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Research Article

Formulation and Evaluation of Gel Containing Crisaborole-Loaded Nano Lipid Carrier for Treatment of Inflammatory Skin Disease

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ABSTRACT

Crisaborole is a non-steroidal phosphodiesterase-4 (PDE-4) inhibitor indicated for mild-to-moderate atopic dermatitis, but its clinical utility is hindered by poor aqueous solubility and limited cutaneous localization. To address these challenges, Crisaborole-loaded Nanostructured Lipid Carriers (NLCs) were formulated via hot emulsification–probe ultrasonication and systematically optimized using a three-factor, three-level Box-Behnken Design (BBD). The independent variables-total lipid concentration (), liquid lipid fraction (), and Poloxamer 188 concentration () significantly influenced particle size (), polydispersity index (PDI,), and entrapment efficiency (%EE,). The optimized NLC formulation (NLC-OPT1) exhibited a nanoscale particle size of 239.89 nm, a narrow PDI of 0.325, an entrapment efficiency of 83.67 ± 1.01%, and a high process yield of 91.62 ± 1.56%. Transmission electron microscopy confirmed predominantly spherical nanostructures with discrete boundaries. Incorporation of the optimized NLCs into a Carbopol 940 hydrogel base afforded a topical gel with favorable rheological and physical properties, including a viscosity of 1952.90 ± 2.59 cP, a dermatologically compatible pH of 7.19 ± 0.05, and excellent spreadability (25.67 ± 0.45 cm). *In vitro* release studies demonstrated sustained drug permeation over 10 h, reaching 96.23% cumulative release, governed by anomalous non-Fickian transport according to the Korsmeyer-Peppas model (,). Accelerated stability testing over 3 months () revealed negligible physicochemical alterations, with release similarity confirmed by an value of 84.70. These findings demonstrate that Crisaborole-loaded NLC gel provides an effective, stable lipid-based nanoplatform for sustained dermal therapy of inflammatory skin disorders.

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INTRODUCTION

Atopic dermatitis (AD) is a prevalent, relapsing inflammatory cutaneous disorder characterized by severe pruritus, localized erythema, and profound disruption of the epidermal permeability barrier (1). While first-line interventions such as topical corticosteroids and calcineurin inhibitors provide clinical relief, their prolonged therapeutic application is frequently hampered by debilitating adverse sequelae, including cutaneous atrophy, telangiectasia, systemic absorption, and potential immunosuppression. Consequently, non-steroidal alternatives with targeted anti-inflammatory activity represent a critical clinical necessity (2,3).

Crisaborole, a selective non-steroidal phosphodiesterase-4 (PDE-4) inhibitor, suppresses inflammatory cascades by elevating intracellular cyclic adenosine monophosphate (cAMP) and downregulating downstream pro-inflammatory cytokines such as TNF-α, IL-4, and IL-13 (4). Approved for mild-to-moderate atopic dermatitis, Crisaborole offers an improved safety margin over steroidal regimens. However, its clinical translation and dermal bioavailability are severely constrained by its unfavorable physicochemical attributes: it is classified as a BCS Class II compound characterized by poor aqueous solubility (~0.02–0.1 mg/mL) and high lipophilicity (5). When delivered via conventional topical vehicles (e.g., ointments or simple creams), Crisaborole exhibits limited percutaneous permeation, poor retention within target epidermal layers, low patient compliance due to greasiness, and occasional burning or stinging at the application site (6).

To circumvent these drug-delivery bottlenecks, nanocarrier systems have garnered substantial interest. Although conventional phospholipid vesicles (liposomes) can enhance transdermal penetration, their commercial viability is plagued by chemical instability (hydrolysis and oxidation of unsaturated fatty acids), physical leakage, aggregation, and complex scale-up procedures in aqueous states (7). Nanostructured Lipid Carriers (NLCs) present a mechanistically distinct, highly robust second-generation colloidal platform designed to overcome these vesicular constraints. Engineered from a spatially disordered blend of solid lipids and liquid lipids, NLCs possess an imperfect crystal matrix that accommodates high loads of hydrophobic drug molecules and effectively suppresses drug expulsion during storage (8). Furthermore, the physiological lipid constituents of NLCs exhibit pronounced biocompatibility and strong affinity for the intercellular stratum corneum lipids, forming an occlusive, hydrating film on the skin that promotes deep cutaneous deposition and prolonged release without irritating inflamed tissues (9).

Despite their advantages, low-viscosity colloidal dispersions of NLCs are impractical for direct dermal application due to poor retention, rapid runoff, and uneven dosing. Incorporating Crisaborole-loaded NLCs into a secondary polymeric hydrogel matrix (such as Carbopol 940) provides an optimal delivery paradigm. The hydrogel base imparts suitable rheological consistency, pseudoplastic flow, and superior spreadability, extending residence time on the skin surface and modulating drug diffusion into sustained kinetics (10-12).

Therefore, the rationale of this study is to engineer, systematically optimize, and evaluate a Crisaborole-loaded Nanostructured Lipid Carrier (NLC) gel system using a Quality by Design (QbD) approach. By synergizing the high encapsulation efficiency and occlusive dermal retention of NLCs with the patient-friendly rheological attributes of a Carbopol hydrogel, this platform aims to overcome the solubility barrier of Crisaborole, eliminate the need for harsh penetration enhancers, provide controlled 10-hour drug release, and ultimately establish a stable, non-greasy, and clinically superior topical modality for the management of inflammatory dermatoses.

