RESEARCH PAPER

DEVELOPMENT OF A PLURONIC LECITHIN ORGANOGEL CONTAINING BETAMETHASONE DIPROPIONATE FOR THE TOPICAL MANAGEMENT OF ATOPIC DERMATITIS.

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Abstract –
Background: Atopic dermatitis is a chronic inflammatory skin disorder requiring effective topical therapy to control inflammation and manage associated symptoms. The development of suitable semisolid formulations is important for achieving desirable physicochemical properties and drug-release characteristics. Pluronic Lecithin Organogel (PLO) represents a potential topical drug delivery platform owing to its structured gel matrix and tunable formulation properties.
Objective: The present study aimed to develop and optimize a betamethasone dipropionate (BD)-loaded PLO formulation using a Quality by Design (QbD) approach to investigate how formulation variables influence physicochemical characteristics and in vitro drug-release behavior.
Methods: A three-factor, three-level Box–Behnken experimental design was employed to investigate the effects of Poloxamer 407 concentration, lecithin concentration, and isopropyl myristate (IPM) volume on formulation performance. The prepared formulations were evaluated for viscosity, pH, spreadability, thermoreversible behavior, and cumulative drug release at predetermined time points. Fourier-transform infrared (FTIR) spectroscopy was used to investigate potential drug–excipient interactions. In vitro drug-release data were analyzed using zero-order, first-order, Higuchi, and Korsmeyer–Peppas kinetic models.
Results: Numerical optimization identified a candidate formulation containing approximately 11.16 g of Poloxamer 407, 1.748 g of lecithin, and 5 mL of IPM. The manuscript reports a viscosity of 199,800 cP, a pH of 6.67, and cumulative drug release of 98.76% at 24 h for the optimized formulation. Among the evaluated release kinetic models, the zero-order model exhibited the highest reported coefficient of determination (R^2 = 0.9797), followed by the first-order model (R^2 = 0.9347), Higuchi model (R^2 = 0.9179), and Korsmeyer–Peppas model (R^2 = 0.9094). These findings suggest that formulation composition influences the physicochemical characteristics and in vitro release behavior of the developed PLO system.
Conclusion: The study provides a preliminary framework for the QbD-guided development and optimization of BD-loaded PLO as a potential topical drug delivery system. However, inconsistencies in the reported formulation and optimization data must be resolved before the quantitative findings can be considered definitive. Further validation, stability assessment, ex vivo skin permeation, and skin compatibility studies are necessary to establish the formulation's suitability for topical application in atopic dermatitis.
Keywords: Betamethasone dipropionate; Pluronic Lecithin Organogel; Poloxamer 407; Quality by Design; Box–Behnken design; In vitro drug release; Atopic dermatitis.
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Introduction

Atopic dermatitis (AD) is a chronic, relapsing inflammatory skin disorder characterized by intense pruritus, xerosis, erythema, and recurrent eczematous lesions that substantially affect patients' quality of life. It affects approximately 20% of children and 10% of adults worldwide and develops through a complex interplay of genetic predisposition, environmental factors, immune dysregulation, and microbial imbalance. Skin barrier dysfunction is a central feature of its pathogenesis, often associated with impaired filaggrin function, thereby facilitating the penetration of allergens and microorganisms into the skin and triggering inflammatory responses. The disease is predominantly associated with type 2 immune responses involving cytokines such as interleukin (IL)-4, IL-13, IL-25, IL-33, and thymic stromal lymphopoietin (TSLP). Effective representation of skin and disease-related immune response is shown in Figures 1 and 2. Keratinocytes, dendritic cells, mast cells, eosinophils, macrophages, and T lymphocytes collectively contribute to the initiation and progression of inflammation. Furthermore, colonization by

Staphylococcus aureus may aggravate skin barrier disruption and inflammatory responses, contributing to disease persistence and recurrence.[1]

