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FORMULATION AND IN VITRO EVALUATION OF CRISABOROLE-LOADED SOLID LIPID NANOPARTICLES - TOPICAL SYSTEM FOR ATOPIC DERMATITIS

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Crisaborole, Solid Lipid Nanoparticles, Box–Behnken design, Atopic dermatitis.

ABSTRACT
Background: Designing and testing a new way to deliver drugs through the skin using Solid Lipid Nanoparticles (SLNs) for sustained as well as enhanced topical delivery of Crisaborole. **Methodology:** Crisaborole was incorporated into SLNs using the Double Emulsification Solvent Evaporation Method. The SLNs were enhanced using a Box-Behnken design. The best-performing formulation was evaluated after optimization for particle size, etc, along with entrapment efficiency and *in vitro* release. **Results:** The SLNs exhibited a remarkable entrapment efficacy of 69.8 ± 1.1% to 80.6 ± 0.3%, and their particle size varied from 222.1 ± 8.5 nm to 440 ± 7.5 nm. In the *in vitro* release study of Crisaborole-SLNs, 92.7 ± 1.17 % was observed at 12 hours. The developed SLN formulation displays no significant change after three months of stability study under accelerated conditions. **Conclusion:** These results suggest that crisaborole-loaded solid lipid nanoparticles (SLNs) represent a promising vehicle for the topical delivery of crisaborole, with potential for enhanced dermal residence due to controlled release and nanoscale size within the skin, while minimizing systemic exposure.

INTRODUCTION

Atopic dermatitis (AD) is a long-lasting skin disease marked by repeated flare-ups of inflammation and skin symptoms that affects nearly 20% of children and adults globally. It is clinically portrayed by pruritus, erythematous laceration, and a compromised skin barrier. The pathogenesis of AD includes a complicated coaction of genetic predisposition, environmental trigger, immune dysregulation, and epidermal barrier dysfunction [1-3]. These factors collectively contribute to significant impairment in quality of life and frequent disease recurrence [4]. Topical therapy remains the mainstay of AD treatment; however, conventional formulations often suffer from limited skin penetration, poor dermal retention, and systemic side effects with prolonged use, particularly in the case of corticosteroids and calcineurin inhibitors [5]. These limitations have necessitated the development of novel, safer, and more

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efficient drug delivery strategies. Crisaborole, a non-steroidal phosphodiesterase-4 (PDE4) inhibitor, has emerged as a promising anti-inflammatory agent with minimal systemic immunosuppression. Despite its potential, its clinical utility is hindered by suboptimal skin permeability and the need for frequent application [6-7]. Nanotechnology-based carriers, especially solid lipid nanoparticles (SLNs), have gained traction in dermatological therapeutic delivery due to their biocompatibility, ability to enhance skin penetration, and controlled drug-release profiles. SLNs provide an occlusive aftermath that boosts skin hydration and facilitates deeper drug retention in the epidermal and dermal layers [8-11]. The research aims to design and test a new skin-based therapeutic delivery system that integrates crisaborole into solid lipid nanoparticles (SLNs) to improve the treatment of atopic dermatitis.

MATERIALS AND METHODS

Materials

Crisaborole, the active drug used to treat atopic dermatitis, was obtained from Dhamtec Pharma and Consultants, India. For the preparation of solid lipid nanoparticles (SLNs), GMS and soya lecithin were sourced from Research Fine Chemi and Loba Chemie. Disodium hydrogen phosphate, NaCl, and potassium Hydrogen phosphate were used to prepare phosphate buffer solutions that simulate physiological conditions. These were also obtained from Loba Chemie. GMS was selected due to its GRAS status, biocompatibility, solid nature at body temperature, and proven ability to enhance barrier properties and dermal drug delivery in SLN-based topical systems.

Formulation of Crisaborole-loaded SLNPs

Crisaborole-loaded SLNs were created by the double emulsification-solvent evaporation method. GMS acts as the solid lipid matrix, while soya lecithin functions as an emulsifier or stabilizer. Dichloromethane serves as an organic solvent to dissolve the lipid components. The aqueous phase (W_1) contains the drug and will later be emulsified with the organic phase to facilitate drug encapsulation within the lipid nanoparticles. The aqueous phase (W_1) containing crisaborole was emulsified into the organic phase using a 22-gauge syringe needle while stirring at 2000 rpm for 10 minutes. The resulting W_1/O emulsion was then injected into 100 mL of a second aqueous phase (W_2) containing Tween 80, again using the same syringe setup. Finally, the organic solvent (dichloromethane) was removed by rotary evaporation, yielding solid lipid nanoparticles (SLNPs) encapsulating the drug [12-13].