MATERIALS AND METHODS

MATERIALS

Crisaborole was acquired from Pure chem. Pvt. Ltd. Cholesterol were procured from Astron Chemicals, India. Span 60, Stearic acid, HPMC, Eudragit and PVP were procured from National chemical, Vadodara. Diethyl Ether, Methanol, Isopropyl Alcohol, Dichloromethane, Polyisobutylene and PEG 400 were procured from Astron Chemicals, India. Other laboratory grade materials were bought from an institutional supplier for the manufacturer of reagents and solutions.

METHODS

2.2.1 Preparation of Crisaborole -Loaded Nanostructured Lipid Carriers (NLCs)

The required quantities of solid lipid and liquid lipid were accurately weighed to obtain a total lipid concentration of 6% w/v, with the liquid lipid constituting 30% of the total lipid content. The weighed lipids were transferred into a beaker and heated at 70–75°C until completely melted (13). The required quantity of crizaborole was added to the molten lipid phase and mixed until uniformly dispersed or dissolved. Separately, the aqueous phase was prepared by dissolving Poloxamer 188 (1.25% w/v) in purified water. The aqueous phase was heated to the same temperature (70–75°C) as the lipid phase to maintain temperature uniformity during emulsification. The hot aqueous phase was gradually added to the molten lipid phase under continuous high-speed stirring at 10,000–15,000 rpm for 5–10 minutes to obtain a coarse emulsion. The resulting emulsion was subsequently subjected to probe ultrasonication at 40–60% amplitude for 5–10 minutes using a pulsed sonication mode to reduce the particle size and obtain a fine nanoemulsion. The prepared nanoemulsion was allowed to cool to room temperature under gentle stirring. During the cooling process, the molten lipid droplets solidified, resulting in the formation of crizaborole-loaded nanostructured lipid carriers. The final NLC dispersion was collected and stored in a suitable, tightly closed container for further characterization and incorporation into the gel formulation (13,14).

2.2.2 Optimization of Crisaborole-Loaded Nanostructured Lipid Carriers Using Box–Behnken Design

The formulation of crisaborole-loaded nanostructured lipid carriers (NLCs) was optimized using a three-factor, three-level Box–Behnken design (BBD) to investigate the influence of formulation variables on the physicochemical characteristics of the prepared nanoparticles. Design-Expert software was used to generate the experimental design and evaluate the effects of independent variables on the selected responses. Three independent formulation variables were selected: total lipid concentration (X_1), liquid lipid fraction of total lipid (X_2), and Poloxamer 188 concentration (X_3). Each factor was studied at three different levels, coded as −1, 0, and +1. Total lipid concentration was varied from 2 to 6% w/v, liquid lipid fraction from 10 to 30%, and Poloxamer 188 concentration from 0.5 to 2% w/v. Particle size (Y_1), polydispersity index (PDI) (Y_2), and entrapment efficiency (Y_3) were selected as dependent variables to evaluate the effect of the formulation variables. Particle size and PDI were considered critical parameters for assessing the physical characteristics and size distribution of the NLCs, whereas entrapment efficiency was used to determine the amount of crisaborole incorporated into the lipid matrix. During the optimization process, the amount of crisaborole (100 mg), type of solid lipid, type of liquid lipid, aqueous phase volume (50 mL), homogenization speed (15,000 rpm), homogenization time (15 min), probe sonication time (10 min), preparation temperature (70°C), and cooling condition (room temperature) were maintained constant to minimize the influence of processing variables on the formulation responses. The experimental runs generated by the BBD were prepared according to the hot emulsification –ultrasonication method. Following preparation, the NLC formulations were evaluated for particle size, PDI, and entrapment efficiency. The experimental response values were entered into the software and analyzed using polynomial regression equations. The relationship between independent variables and dependent responses was evaluated through analysis of variance (ANOVA), response surface plots, and three-dimensional contour plots. The optimized formulation was selected based on the desirability function, considering minimum particle size and PDI along with maximum entrapment efficiency. The predicted responses of the optimized formulation were subsequently compared with the experimentally observed values to assess the adequacy and predictability of the developed optimization model.

2.2.3 Evaluation of Optimized Formulation (NLB-OPT 1)

2.2.3.1 Particle Size and Polydispersity Index

Particle size and size distribution (poly dispersity index) of the optimized Nano Lipid Carrier was determined by dynamic light scattering technique using Zetasizer version 7.13. The Nano Lipid Carrier were

dispersed in nonsolvent vehicle (DM water) and sample was scanned at 25°C± 1°C (15).

2.2.3.2 Transmission Electron Microscopy (TEM)

The morphology of optimized Crisaborole-loaded NLC was examined using Transmission Electron Microscopy (TEM). The suitably diluted NLC dispersion was placed on a TEM grid, dried, and observed at appropriate magnification (16).

2.2.3.3 % Entrapment Efficiency and % Yield

The entrapment efficiency (%EE) of optimized NLC was determined by separating the unentrapped drug from the NLC dispersion and estimating the amount of entrapped Crisaborole. The percentage yield was calculated by comparing the recovered formulation with the total quantity of materials used. Both parameters were determined in triplicate (17).

