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Optimization and Stability Testing of a Nanostructured Lipid Carrier (NLC)-Based Emulgel System for Transdermal Delivery of Anti-Inflammatory Drugs

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ABSTRACT

Nanostructured Lipid Carriers (NLC) are second-generation lipid nanoparticles composed of solid and liquid lipids that improve drug loading, stability, and controlled release. Incorporating NLC into an emulgel enhances transdermal drug delivery by improving skin permeation and prolonging drug release. This study aimed to optimize an NLC-based emulgel using Design of Experiment (DoE) and evaluate its physicochemical properties, drug release, skin permeation, and stability. Diclofenac sodium was selected as the model drug. NLC was prepared using melt-emulsification ultrasonication and optimized with a three-factor Box–Behnken design before incorporation into Carbopol 940 gel. Characterization included particle size, zeta potential, entrapment efficiency, viscosity, spreadability, and drug release analysis. The optimized formulation showed a particle size of 187.4 ± 5.2 nm, zeta potential of −32.6 ± 1.8 mV, and entrapment efficiency of 91.3 ± 2.1%. Drug release reached 85.6% within 24 hours following the Korsmeyer-Peppas model. Skin permeation was significantly higher than conventional gel, and the formulation remained stable for six months at 25°C/60% RH.

Keywords: *Nanostructured Lipid Carriers, Emulgel, Transdermal Delivery, Diclofenac Sodium, Optimization, Stability*

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INTRODUCTION

Inflammation is a complex biological response underlying a wide range of pathological conditions, including rheumatoid arthritis, osteoarthritis, and other musculoskeletal disorders, which collectively contribute to significant global morbidity and impose substantial socioeconomic burdens. The inflammatory process is primarily mediated by cyclooxygenase (COX)-dependent prostaglandin synthesis, accompanied by vascular permeability, tissue edema, and immune cell infiltration, ultimately leading to persistent pain and progressive tissue damage. Nonsteroidal anti-inflammatory drugs (NSAIDs) remain the cornerstone of pharmacological management due to their ability to inhibit COX-1 and COX-2 enzymes; however, their prolonged oral administration is frequently associated with serious adverse effects such as gastrointestinal irritation, ulceration, and renal toxicity, thereby limiting their long-term therapeutic use.

In this context, transdermal drug delivery systems have gained increasing attention as an alternative approach, offering advantages such as avoidance of hepatic first-pass metabolism, reduced systemic exposure, improved patient compliance, and the ability to deliver drugs directly to localized sites of inflammation (Raval et al., 2021). Diclofenac sodium (DS), a widely prescribed NSAID with potent anti-inflammatory and analgesic properties, is considered a suitable candidate for transdermal delivery due to its moderate lipophilicity and relatively low molecular weight (Rowe et al., 2020); nevertheless, conventional topical formulations, including gels and patches, often exhibit limited skin permeation, suboptimal bioavailability, and short residence time on the skin surface.

The primary challenge in transdermal delivery lies in overcoming the barrier function of the stratum corneum, a highly organized lipid-protein matrix that restricts the penetration of most therapeutic molecules. To address this limitation, nanostructured lipid-based delivery systems, particularly Nanostructured Lipid Carriers (NLC), have emerged as promising platforms due to their ability to enhance drug loading, improve stability, and facilitate skin permeation (Iqbal et al., 2020; Patel et al., 2021). NLC are composed of a combination of solid and liquid lipids that form a less-ordered crystalline structure, enabling the accommodation of drug molecules within matrix imperfections while reducing the risk of drug expulsion during storage (Souto et al., 2022). Additionally, the nanoscale size of NLC promotes enhanced interaction with the stratum corneum, increases surface area for drug release, and facilitates penetration through multiple pathways, including intercellular and follicular routes (Joshi & Müller, 2020).

The incorporation of NLC into semi-solid emulgel systems further enhances formulation performance by improving spreadability, skin adhesion, and residence time, while also providing controlled drug release and enhanced patient acceptability. Carbopol-based gel systems are widely used due to their favorable rheological properties, bioadhesive characteristics, and compatibility with topical drug delivery systems (Czajkowska-Kośnik et al., 2022). The development of such complex formulations necessitates the application of systematic optimization strategies, such as Quality by Design (QbD) and Design of Experiments (DoE), which enable the identification and control of critical formulation variables and their interactions affecting key quality attributes

(Charoo et al., 2020). In particular, Box–Behnken Design (BBD) has been widely utilized as an efficient response surface methodology for optimizing pharmaceutical formulations with a reduced number of experimental runs while maintaining statistical robustness.