Formulation Design, Development, and Optimization of SLNs with the aid of Quality by Design (QbD) Approach

Design-Expert® software (version 13.0.5.0) was applied to assess the outcome of independent variables, including GMS concentration (mg), Tween 80 concentration (%), and homogenization speed (rpm), on dependent variables such as particle size, zeta potential, and encapsulation efficiency (EE%) of the nanoparticles. The analysis was assisted using the Box-Behnken response surface methodology, comprising 17 experimental runs [14]. Preliminary experiments guided the selection of independent variables, whereas the amounts of soy lecithin and drug (50 mg each) and the homogenization time (20 minutes) were held constant. Based on Design of Experiments (DoE), 17 formulations were created to establish models described by second-order polynomial functions:

$$Y_{A,B,C} = \beta_0 + \beta_1 X_1 + \beta_2 X_2 + \beta_3 X_3 + \beta_{11} X_{12} + \beta_{22} X_{22} + \beta_{33} X_{32} + \beta_{12} X_1 X_2 + \beta_{13} X_1 X_3 + \beta_{23} X_2 X_3$$

In this model, $Y_{A,\ B,\ and\ C}$ denote the approximated values for encapsulation efficiency (EE%), particle size, and zeta potential, respectively—key physicochemical characteristics of the nanoparticles. β_0 is the intercept; β_1, β_2, and β_3 are Linear coefficients that represent the direct, independent impact of each factor on the response variable (for example, particle size, entrapment efficiency, or drug release), assuming other factors remain constant. β_{11}, β_{22}, and β_{33} are the quadrate coefficients for these same variables. Interaction terms are denoted by β_{12} (GMS and Tween 80), β_{13} (GMS and homogenization speed), and β_{23} (Tween 80 and homogenization speed). The independent variables are represented as X_1, X_2, and X_3. These variables labelled A, B, and C were considered at three levels: low (-1), medium (0), and high (+1). After preparing the formulations and measuring their responses, the data were modelled using a stepwise approach to select the best-fitting equations based on correlation coefficients. Model significance was confirmed by one-way ANOVA, with a critical value < 0.05 indicating statistical significance [15-16]. Various experimental runs with different compositions, labelled F1 to F17.

CHARACTERIZATION OF SOLID LIPID NANOPARTICLES

Transmission Electron Microscopy

TEM serves as a crucial characterization tool to visually confirm the successful formation and nanoscale structure of Crisaborole-loaded SLNs, supporting other analytical results such as particle size and PDI measurements [17-18].

Particle Size, Polydispersity Index, Zeta Potential

The particle size and polydispersity index (PDI) of the Crisaborole-loaded solid lipid nanoparticles (SLNs) were determined by a Nanosight NS 500, an instrument based on nanoparticle tracking analysis (NTA). In contrast, the zeta potential was determined with a Zetasizer SZ 100 (Horiba Scientific) at 25°C. A clear, disposable zeta cell ensured accurate results. These measurements provide crucial data on particle dispersion, charge, and size distribution, key factors in assessing the formulation's stability and efficiency [19-20].

% Entrapment Efficiency (EE) & Total Drug Content (TDC)

The SLN suspension was first subjected to centrifugation at 12,000 rpm for 0.5 hour using a microcentrifuge, which allowed the separation of unencapsulated (free) crisaborole in the aqueous phase from the nanoparticle-bound drug. After centrifugation, the supernatant containing the free drug was discarded, and the pellet comprising crisaborole-loaded SLNs was collected. The pellet was then resuspended in methanol and vortexed thoroughly to disrupt the lipid matrix and release the encapsulated drug. This admixture was centrifuged again at 12,000 rpm for 10 minutes to remove lipid residues, yielding a clear supernatant containing the released crisaborole. Finally, the supernatant was diluted with a pH 7.4 phosphate buffer for subsequent quantitative analysis, enabling accurate determination of the drug encapsulated within the SLNs. Drug concentration was then decided by measuring absorbance at 250 nm, the λmax for Crisaborole, using a UV spectrophotometer [21-22]. UV spectroscopy was selected for routine quantification during formulation screening. Future studies will employ HPLC for degradation profiling and in vivo analysis.