The management of atopic dermatitis involves a comprehensive approach that includes regular moisturization, avoidance of disease triggers, patient education, and pharmacological intervention. Topical corticosteroids remain a cornerstone of treatment for acute inflammatory exacerbations because of their potent anti-inflammatory and immunosuppressive effects. Among these, betamethasone dipropionate (BD) is a highly potent synthetic corticosteroid widely used to manage corticosteroid-responsive dermatoses, including atopic dermatitis, eczema, contact dermatitis, and psoriasis. Its therapeutic activity is primarily mediated by suppression of inflammatory mediators and immune responses, thereby reducing erythema, swelling, and pruritus.[2] However, the clinical performance of a topical corticosteroid depends not only on its pharmacological potency but also on its physicochemical properties, formulation characteristics, and ability to achieve adequate drug deposition at the target site. Prolonged or inappropriate use of potent topical corticosteroids may also increase the risk of local adverse effects, emphasizing the importance of developing suitable delivery systems that support effective topical therapy while minimizing unnecessary drug exposure.[3]

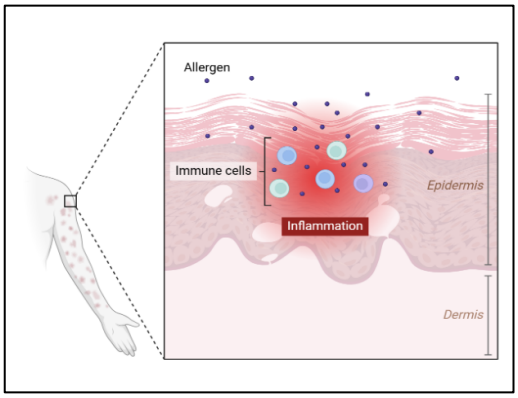


Figure 1: Allergen-induced skin inflammation in atopic dermatitis with immune cell infiltration.

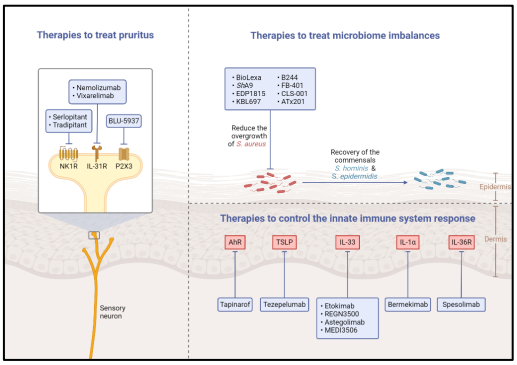


Figure 2: Role of Skin Barrier Dysfunction in the Pathogenesis of Atopic Dermatitis

BD has a molecular weight of approximately 504.6 g/mol, is highly lipophilic (reported log P of 4.5–5.0), and exhibits poor aqueous solubility. Although its lipophilic nature favors partitioning into the stratum corneum, limited aqueous solubility may restrict drug release from conventional topical vehicles and influence its availability within the skin. Consequently, the development of an appropriate topical formulation is important to achieve reproducible drug release, adequate skin permeation, physicochemical stability, and acceptable patient compliance. Conventional creams, ointments, and gels are established approaches for administering corticosteroids; however, their performance may vary with vehicle composition, drug solubilization, skin condition, and the anatomical site of application. These considerations support the investigation of alternative topical delivery platforms to improve BD formulation performance.[4]

Pluronic Lecithin Organogel (PLO) represents a potential approach for addressing these formulation challenges. PLO is a structured topical drug delivery system comprising lecithin, a non-aqueous or oil-based phase, and the hydrophilic block copolymer Pluronic F127 (poloxamer 407), which contributes to gel formation, stability, and desirable rheological characteristics. Additional excipients, such as isopropyl myristate or isopropyl palmitate, may be incorporated to modify the formulation properties and facilitate drug delivery. Lecithin phospholipids can interact with the lipid components of the stratum corneum, potentially promoting temporary changes in lipid organization and enhancing drug partitioning into the skin. The organized gel structure, combined with the solubilizing properties of the formulation components, may support drug release and improve contact between the formulation and the application site. Poloxamer 407 further contributes to the formation of a stable gel network and can impart

thermoreversible behavior, depending on the formulation composition and polymer concentration. These characteristics make PLO a promising platform for investigating the topical delivery of drugs intended for localized dermatological treatment.[5]

