RESEARCH PAPER

Development and Optimization of Crisaborole-Loaded Ethosomes for Enhanced Topical Delivery: Formulation, Characterization and In-Vitro Performance Evaluation

Prathamesh Chaudhari[1], Dr Mital Patani[1*], Dr Bhavna Nangha[3], Harshal Sonawane[1], Ajay Patel[1], Aadil Bokada[1], Dr Siddhi Upadhyay[2]

[1]Sigma Institute of Pharmacy, Sigma University, Vadodara, Gujarat, India-390019
[2]Director, Faculty of Pharmacy, Sigma University, Vadodara, Gujarat, India-390019
[3]Principal, Varsha Goswami College of Pharmacy, Monark University, Vahelal, Gujarat, India-382330

ABSTRACT

Crisaborole, a topical phosphodiesterase-4 (PDE-4) inhibitor, is used to treat inflammatory skin disorders like atopic dermatitis. However, traditional topical formulations often face challenges in penetrating the stratum corneum, limiting drug availability in deeper skin layers. This study aimed to develop and optimize Crisaborole-loaded Ethosomes incorporated into a topical gel to enhance skin permeation and achieve sustained drug release.

Ethosomes were prepared via the cold method by varying phospholipid and ethanol concentrations. Formulations were optimized based on drug content, entrapment efficiency (%EE), and cumulative drug release (%CDR). The optimized ethosomes demonstrated a high entrapment efficiency of 97.43% and satisfactory drug content, indicating effective drug incorporation into vesicular carriers. Morphological and stability assessments confirmed the robustness of the optimized formulation. The ethosomal formulation was incorporated into a gel, which was evaluated for pH, viscosity, spreadability, drug content, and in vitro release. The gel exhibited a pH of 6.55, compatible with skin, suitable viscosity for topical application, and good spreadability, supporting patient acceptability. In vitro release studies revealed sustained drug release, with approximately 90.67% of the drug released over 12 hours. Stability studies showed minimal changes in physicochemical properties and drug release after 30 days at room temperature.

These findings suggest that the Crisaborole-loaded ethosomal gel is a promising topical delivery system that enhances dermal penetration and provides sustained release, potentially improving therapeutic outcomes and patient compliance in managing inflammatory skin conditions.

Keywords: NA

How to cite this article: Chaudhari P, Patani M, Nangha B, Sonawane H, Patel A, Bokada A, Upadhyay S. Development and Optimization of Crisaborole-Loaded Ethosomes for Enhanced Topical Delivery: Formulation, Characterization and In-Vitro Performance Evaluation. Int J Drug Deliv Technol. 2026;16(23s): 261-275. DOI: 10.25258/ijddt.16.23s.27.

Source of support: Nil

Conflict of interest: None

INTRODUCTION

Topical drug delivery remains a preferred route for the management of dermatological disorders due to its localized action, reduced systemic exposure, and improved patient compliance. However, its effectiveness is significantly hindered by the barrier properties of the stratum corneum, which limits drug penetration into deeper skin layers (1,2). Consequently, conventional topical formulations often fail to achieve adequate therapeutic concentrations at the target site.

To address these limitations, various advanced drug delivery systems such as liposomes, niosomes, transferosomes, and microsponges have been investigated (3,4,16). Among these, vesicular and nano-based carriers have demonstrated significant potential in enhancing dermal permeation and sustaining drug release. Recent studies have further highlighted the effectiveness of nanoemulgels and proniosomal systems in improving drug bioavailability and patient compliance in topical therapy (19–21).

Ethosomes, a modified lipid-based vesicular system containing high ethanol content, have emerged as promising carriers for transdermal and dermal delivery. Ethanol enhances membrane fluidity and disrupts the lipid organization of the stratum corneum, thereby facilitating deeper penetration of vesicles (5–7). In addition, the synergistic interaction between phospholipids and ethanol improves vesicle deformability, enabling efficient drug delivery across skin layers.

Crisaborole, a non-steroidal phosphodiesterase-4 (PDE-4) inhibitor, is widely used for the treatment of inflammatory skin disorders such as atopic dermatitis (8,9). Despite its therapeutic potential, its limited penetration through the skin restricts its clinical efficacy. Recent formulation strategies, including microsponges and QbD-based optimized systems, have emphasized the importance of controlled and targeted drug delivery for improving therapeutic outcomes (15,16).

Therefore, the present study focuses on the development and optimization of a Crisaborole-loaded ethosomal gel to enhance dermal penetration and achieve sustained drug release. This approach aims to overcome the limitations of conventional topical formulations and provide an effective and patient-compliant delivery system.

MATERIALS AND METHODS

Materials

Crisaborole was used as the active pharmaceutical ingredient (API). Soya lecithin was used as the phospholipid for vesicle formation and ethanol served as the alcohol phase for ethosome preparation. Cholesterol was incorporated as a stabilizer to improve vesicular membrane rigidity and formulation stability. Propylene glycol was used as a polyol to enhance solubilization and improve formulation characteristics. For preparation of the ethosomal gel, Sangelose 60L was used as the gelling agent and triethanolamine was used for pH adjustment.

Equipment

An electronic weighing balance (US-300, Cyber Lab, USA) was used for accurate weighing of drug and excipients. UV–Visible spectrophotometric analysis was carried out using a UV-1800 spectrophotometer (Shimadzu Corporation) for determination of λmax, preparation of calibration curve, and estimation of drug content. A magnetic stirrer (Remi Equipments Pvt. Ltd.) was used during formulation development. A humidity cabinet (Analytical Technologies) was used for stability storage conditions. Surface morphology of the optimized ethosomes was examined using scanning electron microscopy. FT-IR analysis was performed using an FT-IR spectrophotometer (Shimadzu Corporation) for drug identification and compatibility studies. In-vitro release studies were conducted using a USP dissolution apparatus (Electrolab, TDT-08L). Vesicle size and polydispersity index were determined using a Malvern particle size analyzer (Malvern Instruments Ltd.). Viscosity of the developed gel was measured using a Brookfield viscometer (DV-E viscometer).

Methodology

Preformulation Studies

Preformulation studies were performed to generate essential physicochemical data required for the development of a stable and reproducible topical dosage form.

Organoleptic Evaluation

Crisaborole was evaluated visually for organoleptic properties such as colour, appearance, and odour.

Melting Point Determination

The melting point of Crisaborole was determined using the capillary method. A small quantity of drug was filled into a capillary tube and the melting point was recorded using a melting point apparatus.

Solubility Study

Solubility of Crisaborole was evaluated in different solvents including water, acetone, ethanol, chloroform, ether, and phosphate buffer (pH 7.4). Excess drug was added into glass vials containing 20 mL of each solvent system and kept for 24 h at room temperature. The samples were filtered through a 0.45 µm membrane filter. The filtrate was suitably diluted and analyzed using UV–Visible spectrophotometry at 296 nm.

Partition Coefficient

The partition coefficient of Crisaborole was determined using n-octanol and phosphate buffer (pH 7.4). Both phases were mutually saturated by keeping them in contact for 24 h in a separating funnel. A known quantity of drug (10 mg) was added and the system was intermittently shaken for 4 h. The phases were allowed to separate and drug concentration in each phase was determined spectrophotometrically at 296 nm.

