



**INTERNATIONAL JOURNAL OF
PHARMACEUTICAL SCIENCES**
[ISSN: 0975-4725; CODEN(USA): IJPS00]
Journal Homepage: <https://www.ijpsjournal.com>



Research Article

QbD-Based Development of Lornoxicam Topical Gel Supported by In-Silico Permeation Study

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ARTICLE INFO

Published: 06 Oct 2026

Keywords:

Lornoxicam; topical gel;
Quality by Design;
SwissADME; Taguchi
design; Carbopol 940

DOI:

10.5281/zenodo.23192181

ABSTRACT

The present study aimed to develop and optimize a Lornoxicam topical gel using an in-silico skin permeation assessment integrated with a Quality by Design (QbD) approach. Lornoxicam is a potent oxicam-class non-steroidal anti-inflammatory drug (NSAID), and topical delivery was investigated as a formulation strategy for localized administration. Preformulation studies included organoleptic evaluation, solubility assessment and melting-point determination. SwissADME was used to predict physicochemical and skin-permeation-related descriptors before formulation development. A Carbopol 940-based gel containing Lornoxicam was prepared by dispersion. QbD principles were applied to define the Quality Target Product Profile and Critical Quality Attributes, followed by selection of Carbopol 940, propylene glycol, ethanol and triethanolamine as formulation variables. A Taguchi L9 orthogonal array was used to study their effects on pH, spreadability and viscosity, and the data were analyzed using Design-Expert® software and ANOVA. Lornoxicam showed a melting range of 221–225°C, a λ_{max} of 376 nm in methanol, low aqueous solubility and better solubility in organic solvents. SwissADME predicted a molecular weight of 371.82 g/mol, consensus Log P of 1.59 and skin permeability coefficient (Log Kp) of -7.07 cm/s. The optimized formulation contained 0.5% w/w Carbopol 940, 5% w/w propylene glycol, 5% w/w ethanol and 0.25% w/w triethanolamine. Predicted responses were pH 5.86, spreadability 28.58 g·cm/s and viscosity 20.18 Pa·s, while experimental values were 5.84, 28.41 g·cm/s and 20.05 Pa·s, respectively. The optimized gel showed acceptable homogeneity, smoothness and extrudability and remained physically stable during three months of accelerated storage at $40 \pm 2^\circ\text{C}/75 \pm 5\%$ RH. The study demonstrates the usefulness of combining in-silico permeation prediction with QbD-based formulation optimization for systematic development of Lornoxicam topical gel.

INTRODUCTION

Pain and inflammation are common clinical problems for which non-steroidal anti-

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Relevant conflicts of interest/financial disclosures: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.



inflammatory drugs (NSAIDs) are widely used. Lornoxicam is an oxicam derivative with potent analgesic and anti-inflammatory activity. Although oral administration is effective, conventional systemic NSAID therapy may be associated with gastrointestinal and other systemic adverse effects, particularly during repeated use. Topical delivery offers an alternative route for localized treatment by placing the drug at or near the site of application while potentially reducing systemic exposure.

The stratum corneum is the principal barrier to dermal drug transport. Drug molecular size, lipophilicity, polarity, solubility and formulation composition all influence passive permeation. Lornoxicam has physicochemical characteristics that warrant formulation-assisted delivery, and permeation enhancers such as ethanol and propylene glycol may improve drug solubilization and transport through the skin.

Topical gels are attractive semisolid dosage forms because they are easy to apply, generally non-greasy, readily spreadable and capable of providing localized drug release. Carbopol polymers are commonly used to form clear or translucent gels with controllable viscosity. However, polymer concentration, solvent level and neutralization can substantially affect gel pH, rheology and spreadability.

Quality by Design (QbD) provides a science- and risk-based framework for pharmaceutical development. It begins with a Quality Target Product Profile (QTPP), identifies Critical Quality Attributes (CQAs), links them to Critical Material Attributes (CMAs) and Critical Process Parameters (CPPs), and uses experimental design to understand formulation-variable effects. In the present work, an in-silico permeation assessment was used before formulation development and was

integrated with QbD-based optimization of a Lornoxicam topical gel.