2.2.3.4 In Vitro Drug Release Study

The in-vitro drug release study was carried out using a suitable dissolution or diffusion apparatus. A measured quantity of the drug-loaded formulation was placed in the release medium and maintained at a controlled temperature with continuous stirring. At predetermined time intervals (0–9 hours), aliquots of the release medium were withdrawn and replaced with an equal volume of fresh medium to maintain sink conditions (18). The amount of drug released was determined using a suitable analytical method, such as UV-visible spectrophotometry, at the specified wavelength. The cumulative percentage drug release was calculated at each time point. The experiment was performed in triplicate (N = 3), and the results were expressed as mean ± standard deviation (SD)(19).

2.2.3.5 Drug Release Kinetics

The drug release data obtained from the in-vitro drug release study were fitted to different kinetic models to determine the drug release mechanism. The cumulative percentage of drug released at different time intervals was analyzed using zero-order, first-order, Higuchi, and Korsmeyer–Peppas models. The zero-order model describes drug release at a constant rate, while the first-order model relates drug release to the amount of drug remaining. The Higuchi model evaluates drug release based on diffusion, and the Korsmeyer–Peppas model helps characterize the release mechanism. The regression coefficient (R^2) was determined for each model, and the model with the highest (R^2) value was considered the best fit for the release data (20).

2.2.4 Gel Formulation of Nano Lipid Carrier (NLC)

Carbopol 940 was slowly dispersed in purified water and allowed to hydrate for 4–6 h. Propylene glycol containing the preservative was then added with gentle stirring. The optimized Crisaborole-loaded NLC dispersion was gradually incorporated into the hydrated gel base, followed by dropwise addition of triethanolamine to obtain gel consistency and adjust the pH to 5.0–6.0. Finally, purified water was added to achieve the required final weight, and the formulation was gently mixed and deaerated to obtain a smooth and homogeneous Crisaborole-loaded NLC gel (21).

Table 1: Formulation of Gel Containing Drug Loaded NLC

Sr. No.	Ingredient	Quantity for 100 g gel	Function
1	Optimized Crisaborole-loaded NLC	Quantity equivalent to 2.0 g Crisaborole	Drug-loaded lipid nanocarrier
2	Carbopol 940	1.0 g	Gelling agent
3	Propylene glycol	5.0 g	Humectant / co-solvent
4	Methyl paraben	0.10 g	Preservative
5	Triethanolamine	q.s.	Neutralization / pH adjustment
6	Purified water	q.s. to 100 g	Vehicle

2.2.5 Evaluation of Gel Formulation

2.2.5.1 Viscosity Analysis

The viscosity of Crisaborole-NLC gel was determined using a Brookfield viscometer. The gel sample was placed in the sample container and viscosity was measured using an appropriate spindle at a fixed rotational speed. Measurements were performed in triplicate and expressed as mean ± SD (cP)(22).

2.2.5.2 pH Analysis

The pH of the developed gel was determined using a calibrated digital pH meter. The electrode was immersed in the gel sample and the pH was recorded after stabilization. Measurements were performed in triplicate and expressed as mean ± SD (23).

2.2.5.3 Spreadability Analysis

The spreadability of the developed Crisaborole-NLC gel was determined using the glass-slide method. A fixed quantity of gel was placed between two glass slides and allowed to spread under a specified weight. The spread diameter was measured in cm, and measurements were performed in triplicate (24).

2.2.5.4 In-vitro Drug Release Study

The in-vitro drug release study of the formulated gel was performed using a Franz diffusion cell fitted with a suitable dialysis membrane (25). The membrane was soaked in the appropriate medium before use and mounted between the donor and receptor compartments. A measured quantity of gel was placed in the donor compartment, while the receptor compartment was filled with a suitable dissolution medium and maintained at 37 ± 0.5°C with continuous stirring. Samples were withdrawn from the receptor compartment at predetermined time intervals (0–9 hours) and replaced with an equal volume of fresh medium. The amount of drug released was estimated using a suitable analytical method, such as UV-visible spectrophotometry. The cumulative percentage drug release was calculated, and the experiment was performed in triplicate (N = 3)(26).

2.2.5.5 Stability Study

The prepared nanostructured lipid carrier (NLC)-containing gel was subjected to stability studies under specified storage conditions to evaluate its physical and chemical stability. The formulation was stored in well-closed containers at refrigerated temperature (4 ± 2°C) and room temperature (25 ± 2°C) for a predetermined period. At regular time intervals, the samples were evaluated for physical appearance, colour, odour, homogeneity, pH, viscosity, and drug content. The particle size, polydispersity index (PDI), and zeta potential of the NLCs were also evaluated after suitable extraction or dispersion of the formulation, where feasible. The results were compared with the initial values to determine changes in formulation characteristics and assess the stability of the NLC-containing gel during storage (27).

RESULT AND DISCUSSION

3.1 Optimization of Crisaborole-Loaded Nanostructured Lipid Carriers Using Box–Behnken Design

The formulation of crisaborole-loaded nanostructured lipid carriers (NLCs) was optimized using a three-factor, three-level Box–Behnken design to investigate the influence of total lipid concentration (X_1), liquid lipid fraction (X_2), and Poloxamer 188 concentration (X_3) on particle size (Y_1), polydispersity index (PDI) (Y_2), and entrapment efficiency (Y_3). The experimental results demonstrated variation in all three responses with changes in the formulation composition, indicating that the selected independent variables influenced the characteristics of the prepared NLCs.