Determination of λmax

A stock solution of Crisaborole was prepared by dissolving 100 mg of drug in 100 mL methanol. From this, 1 mL was further diluted to 100 mL to obtain a working solution. Serial dilutions in the concentration range of 2–10 µg/mL were prepared and scanned between 200–400 nm using a double-beam UV–Visible spectrophotometer to determine λmax.

Preparation of Calibration Curve

A stock solution was prepared by dissolving 100 mg of Crisaborole in a small quantity of methanol, followed by sonication and dilution up to 100 mL with phosphate buffer (pH 7.4). Serial dilutions were prepared in the concentration range of 2–10 µg/mL. Absorbance values were recorded at 296 nm and a calibration curve was constructed by plotting concentration versus absorbance. The correlation coefficient (R^2) was calculated to confirm linearity.

FT-IR Spectroscopy (Drug Identification)

FT-IR analysis was performed using the KBr pellet method. A small quantity of drug was mixed with potassium bromide and compressed into a pellet using a hydraulic press. The sample was scanned in the range of 4000–400 cm^{-1} and the obtained spectrum was compared with the reference spectrum of Crisaborole.

Drug–Excipient Compatibility Studies
Compatibility between Crisaborole and excipients was evaluated using FT-IR and DSC. For FT-IR analysis, a physical mixture of drug and phospholipid was prepared and scanned using the KBr pellet method. DSC thermograms of drug and excipients were recorded to evaluate any changes in melting behaviour and possible interaction.

Particle Size Analysis of Drug
Particle size analysis of pure Crisaborole was carried out using optical microscopy and Malvern particle size analysis.

Preparation of Crisaborole-Loaded Ethosomes (Cold Method)
Crisaborole-loaded ethosomes were prepared by the cold method. The drug and phospholipid were dissolved in ethanol under continuous stirring in a closed vessel at room temperature. Propylene glycol was added during stirring and the mixture was maintained at approximately 30°C. The aqueous phase, preheated to the same temperature, was added slowly to the ethanolic phase with continuous stirring to form ethosomal vesicles. Vesicle size was reduced using sonication or extrusion and the prepared ethosomes were stored under refrigerated conditions until further use.

Characterization of Crisaborole Ethosomes
Vesicle Size and Polydispersity Index (PDI)
The mean vesicle size and PDI of the prepared ethosomes were determined using a particle size analyzer. The ethosomal dispersion was diluted with distilled water and measurements were performed at room temperature in triplicate.

Entrapment Efficiency (%EE)
Entrapment efficiency was determined by the centrifugation method. The ethosomal dispersion was centrifuged to separate unentrapped drug in the supernatant. The amount of drug entrapped within vesicles was calculated based on drug estimation of the separated phases.

Scanning Electron Microscopy (SEM)
Morphology of the optimized ethosomal formulation was examined using scanning electron microscopy to confirm vesicle structure and surface characteristics.

In-Vitro Drug Release Study
In-vitro drug release was performed using the dialysis membrane method. Ethosomal samples were placed into dialysis bags and immersed in dissolution medium maintained at 37 ± 0.5°C with stirring at 100 rpm using USP dissolution apparatus. Aliquots were withdrawn at predetermined time intervals and replaced with fresh medium to maintain sink conditions. Samples were diluted appropriately and analyzed spectrophotometrically.

Preparation of Crisaborole Ethosomal Gel
Ethosomal gel was prepared by dispersing a measured quantity of Sangelose 60L in a minimum amount of water and allowing it to swell for 1 h. The optimized ethosomal dispersion was incorporated into the swollen gel base under continuous stirring (700 rpm) while maintaining the temperature at approximately 30°C until a uniform gel was obtained. The pH was adjusted using triethanolamine and the final formulation was subjected to ultrasonication.

Evaluation of Crisaborole Ethosomal Gel
The ethosomal gel was evaluated for pH, spreadability, viscosity, and visual appearance (colour, homogeneity, texture). Stability was assessed at room temperature by monitoring changes in physicochemical properties and drug content at predetermined intervals.

RESULT
Preformulation Studies of Crisaborole
Preformulation studies were carried out to evaluate the physicochemical properties of Crisaborole required for the development of a stable and effective topical ethosomal gel formulation. The studies included organoleptic characterization, melting point determination, solubility analysis, and partition coefficient determination.

Organoleptic Characteristics
Crisaborole was observed as a solid drug substance with a white crystalline powder appearance and a characteristic odour. These observations confirm the physical identity and purity of the drug sample and indicate its suitability for further formulation development.

Melting Point Determination
The melting point of Crisaborole was determined using the capillary method. The observed melting point range was found to be **130–132°C**, which is in close agreement with the reported standard melting point range (**128–134°C**). This confirms the authenticity of the drug and indicates no significant impurity or degradation.

Solubility Study
Solubility studies were performed in different solvents to understand the drug's dissolution behaviour and to assist in solvent selection for analytical and formulation purposes. Crisaborole was found to be very slightly soluble in water (0.053 ± 0.04 mg/mL), indicating poor aqueous solubility. However, the drug showed good solubility in physiological and acidic media such as phosphate buffer pH 7.4 (2.54 ± 0.03 mg/mL) and 0.1N HCl (2.47 ± 0.02 mg/mL). Crisaborole exhibited high solubility in organic solvents, being freely soluble in acetone (12.26 ± 0.038 mg/mL) and methanol (14.35 ± 0.04 mg/mL). These results suggest that Crisaborole is a lipophilic drug with limited water solubility, supporting the need for advanced carrier systems such as ethosomes for improved topical delivery.

Partition Coefficient

The partition coefficient (log P) of Crisaborole was determined using the n-octanol/phosphate buffer (pH 7.4) system. The observed log P value was found to be 3.34, which matches the reported value. Lipophilicity is an important parameter influencing membrane permeation, drug flux, and overall pharmacokinetic behaviour. Since the stratum corneum is lipophilic in nature, a drug with an optimal log P is expected to demonstrate improved skin permeation. The obtained log P value indicates that Crisaborole possesses favourable lipophilicity for transdermal or dermal penetration, supporting its suitability for topical delivery enhancement through ethosomal carriers.

Identification and Determination of Wavelength max (λmax) of Crisaborole:

1000 µg/mL Stock solution of Crisaborole in methanol is prepared. This solution is diluted further to make a 100µg/mL solution. 1mL is taken and adjusted to a concentration of 10µg/mL before being scanned between 200 and 400 nm. The wavelength maxima (λmax) of Crisaborole was determined using UV–Visible spectrophotometry. The drug showed maximum absorbance at 252 nm, which was consistent with the reported (actual) λmax value. (Figure:1) Therefore, 252 nm was selected as the analytical wavelength for further quantitative estimation of Crisaborole.