DRUG EXCIPIENTS COMPATIBILITY STUDY

Fourier Transform Infrared Spectroscopy (FTIR)

Compatibility of the drug and excipients was assessed using a Bruker FTIR spectrometer by analyzing Crisaborole, GMS, Soya Lecithin, Tween 80, a mixture of all ingredients used to formulate SLNs, and an optimized batch of SLNs. A small quantity of the triturated sample was placed on the holder at room temperature and scanned from 400 to 4000 cm^{-1} [23]. The obtained Fourier Transform Infrared (FTIR) spectra were compared to analyze potential interactions between crisaborole and the excipients included in the formulation.

Differential Scanning Calorimetry (DSC)

Differential Scanning Calorimetry (DSC) was observed using a TA Instruments DSC Discovery 250 to investigate the thermal behaviour of crisaborole, glycerol monostearate, and the optimized solid lipid nanoparticle (SLN) formulation. [24-26].

EVALUATION OF SOLID LIPID NANOPARTICLES

In vitro drug release study

An *in vitro* drug release study of the hydrogel containing crisaborole (CRB)–loaded SLNs was performed using the Franz diffusion cell method. The cellophane membrane was activated by overnight soaking in phosphate buffer, pH 7.4. A cellophane membrane was mounted on the receptor compartment. The duration of the drug release studies was 12 hrs. During the *in vitro* drug release study, samples were taken from the receptor compartment of the Franz diffusion cell at predetermined time intervals & analyzed spectrophotometrically to quantify the amount of crisaborole permeated. In parallel, a placebo patch without crisaborole was subjected to the same experimental conditions as the CRB-loaded patch. The placebo patch served as a blank to account for any interference from formulation components or the membrane, ensuring that the measured absorbance was attributable solely to the release of crisaborole [27-32].

Stability Study

To assess stability, the optimized SLN formulations were stored in a stability chamber under two conditions: 25 °C with 60% relative humidity (RH) and at 4 °C. The formulated SLNs were stored in 100 ml glass bottles, tightly sealed. Stability assessments were conducted after 0, 1, 2, and 3 months of storage. Once a sample was tested, it was not returned to the chamber. The formulated systems were assessed using critical parameters that are widely recognized as indicators of the stability and quality of colloidal dispersions, including zeta potential, particle size, PDI, and drug EE [33,34].

Analysis of Data

Mean value ± standard deviation is used to report all data.

RESULTS AND DISCUSSION

Formulation Design, Development, and Optimization of Solid Lipid Nanoparticles with the aid of the design of experiments

The solid lipid nanoparticles were formulated and systematically evaluated with respect to three critical formulation and process variables: the amount of glycerol monostearate (GMS) (X_1), the concentration of Tween 80 (% w/w) (X_2), and the homogenization speed (rpm) (X_3). The design generated 17

experimental runs (Table 1), including five center points. Each formulation was evaluated for key parameters: particle size (Y1), zeta potential (Y2), and drug entrapment efficiency (Y3). The experimental data were analyzed using first-order, second-order, and quadratic models, with the quadratic model providing the best fit ($p < 0.0001$) and an insignificant lack of fit ($p > 0.05$), indicating the model's reliability in predicting outcomes [14].

Table 1: Responses observed for Crisaborole-loaded SLN using BBD

Batch Code	Concentration		Speed of Homogenization (rpm)
	GMS (mg)	Tween 80 (%)	
F1	200	0.5	17500
F2	250	1.5	20000
F3	250	1	17500
F4	300	1	20000
F5	300	1	15000
F6	250	1	17500
F7	250	0.5	15000
F8	300	0.5	17500
F9	250	1	17500
F10	200	1.5	17500
F11	200	1	15000
F12	250	1.5	15000
F13	300	1.5	17500
F14	250	1	17500
F15	250	0.5	20000
F16	200	1	20000
F17	250	1	17500

STATISTICAL OPTIMIZATION AND RESPONSE SURFACE ANALYSIS

Model Selection and ANOVA Analysis

The Box–Behnken design was selected to systematically optimise the formulation parameters of solid lipid nanoparticles by analysing the combined effects of selected independent variables on the desired responses. Model adequacy was confirmed by significant model F-values ($p < 0.05$), non-significant lack-of-fit ($p > 0.05$), high adjusted and predicted R^2 values (difference < 0.20), and acceptable precision > 4. Quadratic models were suggested for all three responses (Y1–Y3), while cubic models were aliased.

