RESEARCH PAPER

Quality by Design-Driven Development and Optimization of Oxaprozin-Loaded Niosomes for Enhanced Topical Delivery

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ABSTRACT

Oxaprozin, a nonsteroidal anti-inflammatory drug (NSAID), is widely used to treat pain and inflammation; however, its oral administration may cause gastrointestinal side effects and limited bioavailability. The present study aimed to develop and optimize oxaprozin-loaded niosomes and incorporate them into a topical gel to enhance drug delivery and therapeutic efficacy. Niosomes were prepared using nonionic surfactants and cholesterol by sonication and optimized using a quality-by-design (QbD) approach with a 3^2 factorial design. Cholesterol and Span 60 concentrations were selected as independent variables, whereas entrapment efficiency and drug release were considered as responses.

The optimized formulation exhibited high entrapment efficiency, an appropriate particle size, and sustained drug release. Scanning electron microscopy confirmed the formation of spherical vesicles. The optimized niosomes were incorporated into a Carbopol 934 gel and evaluated for their physicochemical properties and in vitro drug diffusion. The niosomal gel demonstrated suitable characteristics and prolonged drug release compared to conventional formulations. Stability studies confirmed that the formulation remained stable during the study period. Overall, the developed oxaprozin-loaded niosomal gel shows potential as an effective topical drug delivery system with improved therapeutic performance and reduced systemic side effects.

Keywords: Oxaprozin; Niosomes; Quality by Design; Topical gel; Factorial design; Entrapment efficiency; Controlled drug release; Nanocarriers.

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INTRODUCTION

Inflammatory disorders such as osteoarthritis and rheumatoid arthritis represent a substantial global health burden, necessitating long-term pharmacotherapy for effective management. Nonsteroidal anti-inflammatory drugs (NSAIDs) remain the cornerstone of treatment due to their ability to inhibit cyclooxygenase-mediated prostaglandin synthesis; however, their prolonged systemic administration is frequently associated with gastrointestinal toxicity and other adverse effects, limiting patient compliance and therapeutic outcomes [2,3]. Among these agents, oxaprozin, a propionic acid derivative, exhibits prolonged pharmacological action and potent anti-inflammatory efficacy, yet its oral use is constrained by poor safety in chronic therapy [1].

Topical drug delivery has emerged as a viable alternative strategy to mitigate systemic toxicity while achieving localized therapeutic effects. Despite its advantages, the effectiveness of topical delivery is largely restricted by the barrier properties of the stratum corneum, which significantly limits drug permeation, particularly for lipophilic molecules [4,6]. Consequently, advanced drug delivery systems have been explored to enhance dermal penetration and drug retention at the site of action.

Nanocarrier-based systems, including liposomes, nanoemulsions, and niosomes, have demonstrated significant potential to improve topical drug delivery by enhancing permeation, stability, and controlled-release profiles [7,10]. Among these, niosomes—non-ionic surfactant-based vesicular carriers—have gained considerable attention due to their structural versatility, chemical stability, and ability to encapsulate drugs with varying physicochemical properties [8,9]. Their bilayer architecture facilitates enhanced drug retention within the

skin and sustained drug release, making them particularly suitable for the topical delivery of anti-inflammatory agents.

In parallel, the implementation of the Quality by Design (QbD) paradigm has transformed pharmaceutical development by promoting a systematic, science-based approach to formulation optimization. QbD integrates risk assessment, critical quality attribute (CQA) identification, and statistical design of experiments (DoE) to ensure product robustness and reproducibility [12,13]. Such an approach enables a deeper understanding of formulation variables and their impact on product performance, which is essential for the development of complex nanocarrier systems.

Therefore, the present study aims to develop and optimize oxaprozin-loaded niosomes using a QbD-based factorial design approach and to incorporate the optimized formulation into a carbopol-based topical gel. The study systematically evaluates the influence of formulation variables on entrapment efficiency and drug release, while also assessing physicochemical characteristics and stability. This work provides a rational framework for the development of a robust topical nanocarrier system with improved therapeutic efficacy and reduced systemic exposure [14,16].

MATERIALS AND METHODS

Materials

Oxaprozin was used as the model drug in the present study. Nonionic surfactants, including Span 80, Span 60, Tween 80, and Span 20, were used to prepare the niosomes, and cholesterol served as a membrane stabilizer. Glyceryl monostearate was used as a lipid component. Organic solvents, such as chloroform, methanol, ethanol, and diethyl ether, were utilized during formulation development. Carbopol 934 was used as a gelling agent to prepare the topical gel. Propylene glycol was used as a permeation enhancer, while methyl paraben and propyl paraben were incorporated as preservatives. Sodium hydroxide and triethanolamine were used for pH adjustment. All chemicals and reagents used in the study were of analytical grade.

Equipment

Formulation and evaluation studies were conducted using standard laboratory instruments, including an electronic weighing balance (Cyber Lab, USA), UV–visible spectrophotometer (UV-1800, Shimadzu Corporation), magnetic stirrer (Remi Equipment Pvt. Ltd.), dissolution apparatus USP type I (Electrolab TDT-08L), Brookfield viscometer (DV-E), centrifuge, Fourier-transform infrared (FT-IR) spectrophotometer, and Malvern Zetasizer for particle size and zeta potential analysis.