Table 2: BBD Results for Optimization of Crisaborole-Loaded Nanostructured Lipid Carriers

Std	Run	Total lipid (% w/v)	Liquid lipid fraction (%)	Poloxamer 188 (% w/v)	Particle size (nm)	PDI	Entrapment Efficiency (%)
1	1	2	10	1.25	210.3	0.315	68.12
3	2	2	30	1.25	171.6	0.215	78.96
4	3	6	30	1.25	241.8	0.355	85.79
8	4	6	20	2	219.7	0.325	86.79

Std	Run	Total lipid (% w/v)	Liquid lipid fraction (%)	Poloxamer 188 (% w/v)	Particle size (nm)	PDI	Entrapment Efficiency (%)
7	5	2	20	2	172.8	0.205	76.97
11	6	4	10	2	195.4	0.305	77.52
2	7	6	10	1.25	252.6	0.375	80.51
9	8	4	10	0.5	252.7	0.395	74.48
12	9	4	30	2	179.8	0.215	86.45
13	10	4	20	1.25	192.2	0.26	83.97
5	11	2	20	0.5	212.6	0.345	73.01
14	12	4	20	1.25	191.6	0.267	84.42
6	13	6	20	0.5	278.6	0.425	82.49
10	14	4	30	0.5	221.6	0.365	81.69

3.1.1 Effect on particle size

The particle size of the prepared NLC formulations ranged from 171.6 to 278.6 nm. The minimum particle size was observed in formulation 2, containing 2% w/v total lipid, 30% liquid lipid fraction, and 1.25% w/v Poloxamer 188. In contrast, formulation 13 exhibited the maximum particle size of 278.6 nm, with 6% w/v total lipid, 20% liquid lipid fraction, and 0.5% w/v Poloxamer 188. The results suggest that total lipid concentration and liquid lipid fraction influenced the particle size of the NLCs. An increase in total lipid concentration may contribute to the formation of larger lipid droplets because of the increased amount of dispersed lipid phase. The liquid lipid fraction may also influence the internal lipid matrix and the packing characteristics of the particles. Furthermore, the concentration of Poloxamer 188 may affect particle stabilization by reducing interfacial tension and providing steric stabilization. Lower surfactant concentrations may result in insufficient stabilization of the newly formed droplets, potentially contributing to particle aggregation and increased particle size.

3.1.2 Effect on polydispersity index

The PDI values of the prepared formulations ranged from 0.205 to 0.425, indicating variation in particle size distribution among the experimental batches. Formulation 5 exhibited the lowest PDI value of 0.205, whereas formulation 13 showed the highest PDI value of 0.425. The comparatively lower PDI values observed in certain formulations indicate a more uniform particle size distribution. Poloxamer 188 plays an important role in stabilizing lipid droplets during emulsification and preventing particle aggregation. An appropriate surfactant concentration may provide better coverage of the particle surface, resulting in a relatively homogeneous dispersion. However, variations in lipid concentration and liquid lipid fraction may also influence droplet formation and the uniformity of the resulting NLC dispersion. The observed differences in PDI demonstrate the importance of optimizing the lipid-to-surfactant ratio to obtain a uniform nanoparticulate system.

3.1.3 Effect on entrapment efficiency

The entrapment efficiency of the prepared NLC formulations ranged from 68.12 to 86.79%. The maximum entrapment efficiency of 86.79% was observed in formulation 4, containing 6% w/v total lipid, 20% liquid lipid fraction, and 2% w/v Poloxamer 188. The minimum entrapment efficiency of 68.12% was observed in formulation 1, containing 2% w/v total lipid, 10% liquid lipid fraction, and 1.25% w/v Poloxamer 188. The higher entrapment efficiency observed in formulations containing increased lipid concentration may be associated with the availability of a greater lipid matrix for incorporating the drug. The liquid lipid fraction can also influence the arrangement of the lipid matrix by creating structural imperfections, which may provide additional space for drug incorporation. In addition, Poloxamer 188 may contribute to the stabilization of the lipid dispersion and influence drug retention within the lipid matrix. The maximum entrapment efficiency obtained in formulation 4 indicates that the combination of lipid and surfactant concentrations played an important role in drug incorporation.