The potential utility of PLO for atopic dermatitis is particularly relevant because the disease involves both persistent inflammation and impairment of the skin barrier. A suitable organogel formulation may facilitate BD delivery to the affected skin while providing acceptable spreadability, viscosity, drug content, and formulation stability. Nevertheless, PLO performance is strongly influenced by lecithin and poloxamer concentrations, the selection of the oil phase and penetration-enhancing excipients, and the physicochemical characteristics of the incorporated drug. Therefore, formulation optimization and systematic evaluation are necessary to establish whether the proposed delivery system offers meaningful advantages over conventional topical corticosteroid formulations. In particular, drug release, ex vivo skin permeation, stability, and potential for skin irritation are important parameters for assessing its pharmaceutical performance and suitability for further investigation.[6]

The present study explores the systematic development and Quality by Design (QbD)-guided optimization of a betamethasone dipropionate-loaded Pluronic Lecithin Organogel for potential topical application in atopic dermatitis. The study investigates the combined influence of Poloxamer 407, lecithin, and isopropyl myristate on formulation characteristics and drug-release behavior using a three-factor, three-level Box–Behnken experimental design. Unlike an empirical formulation development approach, this strategy integrates physicochemical characterization, response surface analysis, and multi-response numerical optimization to identify a candidate formulation with a balanced profile of rheological properties and in vitro drug release. The work provides an experimental basis for further evaluating PLO as a topical delivery platform for betamethasone dipropionate.[7]

Research gap and novelty

Although Pluronic-based gels and lecithin-containing topical delivery systems provide established approaches for dermal drug delivery, formulation performance depends on the interactions among polymer concentration, lipid-phase composition, and drug-release characteristics. Therefore, systematic optimization is important for identifying an appropriate balance between the physicochemical properties and the release behavior of a topical formulation. In this context, the present study investigates betamethasone dipropionate-loaded Pluronic Lecithin Organogel using a QbD approach and a three-factor, three-level Box–Behnken design. The distinctive contribution of the study lies in the systematic evaluation of Poloxamer 407, lecithin, and isopropyl myristate as formulation variables, together with the assessment of multiple physicochemical attributes and drug-release responses at different time points. This approach provides a structured basis for identifying an optimized formulation for subsequent investigation of its suitability for topical drug delivery.

In view of these considerations, the present study aims to develop, optimize, and evaluate a BD-loaded Pluronic Lecithin Organogel for the topical management of atopic dermatitis. The study focuses on formulation development and physicochemical characterization, including pH, viscosity, spreadability, thermoreversible behavior, and drug content. In vitro drug release and skin permeation studies will be conducted to investigate the formulation's release characteristics and its potential to facilitate dermal drug delivery. Stability testing, evaluation of potential for skin irritation, and comparative assessment against a marketed topical corticosteroid formulation will further help establish its pharmaceutical performance. The proposed work is intended to determine the feasibility of PLO as an alternative topical delivery platform for BD and to provide a formulation-development basis for improving the localized management of inflammatory skin conditions such as atopic dermatitis.

2. Materials and Methods

2.1. Fourier Transform Infrared (FTIR) Spectroscopy

FTIR spectroscopy was employed to investigate the potential interactions between BD and the selected formulation excipients. The infrared spectra of the pure drug and the physical mixture of BD with the formulation polymers were recorded using a Shimadzu FTIR spectrophotometer over the wavenumber range of 400–4000 cm^{-1}. The obtained spectra were compared to identify characteristic absorption bands and assess possible changes associated with drug–excipient interactions.[8]

2.2. Quality by Design-Based Formulation Optimization

The formulation of BD-loaded PLO was optimized using a QbD approach. A three-factor, three-level Box–Behnken experimental design was developed using Design-Expert software (Demo version 13). The design was used to evaluate the effects of formulation variables and their interactions on drug-release characteristics.[9]

Poloxamer 407 concentration, lecithin concentration, and isopropyl myristate (IPM) volume were selected as the independent variables. The dependent variables were the cumulative drug release at 1, 5, 8, and 24 h. The factor levels were selected based on preliminary formulation studies and the experimental protocol described in the source document.