MATERIALS AND METHODS

Materials

Lornoxicam (pharmaceutical reference standard; MedChemExpress, USA) was used as the active pharmaceutical ingredient. Carbopol 940, triethanolamine, ethanol, propylene glycol, methyl paraben and propyl paraben were used as formulation excipients. Purified water and analytical-reagent-grade solvents and reagents were used for analytical and formulation studies.

In-Silico Permeation Study

The two-dimensional structure of Lornoxicam was obtained from PubChem (CID 54676228), and the corresponding SMILES string was entered into the SwissADME web server. Molecular weight, consensus Log P, topological polar surface area (TPSA), hydrogen-bond donors and acceptors, ESOL solubility, gastrointestinal absorption, bioavailability score, Lipinski compliance and predicted skin permeability coefficient (Log Kp) were recorded. The BOILED-Egg model and bioavailability radar were also examined. The analysis was performed before formulation development to provide preliminary evidence regarding the molecule's suitability for topical delivery.

Preformulation Studies

Organoleptic characteristics were assessed by visual inspection of color, appearance, texture and odor. Solubility was assessed in distilled water, methanol, ethanol, propylene glycol and dimethyl sulfoxide using an equilibrium method. Excess drug was equilibrated in each solvent at $25 \pm 2^\circ\text{C}$ for 24 h, filtered and analyzed spectrophotometrically at 376 nm. Measurements



were performed in triplicate. Melting point was determined by the capillary method.

Preparation of Lornoxicam Gel

Lornoxicam gel was prepared by the dispersion method using Carbopol 940. Carbopol 940 was gradually dispersed in approximately 70% of the required purified water with stirring at 500 rpm, followed by hydration for 24 h. Lornoxicam was dissolved in ethanol and propylene glycol. Methyl paraben and propyl paraben were dissolved in a small quantity of ethanol with gentle heating and incorporated into the drug solution. The drug solution was added slowly to the hydrated polymer with continuous stirring, followed by addition of the remaining water. Triethanolamine was added dropwise to adjust the pH to approximately 5.5–6.5 and to develop the gel structure. The gel was homogenized, allowed to deaerate and filled into suitable containers.

TABLE 1. COMPOSITION OF THE OPTIMIZED LORNOXICAM TOPICAL GEL

Ingredient	Optimized level (% w/w)
Lornoxicam	0.20
Carbopol 940	0.50
Propylene glycol	5.00
Ethanol	5.00
Triethanolamine	0.25
Methyl paraben	0.15
Propyl paraben	0.05
Purified water	q.s. to 100

QbD-Based Formulation Development

The QTPP was defined with emphasis on a smooth topical gel, skin-compatible pH, adequate viscosity, maximum practical spreadability, homogeneity, good extrudability and physical stability. Based on literature and preliminary trials, Carbopol 940 concentration (A), propylene glycol concentration (B), ethanol concentration (C) and triethanolamine concentration (D) were selected as formulation variables.

TABLE 2. INDEPENDENT VARIABLES AND EXPERIMENTAL LEVELS

Factor	Low (-1)	Middle (0)	High (+1)
Carbopol 940 (% w/w)	0.5	1.0	1.5
Propylene glycol (% w/w)	5	10	15
Ethanol (% w/w)	5	10	15
Triethanolamine (% w/w)	0.25	0.50	0.75

A Taguchi L9 orthogonal array was generated in Design-Expert® Version 13. Nine experimental formulations were prepared. The selected responses were pH, spreadability and viscosity. The optimization targets were a skin-compatible pH of 5.5–6.5, maximum spreadability and an appropriate viscosity. ANOVA was used to determine the significance of the models and formulation factors, followed by numerical optimization using a desirability function.

Evaluation Of Gel

Homogeneity, color, transparency, consistency and phase separation were evaluated visually. Grittiness was assessed by rubbing a small amount of gel between the fingertips. Extrudability was assessed from collapsible aluminum tubes and graded according to ease of extrusion. pH was measured using a calibrated digital pH meter after dispersing approximately 1 g of gel in 10 mL of distilled water. Viscosity was measured with a Brookfield DV-E viscometer using spindle No. 64 at 10 rpm and $25 \pm 2^\circ\text{C}$. Spreadability was determined by the parallel-slide method and calculated as $S = ML/T$, where M is the weight attached to the upper slide, L is the length of the slide and T is the time required for separation.