Preformulation Studies

Preformulation studies were performed to evaluate the physicochemical properties of oxaprozin before formulation development.

Organoleptic Properties

The physical characteristics of the drug samples, including color, odor, and appearance, were evaluated.

Melting Point Determination

The melting point of oxaprozin was determined using the capillary method. A small quantity of the drug was filled into a capillary tube and gradually heated. The temperature at which the drug began to melt was recorded.

Determination of λmax

A stock solution of oxaprozin was prepared by dissolving 10 mg of the drug in methanol and diluting to obtain concentrations of 2–10 µg/mL. The solution was scanned in the wavelength range of 200–400 nm using a UV–Visible spectrophotometer to determine the maximum absorbance wavelength (λmax).

Calibration Curve

A standard stock solution was prepared by dissolving 100 mg of oxaprozin in methanol and diluting it with a phosphate buffer (pH 7.4). Serial dilutions ranging from 10 to 50 µg/mL were prepared and analyzed spectrophotometrically at the determined λmax. A calibration curve was plotted for the relationship between absorbance and concentration.

Partition Coefficient

The partition coefficient of oxaprozin was determined using an n-octanol-water (1:1) system. Equal volumes of both phases containing the drug were equilibrated for 24 h, and the concentration in each phase was determined spectrophotometrically.

FT-IR Analysis

Fourier-transform infrared (FT-IR) spectroscopy was used to identify the characteristic functional groups of oxaprozin. Potassium bromide pellets containing the drug were scanned in the range of 4000–400 cm − 1.

Preparation of Oxaprozin Niosomes

Oxaprozin-loaded niosomes were prepared using sonication. The required amount of drug was dissolved in a suitable buffer solution and mixed with non-ionic surfactants and cholesterol in the presence of an organic solvent. The mixture was homogenized using a magnetic stirrer at 1100 rpm. The dispersion was sonicated at 60°C for 15 min to form multilamellar vesicles, followed by a second sonication to obtain unilamellar niosomes.

Characterization of Niosomes

Particle Size and Zeta Potential

The particle size distribution and zeta potential of the niosomal formulation were measured using a Malvern Zetasizer based on dynamic light scattering. Samples were diluted with distilled water before analysis.

Percentage Yield

The percentage yield of niosomes was calculated using the following equation:

$$\text{Percentage Yield} = \frac{\text{Practical weight of niosomes}}{\text{Total theoretical weight of drug and excipients}} \times 100$$

Drug Content

The drug content of the niosomal dispersion was determined by dissolving the formulation in a chloroform:methanol mixture (40:60). The solution was diluted appropriately and analyzed using a UV–Vis spectrophotometer.

Entrapment Efficiency

The entrapment efficiency was determined by centrifuging the niosomal dispersion at 8000 rpm for 1 h at 5°C. The free drug present in the supernatant was analyzed spectrophotometrically.

$$\text{Entrapment Efficiency (\%)} = \frac{\text{Total drug} - \text{Free drug}}{\text{Total drug}} \times 100$$

Vesicle Size Analysis

The vesicle size distribution was determined by dynamic light scattering at 25°C.

Morphological Analysis

The surface morphology of the niosomes was examined using scanning electron microscopy (SEM).

In-Vitro Drug Release

In vitro drug release studies were performed using a USP Type I dissolution apparatus containing phosphate buffer (pH 7.4) maintained at 37 ± 0.5°C and stirred at 150 rpm. Samples were withdrawn at predetermined intervals and analyzed spectrophotometrically.

Preparation of Oxaprozin Niosomal Gel

The optimized niosomal formulation was incorporated into a Carbopol 934 gel base. Carbopol was dispersed in distilled water and allowed to hydrate for several hours. The niosomal dispersion, propylene glycol, and preservatives were added to the hydrated gel base with continuous stirring. The pH was adjusted using triethanolamine to obtain a homogeneous gel.

Evaluation of Niosomal Gel

Physical Appearance

The gel was visually inspected for color, clarity, homogeneity, and grittiness.

pH Measurement

The pH of the gel was measured using a digital pH meter after dispersing a small amount of the gel in distilled water.

Viscosity

Viscosity was determined using a Brookfield viscometer at an appropriate spindle speed.

Spreadability

The spreadability of the gel was evaluated using the glass slide method and calculated using the following equation:

$$S = \frac{M \times L}{T}$$

where S is the spreadability, M is the weight applied, L is the length of the glass slide, and T is the time to separate the slides.

In-Vitro Diffusion Study

Drug diffusion from the gel formulation was studied using a Franz diffusion cell with a phosphate buffer (pH 7.4) as the receptor medium maintained at 37°C. Samples were withdrawn at predetermined intervals and analyzed spectrophotometrically.

Stability Studies

The optimized formulation was stored at room temperature for 30 days. Samples were evaluated at regular intervals to monitor changes in pH, viscosity, spreadability, and drug content.

RESULTS

Preformulation Study of Oxaprozin

Preformulation studies were conducted to evaluate the fundamental physicochemical characteristics of oxaprozin before formulation development. The organoleptic properties of the drug were assessed in terms of color, odor, and appearance. The drug sample appeared as a white, odorless powder, indicating acceptable physical characteristics and the absence of visible impurities.

Melting Point Determination

The melting point of oxaprozin was determined using the capillary method to assess the purity of the drug sample. The observed melting point range was 158–162 °C, confirming the purity and stability of the drug.