Table 1. Formulation design matrix for optimization of BD-loaded PLO

Run	Poloxamer 407 (g)	Lecithin (g)	IPM (mL)
1	7.5	3.0	9
2	10.0	1.5	9
3	12.5	3.0	9
4	12.5	4.5	7
5	7.5	4.5	7
6	10.0	4.5	9
7	7.5	3.0	5
8	12.5	1.5	7
9	10.0	3.0	7
10	7.5	1.5	7
11	10.0	4.5	5
12	10.0	1.5	5
13	12.5	3.0	5
14	10.0	3.0	7
15	10.0	3.0	7

The experimental responses were intended to be evaluated using polynomial regression models to establish the relationship between formulation variables and drug release. The optimized formulation should be identified based on the predefined response criteria and the numerical optimization results.

2.3. Preparation of BD-Loaded PLO Gel

The BD-loaded PLO gel was prepared using an oil phase and an aqueous phase. The combination of hot- and cold-method preparation principles described in the source document was adapted to the specific formulation composition reported for the optimized preparation.[10]

2.3.1. Preparation of the oil phase

Lecithin was mixed with isopropyl myristate and heated to 90°C to facilitate its dissolution. Butylated hydroxytoluene (BHT; 25 mg) and sorbic acid (100 mg) were incorporated into the oil phase. The mixture was stirred until a uniform phase was obtained. The lecithin: IPM ratio in Table 1 is used across various formulation codes.

2.3.2. Preparation of the drug-containing aqueous phase

BD (50 mg) was mixed with polyethylene glycol 400 (PEG 400; 10 mL) to obtain a uniform drug-containing mixture; the same solution was commonly used for all 15 and optimized batches. Poloxamer 407 (quantity as per DOE) was dissolved in the required quantity of distilled water to prepare the aqueous polymer phase. The prepared Poloxamer 407 solution was stored at a low temperature overnight to facilitate polymer dissolution and obtain a homogeneous solution.

2.3.3. Formation of the PLO gel

The oil phase was gradually incorporated into the aqueous Poloxamer 407 phase under mechanical stirring. Mixing was continued until a uniform semisolid formulation was obtained. All the batches were cross-checked for homogeneity, room-temperature stability for 15 days, and drug uniformity using a validated UV method, as reported later. The resulting BD-loaded PLO gel was evaluated for pH, viscosity, spreadability, thermoreversibility, and in vitro drug release.[11] After evaluation, the optimized batch suggested by Design-Expert was used, and confirmation was performed accordingly. The final optimized formula is presented in Table 2.

Table 2. Composition of the reported BD-loaded PLO formulation

Ingredient	Quantity
Betamethasone dipropionate	50 mg
Poloxamer 407	11.166 g
Isopropyl myristate	5 mL
Lecithin	1.748 g
Sorbic acid	100 mg
Butylated hydroxytoluene	25 mg
PEG 400	10 mL

Distilled water	Up to 50 mL

2.4. Physicochemical Characterization of PLO Gel

2.4.1. Determination of viscosity

The viscosity of the prepared PLO gel was measured using a thermostatically controlled Brookfield viscometer (Model LV) equipped with spindle LV-7. Measurements were performed at 20 rpm and room temperature. The viscosity values were recorded in triplicate to evaluate the consistency and flow characteristics of the prepared formulations, and the average is presented.[12]

2.4.2. Determination of spreadability

The spreadability of the PLO gel was assessed using the glass-slide method. Approximately 1 g of the formulation was placed on a clean glass slide and covered with a second slide. A 100 g weight was applied for 5 s to facilitate spreading. After the weight was removed, the spread area was marked on butter paper and measured.[13]

Spreadability was calculated using the following equation:

$$S = M \times L/T$$

where:

- (S) = spreadability (g·cm/s);
- (M) = applied weight (g);
- (L) = distance traveled by the slide (cm);
- (T) = time taken for the slide to travel the specified distance (s).

The spreadability value was used to assess the gel's ease of application. The manuscript should report the actual measured slide displacement and the corresponding spreadability values.