RESPONSE SURFACE ANALYSIS

Effect on Particle Size (Y1)

Particle size significantly influenced SLN performance, ranging from 164 to 745 nm. The optimized quadratic model (F-value: 138.32, $p < 0.0001$) showed a strong signal (adequate precision = 35.08) with an adjusted R^2 of 0.9872. Size increased with GMS concentration and decreased with Tween 80 and homogenization speed up to an optimal point. The regression equation for particle size was:

$$Y1 = 180.2 + 35.5A - 27.875B - 69.88C + 115.75AB - 48.25AC - 17BC + 175.4A^2 + 84.65B^2 + 211.65C^2$$

Effect on Zeta Potential (Y2)

Zeta potential ranged from −26.8 to −17.5 mV, indicating colloidal stability. The model was significant ($F = 17.34$, $p = 0.0005$), with predicted and adjusted R^2 of 0.7264 and 0.9019, respectively. Increased GMS raised the zeta potential (more negative), while Tween 80 and higher homogenization speeds reduced it due to destabilization of particles. Regression equation:

$$Y2 = -23.68 + 1.79A - 1.83B - 0.34C + 0.63AB + 0.25AC + 0.78BC + 1.57A^2 - 0.46B^2 + 2.37C^2$$

Effect on Entrapment Efficiency (Y3)

The entrapment efficiency of the formulation was significantly influenced by the selected formulation variables, as evidenced by a high model F-value of 79.73 ($p < 0.0001$) and an adjusted R^2 of 0.9779. Higher GMS improved entrapment, while excessive surfactant or homogenization could lead to leakage or reduced loading, as depicted in Figure 1.

Numerical Optimization and Validation

Numerical optimization targeting minimal particle size, maximal entrapment, and suitable zeta potential yielded optimal conditions: GMS 262.49 mg, Tween 80 1.177%, homogenization speed 18,092.78 rpm (desirability = 0.892). The optimized formulation represents a checkpoint batch predicted by the numerical optimization model and prepared independently for validation, rather than a direct formulation within the original Box–Behnken experimental design matrix. Therefore, the particle size of 183±3.24nm reflects the validated model prediction under optimized conditions and does not contradict the experimental design range (222–440 nm) [15-16].

CHARACTERIZATION OF SOLID LIPID NANOPARTICLES

Transmission Electron Microscopy

The Transmission Electron Microscopy (TEM) analysis (Figure 2) of the optimized Solid Lipid Nanoparticles (SLNs) revealed predominantly rounded particles with even surfaces. The

particles were well-dispersed, with nominal aggregation, indicating good colloidal stability and a dense lipid core, thereby confirming structural integrity, which is crucial for drug encapsulation [18]. Some degree of size variation was observed, which is consistent with dynamic light scattering measurements.

Particle Size, Polydispersity Index, Zeta Potential

The particle size and zeta potential study of the optimized batch of solid lipid nanoparticles (SLNs) revealed favorable physicochemical characteristics for topical delivery in the therapy of atopic dermatitis. The optimized SLN formulation exhibited a mean particle size of 183 ± 3.24 nm, which lies within the optimal nanoscale range for efficient skin penetration and enhanced drug delivery through the stratum corneum. The Polydispersity Index (PDI) of 0.263 ± 0.013 indicates a relatively narrow size distribution, contributing to consistent and predictable release profiles. The Zeta potential, recorded at -26.1 ± 0.73 mV, suggests that the nanoparticles possess sufficient surface charge to provide electrostatic stabilization, thereby minimizing aggregation and contributing to the overall stability of the dispersion [19].