Despite the growing interest in NLC-based transdermal systems, studies that comprehensively integrate formulation optimization, detailed physicochemical characterization, drug release kinetics, ex vivo skin permeation, and stability evaluation remain relatively limited (Agrawal et al., 2021; Fitriani et al., 2024). Therefore, the present study aims to develop and optimize a diclofenac sodium-loaded NLC emulgel using Box–Behnken Design and to systematically evaluate its physicochemical properties, in vitro drug release behavior, ex vivo permeation profile, and stability, with the goal of enhancing transdermal delivery performance and therapeutic efficacy.

METHODS

Diclofenac sodium (DS, purity ≥ 99%) was obtained from Sigma-Aldrich (St. Louis, MO, USA). Glyceryl monostearate (GMS) and Miglyol 812 were supplied by Gattefossé (Saint-Priest, France), while Poloxamer 188 and Tween 80 were procured from BASF (Ludwigshafen, Germany). Carbopol 940 was obtained from Lubrizol (Wickliffe, OH, USA), and triethanolamine (TEA), propylene glycol, methylparaben, and propylparaben were purchased from Merck KGaA (Darmstadt, Germany). All chemicals and solvents were of analytical grade and used as received. Fresh abdominal skin was excised from male Wistar rats (200–250 g) obtained from the Laboratory Animal Center, Faculty of Medicine, Universitas Indonesia, and all procedures were conducted in accordance with ethical guidelines under approval number 2023/FKUI/0187.

Nanostructured Lipid Carriers (NLC) were prepared using the melt-emulsification ultrasonication technique with slight modifications from previously reported methods (Agrawal et al., 2021). Briefly, the solid lipid (GMS) and liquid lipid (Miglyol 812) were melted together at 80°C to form a homogeneous lipid phase, and diclofenac sodium was dissolved in the molten lipids. The aqueous phase containing Poloxamer 188 and Tween 80 was heated to the same temperature and added dropwise into the lipid phase under continuous stirring at 1500 rpm for 5 minutes to form a coarse emulsion. The resulting emulsion was subjected to probe ultrasonication (Sonics Vibra-Cell, Newtown, CT, USA) at 80% amplitude for a predetermined time, followed by cooling to room temperature under stirring and storage at 4°C for further use.

A three-factor, three-level Box–Behnken Design (BBD) was employed for formulation optimization using Design-Expert® software (Version 12.0; Stat-Ease Inc., Minneapolis, MN, USA). The independent variables were solid-to-liquid lipid ratio (2:1–4:1), surfactant concentration (1–3% w/v), and sonication time (3–9 minutes), while the dependent variables included particle size, zeta potential, and entrapment efficiency. A total of 17 experimental runs, including five center points, were generated to evaluate the effects of formulation variables and their interactions on critical quality attributes.

The optimized NLC dispersion was incorporated into a Carbopol 940-based emulgel. Carbopol 940 (0.5% w/w) was dispersed in distilled water and allowed to hydrate overnight,

followed by the addition of preservatives (methylparaben 0.18% and propylparaben 0.02%) dissolved in propylene glycol. The NLC dispersion was then gradually incorporated into the gel base under gentle stirring to maintain nanoparticle integrity, and the pH was adjusted to 6.0–6.5 using triethanolamine. A conventional gel containing an equivalent amount of diclofenac sodium without NLC was prepared as a control formulation.

Physicochemical characterization of the formulations included measurement of particle size, polydispersity index (PDI), and zeta potential using dynamic light scattering (Zetasizer Nano ZS, Malvern Instruments, UK). Morphological analysis was performed using transmission electron microscopy (JEOL JEM-1400, Japan) following negative staining with 2% phosphotungstic acid. Entrapment efficiency was determined by ultracentrifugation at 30,000 rpm for 1 hour at 4°C, and the amount of free drug in the supernatant was quantified using high-performance liquid chromatography. Viscosity was measured using a Brookfield viscometer (RVT model), spreadability was evaluated using a cone-plate method, and pH was measured with a calibrated digital pH meter (Mettler-Toledo, Switzerland).

In vitro drug release studies were conducted using a Franz diffusion cell equipped with a dialysis membrane (MWCO 12,000 Da), with phosphate-buffered saline (PBS, pH 7.4) maintained at 37 ± 0.5°C as the receptor medium. Samples were withdrawn at predetermined intervals up to 24 hours and replaced with fresh medium to maintain sink conditions, and drug content was analyzed using UV–Vis spectrophotometry at 276 nm. The release data were fitted to various kinetic models, including zero-order, first-order, Higuchi, and Korsmeyer–Peppas models.