Determination of Maximum Absorption Wavelength (λmax)

The UV-Vis absorption spectrum of oxaprozin was obtained by scanning the drug solution in the wavelength range of 200–400 nm. The maximum absorption wavelength (λmax) was 252 nm, and was selected for further spectrophotometric analysis (Fig. 1).

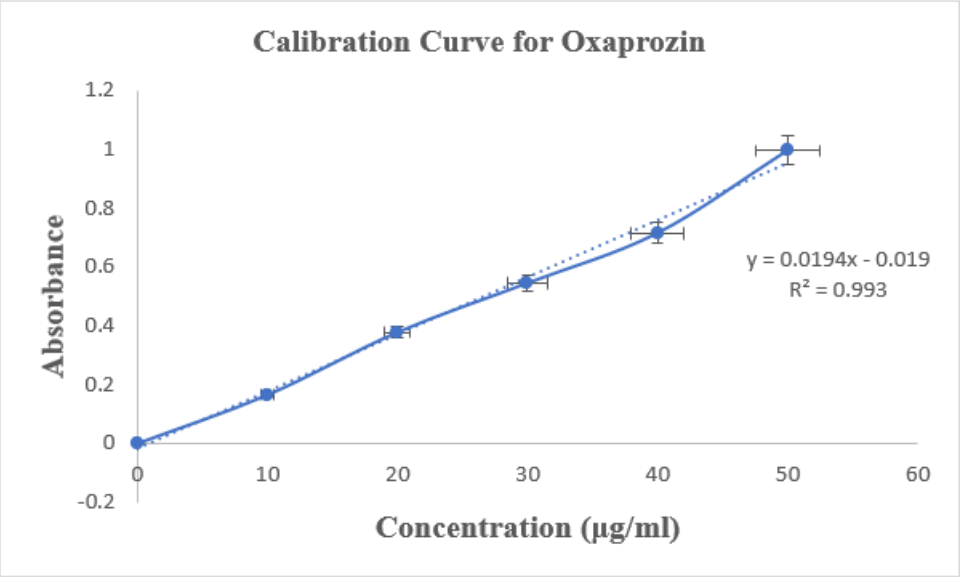

Figure 1 Calibration Curve for Oxaprozin

Calibration Curve of Oxaprozin

A calibration curve was constructed using Oxaprozin standard solutions in the concentration range of 10–50 µg/mL. Absorbance values were measured at 252 nm using a UV–visible spectrophotometer. The calibration curve showed a linear relationship between concentration and absorbance (Table 1 and Fig. 2). Regression analysis demonstrated a correlation coefficient (R^2) of 0.993, indicating good linearity within the studied concentration range.

Table 1. Calibration data of Oxaprozin

Concentration (µg/ml)	**0**	**10**	**20**	**30**	**40**	**50**
Absorbance (nm) (Mean ± S.D.) (n = 3)	**0**	**0.165 ±1.57**	**0.378 ±1.34**	**0.545 ±1.67**	**0.715 ±1.31**	**0.996 ±1.34**

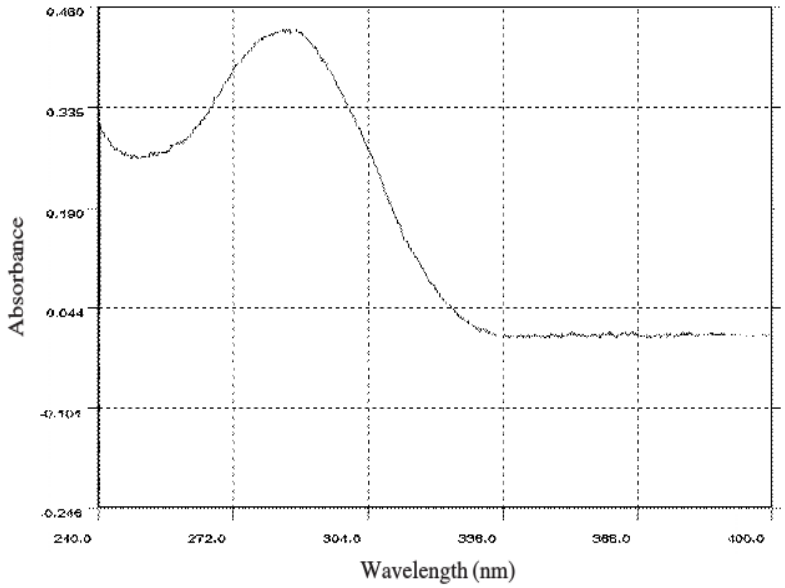

Figure 2 Wavelength max (λmax) of Oxaprozin

Solubility Study

The solubility of oxaprozin was evaluated in different solvents, including water, ethanol, acetone, methanol, and chloroform. The results are summarized in Table 2. Oxaprozin was found to be poorly soluble in water but exhibited good solubility in organic solvents, particularly acetone, ethanol, and methanol.