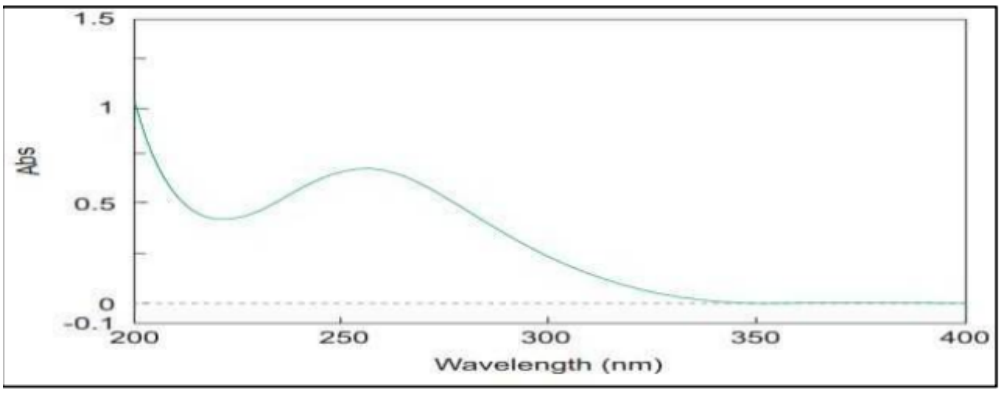

Figure:1 Wavelength max (λmax) of Crisaborole

Preparation of calibration curve of Crisaborole:

A calibration curve of Crisaborole was prepared in the concentration range of 2–6 µg/mL. (Figure-2) The absorbance values increased proportionally with concentration, indicating a linear relationship suitable for quantitative analysis. The recorded absorbance values were 0.258, 0.424, 0.550, 0.638, and 0.759 for concentrations of 2, 3, 4, 5, and 6 µg/mL, respectively. This confirms that the method is appropriate for estimation of Crisaborole in further formulation studies.

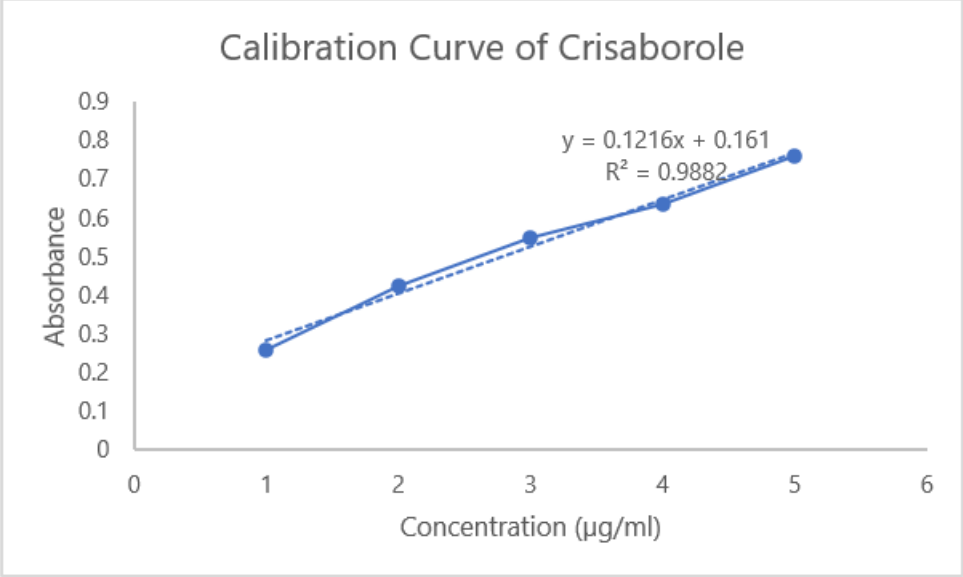

Figure:2 Calibration Curve of Crisaborole

Identification of Crisaborole by FT-IR Spectroscopy

Fourier transform infrared (FT-IR) spectroscopy was performed to confirm the identity and purity of Crisaborole. A potassium bromide (KBr) pellet was prepared using approximately 1 mg of Crisaborole and compressed using a hydraulic pellet press. The sample was scanned in the range of 4000–400 cm^{-1}, and the obtained spectrum was compared with the standard reference spectrum.

The FT-IR spectrum of Crisaborole showed characteristic peaks corresponding to functional group vibrations, confirming the presence of the drug. (Figure:3) The spectrum exhibited major absorption bands at 2847.68 cm^{-1} (O–H stretching region), 2199.12 cm^{-1} (C–H stretching region), 1192.74 cm^{-1} (C=O stretching region), and 678.37 cm^{-1} (C=C vibration region). The observed peaks were found to be consistent with reported standard values, thereby confirming the identity and purity of Crisaborole used for further formulation studies.

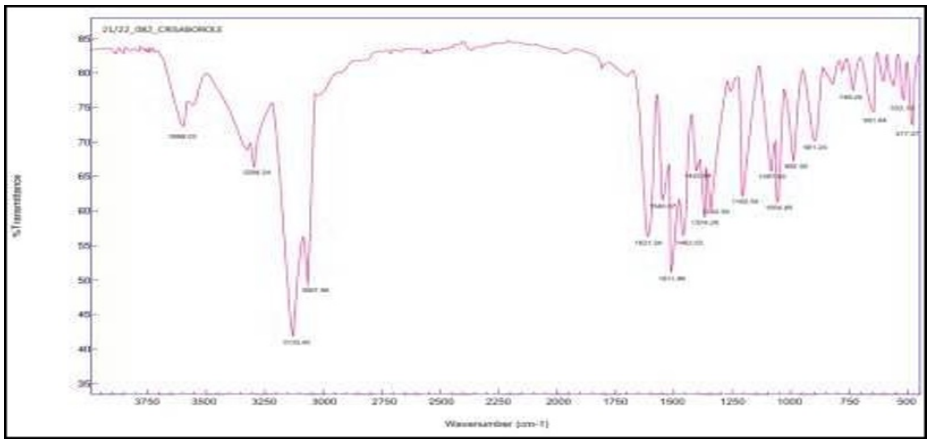

Figure 3: FTIR of Crisaborole

Differential Scanning Calorimetry (DSC) of Crisaborole

Differential scanning calorimetry (DSC) was performed to confirm the thermal behaviour, identity, and purity of Crisaborole. (Figure:4) The DSC thermogram of Crisaborole showed a characteristic endothermic peak corresponding to its melting point, which was found to agree with the reported standard data. The absence of additional unexpected peaks indicated that the drug sample was pure and suitable for further formulation development.