Stability Study

The optimized formulation was subjected to accelerated stability testing according to ICH Q1A(R2). Samples were stored at $40 \pm 2^\circ\text{C}/75 \pm 5\%$ relative humidity for three months and evaluated at 0, 1, 2 and 3 months for appearance,



color, homogeneity, pH, spreadability, viscosity and extrudability.

RESULTS

In-Silico Permeation and Physicochemical Prediction

SwissADME predicted a molecular weight of 371.82 g/mol and a consensus Log P of 1.59. The predicted skin permeability coefficient was -7.07 cm/s. TPSA was $136.22 \text{ \AA}^2$, with five hydrogen-bond acceptors and two hydrogen-bond donors. Lipinski's Rule of Five showed no violations and the predicted bioavailability score was 0.56. The predicted Log Kp indicated that passive skin permeation may be limited, supporting the inclusion of formulation-assisted permeation enhancers.

TABLE 3. SWISSADME-PREDICTED PHYSICOCHEMICAL AND PERMEATION PARAMETERS OF LORNOXICAM

Parameter	Predicted value
Molecular formula	C13H10CIN3O4S2
Molecular weight	371.82 g/mol
Consensus Log P	1.59
TPSA	$136.22 \text{ \AA}^2$
H-bond acceptors	5
H-bond donors	2
Rotatable bonds	3
Skin permeability (Log Kp)	-7.07 cm/s
ESOL Log S	-3.63
GI absorption	High
BBB permeability	No
P-gp substrate	No
Lipinski violations	0
Bioavailability score	0.56

Preformulation Findings

Lornoxicam appeared as a light-yellow to yellow, odorless crystalline fine powder. The drug was slightly soluble in distilled water, freely soluble in methanol and dimethyl sulfoxide, soluble in ethanol and moderately soluble in propylene glycol. The observed melting range was $221-225^\circ\text{C}$. These findings were consistent with the expected physicochemical characteristics and supported further formulation development.

TABLE 4. SOLUBILITY PROFILE OF LORNOXICAM

Solvent	Solubility observation
Distilled water	Slightly soluble
Methanol	Freely soluble
Ethanol	Soluble
Propylene glycol	Moderately soluble
DMSO	Freely soluble

Optimization By Taguchi L9 Design

The nine experimental batches produced pH values from 5.78 to 7.12, spreadability values from 16.74 to $30.15 \text{ g}\cdot\text{cm/s}$ and viscosity values from 18.76 to $43.28 \text{ Pa}\cdot\text{s}$. Increasing Carbopol concentration generally increased viscosity and reduced spreadability. Triethanolamine had a pronounced effect on pH because of its neutralizing action on Carbopol.

TABLE 5. EXPERIMENTAL RESPONSES OF THE TAGUCHI L9 BATCHES

Run	Carbopol (%)	PG (%)	Ethanol (%)	TEA (%)	pH	Spreadability ($\text{g}\cdot\text{cm/s}$)	Viscosity ($\text{Pa}\cdot\text{s}$)
G1	0.75	5	10	0.75	6.92	18.45	34.82
G2	0.5	5	5	0.25	5.78	26.84	18.76
G3	0.75	15	5	0.5	6.41	22.18	29.65
G4	0.5	10	10	0.5	6.32	28.76	20.41
G5	1.0	5	15	0.5	6.36	17.42	41.53
G6	0.75	10	15	0.25	5.94	23.87	27.34



G7	1.0	15	10	0.25	5.86	19.56	38.92
G8	1.0	10	5	0.75	7.05	16.74	43.28
G9	0.5	15	15	0.75	7.12	30.15	21.36

Statistical Analysis And Model Validation

The pH model was statistically significant ($F = 165.48$, $p < 0.0001$), with triethanolamine identified as the significant factor. The

spreadability model was significant ($F = 21.05$, $p = 0.0019$), with Carbopol 940 as the significant factor. The viscosity model was also significant ($F = 47.07$, $p = 0.0002$), again showing a significant contribution from Carbopol 940.