Table 2. Solubility profile of Oxaprozin

Sr. NO.	SOLVENTS	SOLUBILITY (mg/mL) (Mean ± S.D.) (n = 3)	INTERPRETATION
1.	**Water**	0.012±0.004	Poorly Soluble
2.	**Ethanol**	14.18±0.013	Freely Soluble
3.	**Acetone**	17.26±0.029	Freely Soluble
4.	**Methanol**	13.78±0.024	Freely Soluble
5.	**Chloroform**	8.67±0.067	Soluble

FT-IR Analysis

FT-IR spectroscopy was performed to identify the characteristic functional groups of oxaprozin. The FT-IR spectrum showed characteristic peaks corresponding to the functional groups present in the drug molecule. The major peaks observed were 1717 cm^{-1} (C=O stretching), 2914 cm^{-1} (aromatic C–H stretching), 1568 cm^{-1} (aromatic C=C stretching), 2603 cm^{-1} (O–H stretching), 1266 cm^{-1} (C–N stretching), and 1059 cm^{-1} (C–F stretching). These results confirmed the identity of the drug (Fig. 3).

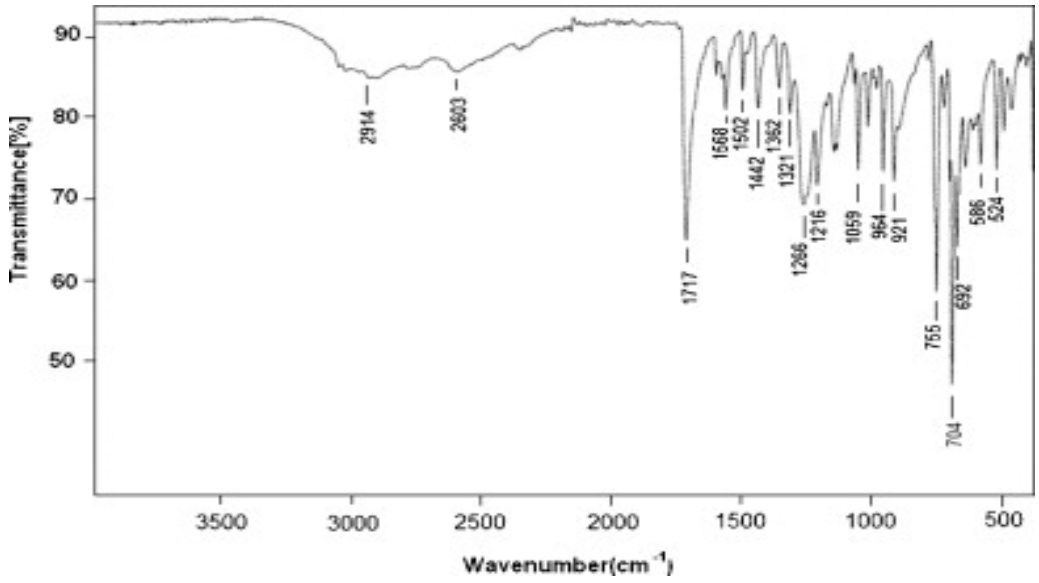

Figure 3 Identification of Pure Drug Oxaprozin by IR Spectrum

Preparation and Characterization of Niosomes

Nine formulations (F1–F9) of oxaprozin-loaded niosomes were prepared using different surfactant compositions. The formulations were evaluated for percentage yield, entrapment efficiency, drug content, and cumulative drug release, and the results are presented in Table 3.

Table 3. Characterization of Oxaprozin-Loaded Niosomal Formulations

Parameter	F1	F2	F3	F4	F5	F6	F7	F8	F9
% Yield	88.73	94.90	91.87	90.95	95.11	91.68	91.17	92.23	95.04
% EE	93.34	95.08	93.33	91.16	93.01	92.34	93.61	96.23	96.53
% Drug Content	94.46	96.00	94.68	93.33	94.01	93.19	95.36	96.55	97.23
% CDR	88.23	93.42	93.09	92.70	91.37	92.75	91.82	90.55	96.03

The percentage yield ranged from 88.73% to 95.11%, and the entrapment efficiency ranged from 91.16% to 96.53%. The drug content was found to be within the range of 93.19%–97.23%, indicating efficient drug incorporation within the vesicles. The cumulative drug release ranged from 88.23% to 96.03%.

Risk Assessment of Critical Quality Attributes

A risk assessment was conducted to evaluate the impact of formulation variables on the critical quality attributes (CQAs) of the niosomal formulations. The evaluated CQAs included percentage yield, entrapment efficiency, vesicle size, and drug release. The results of the risk assessment are summarized in Table 4.

Table 4. Risk Assessment of Critical Quality Attributes (CQAs)

Drug Product CQAs	Surfactant Concentra-tion	Cholesterol Concentrati-on	Lipid Concentration	Organic phase Composition	Organic Phase Volume	Aqueous Phase Volume	Stirring Speed	Stirring Time
%Yield	High	High	Low	Low	Low	Low	High	Medium
Entrapment Efficiency	High	High	Low	Medium	Low	Low	High	Medium
Vesicle Size	High	High	Low	Medium	Low	Low	High	Low
Drug Release	High	High	Low	Low	Low	Low	High	Low

Formulation and Development of Oxaprozin Niosomes Using Design of Experiments (DoE) Based on QbD Approach

3^2 Factorial Design

A 3^2 factorial design was employed to optimize the formulation variables using the quality by design (QbD) approach. Two formulation variables were selected as independent variables, and two responses were selected as dependent variables.

The selected independent variables were as follows:

- X1: Cholesterol concentration
- X2: Span 60 concentration

Each variable was studied at three levels: low (-1), medium (0), and high (+1).