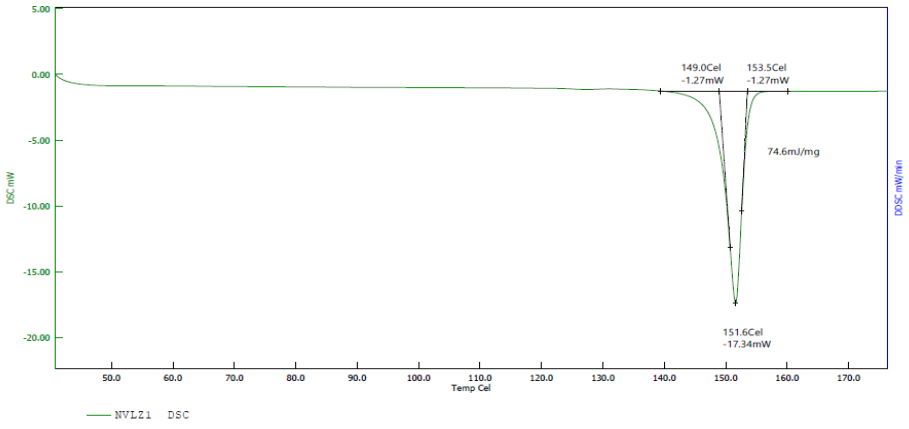

Figure 4: Differential Scanning Calorimetry of Crisaborole

Particle Size Study of Crisaborole- API:

The particle size analysis suggests that Crisaborole API has an average size in the submicron range but shows broad distribution and aggregation, as supported by the high PDI and multiple peaks. This justifies the need for a vesicular carrier system (ethosomes) to improve drug dispersion, stability, and skin penetration. (Figure-5)

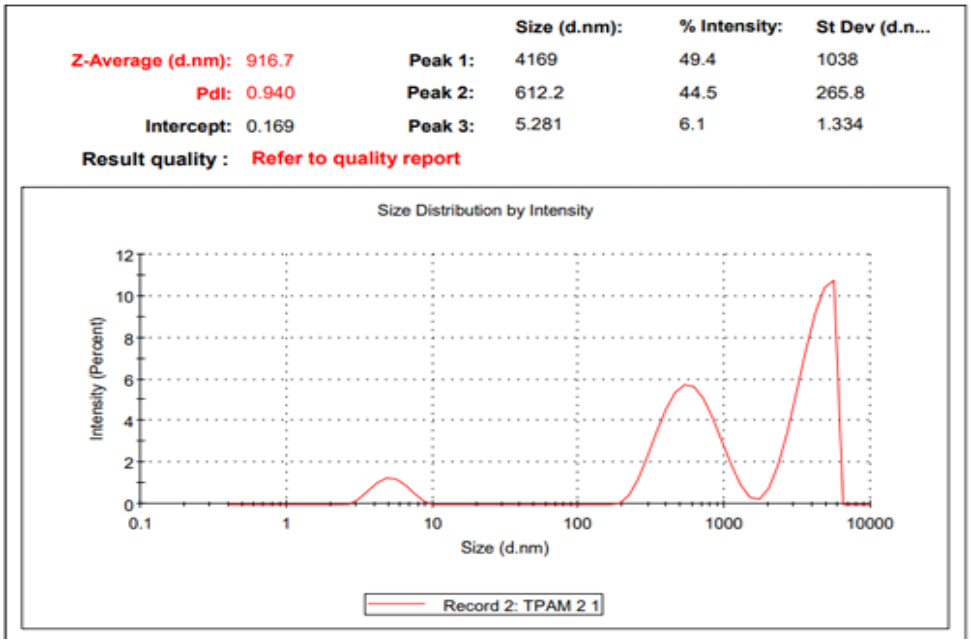

Figure 5: Particle Size Study

Preliminary Trial Batch of Crisaborole loaded ethosomes

Table 1: Preliminary Trial Batch of Crisaborole loaded ethosomes

Batch	Conc. Of Phospholipid (W/V)	Ethanol (V/V)	Cholesterol (W/V)	Propylene Glycol (V/V)	Composition Ethanol: IPA (V/V)	Distilled water (V/V)
Selection of Conc. Of Phospholipid						
CRE 1	0.5 %	1%	0.2%	1%	1:1	q. s
CRE 2	1%	1%	0.2%	1%	1:2	q. s
CRE 3	1.5%	1%	0.2%	1%	1:1	q. s
CRE 4	2%	1%	0.2%	1%	1:1	q. s
CRE 5	2.5 %	1%	0.2%	1%	1:2	q. s
Selection of conc. Of Ethanol						
CRE 6	2%	1%	0.2%	1%	1:1	q. s
CRE 7	2%	2%	0.2%	1%	2:1	q. s
CRE 8	2%	3%	0.2%	1%	3:1	q. s

CRE 9	2%	4%	0.2%	1%	1:1	q. s
CRE 10	2%	5%	0.2%	1%	2:1	q. s
Selection of conc. Of Cholesterol						
CRE 11	2%	1%	0.1%	1%	1:1	q. s
CRE 12	2%	1%	0.2%	1%	1:1	q. s
CRE 13	2%	1%	0.3%	1%	1:1	q. s
CRE 14	2%	1%	0.4%	1%	1:1	q. s
CRE 15	2%	1%	0.5%	1%	1:1	q. s
Selection of conc. Of Propylene Glycol						
CRE 16	2%	1%	0.2%	1%	1:1	q. s
CRE 17	2%	1%	0.2%	2%	1:1	q. s
CRE 18	2%	1%	0.2%	3%	1:1	q. s
CRE 19	2%	1%	0.2%	4%	1:1	q. s
CRE 20	2%	1%	0.2%	5%	1:1	q. s

Characterization of Preliminary Trial Batch

Table 2: Selection of Conc. Of Phospholipid

Batch	% Drug Content	EE(%)	% CDR
CRE 1	94.26	92.56	84.68
CRE 2	94.68	96.28	85.68
CRE 3	95.59	97.43	93.68
CRE 4	86.67	95.85	90.35
CRE 5	87.95	96.71	91.68

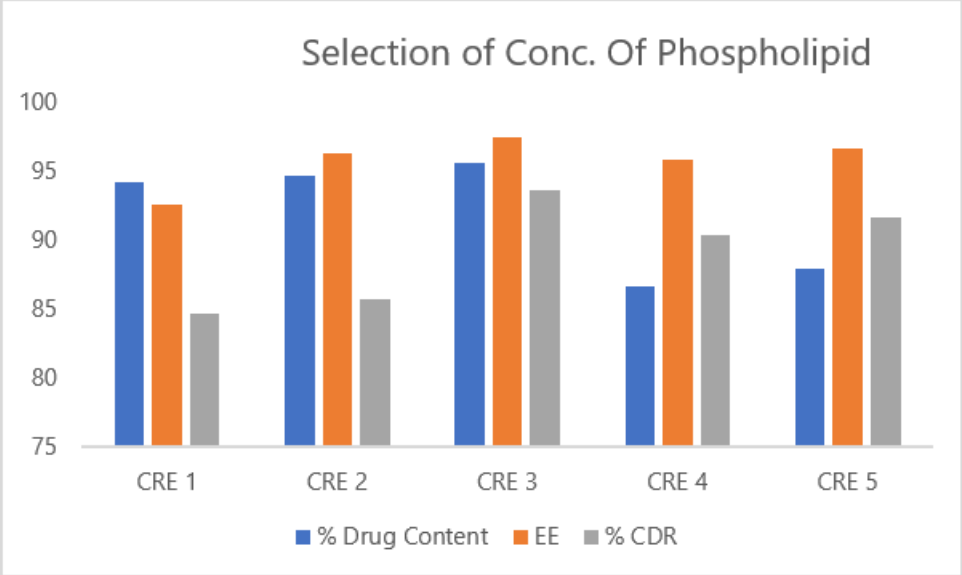

Figure 6: Selection of Conc. Of Phospholipid

The data for the five CRE batches indicate the formulation performance in terms of drug content, encapsulation efficiency (EE), and cumulative drug release (% CDR). The % drug content of the batches ranges from 86.67% to 95.59%, reflecting slight variations in the uniformity of drug incorporation during preparation. Batches CRE 1, CRE 2, and CRE 3 show higher drug content (>94%), whereas CRE 4 and CRE 5 exhibit relatively lower values (≈87%), suggesting minor inconsistencies in drug loading. The encapsulation efficiency is consistently high across all batches, ranging from 92.56% to 97.43%, indicating effective entrapment of the drug within the carrier system. Regarding the % CDR, which measures the extent of drug released, values range from 84.68% to 93.68%, with CRE 3 showing the highest release and CRE 1 the lowest. Overall, the data suggest that while all batches demonstrate satisfactory drug encapsulation and release, CRE 3 appears to provide the optimal combination of high drug content, maximum encapsulation efficiency, and superior cumulative drug release. Minor variations among batches are likely due to differences in formulation handling or process parameters.