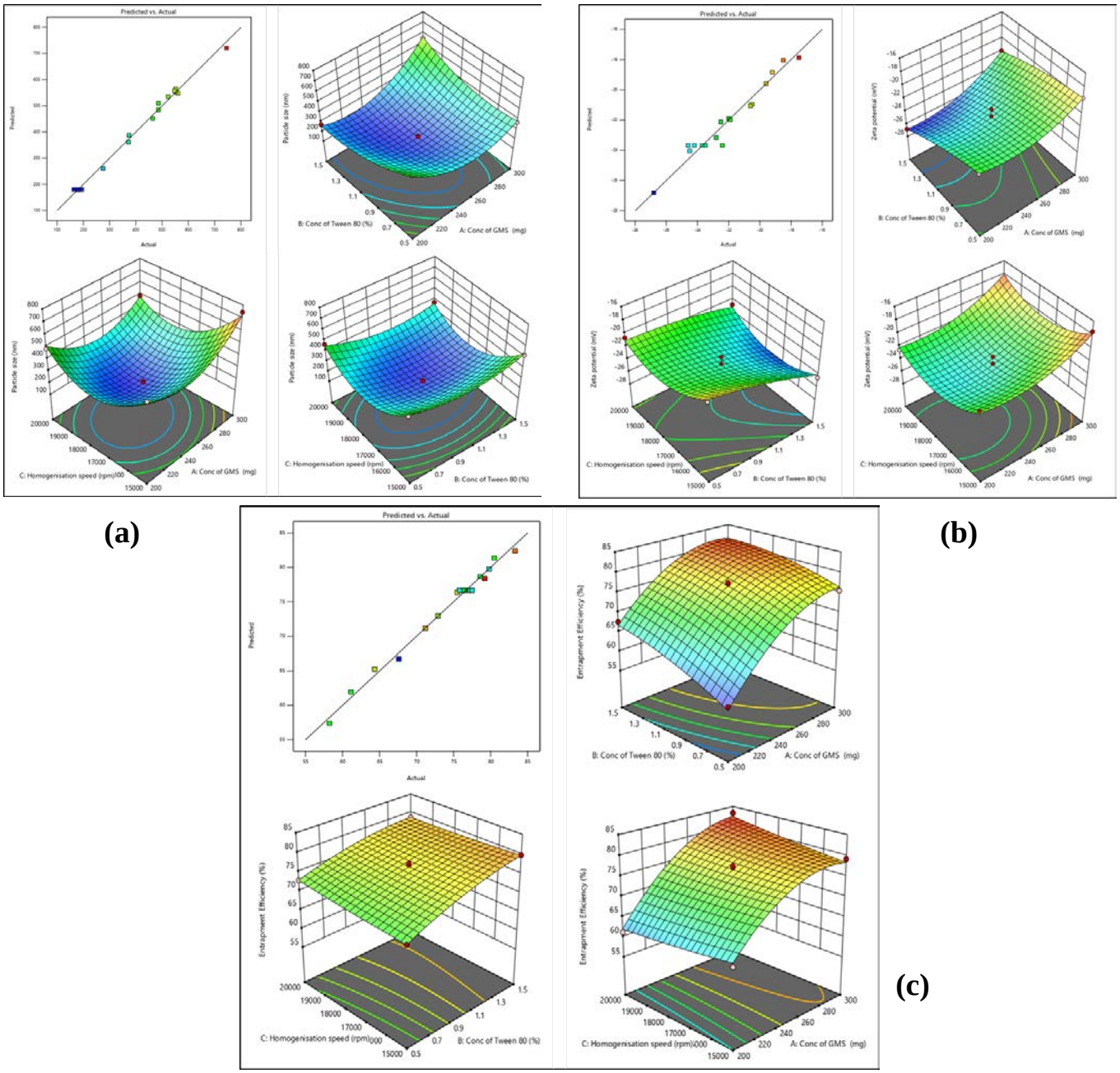

Figure 1: Response surface graphs were generated to visually illustrate the impact of the independent formulation and process variables on the key responses: (a) particle size, (b) zeta potential, and (c) entrapment efficiency.

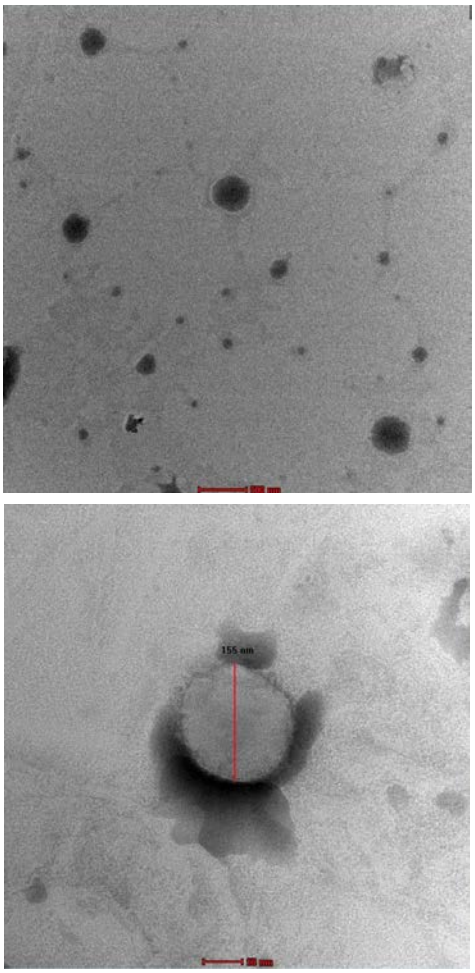

Figure 2: TEM images of the optimized batch of SLNPs

% Entrapment Efficiency (EE) & Total Drug Content (TDC)

The solid lipid nanoparticles designed for Atopic Dermatitis showed an entrapment efficiency of 78.5 ± 1.25 %, indicating that a significant amount of the drug is well encapsulated within the nanoparticles, ensuring sustained release and making them effective for delivering therapeutic levels of the drug over an extended period. Additionally, the total drug content of 66.23 ± 0.38 % reflects a substantial loading capacity, meaning that a large fraction of the nanoparticle formulation is composed of the therapeutic agent. These results suggest that the nanoparticles are well-suited for delivering an effective dose of the drug for the treatment of Atopic Dermatitis [21,35].