3.1.3.1 Model fitting and regression analysis

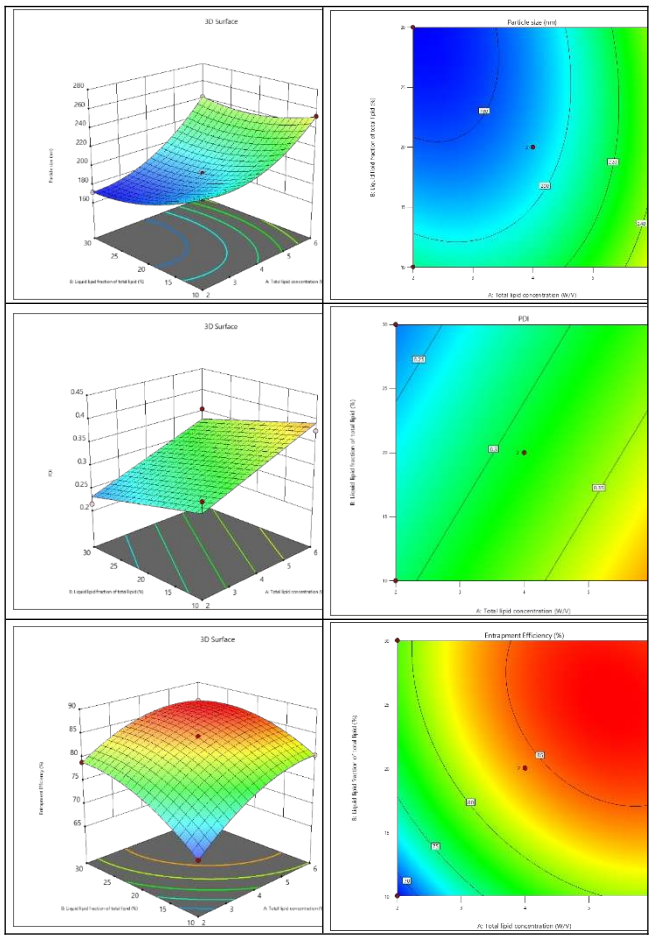
To evaluate the mathematical relationship between the independent variables-amount of Soy Phosphatidylcholine (X_1), amount of Poloxamer 188 (X_2), and amount of Sorbitol (X_3) and the selected critical quality attributes (CQAs), different polynomial models (linear, two-factor interaction [2FI], quadratic, and cubic) were fitted to the experimental response data (Table X). The selection of the most suitable mathematical model was governed by key diagnostic statistical metrics, including standard deviation (SD), coefficient of determination (R^2), adjusted R^2, predicted R^2, and the predicted residual error sum of squares (PRESS). A model demonstrating a low SD, high R^2 approaching unity, reasonable agreement between adjusted and predicted R^2 (difference < 0.2), and a minimized PRESS statistic was selected to ensure predictive accuracy.

Dependent Variable	Source	Std. Dev.	R^2	Adjusted R^2	Predicted R^2	PRESS	
Y1: PS	Linear	12.76	0.8839	0.849	0.8171	2565.75	
	2FI	13.54	0.9085	0.8301	0.7953	2871.31	
	Quadratic	**0.5477**	**0.9999**	**0.9997**	**0.9988**	**17.04**	**Suggested**
	Cubic	0.4243	1	0.9998		*	Aliased
Y2: PDI	Linear	0.0293	0.8669	0.827	0.7848	0.0139	
	2FI	0.0285	0.9118	0.8362	0.8326	0.0108	
	Quadratic	**0.0025**	**0.9996**	**0.9988**	**0.9985**	**0.0001**	**Suggested**
	Cubic	0.0049	0.9996	0.9951		*	Aliased
Y3: %EE	Linear	2.34	0.8638	0.823	0.7895	84.74	
	2FI	2.57	0.8849	0.7863	0.7344	106.92	
	Quadratic	**0.1793**	**0.9997**	**0.999**	**0.9979**	**0.8418**	**Suggested**
	Cubic	0.3182	0.9997	0.9967		*	Aliased

Table 3: Statistical Model Summary for Response Surface Optimization of Crisaborole NLC

For vesicle size (Y_1), the quadratic model was suggested as the optimal fit, showing an R^2 of 0.9999, adjusted R^2 of 0.9997, and predicted R^2 of 0.9988, accompanied by a markedly low standard deviation (0.5477) and PRESS value (17.04). The linear ($R^2 = 0.8839$) and 2FI ($R^2 = 0.9085$) models exhibited higher standard deviations (> 12.0) and elevated PRESS values (> 2500), indicating inadequate mathematical representation. Although the cubic model demonstrated high mathematical correlation ($R^2 = 1.0000$), it was found to be aliased due to insufficient degrees of freedom and was consequently rejected. Regarding the polydispersity index (Y_2), the quadratic model provided the highest statistical adequacy, yielding an R^2 of 0.9996, adjusted R^2 of 0.9988, and predicted R^2 of 0.9985, alongside minimal residual variance (SD = 0.0025; PRESS = 0.0001). The linear and 2FI alternatives were insufficient, exhibiting lower coefficients of determination ($R^2 = 0.8669$ and 0.9118, respectively). For entrapment efficiency (Y_3), the quadratic model demonstrated superior predictive capability over linear ($R^2 = 0.8638$) and 2FI ($R^2 = 0.8849$) models, achieving an R^2 of 0.9997, adjusted R^2 of 0.9990, and predicted R^2 of 0.9979, with an SD of 0.1793 and PRESS of 0.8418. Across all three measured responses (Y_1, Y_2, and Y_3), the selected quadratic models showed close concordance between predicted and adjusted R^2 values (differences < 0.002), confirming the absence of over-fitting and verifying the adequacy of the second-order polynomial equations to navigate the design space for formulation optimization.

Figure 1: Contour Plots and 3D Surface Plots for Response Y1, Y2 & Y3



The interactive effects of the independent formulation variables—total lipid concentration (Factor A, % w/v) and liquid lipid fraction of total lipid (Factor B, %)—on the critical quality attributes, namely particle size (Y_1), polydispersity index (Y_2), and entrapment efficiency (Y_3), were investigated using 3D response surface and 2D contour plots. The 3D response surface and 2D contour plots demonstrated the significant impact of total lipid concentration (Factor A) and liquid lipid fraction (Factor B) on the critical quality attributes of the nanocarriers. Elevating total lipid concentration from 2% to 6% w/v predominantly drove an increase in particle size (Y_1) from ~160 nm to >240 nm and broadened the polydispersity index (Y_2) from ~0.20 to >0.35 due to increased dispersion viscosity and reduced shearing efficiency during homogenization, whereas the liquid lipid fraction exerted negligible influence on size distribution. Conversely, both factors displayed a pronounced synergistic and quadratic effect on entrapment efficiency (Y_3), which rose markedly from ~65% to >85%; this enhancement is attributed to the expanded hydrophobic matrix volume at higher total lipid concentrations and increased crystal lattice imperfections induced by the liquid lipid fraction that prevent drug expulsion.