Ex vivo skin permeation studies were performed using excised rat abdominal skin mounted on a Franz diffusion cell with a diffusion area of 1.77 cm^2, with the stratum corneum facing the donor compartment. Each formulation (500 mg) was applied to the donor chamber, while the receptor chamber contained PBS (pH 7.4) maintained at 37°C and stirred at 600 rpm. Samples were collected at predetermined time intervals up to 24 hours and analyzed for drug content, and permeation parameters such as steady-state flux (Jss), permeability coefficient (Kp), and enhancement ratio (ER) were calculated.

Stability studies were carried out in accordance with ICH Q1A(R2) guidelines by storing samples in amber glass containers under long-term (25 ± 2°C/60 ± 5% RH) and accelerated (40 ± 2°C/75 ± 5% RH) conditions. Evaluations were conducted at 0, 1, 2, 3, and 6 months for particle size, zeta potential, entrapment efficiency, viscosity, pH, and drug content. Additionally, freeze–thaw stability was assessed over six cycles between −20°C and 25°C.

All experiments were performed in triplicate (n = 3), and the results are presented as mean ± standard deviation. Statistical analysis was conducted using one-way analysis of variance (ANOVA) followed by Tukey's post hoc test (SPSS version 25.0), with a p-value < 0.05 considered statistically significant. The optimal formulation was determined using the desirability function approach in Design-Expert® software.

RESULTS

1. Box-Behnken Design Optimization

The 17 experimental runs generated by the Box–Behnken Design (BBD), along with the observed responses, are presented in Table 1. The particle size ranged from 118.3 to 295.6 nm, zeta potential from −18.4 to −38.7 mV, and entrapment efficiency (EE%) from 74.2 to 94.8%. Analysis of variance (ANOVA) of the quadratic models demonstrated high statistical significance for all responses ($p < 0.0001$), with adequate precision values exceeding 4, indicating good model discrimination. The lack-of-fit was non-significant ($p > 0.05$), confirming the validity of the developed models.

Values are expressed as mean (n = 3). X_1: solid-to-liquid lipid ratio; X_2: surfactant concentration (% w/v); X_3: sonication time (min); Y_1: particle size (nm); Y_2: zeta potential (mV); Y_3: entrapment efficiency (%); PDI: polydispersity index.

Table 1. Experimental design matrix and observed responses for NLC optimization using Box–Behnken Design (BBD)

Run	X1 (Ratio)	X2 (% w/v)	X3 (min)	Y1 Size (nm)	Y2 ZP (mV)	Y3 EE (%)	PDI	Drug Content (%)
1	2:1	1	6	241.5	−24.3	79.8	0.312	97.2
2	4:1	1	6	275.3	−21.7	76.4	0.341	96.8
3	2:1	3	6	178.4	−36.5	92.3	0.198	98.1
4	4:1	3	6	195.8	−34.2	88.7	0.224	97.6
5	2:1	2	3	213.6	−29.8	83.5	0.265	97.9
6	4:1	2	3	235.2	−27.1	81.2	0.287	97.3
7	2:1	2	9	182.1	−35.4	91.5	0.213	98.3
8	4:1	2	9	199.4	−33.1	89.2	0.231	98.0
9	3:1	1	3	258.7	−22.4	77.9	0.328	96.9
10	3:1	3	3	186.3	−35.8	90.1	0.205	98.2
11	3:1	1	9	235.4	−24.8	80.3	0.306	97.1
12	3:1	3	9	173.6	−37.9	93.4	0.188	98.5
13	3:1	2	6	189.2	−33.6	91.0	0.219	98.1
14	3:1	2	6	191.5	−32.9	90.7	0.223	98.0
15	3:1	2	6	188.7	−33.2	91.3	0.216	98.2

Fundamental and Applied Research in Medicine and Allied Sciences Indonesia (FARMASI)
Vol. 02, No. 1, May 2026

16	3:1	2	6	190.1	−33.8	90.9	0.221	98.1
17	3:1	2	6	187.4	−32.6	91.5	0.218	98.3

The solid-to-liquid lipid ratio (X_1) significantly affected particle size ($p = 0.0023$) and EE% ($p = 0.0041$). Increasing solid lipid content resulted in larger particle sizes due to increased viscosity of the lipid phase, while an optimal ratio of 3:1 provided a balanced crystalline structure for efficient drug entrapment. Surfactant concentration (X_2) showed the most pronounced influence on all responses, where higher concentrations reduced interfacial tension, leading to smaller particle size and increased zeta potential magnitude. Sonication time (X_3) significantly reduced particle size; however, excessive sonication (>9 min) may induce thermal instability, necessitating optimization.