The dependent variables were as follows:

- Y1: Entrapment efficiency (%EE)
- Y2: Percentage cumulative drug release (%CDR)

Table 5. Independent variables and their levels in factorial design

Independent variables of formulations			
Independent variables (X1)	**Low (-1)**	**Medium (0)**	**High (+1)**
Cholesterol (mg)	7	12	17
Span 60 (mg)	12	17	22
Dependent variables			
Y1= Entrapment Efficiency			
Y2= % CDR			

Composition of Factorial Batches (Coded Form)

Nine experimental batches (ONS1–ONS9) were prepared based on the factorial design. The coded levels of the formulation variables used in each batch are shown in Table 6.

Table 6. Factorial design batches in coded form

FENS 3^2 = batches		
Batches	**Variable level in coded form**	
	Conc. of Cholesterol (mg) (X1)	**Conc. of Span 60 (mg) (X2)**
ONS1	-1	-1
ONS2	0	-1
ONS3	+1	-1
ONS4	-1	0
ONS5	0	0
ONS6	+1	0
ONS7	-1	+1
ONS8	0	+1
ONS9	+1	+1

Composition of Factorial Batches (Actual Values)

The coded levels of the variables were converted into actual values for formulation preparation, as shown in Table 7.

Table 7. Factorial batches in actual values

ONS 3^2 = batches		
Batches	**Variable level in coded form**	
	Vol. of Cholesterol (mg) (X1)	**Vol. of Cholesterol (mg) (X2)**
ONS1	7	12
ONS2	12	12
ONS3	17	12
ONS4	7	17
ONS5	12	17
ONS6	17	17
ONS7	7	22
ONS8	12	22
ONS9	17	22

Characterization of Factorial Batches

All factorial batches were evaluated for entrapment efficiency (%EE) and percentage cumulative drug release after 8 h (%CDR). The results obtained for each batch are presented in Table 8.

Table 8. Evaluation of factorial design batches

Batch No	% E. E (Mean ± S.D.) (n = 3)	Drug Release 8h (%) (Mean ± S.D.) (n = 3)
ONS1	92.41±1.45	92.23±1.32
ONS2	72.40±1.64	89.82±0.50
ONS3	64.19±1.15	85.23±1.80
ONS4	84.30±2.424	94.42±1.55
ONS5	67.69±0.45	83.69±1.85
ONS6	60.04±1.34	84.42±1.39
ONS7	82.89±1.78	93.94±1.85
ONS8	66.98±0.97	79.02±1.45
ONS9	55.89±1.14	72.98±2.90

Statistical Analysis

The experimental data obtained from the factorial design batches were analyzed using response surface methodology (RSM) to evaluate the influence of formulation variables on the selected response parameters. The independent variables considered in the study were cholesterol concentration (X1) and Span 60 concentration (X2), whereas the dependent responses were entrapment efficiency (Y1) and percentage cumulative drug release (Y2).

A quadratic polynomial equation was generated to establish the relationship between the independent variables and responses**.**

Effect of Formulation Variables on Entrapment Efficiency (Y1)

The regression equation obtained for the entrapment efficiency is shown below:

$$EE = +69.70 - 13.26A - 4.06B + 0.33AB + 4.58A^2 + 1.60B^2$$

where A= Cholesterol concentration

B = Span 60 concentration

The statistical significance of the model was evaluated using analysis of variance (ANOVA).

Table 9. ANOVA for Entrapment Efficiency (Response Surface Quadratic Model)

Analysis of variance table [Partial sum of squares - Type III]						
	Sum of		**Mean**	**F**	**p-value**	
Source	**Squares**	**df**	**Square**	**Value**	**Prob > F**	
Model	1201.74	5	240.35	120.10	0.0012	significant
A-Cholesterol (mg)	*1055.50*	*1*	*1055.50*	*527.41*	*0.0002*	
B-Span 60 (mg)	*98.74*	*1*	*98.74*	*49.34*	*0.0059*	
AB	*0.44*	*1*	*0.44*	*0.22*	*0.6726*	
A^2	*41.95*	*1*	*41.95*	*20.96*	*0.0196*	

B^2	*5.12*	*1*	*5.12*	*2.56*	*0.2080*	
Residual	6.00	3	2.00			
Cor Total	1207.75	8				

The model was found to be statistically significant ($p < 0.05$), indicating that the selected variables significantly influenced the entrapment efficiency. The three-dimensional response surface and contour plots illustrating the relationship between formulation variables and entrapment efficiency are presented in Figs. 8 and 9, respectively.