DRUG-EXCIPIENT COMPATIBILITY STUDY

Fourier Transform Infrared Spectroscopy (FTIR)

The FTIR spectra of crisaborole, glyceryl monostearate (GMS), soya lecithin, and Tween 80, as well as their physical mixture, were recorded to assess possible interactions between the drug and excipients. The FTIR spectrum of crisaborole exhibited distinct characteristic peaks (Figure 3) analogous to the functional groups present in its molecular structure. These absorption bands confirm the chemical identity of crisaborole and serve as reference peaks for comparison. Crisaborole contains a boron atom, is a benzoxaborole, an aromatic ether, and a nitrile. These functional groups contribute to the characteristic absorption bands in the FTIR spectrum. The physical mixture retains characteristic peaks from all components, indicating compatibility [23]. The FTIR spectra of the pure drug and the optimized SLN formulation confirm that no significant interactions occurred between the lipids and the Crisaborole. The characteristic peaks of crisaborole were either reduced in intensity or overlapped in the SLN spectrum, which may be attributed to dilution effects and dispersion within the lipid matrix. These findings suggest compatibility between the drug and excipients; however, FTIR alone cannot conclusively confirm molecular encapsulation. Complementary techniques such as XRD or DSC provide stronger evidence of drug incorporation within the lipid matrix.

Differential Scanning Calorimetry (DSC)

DSC thermograms were analyzed to evaluate the melting behavior of Crisaborole (Figure 4) and Crisaborole-loaded solid lipid nanoparticles (SLNs) (Figure 5). Crisaborole exhibited an endothermic peak around 136.5 °C (127.21 J/g), confirming its crystalline structure. For the Crisaborole-loaded SLNs, the DSC thermogram showed a broad endothermic peak at 50.02°C, along with a disappearance of the characteristic peaks seen in the unencapsulated Crisaborole. The broad peak and the absence of original endothermic peaks suggest that the Crisaborole was productively entrapped within the lipid matrix of SLNs [24,25].

In vitro drug release study

The drug release profiles of CRB-loaded SLN hydrogel and the placebo formulation were determined in vitro using a Franz diffusion cell over 12 h. The cumulative amount of crisaborole (CRB) released through the cellophane membrane increased progressively over time, indicating a sustained, controlled drug-release pattern from the formulation. An initial drug release of approximately 12.5 ± 0.23% was observed within the first hour, suggesting a moderate early release. This was followed by a continuous increase in drug release, reaching 63.5 ± 1.58% at the sixth hour and 92.7 ± 1.17% after 12 hours. The placebo patch showed no detectable drug release during the study period, establishing that the drug release detected was attributable solely

to CRB from the SLNP matrix. The drug release profile (Figure 6) showed continuous, sustained release of the drug until 12 hours. The sustained release profile observed may be associated with the effective encapsulation of crisaborole (CRB) within the solid lipid matrix of the nanoparticles. The solid lipid core acts as a diffusion barrier, controlling the drug's movement from the nanoparticles into the surrounding medium and, subsequently, through the membrane.

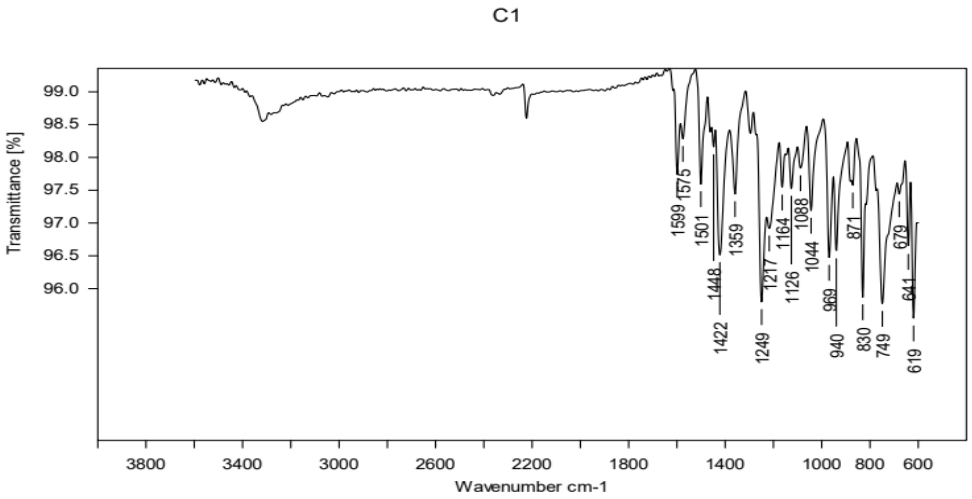

Figure 3: FTIR Spectra of Crisaborole plus excipients after drug-excipient compatibility study