2.4.3. Evaluation of thermoreversibility

The thermoreversible behavior of the PLO gel was evaluated by placing the formulation in borosilicate glass containers and heating the samples in a hot-air oven over the temperature range of 27–50°C at a heating rate of 1°C/minute. The temperature at which the gel began to flow upon inversion of the container was recorded as the gel-to-sol transition temperature.[14]

The formulation's ability to regain its gel structure upon cooling was also examined qualitatively. The cooling rate was fixed at 2°C/minute. This assessment was used to characterize the temperature-dependent sol–gel behavior of the formulation. Studies were done in triplicate.

2.4.4. Determination of pH

The pH of the PLO gel was determined using a calibrated digital pH meter at room temperature. Briefly, 1 g of the formulation was dispersed in 25 mL of deionized water, and the pH of the resulting dispersion was measured. The pH was evaluated to assess the formulation's suitability for topical application.

2.5. In Vitro Drug Release Study

The in vitro release of BD from the optimized PLO gel was investigated using the dialysis membrane method. The dialysis membranes (Himedia, LA387-5MT; molecular cut-off 1200 Dalton) were pre-cleaned and soaked in distilled water overnight before use. Approximately 2 g of the formulation was placed in a dialysis bag, which was then immersed in 100 mL of phosphate-buffered saline (PBS; pH 7.4) containing 10% ethanol.

The release study was conducted at 37°C under continuous magnetic stirring at 100 rpm. Samples of 5 mL were withdrawn at predetermined intervals of 1, 2, 3, 5, 8, and 24 h. Following each withdrawal, an equal volume of fresh release medium was added to maintain a constant volume and concentration gradient.[15]

The collected samples were analyzed by UV spectrophotometry at 240 nm to determine the concentration of released BD by the validated method. The cumulative percentage of drug released was calculated using the appropriate concentration and sampling volume corrections. The release profile was constructed by plotting cumulative percentage drug release against time.

2.6. Analysis of Drug Release Kinetics

The in vitro release data obtained from the optimized PLO gel were fitted to zero-order, first-order, Higuchi, and Korsmeyer–Peppas kinetic models to investigate the release pattern. For the zero-order model, the cumulative amount of drug released was plotted against time. In the first-order model, the logarithm of

the percentage of drug remaining was plotted against time. In the Higuchi model, the cumulative percentage of drug released was plotted against the square root of time to evaluate the applicability of the diffusion-based model. Korsmeyer–Peppas model. The logarithm of the fractional drug release was plotted against the logarithm of time. The release exponent was interpreted based on the formulation's geometry and the applicable model-specific criteria.

The kinetic models were compared using their coefficients of determination (R^2), with higher values indicating a closer fit to the corresponding model. The model with the best statistical fit was considered alongside the assumptions and limitations of each kinetic equation to interpret the release behavior.[16]

3. Results and Discussion

3.1. FTIR Spectroscopic Analysis

FTIR spectroscopy was used to examine the characteristic functional groups of the drug and to assess potential interactions between the drug and the excipients incorporated into the PLO formulation. Spectra are shown in Figure 3, a: PLO placebo, b: BD, c: BD loaded PLO.

The FTIR spectrum of the PLO placebo exhibited absorption bands at 3417.84 cm^{-1}, associated with O–H stretching, and at 2876.52 cm^{-1}, attributed to aliphatic C–H stretching. Additional bands at 1732.22 and 1627.54 cm^{-1} were assigned to carbonyl and C=C vibrations, respectively. In comparison, bands at 1251.85 and 1123.51 cm^{-1} were attributed to C–O–C and C–O stretching vibrations of the formulation components. These spectral features were consistent with the presence of Poloxamer 407, lecithin, isopropyl myristate, and sorbic acid in the formulation.[17] The spectrum of the pure drug showed characteristic absorption bands at 3478.79, 3088.33, 2923.84, 1712.15, 1612.49, 1271.70, and 1069.02 cm^{-1}, corresponding to the reported hydroxyl, C–H, carbonyl, C=C, C–F, and C–O vibrations, respectively. These absorption bands provided the reference spectral profile for comparison with the placebo and drug-loaded gel.[18]