Table 3: Selection of conc. Of Ethanol

Batch	% Drug Content	EE (%)	% CDR
CRE 6	89.35	96.36	90.35
CRE 7	87.68	87.79	88.67
CRE 8	89.68	91.65	86.59
CRE 9	85.68	90.51	84.26
CRE 10	86.69	90.35	90.35

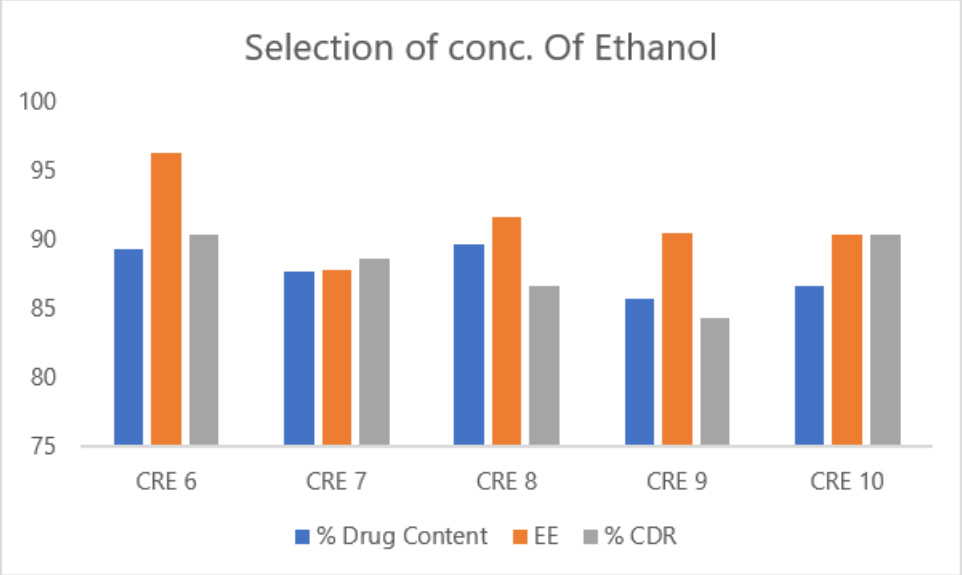

Figure 7: Selection of conc. Of Ethanol

The data for batches CRE 6 to CRE 10 reflect their performance in terms of drug content, encapsulation efficiency (EE), and cumulative drug release (% CDR). The % drug content ranges from 85.68% to 89.68%, showing slightly lower drug incorporation compared to earlier batches, with CRE 9 having the lowest drug content. Encapsulation efficiency varies from 87.79% to 96.36%, with CRE 6 exhibiting the highest EE, indicating effective drug entrapment, whereas CRE 7 shows the lowest, suggesting some inefficiency in encapsulation. The % CDR values range from 84.26% to 90.35%, demonstrating good but moderate drug release across the batches, with CRE 6 and CRE 10 showing the highest release. Overall, these batches display acceptable formulation characteristics, although CRE 6 stands out for combining relatively high drug content, maximum encapsulation efficiency, and favorable drug release, making it potentially the most efficient among this set. Slight variations among batches are likely due to minor differences in preparation or processing conditions.

Table 4: Selection of conc. of Cholesterol

Batch	% Drug Content	EE(%)	% CDR
CRE 11	84.36	91.26	90.35
CRE 12	86.57	92.35	91.02
CRE 13	82.35	90.26	87.68
CRE 14	81.36	93.35	89.68
CRE 15	87.68	94.26	87.59

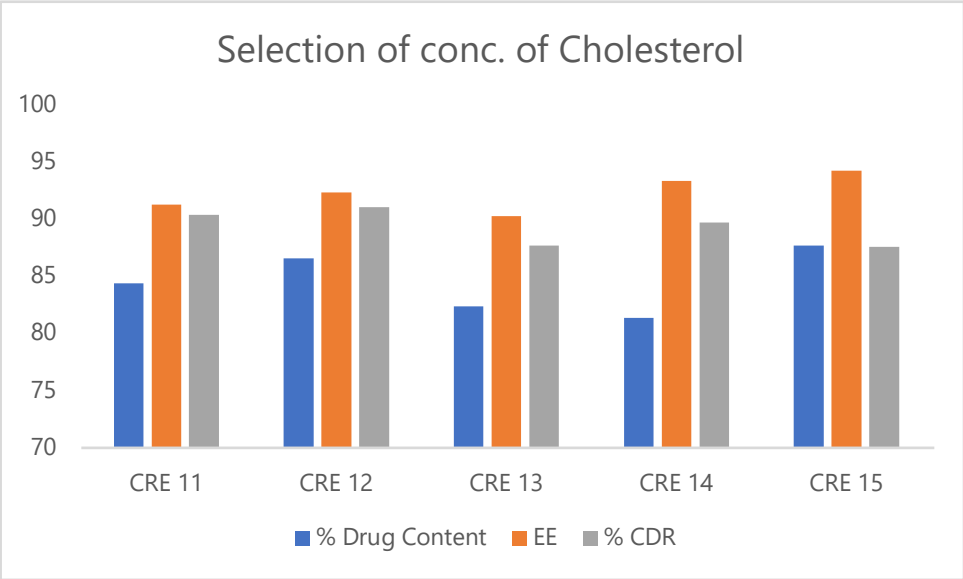

Figure 8: Selection of conc. of Cholesterol

The data for batches CRE 11 to CRE 15 indicate their performance in terms of % drug content, encapsulation efficiency (EE), and cumulative drug release (% CDR). The % drug content ranges from 81.36% to 87.68%, showing slightly lower drug incorporation in some batches, with CRE 14 having the lowest drug content. Encapsulation efficiency is consistently high, ranging from 90.26% to 94.26%, indicating effective drug entrapment in all batches. The % CDR values vary between 87.59% and 91.02%, suggesting satisfactory drug release, with CRE 12 showing the highest release and CRE 15 the lowest. Overall, while minor variations exist among batches, all formulations demonstrate acceptable encapsulation and drug release characteristics, with CRE 12 appearing to be the most balanced batch in terms of drug content, EE, and % CDR. These variations are likely due to small differences in formulation handling or processing conditions.

