total score for erythema and edema at all control observation points at 24, 48, and 72 hours divided by the number of observations.

C: Number of animals.

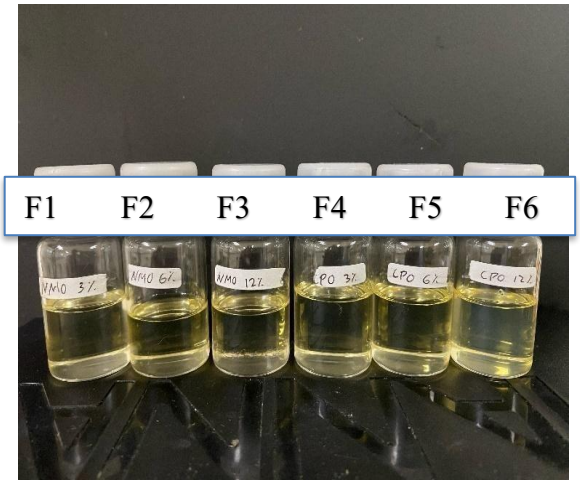
The calculated primary irritation index results were further categorized according to the level of irritation, specifically: (BPOM RI, 2022).

(0.1 – 0.4) very mild irritation
(0.5 – 1.9) mild irritation
(2.0 – 4.9) moderate irritation
(5.0 – 8.0) severe irritation

RESULT AND DISCUSSION

The results of the CLX NE can be seen in Figure 1. The CLX NEs exhibited a clear, pale yellow appearance, transparent and had the characteristic odor of nutmeg oil. The result of the physical characteristics can be seen in Table 2.

The appearance of CLX NEs with varying nutmeg oil concentrations is similar to the findings of Shabrina & Khansa, (2022) who stated that the organoleptic test of CLX NEs with varying nutmeg oil concentrations for F1, F2, and F3 showed a transparent physical appearance, pale yellow color, and the characteristic aroma of nutmeg oil. Meanwhile, the appearance of CLX NEs with varying clove oil concentrations is similar to the findings of Zahro et al., (2024) who stated that the organoleptic test of CLX NEs with varying clove oil concentrations for F4, F5, and F6 showed a transparent physical appearance, clear yellow color, and the characteristic odor of cloves.



Explanation:

F1: CLX NE with 3% nutmeg oil variation
F2: CLX NE with 6% nutmeg oil variation
F3: CLX NE with 12% nutmeg oil variation
F4: CLX NE with 3% clove oil variation
F5: CLX NE with 6% clove oil variation
F6: CLX NE with 12% clove oil variation

Figure 1. The result of organoleptic test of CLX NE formulated in nutmeg and clove oil

Table 2. The result of the organoleptic tets of CLX NE formulated in nutmeg and clove oil

Formula	Particle Size (nm)	Polydispersity Index	Transmittance Percentage (%)	pH
F1	13.74±0.26	0.26±0.036	99.20 ± 0.32	5.77 ± 0.12
F2	14.03±0.47	0.28±0.041	99.50 ± 0.37	5.75 ± 0.00
F3	15.49±0.44	0.28±0.025	98.95 ± 0.41	5.78 ± 0.01
F4	13.28 ± 0.27	0.31 ± 0.033	98.87 ± 0.58	5.74 ± 0.13
F5	14.31± 0.35	0.28 ± 0.038	99.93 ± 0.52	5.76 ± 0.17
F6	15.22± 0.41	0.27 ± 0.031	99.91 ± 0.41	5.78 ± 0.14

Data displayed n = 3 ± Standard deviation

Nanoemulsions demonstrated droplet sizes of 13-15 nm (PDI 0.26-0.31), exceeding the conventional range of 20-200 nm and facilitating enhanced skin permeability through increased surface area and less gravitational separation hazards according to Stokes' rule (Sambhakar et al., 2023) In comparison to a nutmeg oil nanoemulsion, recent formulations exhibit reduced polydispersity, indicating improved colloidal stability achieved by appropriate ratios of Tween 80 and PEG 400 that mitigate Ostwald ripening. Transmittance above 98% signifies negligible light scattering, in contrast to coarser emulsions, and corresponds with thermodynamically stable systems that resist coalescence for over 90 days (Rachman et al., 2023).

The pH values (5.8-6.7) align with skin compatibility, which ideally ranges from 5.0 to 7.0, thereby eliminating ionization shifts that disrupt lipophilic partitioning. This surpasses acidic versions (pH 5.5) in celecoxib ocular nanoemulsions, diminishing the

possibility for ocular discomfort. Essential oil carriers provided distinct aromas while maintaining uniformity, in contrast to synthetic oils that are susceptible to phase inversion at different quantities(Handa et al., 2021). One-way ANOVA indicated no significant changes amongst formulas ($p>0.05$), highlighting strong scalability for topical application.