The spectrum of the drug-loaded PLO gel displayed absorption bands at 3551.96, 3423.58, 3231.43, 2996.26, 2877.24, 1732.94, 1626.83, 1512.83, 1251.85, 1117.06, and 833.85 cm^{-1}. The bands in the higher-wavenumber region were assigned to hydroxyl and C–H stretching vibrations. In contrast, those in the fingerprint region were attributed to vibrations associated with the excipients and the drug-containing formulation. The carbonyl absorption at 1732.94 cm^{-1} and the C–O–C absorption at 1251.85 cm^{-1} were particularly relevant to the ester-containing components and the ether linkages of Poloxamer 407, respectively.[19]

Overall, the observed spectra demonstrate characteristic functional-group vibrations in the drug-loaded formulation. A conclusion derived from a direct comparison of the drug-specific bands in the pure-drug and formulation spectra, including assessment, confirms the absence of peak shifts, disappearance, broadening, or changes in intensity.

3.2. Effect of Formulation Variables on the Physicochemical Characteristics of PLO Gel

A three-factor, three-level Box–Behnken design was used to investigate the influence of Poloxamer 407, lecithin, and isopropyl myristate on the physicochemical characteristics and drug-release behavior of the PLO formulations. The measured responses included viscosity, thermoreversibility, pH, spreadability, and cumulative drug release at 1, 5, 8, and 24 h. The experimental results demonstrated considerable variation among formulations, indicating that the composition of the organogel influenced its rheological characteristics and release profile. 3D graph models representing relationships between independent variables, a. viscosity; b. Spreadability; c.Thermoreversibility; d. pH is presented in Figure 4, and for *in-vitro* release at e.1; f.5; g.8; and h.24 Hours in Figure 5

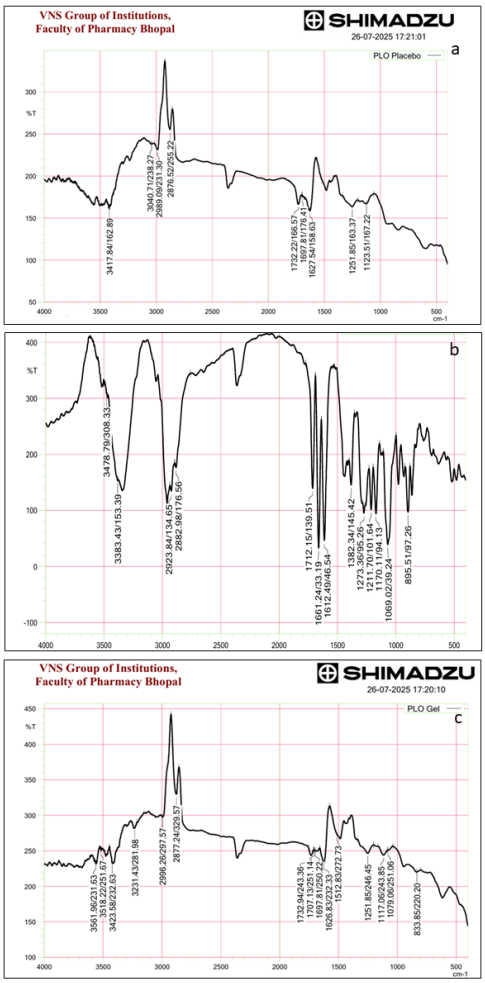


Figure 3, FTRI spectra: a: PLO placebo, b: BD, c: BD loaded PLO.

Table 3: Box Behnken Experimental Design with Observed Responses of PLO Gel

Formulations	Poloxamer 407 (g)	Lecithin (g)	IPM (ml)	Viscosity (cP)	Thermoreversibility (°C)	pH	Spreadability (g.cm/s)	1hr Drug Release (%)	5hr Drug Release (%)	8hr Drug Release (%)	24hr Drug Release (%)
1	12.5	3	7	112800	36.5	7.73	0.89	63.81	69.05	75.39	83.31
2	10	1.5	9	126700	36	6.93	0.92	66.76	70.3	74.56	93.36
3	7.5	3	9	147700	33.5	7.28	3.06	59.93	66.43	76.81	82.77
4	7.5	3	7	199880	36.5	7.77	1.46	59.21	65.04	73.42	83.92
5	12.5	4.5	7	129200	35.5	6.26	0.65	53.23	60.5	71.9	96.92
6	10	3	9	183400	34	6.55	0.83	38.55	47.91	58.83	99.99
7	10	3	5	57000	32.5	6.25	0.93	73.04	79.07	81.84	86.58
8	7.5	1.5	7	157400	35	6.67	0.74	48.23	57.91	69.05	92.51
9	7.5	3	5	198600	35.5	6.82	0.75	54.13	62.78	76.9	99.66