Table 5: Selection of conc. of Propylene Glycol

Batch	% Drug Content	EE(%)	% CDR
CRE 16	89.59	95.68	85.67
CRE 17	89.68	9.35	84.59
CRE 18	87.35	91.26	79.35
CRE 19	90.35	95.67	80.26
CRE 20	92.35	94.68	83.68

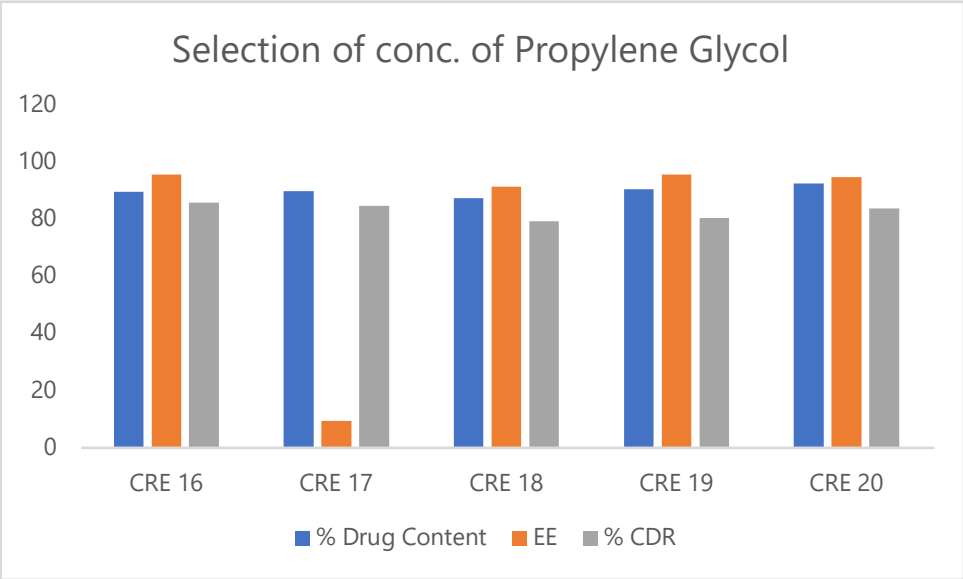

Figure 9: Selection of conc. of Propylene Glycol

The data for batches CRE 16 to CRE 20 reflect their performance in terms of % drug content, encapsulation efficiency (EE), and cumulative drug release (% CDR). The % drug content ranges from 87.35% to 92.35%, indicating generally good drug incorporation, with CRE 20 showing the highest content. Encapsulation efficiency is high for most batches (91.26%–95.68%), except for CRE 17, which shows an unusually low value of 9.35%, likely due to a formulation or measurement error. The % CDR values range from 79.35% to 85.67%, indicating moderate drug release, with CRE 16 showing the highest release and CRE 18 the lowest. Overall, most batches demonstrate satisfactory drug content and encapsulation, although drug release is somewhat lower compared to previous sets. CRE 16 and CRE 20 appear relatively balanced in terms of drug content, EE, and % CDR, while CRE 17 requires further investigation due to its anomalously low EE. Variations among batches may be attributed to differences in formulation handling or process parameters.

Optimization of batch

F3 batch was selected for optimized batch because Drug Content, % EE&%CDR were found to be 98.59, 97.43&93.68 %.

Characterization of optimized batch

Scanning Electron Microscopy (SEM)

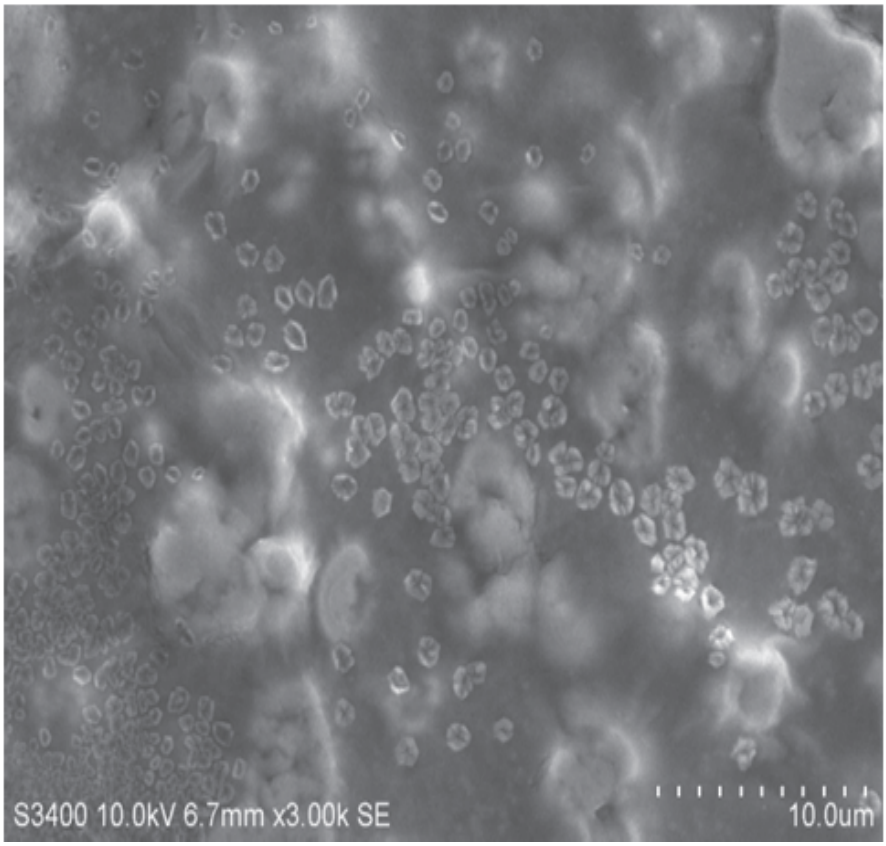

Figure 10: Scanning Electron Microscopy (SEM)

Particle Size Analysis

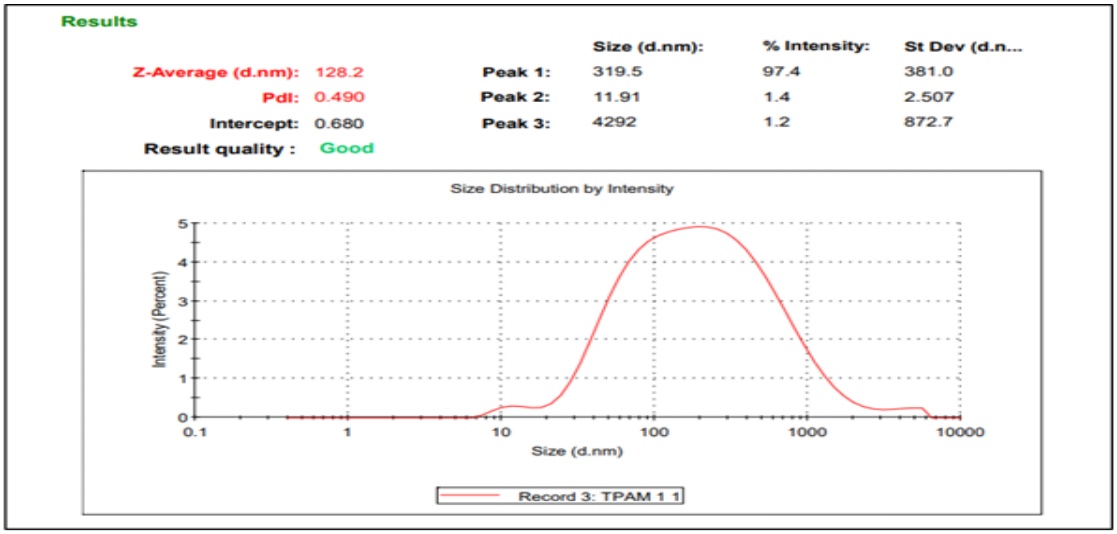

Figure 11: Particle Size Analysis

Zeta Potential

The optimized ethosomal formulation showed a zeta potential of –27.1 mV, indicating a negatively charged vesicular surface. The major peak around –28.7 mV (92% area) suggests good charge uniformity and moderate colloidal stability with reduced aggregation tendency. (Figure:12)