2. Optimized NLC Characterization

The desirability function identified the optimal formulation at $X_1 = 3:1$, $X_2 = 2.0\%$ w/v, and $X_3 = 6$ minutes, with predicted responses of 188 nm particle size, −33 mV zeta potential, and 91.2% EE. Experimental results showed excellent agreement with predicted values, confirming model reliability (Table 2).

Table 2. Physicochemical properties of optimized NLC and NLC-emulgel formulations.

Values are expressed as mean ± SD (n = 3). N/A: not applicable.

Parameter	Optimized NLC (Predicted)	Optimized NLC (Observed)	NLC-Emulgel
Particle Size (nm)	188.0 ± 0.0	187.4 ± 5.2	192.8 ± 6.1
PDI	0.215 ± 0.000	0.218 ± 0.012	0.235 ± 0.018
Zeta Potential (mV)	−33.0 ± 0.0	−32.6 ± 1.8	−29.3 ± 2.1
Entrapment Efficiency (%)	91.2 ± 0.0	91.3 ± 2.1	88.9 ± 1.8
Drug Content (%)	N/A	98.2 ± 0.9	97.6 ± 1.2
pH	N/A	5.8 ± 0.1	6.2 ± 0.1
Viscosity (cPs)	N/A	—	18,450 ± 620
Spreadability (g·cm/s)	N/A	—	8.24 ± 0.42

N/A: Not applicable. Data presented as mean ± SD (n = 3).

The optimized NLC exhibited a narrow size distribution (PDI = 0.218), indicating a monodisperse system. The high negative zeta potential (−32.6 mV) suggests strong electrostatic repulsion and good colloidal stability. Entrapment efficiency above 90% confirms efficient drug incorporation into the lipid matrix. Incorporation into the emulgel resulted in a slight increase in particle size, likely due to immobilization within the gel network, while maintaining acceptable

physicochemical properties. The emulgel demonstrated suitable viscosity (18,450 cPs) and spreadability (8.24 g·cm/s) for topical application.

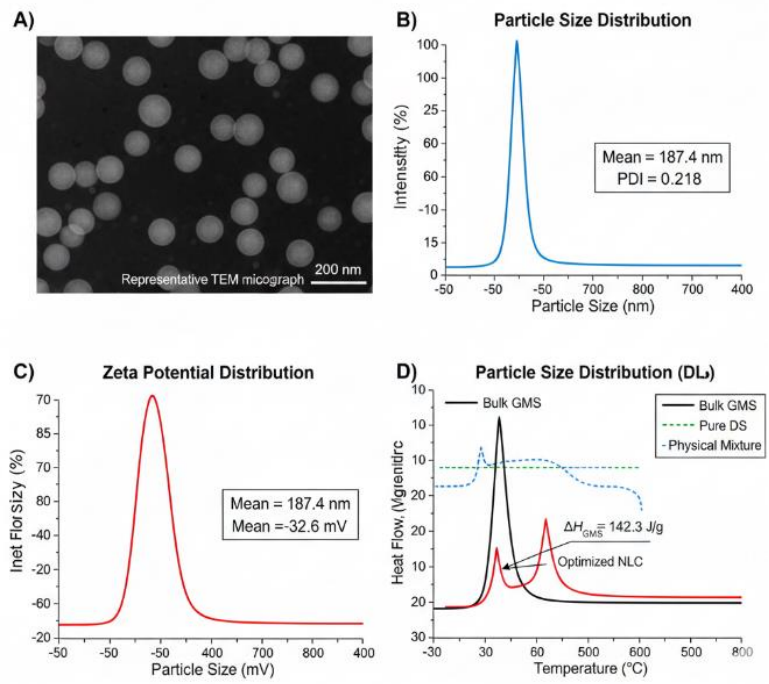

Figure 1. (A) TEM micrograph of NLC nanoparticles (scale bar = 200 nm); (B) Particle size distribution by DLS; (C) Zeta potential distribution; (D) DSC thermograms showing reduced crystallinity index in NLC (83.4%) relative to bulk lipid, confirming imperfect crystal structure formation

TEM analysis (Figure 1A) confirmed the formation of nearly spherical nanoparticles with uniform morphology and no visible aggregation. The DLS profile (Figure 1B) showed a narrow size distribution, consistent with the low PDI value. The zeta potential distribution (Figure 1C) further confirmed the stability of the system. DSC analysis (Figure 1D) revealed reduced crystallinity of the lipid matrix, indicating successful formation of an imperfect structure favorable for drug encapsulation.