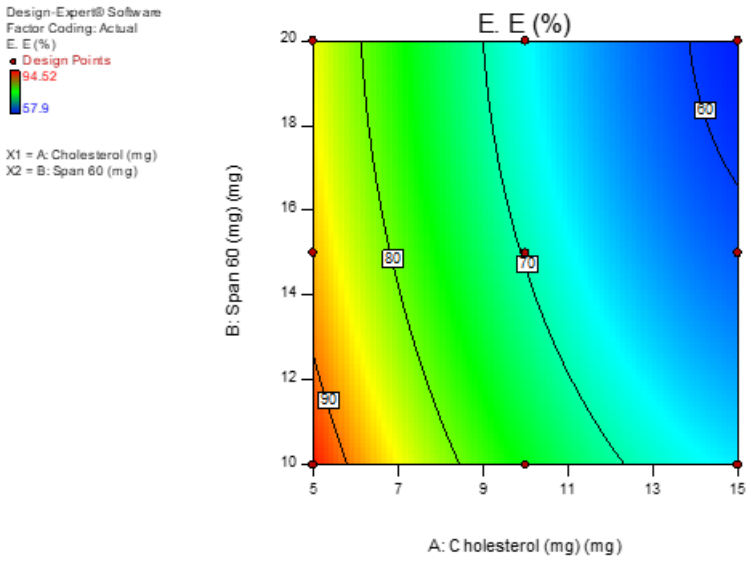

Figure 8 Response surface plot

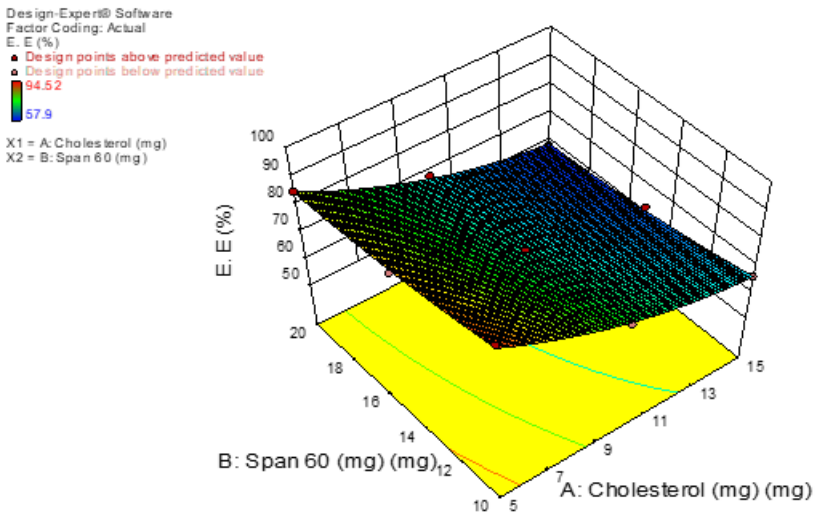

Figure 9: 3-D surface plot

Effect of Formulation Variables on Cumulative Drug Release (Y2)

The regression equation obtained for cumulative drug release is presented below:

$$\text{Drug Release} = +83.50 - 6.30A - 3.35B - 3.45AB + 2.68A^2 - 1.77B^2$$

where A = Cholesterol concentration

B = Span 60 concentration

The statistical significance of the model was evaluated using ANOVA.

Table 10. ANOVA for Cumulative Drug Release

Analysis of variance table [Partial sum of squares - Type III]						
	Sum of		**Mean**	**F**	**p-value**	
Source	**Squares**	**df**	**Square**	**Value**	**Prob > F**	
Model	374.12	5	74.82	10.62	0.0400	significant
A-Cholesterol (mg)	*238.39*	*1*	*238.39*	*33.85*	*0.0101*	
B-Span 60 (mg)	*67.34*	*1*	*67.34*	*9.56*	*0.0536*	
AB	*47.75*	*1*	*47.75*	*6.78*	*0.0801*	
A^2	*14.40*	*1*	*14.40*	*2.04*	*0.2481*	
B^2	*6.24*	*1*	*6.24*	*0.89*	*0.4159*	
Residual	21.13	3	7.04			
Cor Total	395.25	8				

The ANOVA results demonstrated that the developed model was statistically significant, indicating the notable influence of formulation variables on drug release.

The response surface plot and three-dimensional surface plot representing the effect of cholesterol and Span 60 concentrations on cumulative drug release are shown in Fig. 10 and Fig. 11.