3.1.3.2 Checkpoint Analysis and Model Validation of Optimized Formulations

To validate the reliability and predictive capability of the established mathematical models, checkpoint analysis was performed by evaluating two independent optimized formulations (**NLC-OPT1** and **NLC-OPT2**) obtained through numerical optimization using a desirability function equal to 1. The experimental (observed) responses for particle size (PS), polydispersity index (PDI), and percentage entrapment efficiency (%EE) were compared with the software-predicted values to determine the percentage prediction error. For the primary optimized batch, **NLC-OPT1** (composed of 6% w/v total lipid concentration, 30% liquid lipid fraction, and 1.25% w/v Poloxamer 188), the observed values were found to be 239.89 nm for particle size, 0.325 for PDI, and 83.67 % for entrapment efficiency, in close concordance with the predicted values of 242.2 nm, 0.332, and 85.802 %, respectively. This resulted in low percentage prediction errors of 0.95% for PS, 2.10% for PDI, and 2.50% for %EE. Similarly, the second checkpoint formulation, **NLC-OPT2** (4% w/v total lipid concentration, 30% liquid lipid fraction, and 0.5% w/v Poloxamer 188), yielded observed values of 226.56 nm (predicted: 221.2 nm), 0.356 (predicted: 0.342), and 78.11 % (predicted: 81.63 %), corresponding to minimal prediction errors of 2.42%, 4.09%, and 4.31%, respectively. Across both test checkpoints, the percentage prediction errors for all evaluated critical quality attributes remained well within the acceptable threshold of < 5 %. The close agreement between the predicted and observed responses confirms the high predictive precision, robustness, and mathematical validity of the response surface optimization models for formulating the lipid nanocarrier system.

The overlay plot generated via Design-Expert® software delineated the operable design space satisfying the predetermined optimization criteria for the nanocarrier formulation, wherein the yellow-shaded region designates the acceptable space fulfilling all response constraints, while the grey area represents non-compliant formulation combinations. Graphical optimization identified an optimal coordinate situated within the demarcated design boundary at a total lipid concentration (X_1) of 2.06% w/v and a liquid lipid fraction of total lipid (X_2) of 28.70%, yielding a predicted particle size of 165.82 nm (with a 95% confidence interval ranging from 164.74 to 166.90 nm). The presence of a broad, continuous yellow zone underscores the robustness of the established mathematical models and confirms substantial processing flexibility for consistently fabricating nanoparticles within targeted critical quality specifications.

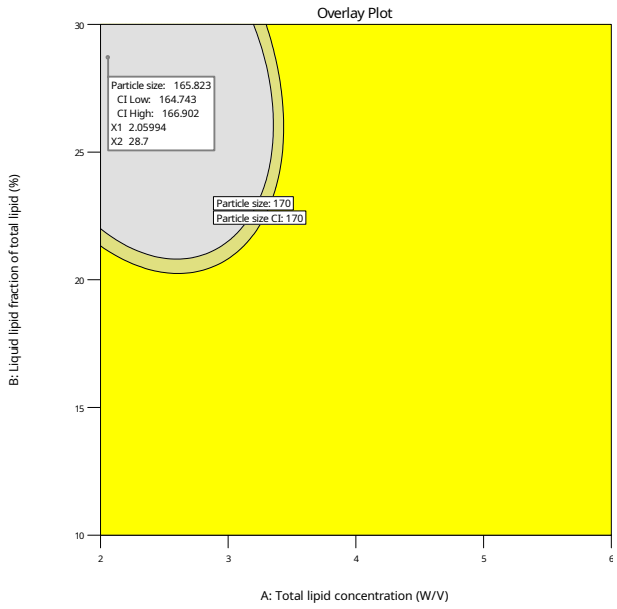


Figure 2: Overlay Plot

Batch Code	Total Lipid Concentration (% w/v)	Liquid Lipid Fraction (%)	Poloxamer 188 (% w/v)	Predicted			Observed			% Error			Desirability
				PS (nm)	PDI	EE (%)	PS (nm)	PDI	EE (%)	PS	PDI	% EE	
NLC-OPT1	**6**	**30**	**1.25**	**242.2**	**0.332**	**85.802**	239.89	0.325	83.67	0.95	2.1	2.5	**1**
NLC-OPT2	**4**	**30**	**0.5**	**221.2**	**0.342**	**81.63**	226.56	0.356	78.11	2.42	4.09	4.31	**1**
n = 3													

Table 4: Checkpoint Analysis and Optimized Batch

3.2 Evaluation of Optimized Crisaborole-Loaded Nanostructured Lipid Carriers

3.2.1 Particle Size and Polydispersity Index

The optimized Crisaborole-loaded NLC (NLC-OPT1) showed a mean particle size (Z-average) of 239.8 nm with a PDI of 0.325. The single major intensity peak indicates a predominantly unimodal particle-size distribution. The obtained particle size confirms the nanoscale nature of the optimized formulation, while the PDI indicates a moderately narrow and acceptable size distribution.