10	10	1.5	7	34400	34.5	6.34	0.88	55.78	64.09	77.63	84.85
11	10	4.5	7	1164000	33.5	6.17	0.77	41.92	50.87	68.73	84.18
12	12.5	1.5	5	1844000	36.5	6.45	0.66	37.91	45.01	59.83	83.33
13	12.5	3	5	1996000	35.5	6.43	0.67	31.76	40.16	52.99	83.52
14	10	3	9	780000	34	6.55	1.36	44.29	51.48	63.66	73.94
15	10	3	7	1768000	33	6.72	0.7	33.55	41.31	53.84	78.92

3.2.1. Viscosity

The viscosity of the prepared formulations ranged from 34,400 to 376,800 cP. The lowest value was observed for the formulation containing 10 g of Poloxamer 407, 1.5 g of lecithin, and 7 mL of IPM. In contrast, the highest value was reported for the formulation containing 10 g of Poloxamer 407, 3 g of lecithin, and 7 mL of IPM.

The variation in viscosity indicates that the rheological behavior of the formulations was not governed solely by the amount of Poloxamer 407. Lecithin and IPM also contributed to differences in the formulation structure and consistency. Changes in the relative proportions of the aqueous polymer phase and lipid-containing phase may influence the organization of the gel network and, consequently, its apparent viscosity.[20]

The quadratic response-surface model reported for viscosity was:

$$\textbf{Viscosity} = 217800 + 46397.5 \cdot A + 15747.5 \cdot B + 1650 \cdot C - 13080 \cdot AB - 26925 \cdot AC + 31175 \cdot BC - 55515 \cdot A^2 - 32065 \cdot B^2 - 33010 \cdot C^2$$

where (A), (B), and (C) represent the coded levels of Poloxamer 407, lecithin, and IPM, respectively.

The model includes linear, interaction, and quadratic terms, suggesting that the relationship between composition and viscosity may be nonlinear. Nevertheless, the magnitude and statistical significance of the individual effects cannot be established from the regression equation alone. Analysis of variance (ANOVA), model-fit statistics, and diagnostic plots are needed to assess the model's adequacy and predictive reliability.

From a formulation perspective, viscosity is an important parameter because it affects handling, spreading, residence time, and the diffusion of drug molecules through the semisolid matrix. However, the highest viscosity should not automatically be considered optimal, since excessive consistency may reduce ease of application and may not necessarily improve drug release.

3.2.2. Spreadability

The measured spreadability values ranged from 0.65 to 3.06, as reported in the experimental dataset. The highest value, 3.06, was obtained for the formulation containing 7.5 g of Poloxamer 407, 3 g of lecithin, and 9 mL of IPM. In contrast, a value of 0.65 was observed for the formulation containing 12.5 g of Poloxamer 407, 4.5 g of lecithin, and 7 mL of IPM.

These observations indicate that the ease of spreading varied substantially with formulation composition. The formulation with the highest spreadability contained less Poloxamer 407 and a higher volume of IPM than several formulations with lower spreadability. This pattern is consistent with the possibility that changes in polymer concentration and in the relative proportion of the oil phase alter the gel's resistance to deformation during spreading.

The reported response-surface equation was:

$$\textbf{Spreadibility} = 1.0087 + 0.3225A + 0.0463B + 0.3163C + 0.2375AB + 0.6075AC - 0.085BC$$

The positive coefficients of the linear and most interaction terms suggest positive contributions to the predicted response within the fitted model. In contrast, the negative (BC) coefficient indicates a negative interaction between the coded lecithin and IPM factors. These interpretations are contingent on the coding scheme and the model's adequacy.[21]

The spreadability findings also demonstrate that a high-viscosity formulation does not necessarily exhibit good spreading performance. Therefore, both parameters should be considered together during optimization to balance semisolid consistency and ease of topical application.