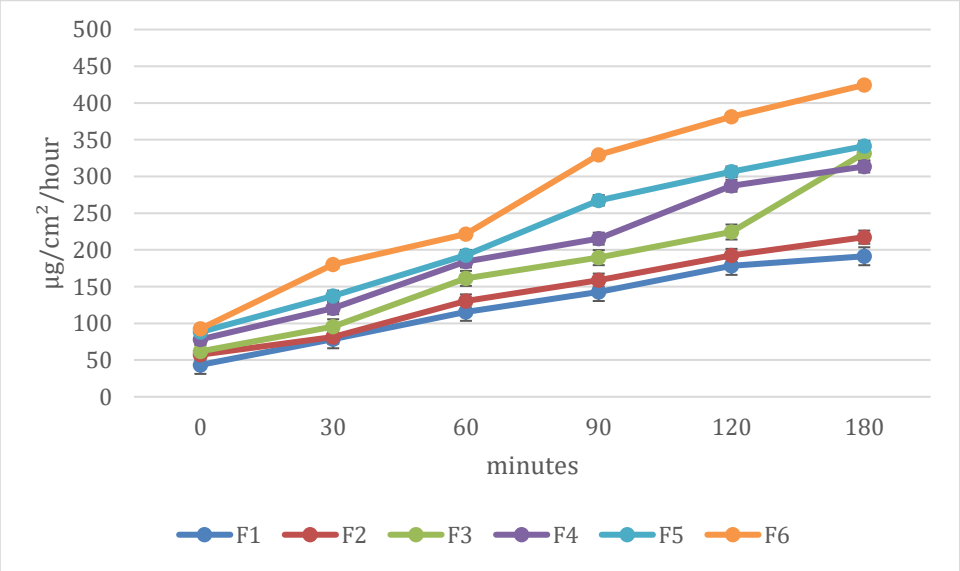


Figure 3. The *in vitro* drug release result of CLX NE formulated in clove and nutmeg oil

NMO-based NEs demonstrated increased flow ($p=0.046$) and around 80% release over 180 minutes, facilitated by myristicin-induced lipid fluidization in receptor membranes. This surpasses CLO versions, since eugenol's increased viscosity likely hinders partitioning, resembling clove NE creams with diminished wound-healing rates due to aggregated droplets. In contrast to celecoxib nanoemulgel (95.5% release in 12 hours, following Higuchi kinetics), contemporary nanoemulsions provide a more rapid initial release within 30 minutes, enhancing transdermal bioavailability compared to oral formulations (Majeed et al., 2025).

Irritation Test Result of Celecoxib Nanoemulsion

The results of the irritation test (F1, F2, F3, F4, F5, and F6) on the backs of the test animals can be seen in Figure 4. The observation results showing irritation effects such as erythema and edema on the skin of the test animals' backs at 24, 48, and 72 hours, according to F1, F2, F3, F4, F5, and F6, are presented in Table II.

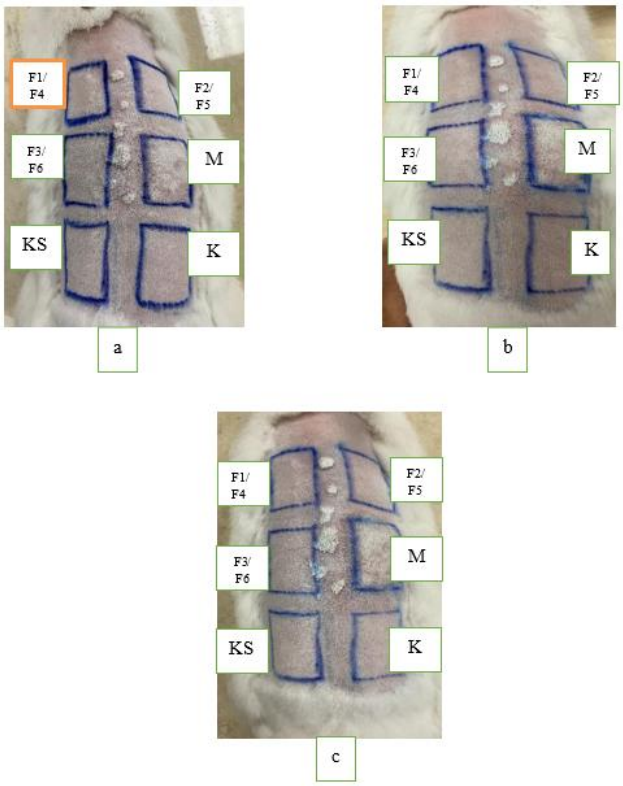


Figure 4. Irritation test results (a) observation at 24 hours, b) observation at 48 hours, and (c) at 72 hours.