TABLE 6. ANOVA AND MODEL-FIT SUMMARY

Response	Significant factor	Model F-value	p-value	R ²	Adjusted R ²	Predicted R ²
pH	Triethanolamine	165.48	<0.0001	0.9822	0.9763	0.9599
Spreadability	Carbopol 940	21.05	0.0019	0.8753	0.8337	0.7193
Viscosity	Carbopol 940	47.07	0.0002	0.9401	0.9201	0.8652

Optimization And Confirmation

Numerical optimization generated solutions with a desirability value of 1.000. The selected optimized formulation contained 0.5% Carbopol 940, 5% propylene glycol, 5% ethanol and 0.25% triethanolamine. The predicted and experimentally observed responses were closely comparable, indicating satisfactory predictive performance of the optimization models.

TABLE 7. PREDICTED AND OBSERVED RESPONSES OF THE OPTIMIZED FORMULATION

Response	Predicted	Observed
pH	5.86	5.84
Spreadability (g·cm/s)	28.58	28.41
Viscosity (Pa·s)	20.18	20.05

Evaluation and Stability

The optimized gel was smooth, homogeneous and free from visible aggregates and phase separation. No appreciable grittiness was observed, and the formulation was extruded smoothly from the collapsible tube. During accelerated storage at $40 \pm 2^\circ\text{C}/75 \pm 5\% \text{ RH}$ for three months, no significant visual change, phase separation, liquefaction or precipitation was reported. The measured pH,

spreadability and viscosity remained within acceptable ranges over the study period.

DISCUSSION

The in-silico assessment provided an early estimate of the molecular characteristics relevant to dermal delivery. Lornoxicam showed a molecular weight below the commonly used 500 Da reference threshold and moderate lipophilicity, which can favor partitioning into the lipid-rich stratum corneum. At the same time, the relatively high TPSA and the predicted Log K_p of -7.07 cm/s indicate that passive permeation may be limited. Thus, the computational findings support the need for formulation strategies rather than implying that topical delivery will necessarily produce a specific in vivo therapeutic exposure.

The preformulation results supported the use of ethanol and propylene glycol in the gel. Their solvent and co-solvent properties can improve drug solubilization, while both can contribute to dermal permeation enhancement. Carbopol 940 provided the polymeric network required for gel formation. The optimization results demonstrated the expected formulation relationships: higher



polymer concentration increased viscosity and reduced spreadability, whereas triethanolamine strongly influenced pH through neutralization of Carbopol.

The QbD strategy reduced the number of experimental batches needed to examine four formulation variables and linked formulation composition to measurable CQAs. The significant ANOVA results and high coefficients of determination indicate that the selected models described the observed response variation within the studied design space. The close agreement between predicted and observed responses in the confirmation experiment further supports the selected formulation conditions.

The optimized formulation showed acceptable physical characteristics and maintained its properties during the three-month accelerated study. Nevertheless, the present work was primarily a formulation-development and computational study. The predicted skin permeability should be interpreted as a theoretical estimate, and additional experimental permeation, drug-content, release, skin-retention, irritation and pharmacodynamic studies would be required to establish clinical performance.

CONCLUSION

A Lornoxicam topical gel was successfully developed using an integrated in-silico and QbD-based approach. SwissADME analysis provided preliminary evidence regarding molecular properties relevant to skin delivery and supported the use of permeation-enhancing excipients. The Taguchi L9 design efficiently identified the effects of Carbopol 940 and triethanolamine on viscosity/spreadability and pH, respectively. The optimized formulation containing 0.5% Carbopol 940, 5% propylene glycol, 5% ethanol and 0.25% triethanolamine showed predicted and

experimental responses in close agreement and acceptable physical stability under accelerated conditions. The findings demonstrate a systematic formulation-development strategy for Lornoxicam topical gel, while further experimental skin-permeation and biological studies are warranted before therapeutic conclusions are drawn.

ACKNOWLEDGEMENT

The authors acknowledge Yash Institute of Pharmacy, Chhatrapati Sambhajanagar, for providing laboratory facilities and academic support for this research work.

CONFLICT OF INTEREST

The authors declare no conflict of interest related to this work.

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HOW TO CITE: Rutuja Salunke, S. S. Angadi, Reshma Patil, Vadana Patil, QbD-Based Development of Lornoxicam Topical Gel Supported by In-Silico Permeation Study, *Int. J. of Pharm. Sci.*, 2026, Vol 4, Issue 10, 891-897. <https://doi.org/10.5281/zenodo.23192181>