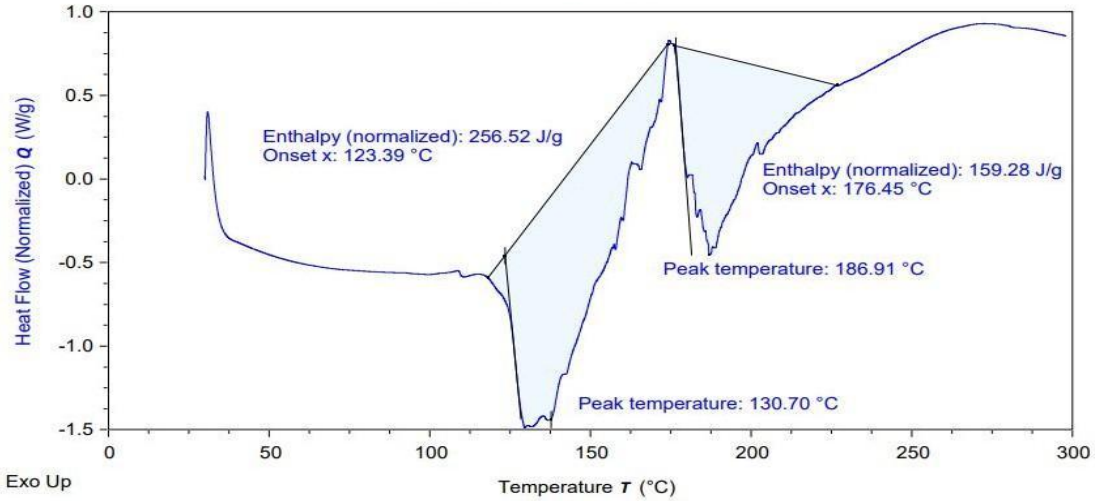

Figure 4: DSC Thermogram of pure Crisaborole

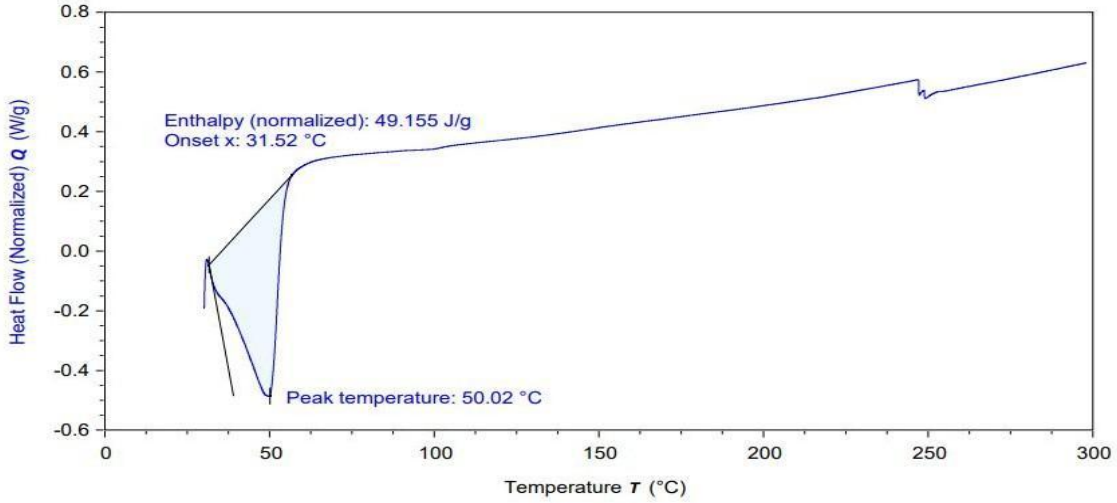

Figure 5: DSC Thermogram of Crisaborole SLN

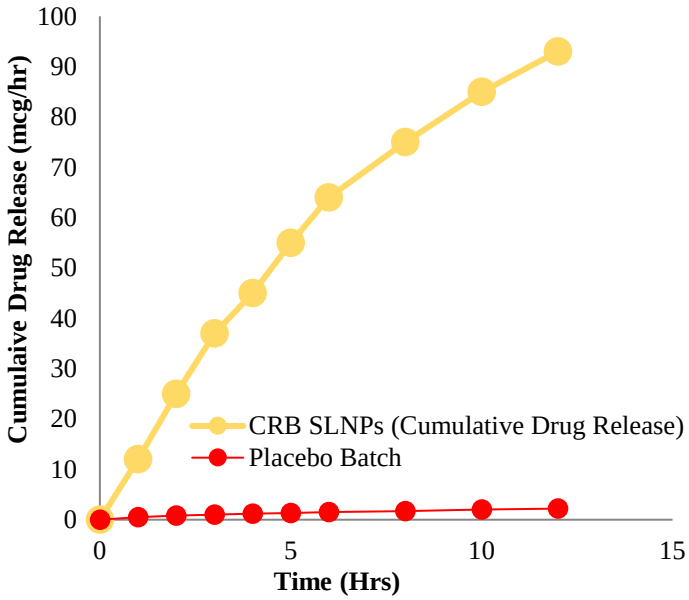

Figure 6: *In vitro* drug release profile of CRB-loaded SLNPs

Release Kinetics Modeling

To further demonstrate the mechanism of drug release from the SLN formulation, the *in vitro* release data were fitted to various kinetic models, including Zero-order, First-order, Higuchi, and Korsmeyer–Peppas models. The regression coefficients (R^2) were calculated for each model to determine the best fit. The release profile signifies the highest correlation with the Higuchi model ($R^2 = 0.987$), suggesting that drug release predominantly follows a diffusion-controlled mechanism from the lipid matrix. Additionally, the Korsmeyer–Peppas model yielded an R^2 value of 0.981 with a release exponent (n) value of 0.46, indicating Fickian diffusion-controlled drug release. (Fickian diffusion if $n \leq 0.5$; anomalous transport if $0.5 < n < 1$). These findings support the sustained-release behavior observed and confirm that the solid lipid core functions as a diffusion barrier that regulates the release of crisaborole.

Stability Study

The stability analysis of the optimized batch of SLNs showed a minor decrease in drug content, from 78.3% to 75.2% at room temperature and from 78.3% to 77.4% upon freezing. Drug leaching from the nanoparticles, which is less noticeable at freezing temperatures than at room temperature, could be responsible for this decrease. Additionally, particle size analysis revealed that during a three-month stability period, the nanoparticles' sizes increased from 183 nm to 213 nm at 25°C and 60% relative humidity, and from 183 nm to 198 nm at freezing temperatures [31]. A decrease in zeta potential (ZP) was associated with this increase in particle size. Notwithstanding these modifications, the low and steady PDI values indicated that the SLNs maintained their physical stability, with respect to particle size