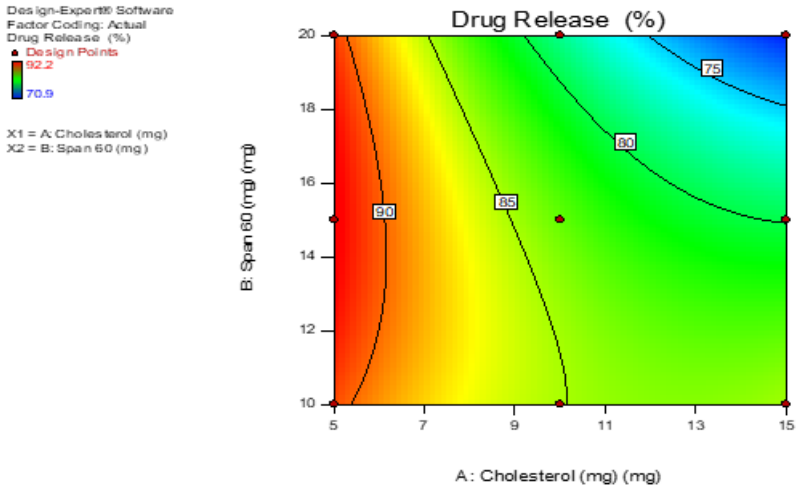

Figure 10 Response surface plot

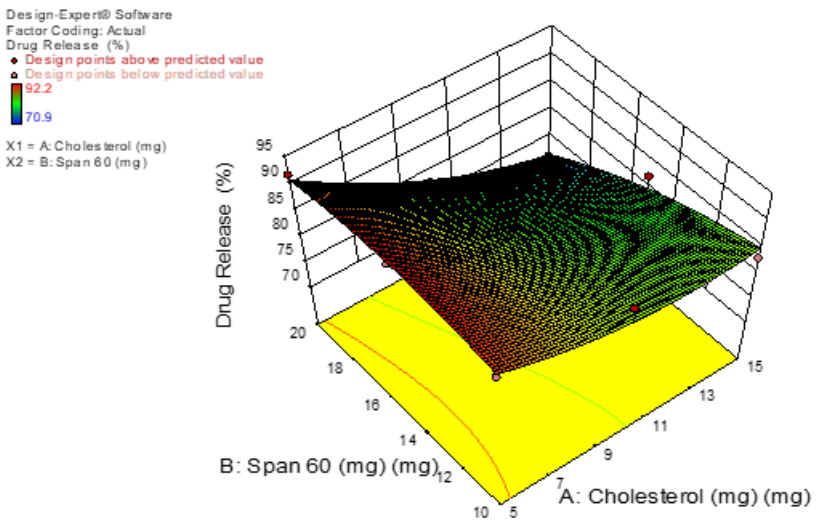

Figure 11 3-D surface plot

Checkpoint Analysis and Model Validation

Checkpoint analysis was performed to validate the polynomial models developed from the factorial design. The responses predicted by the statistical model were compared with the experimentally obtained values for the selected checkpoint formulations. The results showed that the predicted values of entrapment efficiency (EE, %) and percentage cumulative drug release (CDR, %) were in close agreement with the experimentally observed values.

The minor variations between the predicted and experimental results indicate the reliability and predictive capability of the developed response surface model. These findings confirm that the quality by design (QbD)–based optimization approach successfully predicted the formulation responses within the studied design space.

Based on these results, Batch 1 was identified as the optimized formulation, exhibiting satisfactory entrapment efficiency and cumulative drug release. Therefore, this optimized batch was selected for further incorporation into the topical niosomal gel formulation and subsequent evaluation studies.

Morphological Analysis by SEM

The morphology of the optimized niosomal formulation was evaluated using **scanning electron microscopy (SEM)**. SEM images revealed the formation of **spherical vesicles with smooth surfaces**, confirming the successful formation of niosomes (Fig. 12). 12).

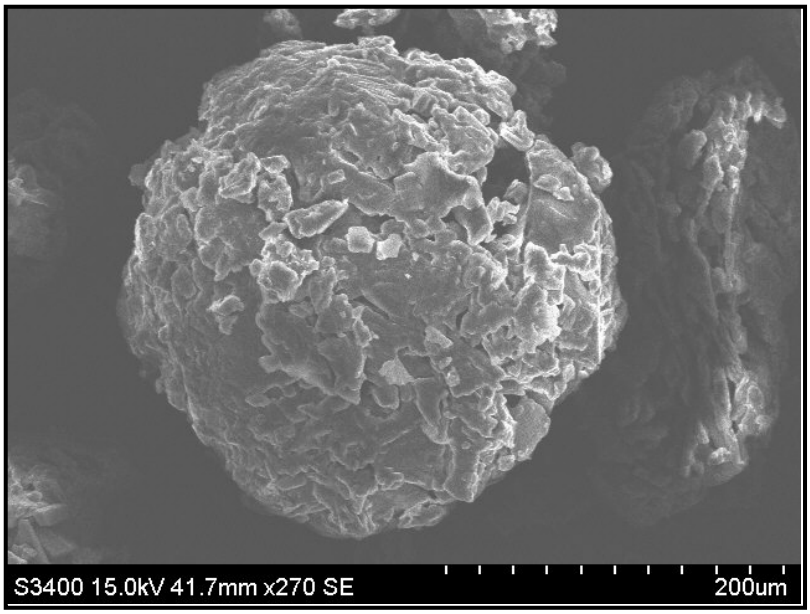

Figure 12 SEM image of Validated optimized Batch Niosomes

Preparation of Oxaprozin-Loaded Niosomal Gel

Dose Calculation for Topical Gel

The amount of oxaprozin required to prepare a 30 g gel containing 2% drug was calculated using the following formula:

$$30 \times \frac{2}{100} = 0.6\ g$$

$$0.6\ g = 600\ mg$$

Thus, 600 mg of oxaprozin is required for a 30 g gel formulation.

From the drug content analysis of the niosomes, 100 mg of niosomes contained 97.62 mg of oxaprozin. Therefore, the quantity of niosomes required to obtain 600 mg of drug was calculated as follows:

$$\frac{600 \times 100}{97.62} = 614.62\ mg$$

Hence, 614.62 mg of oxaprozin-loaded niosomes was incorporated into 30 g of carbopol gel to achieve a final drug concentration of 2% w/w.

Preliminary Trial Batches of Carbopol Gel

Different concentrations of carbopol 934 (1–2.5% w/v) were used to prepare four preliminary gel formulations (ONG1–ONG4). Each formulation contained propylene glycol (10 mL), methyl paraben (0.1 g), propyl paraben (0.05 g), triethanolamine (0.25 mL), and distilled water as the base components. The prepared gel formulations were evaluated for their appearance, odor, pH, viscosity, and spreadability. All formulations were colorless and odorless.