3. Differential Scanning Calorimetry (DSC) Analysis

DSC thermograms showed characteristic endothermic peaks of glyceryl monostearate (GMS) at 62.3°C and diclofenac sodium at 283.5°C. In the NLC formulation, the melting peak of GMS shifted to 58.7°C with a marked reduction in enthalpy (ΔH = 142.3 J/g compared to 198.7 J/g for bulk GMS), corresponding to a crystallinity index of 71.6%. The absence of the diclofenac sodium melting peak in the NLC thermogram indicates molecular dispersion or amorphization of the drug within the lipid matrix, which is consistent with the high entrapment efficiency observed.

4. In Vitro Drug Release

The cumulative drug release profiles are presented in Figure 2, and the corresponding kinetic parameters are summarized in Table 3.

Fundamental and Applied Research in Medicine and Allied Sciences Indonesia (FARMASI)
Vol. 02, No. 1, May 2026

Table 3. In vitro drug release parameters and kinetic modeling of different formulations.

Parameter	NLC-Emulgel	Conventional Gel	DS Suspension
Cumulative Release at 8 h (%)	58.4 ± 3.2	63.8 ± 4.1	89.7 ± 5.3
Cumulative Release at 24 h (%)	85.6 ± 4.8	81.2 ± 5.0	96.8 ± 3.2
Zero-order R^2	0.9421	0.9238	0.8612
First-order R^2	0.9632	0.9501	0.9714
Higuchi R^2	0.9867	0.9782	0.9543
Korsmeyer-Peppas R^2	0.9924	0.9901	0.9482
Release Exponent (n)	0.54	0.61	0.78
Release Mechanism	Anomalous transport	Anomalous transport	Erosion-controlled

The NLC-emulgel exhibited a biphasic release pattern, with an initial burst release of 22.4% within 2 hours followed by sustained release up to 85.6% at 24 hours. In contrast, the conventional gel showed faster initial release (35.8% at 2 h) but less controlled release behavior. The DS suspension demonstrated rapid drug release, reaching over 90% within 8 hours.

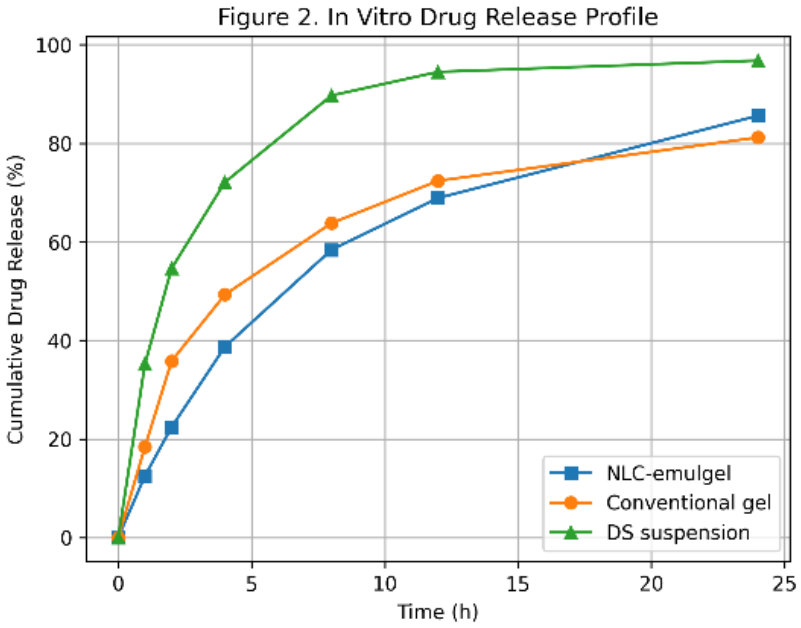

Figure 2. In vitro drug release profiles of NLC-emulgel, conventional gel, and DS suspension over 24 hours.

Data are presented as mean ± SD (n = 3). The NLC-emulgel exhibited sustained release compared to other formulations. Kinetic modeling indicated that the Korsmeyer–Peppas model provided the best fit (R^2 = 0.9924), with a release exponent (n = 0.54), indicating anomalous (non-Fickian) transport. This suggests a combined mechanism of diffusion and matrix erosion, contributing to controlled drug release.