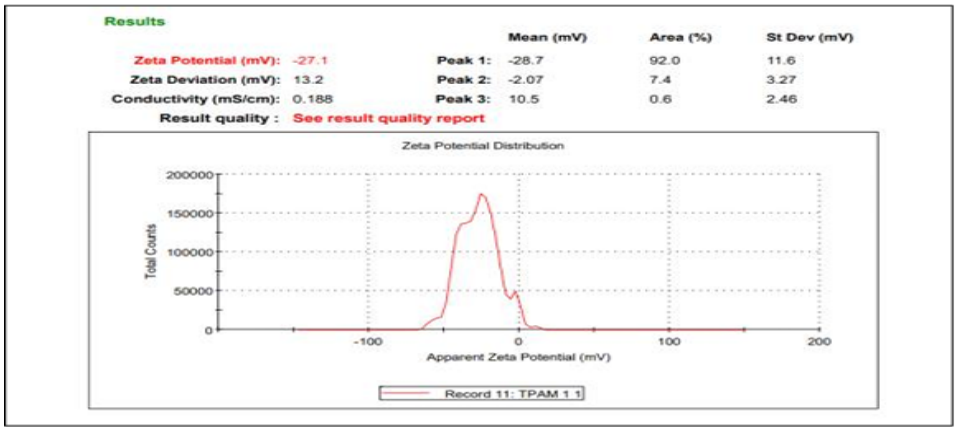

Figure 12: Zeta Potential

% Entrapment efficiency

Prepared ethosomes formulation showed good entrapment efficiency of 97.43 %. This behavior may be due to the presence of a higher concentration of ethanol which increases Drug solubility in ethosomes.

Drug content

Drug content (%) of optimized batch was found to be 95.59. This indicates good amount of drug in ethosomes.

Preliminary trial batch of Ethosomal gel

Evaluation of Topical Ethosomal Gel

The prepared Crisaborole ethosomal gels were evaluated for organoleptic characteristics, pH, viscosity, and spreadability. Both formulations (G1 and G2) were found to be colorless and odorless, indicating good patient acceptability. The pH of the gels was found to be 6.62 (G1) and 6.87 (G2), which lies within the acceptable range for topical application and is close to normal skin pH. Viscosity was measured using a Brookfield viscometer (spindle no. 62). The viscosity values were 12,357 cP for G1 and 153,786 cP for G2, indicating that G2 was significantly more viscous than G1. Spreadability values were 15.67 g·cm/sec (G1) and 8.67 g·cm/sec (G2), suggesting that G1 exhibited better spreading characteristics, whereas G2 showed reduced spreadability due to higher viscosity.

Dose Calculation for Crisaborole Ethosomal Gel

The marketed Crisaborole topical gel contains 2% w/w Crisaborole, which corresponds to 0.6 g (600 mg) of Crisaborole in 30 g gel.

$$\text{Drug required} = 30 \times \frac{2}{100} = 0.6\text{ g} = 600\text{ mg}$$

For incorporation of Crisaborole-loaded ethosomes into gel, the drug loading was considered as 4.3 mg of Crisaborole per 100 mg of ethosomes. Therefore, the amount of ethosomes required to provide 600 mg of drug was calculated as:

$$4.3\text{ mg drug} \rightarrow 100\text{ mg ethosomes}$$

$$600\text{ mg drug} \rightarrow X\text{ mg ethosomes}$$

$$X = \frac{600 \times 100}{4.3} = 13{,}953.48\text{ mg ethosomes}$$

$$X \approx 13.95\text{ g ethosomes}$$

Thus, approximately 13.95 g of ethosomes would be required to incorporate 600 mg Crisaborole into a 30 g gel batch containing 2% w/w drug.

Characterization of Crisaborole Ethosomes for Topical Gel

The optimized Crisaborole-loaded ethosomal gel was evaluated for physicochemical and formulation characteristics to ensure suitability for topical application. The formulation was prepared as a 2% w/w gel (30 g batch size) containing 600 mg of Crisaborole. The gel exhibited an opaque appearance, indicating uniform dispersion of ethosomal vesicles within the gel base. The pH of the formulation was found to be 6.55, which is close to skin pH and suggests good dermal compatibility. The viscosity of the gel was 9764 cP, indicating adequate consistency for topical application and retention on the skin surface. The spreadability was 14.59 g·cm/sec, confirming good ease of application and uniform spreading. The drug content was found to be 95.48%, demonstrating efficient incorporation and uniform distribution of Crisaborole in the formulation. Overall, the optimized ethosomal gel showed suitable properties for topical delivery

In-Vitro Drug Release Study

The in-vitro drug release profile of the optimized Crisaborole ethosomal gel showed a sustained and controlled release pattern over 12 h. No drug release was observed at 0 h, indicating formulation integrity at the initial stage. An initial release of 23.51% was obtained within 1 h, which may be attributed to the drug present near the surface of the gel and vesicles. Thereafter, the release increased gradually, reaching 45.01% at 4 h and 60.20% at 7 h, suggesting controlled diffusion of Crisaborole from

the ethosomal vesicles through the gel matrix. At the end of 12 h, the formulation exhibited 90.67% cumulative drug release, confirming sustained release and near-complete drug availability. Overall, the release pattern supports the potential of the ethosomal gel to provide prolonged topical drug delivery, which may improve therapeutic efficacy and reduce dosing frequency.

Stability Study

The stability of the optimized Crisaborole ethosomal gel was evaluated at room temperature for 30 days by monitoring physical appearance, pH, viscosity, spreadability, and cumulative drug release (%CDR). The formulation remained opaque throughout the study period, indicating no visible phase separation or physical instability. The pH showed only a slight reduction from 6.55 (day 1) to 6.51 (day 30), remaining within the acceptable range for topical application. Viscosity demonstrated negligible variation, decreasing marginally from 9764 cP to 9753 cP, suggesting that the gel maintained its consistency during storage. Similarly, spreadability showed minimal change from 14.59 to 14.50 g·cm/sec, confirming good retention of application properties. The %CDR remained nearly constant, with a minor reduction from 90.67% to 90.34%, indicating that the formulation preserved its sustained drug release behaviour. Overall, the results confirm that the optimized ethosomal gel remained stable under room temperature conditions for at least 30 days.