The pH of the formulations ranged between 6.40 and 6.78, which is suitable for topical application. The viscosity values varied from 9267 to 19878 cps, while the spreadability ranged between 10.30 and 15.78 g·cm/sec. Among the prepared formulations, ONG1 exhibited appropriate viscosity and better spreadability; therefore, it was selected as the optimized gel base for the incorporation of the oxaprozin niosomal formulation.

Characterization of Optimized Oxaprozin Niosomal Gel

The optimized oxaprozin niosomal gel was evaluated for its physicochemical properties. The formulation was transparent and odorless. The pH of the gel was found to be 6.40 ± 0.013, which is within the acceptable range for topical formulations.

The viscosity of the gel was 9267 ± 45 cps, indicating appropriate consistency for topical application. The spreadability of the gel was 15.78 ± 0.14 g· cm/s, suggesting good spreading ability. The drug content of the optimized formulation was 94.44 ± 0.48%, confirming uniform drug distribution within the gel.

In-Vitro Drug Release Study

The in vitro drug release profile of the optimized Oxaprozin niosomal gel was evaluated for 12 h using a phosphate buffer (pH 7.4) as the dissolution medium. The formulation exhibited a gradual and sustained release pattern.

The cumulative drug release increased from 6.66% at 1 h to 84.05% at 12 h, indicating the sustained-release behavior of the niosomal gel formulation.

Stability Studies

Stability studies of the optimized oxaprozin niosomal gel were performed at room temperature for 30 days. The formulation was evaluated at 0, 10, 20, and 30 days for parameters such as pH, viscosity, spreadability, and drug content. The results indicated no significant changes in the evaluated parameters during the storage period, confirming the stability of the optimized formulation.

DISCUSSION

The present study provides a systematic and QbD-driven approach for the development of an oxaprozin-loaded niosomal gel, demonstrating the potential of vesicular nanocarriers in enhancing topical drug delivery. Unlike conventional formulations, the developed system integrates formulation optimization with statistical modeling, thereby ensuring reproducibility and robustness of the final product.

Preformulation studies confirmed that oxaprozin possesses physicochemical properties compatible with vesicular encapsulation. The observed solubility profile and lipophilic nature of the drug contributed to its high affinity for the niosomal bilayer, resulting in elevated entrapment efficiency. This observation aligns with previously reported studies indicating that lipophilic drugs exhibit enhanced incorporation within surfactant-based vesicles [8,11].

The factorial design-based optimization revealed that both cholesterol and surfactant concentrations significantly influence the performance of the niosomal system. Cholesterol plays a critical role in modulating membrane rigidity and permeability; increased cholesterol content enhances vesicle stability and entrapment efficiency but may retard drug release due to reduced bilayer fluidity [12]. Conversely, surfactant concentration influences vesicle formation and drug solubilization, thereby impacting both encapsulation and release characteristics. The statistical significance of these variables highlights the importance of QbD principles in understanding formulation behavior.

The optimized formulation exhibited spherical morphology with uniform vesicle distribution, as confirmed by SEM analysis, indicating successful vesicle formation and structural integrity. Incorporation of the optimized niosomes into a carbopol gel resulted in a formulation with desirable rheological and physicochemical properties suitable for topical application. The pH, viscosity, and spreadability values were within acceptable limits, ensuring patient compliance and effective application [6].

A key outcome of this study is the sustained drug release profile observed over 12 hours, which can be attributed to the dual mechanism of drug release from the vesicular system and diffusion through the gel matrix. Such controlled release behavior is advantageous for maintaining therapeutic drug levels and reducing dosing frequency. Similar findings have been reported in other nanocarrier-based systems, including nanoemulgels and microsponges, where sustained release significantly improved therapeutic outcomes [10,15].

Furthermore, the stability studies demonstrated that the optimized formulation maintained its physicochemical integrity over the study period, indicating its suitability for practical application. This stability can be attributed to the presence of cholesterol, which enhances vesicle rigidity, and the structured gel matrix that minimizes drug leakage.

From a translational perspective, the developed formulation offers a promising alternative to oral NSAID therapy by reducing systemic exposure and associated adverse effects. However, while the in vitro findings are encouraging, further studies involving ex vivo skin permeation and in vivo pharmacodynamic evaluation are essential to establish clinical efficacy.

Overall, this study underscores the significance of integrating nanotechnology with QbD principles to develop advanced topical drug delivery systems. The findings provide a strong foundation for future research aimed at translating such formulations into clinically viable therapies [13,16].

CONCLUSION

In the present study, we successfully developed and optimized oxaprozin-loaded niosomes incorporated into a carbopol-based topical gel using a quality-by-design (QbD) approach. The prepared niosomal formulations demonstrated high entrapment efficiency, satisfactory drug content, and sustained drug release characteristics. Optimization through factorial design confirmed that formulation variables, such as cholesterol and surfactant concentration, significantly influenced the performance of the niosomal system. The optimized niosomal gel exhibited acceptable physicochemical properties, suitable pH, good spreadability, and prolonged drug release over 12 hours. Stability studies indicated that the formulation remained stable under storage conditions.

However, the study was limited to in vitro evaluation, and further investigations, including ex vivo skin permeation studies, in vivo pharmacological evaluation, and long-term stability studies, are required to confirm the clinical potential of the developed formulation. These findings suggest that niosomal gel systems may represent a promising strategy for improving the topical delivery of anti-inflammatory drugs.

Conflict of Interest

The authors declare no conflicts of interest related to the publication of this paper.

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