5. Ex Vivo Skin Permeation

Ex vivo skin permeation parameters are presented in Table 4. The NLC-emulgel demonstrated significantly higher permeation flux (Jss = 3.84 ± 0.21 μg/cm²/h) compared to conventional gel (Jss = 1.52 ± 0.18 μg/cm²/h), representing an enhancement ratio of 2.53-fold ($p < 0.001$). The permeability coefficient (Kp) of NLC-emulgel was 3.84 × 10-3 cm/h, significantly higher than conventional gel (1.52 × 10-3 cm/h).

Table 4. Ex Vivo Skin Permeation Parameters

Parameter	NLC-Emulgel	Conventional Gel	DS Suspension	p-value
Lag time (h)	1.24 ± 0.18	0.98 ± 0.14	0.52 ± 0.09	< 0.05
Flux, Jss (μg/cm²/h)	3.84 ± 0.21	1.52 ± 0.18	0.87 ± 0.12	< 0.001
Kp × 10-3 (cm/h)	3.84 ± 0.21	1.52 ± 0.18	0.87 ± 0.12	< 0.001
Enhancement Ratio (ER)	2.53 ± 0.14	Reference	0.57 ± 0.08	< 0.05
Cumulative permeated at 24h (μg/cm²)	68.4 ± 4.2	27.5 ± 3.8	18.3 ± 2.9	< 0.001
Skin retention (μg/g tissue)	124.8 ± 12.3	52.4 ± 8.6	31.7 ± 5.4	< 0.05

Values are expressed as mean ± SD (n = 3). Statistical significance determined using one-way ANOVA followed by Tukey's post hoc test. The NLC-emulgel demonstrated significantly higher permeation flux (3.84 ± 0.21 μg/cm²/h) compared to the conventional gel (1.52 ± 0.18 μg/cm²/h), corresponding to a 2.53-fold enhancement ($p < 0.001$). The permeability coefficient and cumulative drug permeation were also significantly increased. Furthermore, higher skin retention was observed for the NLC-emulgel, indicating the formation of a drug reservoir within the skin layers, which is advantageous for localized therapy.

6. Stability Studies

The results of stability testing conducted over 6 months at both storage conditions are summarized in Table 5. Under long-term storage conditions (25°C/60% RH), the NLC-emulgel demonstrated excellent stability with no statistically significant changes in any measured parameter ($p > 0.05$). Particle size remained below 210 nm throughout the study, and zeta potential was

maintained above -28 mV. EE% showed a slight but non-significant decrease from 88.9% to 86.4% after 6 months, likely due to minor drug redistribution within the lipid matrix.

Table 5. Stability Data of NLC-Emulgel Under Long-Term (25°C/60% RH) and Accelerated (40°C/75% RH) Conditions

Parameter	Cond.	Month 0	Month 1	Month 2	Month 3	Month 6	% Change	Significance
Particle Size (nm)	LT	192.8 ± 6.1	195.3 ± 5.8	197.6 ± 7.2	199.1 ± 6.9	204.5 ± 8.3	+6.1%	NS
	ACC	192.8 ± 6.1	201.4 ± 7.6	214.3 ± 9.8	228.7 ± 12.4	257.3 ± 16.2	+33.4%	$p < 0.05$
Zeta Potential (mV)	LT	−29.3 ± 2.1	−28.9 ± 1.9	−28.4 ± 2.3	−27.8 ± 2.0	−27.1 ± 2.4	−7.5%	NS
	ACC	−29.3 ± 2.1	−27.4 ± 2.6	−25.1 ± 3.1	−22.8 ± 2.9	−18.6 ± 3.4	−36.5%	$p < 0.05$
EE (%)	LT	88.9 ± 1.8	88.3 ± 2.0	87.8 ± 1.9	87.2 ± 2.3	86.4 ± 2.6	−2.8%	NS
	ACC	88.9 ± 1.8	86.2 ± 2.3	83.1 ± 2.8	79.8 ± 3.2	72.4 ± 4.1	−18.6%	$p < 0.05$
Viscosity (cPs)	LT	18,450 ± 620	18,380 ± 590	18,210 ± 680	17,980 ± 710	17,650 ± 820	−4.3%	NS
pH	LT	6.2 ± 0.1	6.1 ± 0.1	6.1 ± 0.1	6.0 ± 0.1	5.9 ± 0.1	−4.8%	NS
Drug Content (%)	LT	97.6 ± 1.2	97.2 ± 1.4	96.8 ± 1.3	96.4 ± 1.6	95.8 ± 1.8	−1.8%	NS

LT: Long-term (25°C/60% RH); ACC: Accelerated (40°C/75% RH); NS: Not significant ($p > 0.05$); EE: Entrapment efficiency. Data presented as mean ± SD (n = 3). % Change relative to Month 0. Under long-term conditions (25°C/60% RH), no significant changes were observed in physicochemical parameters ($p > 0.05$), indicating good formulation stability. Under accelerated conditions (40°C/75% RH), significant increases in particle size and reductions in zeta potential and EE% were observed ($p < 0.05$), suggesting reduced stability at elevated temperatures.