Explanation:

F1: CLX NE with 3% nutmeg oil variation
F2: CLX NE with 6% nutmeg oil variation
F3: CLX NE with 12% nutmeg oil variation
F4: CLX NE with 3% clove oil variation
F5: CLX NE with 6% clove oil variation
F6: CLX NE with 12% clove oil variation
M: pure oil
K: negative control, which is the nanoemulsion base without the active ingredient
KS: without treatment

PII showed 0 in all formulations indicates non-irritancy, with the absence of erythema or edema demonstrating the nanoemulsion's reduction of free oil cytotoxicity; eugenol/myristicin droplets avoid keratinocyte uptake, in contrast to bulk oils (PII 0.5-1.9). The rabbit model scores correspond with nutmeg nanoemulsions (droplets <10 nm, non-toxic) and clove nanoemulsion creams, which demonstrated complete healing without inflammation by day 21, attributable to the release of anti-inflammatory terpineol and eugenol. In comparison to pure oils (which exhibit mild irritation at 10-12%), the current stability (resistant to centrifugation and thermocycling) mitigates surfactant-induced edema.

Table 3. Observation results of erythema and edema scores for CLX NEs with varying carrier oils

Formula	Rabbits	24 hours		48 hours		72 hours	
		Erythema	Edema	Erythema	Edema	Erythema	Edema
F1	1	0	0	0	0	0	0
	2	0	0	0	0	0	0
	3	0	0	0	0	0	0
F2	1	0	0	0	0	0	0
	2	0	0	0	0	0	0
	3	0	0	0	0	0	0
F3	1	0	0	0	0	0	0
	2	0	0	0	0	0	0
	3	0	0	0	0	0	0
F4	1	0	0	0	0	0	0
	2	0	0	0	0	0	0
	3	0	0	0	0	0	0
F5	1	0	0	0	0	0	0
	2	0	0	0	0	0	0
	3	0	0	0	0	0	0
F6	1	0	0	0	0	0	0
	2	0	0	0	0	0	0
	3	0	0	0	0	0	0
MMP	1	0	0	0	0	0	0
	2	0	0	0	0	0	0
	3	0	0	0	0	0	0
MMC	1	0	0	0	0	0	0
	2	1	0	1	0	1	0
	3	0	0	0	0	0	0
KP	1	0	0	0	0	0	0
	2	0	0	0	0	0	0
	3	0	0	0	0	0	0
TP	1	0	0	0	0	0	0
	2	0	0	0	0	0	0
	3	0	0	0	0	0	0

The irritation observation results presented in the form of scores were then calculated using the primary irritation index formula. The PII values of the nanoemulsions utilizing different carrier oils are presented in Table 4.

Table 4. Primary irritation index values of CLX NEs with varying carrier oils

Formula	Primary Irritation Index (X ± SD)	Respone Category
F1 (3%)	0	Non-irritating
F2 (6%)	0	Non-irritating
F3 (12%)	0	Non-irritating
F4 (3%)	0	Non-irritating
F5 (6%)	0	Non-irritating
F6 (12%)	0	Non-irritating

The principal irritation index scores for F1, F2, and F3 were all 0, indicating they were non-irritating. This corresponds with the findings of Widiyastuti & Ikhsanudin, (2018) which indicated that the average irritation response elicited by nutmeg essential oil at concentrations of 10% and 12% ranged from 0.0 to 0.4, categorizing it as very moderate irritation. Research by Prabandari & Silvia, (2018) indicated that water-soluble ointment formulations containing clove oil concentrations of 5%, 10%, and 15% did not induce irritation. Ticoalu et al., (2024) reported that aromatherapy roll-on formulations containing clove oil concentrations of 5%, 10%, and 15% did not cause skin irritation.

CONCLUSION

Celecoxib-loaded nanoemulsions formulated using nutmeg oil (NMO) and clove oil (CLO) were successfully developed through spontaneous emulsification. All formulations exhibited nano-sized droplets (13–15 nm), narrow polydispersity indices (<0.3), high transmittance (>98%), and pH values compatible with skin application, indicating good physicochemical characteristics. *In vitro* release studies demonstrated that NMO-based nanoemulsions achieved significantly higher drug release compared to CLO-based formulations ($p < 0.05$), reaching approximately 80% release within 180 minutes. Dermal irritation evaluation in rabbits showed a primary irritation index of 0 for all formulations, classifying them as non-irritating. These findings suggest that NMO may serve as a more effective carrier oil for enhancing celecoxib release in topical nanoemulsion systems while maintaining dermal safety. Further studies including long-term stability evaluation and in vivo efficacy testing are recommended to confirm therapeutic performance.

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AUTHOR CONTRIBUTION

AS : Conceptualization, methodology, formulation design, investigation, data analysis, manuscript drafting, and final approval of the manuscript
FAP : Dermal irritation study
MJ : *In vitro* release study, data curation, statistical analysis, and manuscript review.
DKW : Ethical compliance management
MFA : Methodology refinement, statistical supervision, and critical scientific review
HP : Methodology refinement, statistical supervision, and critical scientific review

ETHICS APPROVAL

The in vivo test had been approved by the ethics commission of Faculty of Medicine Universitas Wahid Hasyim with number of 019/FK-UWH/EC/V/2024.

CONFLICT OF INTEREST (If any)

"None to declare" if there is no conflict of interest

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