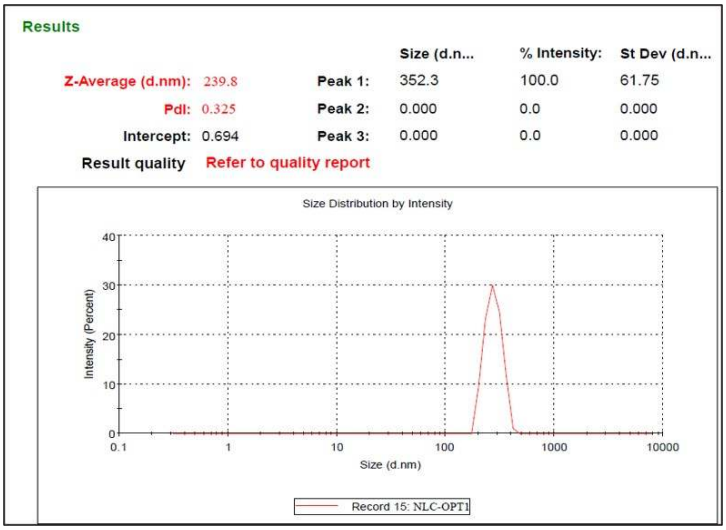


Figure 3: Particle Size and PDI

3.2.2 Transmission Electron Microscopy (TEM)

TEM revealed predominantly spherical to nearly spherical nanosized particles with distinguishable boundaries. Some particle association was observed, which may be attributed to sample drying during TEM preparation. Overall, the image confirmed the successful formation of Crisaborole-loaded NLCs with nanoscale morphology.

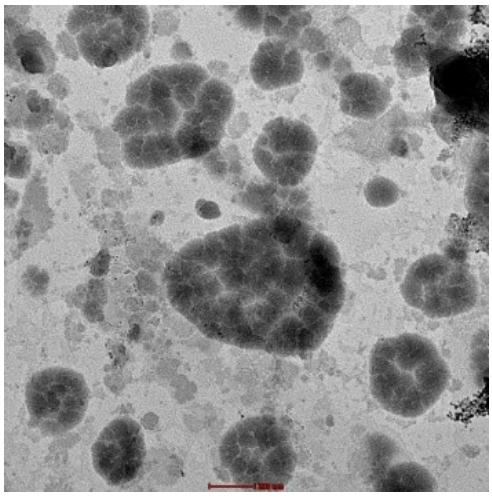


Figure 4: TEM Image of Optimized Crisaborole-loaded NLCs

3.2.3 % Entrapment Efficiency and % Yield

The optimized NLC showed an entrapment efficiency of 83.67 ± 1.01%, indicating effective incorporation of Crisaborole within the lipid matrix. A percentage yield of 91.62 ± 1.56% demonstrated good formulation recovery with minimal processing loss. Overall, the results indicate satisfactory drug entrapment and reproducibility of the optimized NLC formulation.

Table 5: Result of % Entrapment Efficiency

Batch	% Entrapment Efficiency			Mean	SD
OPT1	83.56	84.96	82.5	83.67333	1.007483
Result of % Yield					
OPT1	91.56	89.74	93.56	91.62	1.560085

3.2.4 In Vitro Drug Release Study

The drug release study showed a progressive increase in cumulative drug release with time, reaching 9.56 ± 3.56% at 1 hour and 92.56 ± 4.23% at 9 hours (N = 3). The maximum drug release was observed at 9 hours, indicating sustained drug release over the study period. The results are expressed as mean ± standard deviation (SD), demonstrating variability among the three replicates.

Table 6: Result of in Vitro Drug Release Study

Time (hr)	Mean	SD
0	0	0
1	9.56	3.56
2	25.82	4.56
3	36.44	2.65
4	48.24	2.74
5	57.96	4.69
6	64.87	5.64
7	76.94	2.95

Time (hr)	Mean	SD
8	86.56	5.32
9	92.56	4.23
N = 3		

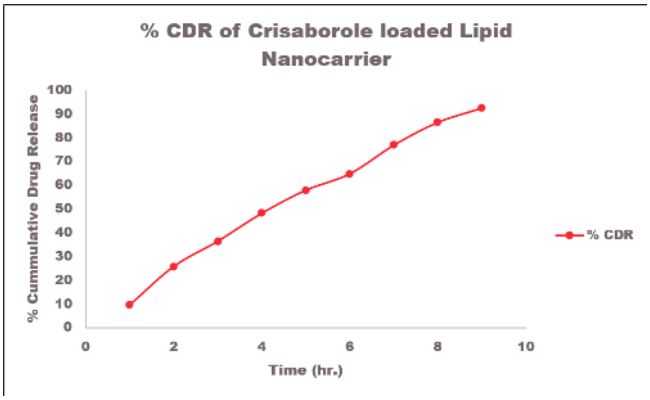


Figure 5: Result of in Vitro Drug Release Study

3.2.5 Drug Release Kinetics

The Korsmeyer–Peppas model showed the highest R^2 value (0.9949), indicating the best fit among the evaluated kinetic models. The release exponent n = 0.876 suggests anomalous/non-Fickian transport, indicating that Crisaborole release was likely governed by a combination of drug diffusion and matrix-related processes.