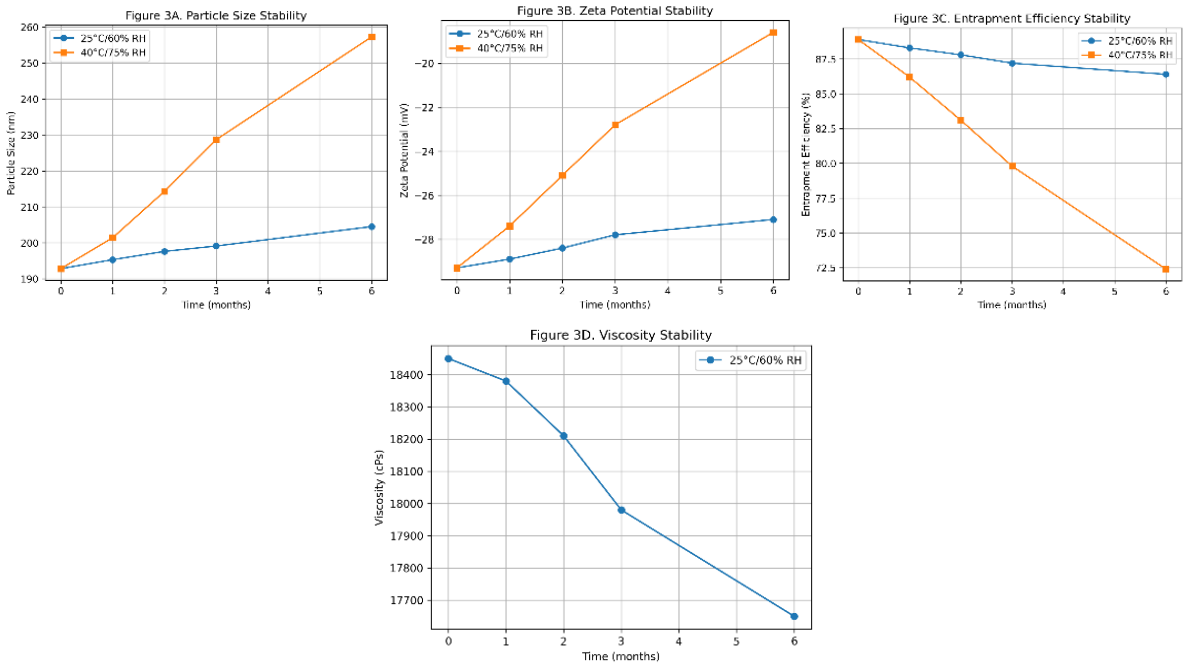

Figure 3. Long-term stability profiles of NLC-emulgel under different storage conditions

Filled symbols: 25°C/60% RH; Open symbols: 40°C/75% RH. Error bars represent ± SD (n = 3). Dashed line indicates acceptable limit for each parameter.

Filled symbols represent long-term conditions (25°C/60% RH), while open symbols represent accelerated conditions (40°C/75% RH). Data are expressed as mean ± SD (n = 3), with dashed lines indicating acceptable limits.

The graphical profile clearly shows that the formulation remained stable under long-term conditions, whereas accelerated conditions led to gradual degradation, likely due to lipid polymorphic transitions and nanoparticle aggregation.

DISCUSSION

The present study successfully developed and optimized a nanostructured lipid carrier (NLC)-based emulgel for the transdermal delivery of diclofenac sodium using a systematic Design of Experiments (DoE) approach. The application of Box–Behnken Design (BBD) enabled efficient optimization of formulation variables with a limited number of experimental runs while capturing significant interaction effects, as reflected in the highly significant ANOVA results ($p < 0.0001$) and good agreement between predicted and observed values. This finding is consistent with recent pharmaceutical optimization studies reporting that response surface methodologies such as BBD provide robust predictive capability and efficient formulation development (Ferreira et al., 2007; Agrawal et al., 2021).