DISCUSSION

The present study successfully developed and optimized a Crisaborole-loaded ethosomal gel for enhanced topical delivery. Preformulation studies confirmed the purity and physicochemical suitability of the drug, while its poor aqueous solubility justified the need for a lipid-based carrier system (1). Similar challenges associated with poorly soluble drugs have been effectively addressed using vesicular and nano-carrier systems such as proniosomes and nanoemulgels (19,20).

Ethosomal systems are known to enhance dermal penetration due to the synergistic effect of ethanol and phospholipids, which increase lipid fluidity and vesicle deformability (4,6). Comparable findings have been reported for microsponges and proniosomal formulations, where improved drug retention and controlled release were observed (16,21). The high entrapment efficiency observed in the optimized formulation further supports the suitability of ethosomes for lipophilic drugs such as Crisaborole.

The optimized gel exhibited physicochemical properties suitable for topical application, including a pH close to that of the skin, appropriate viscosity, and good spreadability. These parameters are critical for patient acceptability and therapeutic performance (12,13). Similar characteristics have been reported in controlled-release and in-situ gel systems designed for sustained drug delivery (17).

The in-vitro drug release profile demonstrated a sustained release pattern over 12 h, which can be attributed to the reservoir effect of ethosomal vesicles combined with the gel matrix. This behavior aligns with previously reported vesicular systems that provide prolonged drug release and improved therapeutic efficacy (7,10).

Furthermore, stability studies indicated minimal variation in formulation parameters over 30 days, confirming the robustness of the developed system. This is consistent with QbD-based and factorial design approaches reported in recent studies, which ensure formulation stability and reproducibility (15,20).

Overall, the findings suggest that the developed ethosomal gel is a promising strategy for enhancing dermal delivery of Crisaborole and may offer improved clinical outcomes compared to conventional formulations.

CONCLUSION

Crisaborole-loaded ethosomal gel was successfully developed and optimized for topical delivery. The formulation showed good physicochemical properties, high drug content, sustained drug release up to 12 h, and stability for 30 days at room temperature. Overall, the ethosomal gel is a promising system to enhance topical delivery and improve therapeutic effectiveness of Crisaborole.

Conflict of Interest

All the authors affirm there are no conflicts of interest.

Acknowledgement

I would like to express my heartfelt gratitude to my guide Dr. Mital Patani for her valuable guidance, constant support, and encouragement throughout my research work. I am also deeply thankful to my parents for their unconditional love, motivation, and blessings. Finally, I extend my sincere thanks to all those who directly or indirectly helped me in completing my research work successfully.

REFERENCES

1. Barry BW. Dermatological formulations: percutaneous absorption. New York: Marcel Dekker; 1983.
2. Elias PM. Stratum corneum barrier function: permeability and antimicrobial defense. J Invest Dermatol. 2005;125(2):183–200.
3. Mezei M, Gulasekharam V. Liposomes—a selective drug delivery system for the topical route. Life Sci. 1980;26(18):1473–7.
4. Touitou E, Dayan N, Bergelson L, Godin B, Eliaz M. Ethosomes—novel vesicular carriers for enhanced delivery: characterization and skin penetration properties. J Control Release. 2000;65(3):403–18.

5. Touitou E. Composition of ethosomes and their mechanism of skin delivery. Adv Drug Deliv Rev. 2008;60(13–14):1526–32.
6. Verma DD, Fahr A. Synergistic penetration enhancement effect of ethanol and phospholipids on the topical delivery of cyclosporin A. Eur J Pharm Biopharm. 2004;57(2):293–9.
7. Elsayed MMA, Abdallah OY, Naggar VF, Khalafallah NM. Deformable liposomes and ethosomes as carriers for skin delivery: a comparative study. Int J Pharm. 2007;332(1–2):1–16.
8. US Food and Drug Administration. Crisaborole ointment prescribing information. Silver Spring (MD): FDA; 2016.
9. Paller AS, Tom WL, Lebwohl MG, Blumenthal RL, Boguniewicz M, Call RS, et al. Efficacy and safety of crisaborole ointment in patients with atopic dermatitis. J Am Acad Dermatol. 2016;75(3):494–503.
10. Benson HAE. Transfersomes for transdermal drug delivery. Curr Drug Deliv. 2005;2(1):23–33.
11. Jain S, Tiwary AK, Sapra B, Jain NK. Ethosomes: a novel vesicular carrier for enhanced transdermal drug delivery. Drug Dev Ind Pharm. 2003;29(9):1013–26.
12. Schmid-Wendtner MH, Korting HC. The pH of the skin surface and its impact on the barrier function. Skin Pharmacol Physiol. 2006;19(6):296–302.
13. Jones DS, Woolfson AD, Brown AF. Textural, viscoelastic and mucoadhesive properties of pharmaceutical gels. Int J Pharm. 1997;151(2):223–33.
14. International Council for Harmonisation (ICH). ICH Q1A(R2): Stability testing of new drug substances and products. Geneva: ICH; 2003.
15. Patel S, Patani M, Talaviya N, Soni K, Shah M, Kalsara K, et al. Development of a QbD-based stability-indicating RP-HPLC method for glimepiride and gemigliptin. J Appl Bioanal. 2025;11(8 Suppl):778–91. doi:10.53555/jab.v11si8.1183
16. Sodha A, Patani M, Nangha B, Upadhyay S, Solanki A, Maske P, et al. Optimization and characterization of desonide-loaded Eudragit RS100 microsponges by quasi-emulsion solvent diffusion for sustained topical delivery. Int J Drug Deliv Technol. 2026;16(2 Suppl):391–6. doi:10.25258/ijddt.16.391-396
17. Talaviya N, Mathukiya Z, Patel S, Patani M, Kalsara K, Soni K, et al. Floating oral in-situ gel of risedronate sodium for sustained gastro-retentive delivery. Int J Drug Deliv Technol. 2026;16(2 Suppl):832–50. doi:10.25258/ijddt.16.832-850
18. Koli M, Dutta P, Patel N, Patel AK, Ghosh B, Singh A, Pal R. Non-ionic surfactants (niosomes) in drug delivery: clinical trials and patents in tuberculosis and oncology. Curr Nanomedicine. 2026;16.
19. Patel Y, Patani M, Patel R, Nangha B, Upadhyay S, Shah T, Kalsara K, et al. Nanoemulgel for topical delivery of flecainide acetate to improve patient compliance in arrhythmia management. Int J Drug Deliv Technol. 2026;16(3Suppl):88–96. doi:10.25258/ijddt.16.3s.12
20. Kachhiya P, Patani M, Nangha B, Chauhan D, Upadhyay S, Patel S, Agrawal M. Crisaborole-loaded proniosomes: formulation, optimization and characterization using factorial design. Int J Drug Deliv Technol. 2026;16(6 Suppl):665–75. doi:10.25258/ijddt.16.6s.92
21. Chauhan D, Patani M, Modi D, Nangha B, Kachhiya P, Singh J, Upadhyay S, et al. Development and evaluation of luliconazole-loaded proniosomal gel for enhanced topical delivery. Int J Drug Deliv Technol. 2026;16(11Suppl):987–98. doi:10.25258/ijddt.16.11s.97