Table 7: Result of Drug Release Kinetics

Batch	Zero order	First order	Higuchi	K-P	H-C	
	R2	R2	R2	R2	n	R2
In-vitro Drug Release Study						
CR-NLCs	0.9846	0.9395	0.8617	0.9949	0.876	0.9743

3.3 Evaluation of Gel Formulations

3.3.1 Viscosity Analysis of Developed Gel

The NLC gel showed viscosities of 1952.90 ± 2.59 cP. The viscosity value indicate that formulation possessed uniform and suitable consistency for topical application, with minimal variability among replicate measurements.

3.3.2 pH Analysis of Developed Gel

The mean pH values of the NLC gel was 7.19 ± 0.05. The formulation showed near-neutral with low variability among replicate measurements, indicating consistent pH characteristics of the developed gel formulations.

3.3.3 Spreadability Analysis of Developed Gel

The spreadability of the NLC gel was 25.67 ± 0.45 cm. The formulation exhibited good spreading characteristics, indicating their ability to spread easily over the skin surface and supporting their suitability for topical application.

3.3.4 In-vitro Drug Release Study

In-vitro drug release was evaluated over 10 h and expressed as cumulative drug release (% CDR). The Crisaborole-NLC gel showed 96.23% release at 10 h. The formulation demonstrated a gradual and sustained drug-release profile over the study period.

Table 8: Result of In-Vitro Drug Release Study of Gel

Time (Hr.)	Crisa NLC Gel
1	4.97
2	14.63
3	25.96
4	40.88
5	54.63

Time (Hr.)	Crisa NLC Gel
6	69.89
7	74.56

Time (Hr.)	Crisa NLC Gel
8	85.56
10	96.23

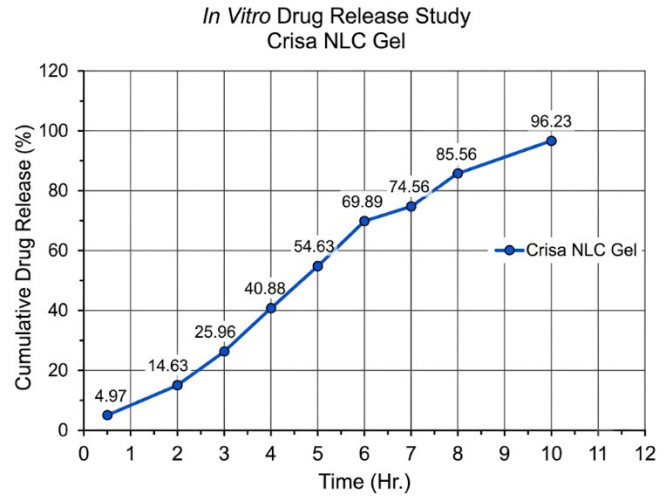


Figure 6: Result of In-Vitro Drug Release Study of Gel

3.3.5 Stability Study for Proliposomes gel

The optimized Crisaborole-NLC gel was stored at 40 ± 2°C/75 ± 5% RH for 3 months and evaluated for stability parameters. The formulation remained smooth and homogeneous, with only minor changes in pH, viscosity and spreadability. The f_2 value of 84.70 confirmed similarity of the drug-release profiles, indicating satisfactory stability after 3 months.

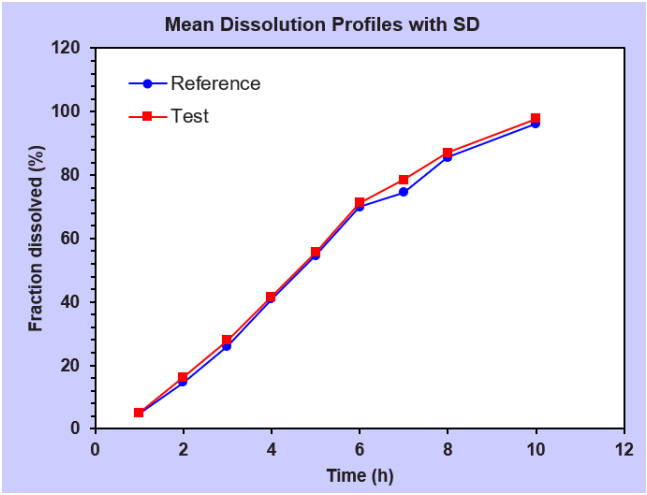


Figure 7: Similarity Factor for NLC Gel

CONCLUSION

The present study successfully engineered and optimized a Crisaborole-loaded nanostructured lipid carrier (NLC) topical gel system to overcome the aqueous solubility and dermal retention constraints of Crisaborole. Application of the Box–Behnken experimental design permitted systematic mapping of formulation parameters, identifying an optimal lipid and surfactant architecture that imparted favorable nanoscale attributes, narrow polydispersity, and robust drug encapsulation exceeding 83%. Transmission electron microscopy substantiated the formation of uniform, spherical nanoparticles. Incorporation of the colloidal NLC dispersion into a Carbopol 940 hydrogel vehicle produced a topically suitable formulation exhibiting

desirable consistency, skin-compatible near-neutral pH, and superior spreadability. The developed NLC gel sustained the release of Crisaborole over 10 hours (achieving 96.23% cumulative release) via an anomalous diffusion-controlled mechanism. Furthermore, the formulation preserved its structural homogeneity and release characteristics under accelerated stability testing for 3 months, as evidenced by an f_2 metric of 84.70. Consequently, the Crisaborole-loaded NLC gel stands as a viable, stable, and clinically promising lipid-based topical platform for the prolonged management of mild-to-moderate atopic dermatitis and related inflammatory dermatoses.

Conflict of interest

The authors disclose that they have no conflicting financial interests.

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