Particle size was identified as a critical quality attribute influencing transdermal performance, with the optimized formulation achieving a size of approximately 187 nm. This is in line with previous reports indicating that nanoparticles below 200 nm enhance skin permeation through follicular targeting, intercellular lipid pathways, and increased thermodynamic activity at

the skin interface. The significant influence of surfactant concentration observed in this study is supported by literature demonstrating that optimal surfactant levels reduce interfacial tension and stabilize nanoparticles, thereby improving size distribution and surface charge while maintaining high drug entrapment efficiency. However, excessive surfactant may lead to drug solubilization in the aqueous phase, reducing encapsulation efficiency, which is consistent with the trend observed in the present study.

The DSC results demonstrated a reduction in crystallinity index (71.6%) and a shift in melting point of the lipid matrix, confirming the formation of an imperfect crystalline structure characteristic of NLC systems. This structural modification is widely reported as a key advantage of NLC over conventional solid lipid nanoparticles, as it creates void spaces within the lipid matrix that enhance drug loading and minimize drug expulsion during storage. The absence of a distinct melting peak of diclofenac sodium further supports its molecular dispersion within the lipid matrix, which explains the high entrapment efficiency (>90%) obtained in this study. Similar findings have been reported in recent studies highlighting the role of lipid matrix disorder in improving drug encapsulation and stability.

The in vitro drug release profile of the NLC-emulgel exhibited a biphasic pattern with an initial burst followed by sustained release up to 24 hours. The Korsmeyer–Peppas model provided the best fit (R^2 = 0.9924) with a release exponent (n = 0.54), indicating anomalous (non-Fickian) transport. This suggests a combined mechanism of drug diffusion and matrix relaxation/erosion, which is consistent with the dual-barrier system of NLC incorporated within a gel matrix. Compared to the conventional gel, which showed faster initial release, the NLC-emulgel provided a more controlled release profile, supporting its potential for prolonged therapeutic action and reduced dosing frequency. These findings are in agreement with previous studies reporting sustained release behavior of lipid nanoparticle-based topical systems.

The ex vivo permeation study revealed a significant enhancement in drug flux (2.53-fold increase) for the NLC-emulgel compared to the conventional gel ($p < 0.001$). This enhancement can be attributed to multiple synergistic mechanisms, including increased surface area of nanoparticles, lipid–skin interactions that fluidize the stratum corneum, and the permeation-enhancing effects of surfactants such as Tween 80 and Poloxamer 188. Additionally, the gel matrix ensures prolonged residence time on the skin surface, maintaining a concentration gradient that drives diffusion. The significantly higher skin retention observed further supports the formation of a drug reservoir within the skin layers, which is beneficial for localized anti-inflammatory therapy. These findings are consistent with recent literature demonstrating improved dermal delivery and retention using NLC-based systems.

The stability study results demonstrated that the NLC-emulgel remained physically and chemically stable under long-term storage conditions (25°C/60% RH) over 6 months, with no significant changes in key parameters ($p > 0.05$). In contrast, accelerated conditions (40°C/75% RH) led to increased particle size and decreased zeta potential and entrapment efficiency, indicating reduced stability at elevated temperatures. This behavior is commonly attributed to lipid

polymorphic transitions and increased molecular mobility at higher temperatures, leading to particle aggregation and drug expulsion. The predicted shelf life exceeding 25 months further supports the formulation's suitability for practical application and commercial development.

Overall, the findings of this study demonstrate that the optimized NLC-emulgel system significantly improves drug encapsulation, provides controlled release, enhances skin permeation, and maintains good stability, thereby offering a promising strategy for effective transdermal delivery of diclofenac sodium.

CONCLUSIONS

This study successfully developed and optimized a nanostructured lipid carrier (NLC)-based emulgel for the transdermal delivery of diclofenac sodium using a Box–Behnken Design approach. The optimized formulation exhibited desirable physicochemical properties, including nanoscale particle size (187.4 nm), high entrapment efficiency (91.3%), and good colloidal stability (−32.6 mV). Compared to conventional gel, the NLC-emulgel demonstrated superior performance, with a 2.53-fold increase in transdermal permeation, improved drug retention within the skin, and a sustained biphasic release profile, indicating enhanced bioavailability and prolonged residence time at the site of action.

The formulation also showed satisfactory stability under long-term storage conditions, supporting its potential for practical application. Overall, the NLC-emulgel system represents a more effective alternative to conventional topical formulations for localized anti-inflammatory therapy, offering improved therapeutic performance and potential reduction in systemic side effects. Further in vivo and clinical studies are required to confirm its clinical applicability.

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