and distribution, under both storage conditions. Furthermore, when stored at 25°C and 60% relative humidity, the ZP values for the optimized SLNs ranged from -26.5 mV to -25 mV, and when stored at freezing temperatures, they ranged from -26.5 mV to -25.8 mV. The nanoparticles' good physical stability (ZP values of about 30 mV) during the three-month storage period under both conditions is indicated by these ZP values [36]. Extended ICH-compliant stability studies are underway to determine the long-term shelf life and formulation robustness.

CONCLUSION

A topical drug delivery system incorporating Crisaborole-Loaded Solid Lipid Nanoparticles (SLNs) was successfully developed and evaluated for the treatment of atopic dermatitis. The optimized SLN formulation exhibited favorable physicochemical characteristics, including nanoscale particle size, high drug entrapment efficiency, and good formulation stability, which are crucial for compelling in vitro drug release and drug retention within the targeted skin layers. These outcomes demonstrate that Crisaborole-Loaded SLNs offer a promising approach for enhancing therapeutic efficacy, reducing dosing frequency, and improving patient compliance in the management of atopic dermatitis. Furthermore, this nanotechnology-based topical delivery approach has the potential to represent an important advancement in the therapy of chronic inflammatory skin disorders. Further studies, including *in vitro* cytotoxicity, *ex vivo* skin retention, and *in vivo* therapeutic evaluation, are required to demonstrate the potential for a complete clinical shift of the developed SLN system.

FINANCIAL ASSISTANCE

NIL

CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTION

Nisha V Kalayil and Tularam Barot contributed to the conceptualization, experimental part, writing the manuscript, and data analysis. Tularam Barot also contributed to critical editing. Aarati Budar edited and analyzed the result. All authors have read and approved the final manuscript.

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