3.2.3. Thermoreversibility

The measured gel-to-sol transition temperatures ranged from 32.5 to 36.5°C across the reported formulations. The highest transition temperature, 36.5°C, was observed in formulations 1, 4, and 12, while the lowest, 32.5°C, was recorded for formulation 7.

The observed temperature range indicates that the formulations exhibited differences in their temperature-dependent flow behavior. Poloxamer 407 is a thermoresponsive polymer, and its organization in aqueous systems is sensitive to temperature and concentration. The

presence of lecithin and IPM may further modify the structure and flow behavior of the composite formulation.[22]

The reported quadratic model was:

Thermoriversibility = 34.16667 + 0.1875·A - 0.0625·B + 0·C + 0.125·AB - 1.5·AC - 0.25·BC + 0.10417·A² + 1.10417·B² + 0.22917·C²

The relatively large negative coefficient for the (AC) interaction suggests that the combined effect of Poloxamer 407 and IPM may influence the predicted transition temperature in a direction different from their individual linear effects. This remains a model-based interpretation rather than proof of a specific molecular mechanism.

The ability of a topical formulation to maintain an appropriate consistency during storage and application is an important consideration. Nevertheless, the measured transition temperature should be interpreted in relation to the intended application conditions, and thermoreversibility should be confirmed by reproducible heating–cooling measurements.

3.2.4. pH

The pH of the experimental formulations ranged from 6.17 to 7.77. The lowest pH was recorded for the formulation containing 10 g of Poloxamer 407, 4.5 g of lecithin, and 7 mL of IPM. In comparison, the highest value was observed for the formulation containing 7.5 g of Poloxamer 407, 3 g of lecithin, and 7 mL of IPM.

The variation in pH indicates that the formulation's composition influenced the measured acidity or alkalinity of the aqueous dispersion. Differences in the concentration of acidic components, including sorbic acid, and variations in the formulation matrix may contribute to the observed changes. However, the relative contributions of individual excipients cannot be established from the available data because sorbic acid was not explicitly varied as a factor in the reported three-factor design.[23]

The reported linear response model was:

pH = 6.748 + 0.1963A + 0.0825B + 0.4363C

The coefficients indicate positive predicted relationships between the coded factors and pH within the model. The relatively larger coefficient for (C) suggests a greater modeled effect of the IPM factor than that of the other two factors.

The pH results provide an initial indication of the formulation's physicochemical characteristics. However, topical tolerability cannot be established from pH alone; it requires suitable safety and skin-compatibility studies.[24]

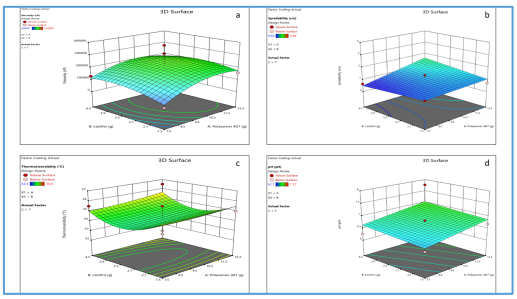


Figure 4: 3D graphs representing relationships between independent variables, a. viscosity; b. Spreadability; c.Thermoreversibility; d. pH

3.3. Effect of Formulation Variables on In Vitro Drug Release

The in vitro drug-release profiles showed that the cumulative release of BD varied with PLO gel composition. Across the 15 experimental runs, the reported drug release ranged from 31.76% to 73.04% at 1 h, 40.16% to 79.07% at 5 h, 52.99% to 81.84% at 8 h, and 73.94% to 99.99% at 24 h. These results demonstrate that the formulation variables influenced both the early and longer-term release profiles.[25]

3.3.1. Drug release at 1 h

At 1 h, the highest reported release was 73.04%, observed for the formulation containing 10 g of Poloxamer 407, 3 g of lecithin, and 5 mL of IPM. The lowest release was 31.76%, observed in the formulation containing 12.5 g of Poloxamer 407, 3 g of lecithin, and 3 mL of IPM, as shown in Table 3.

The relatively high initial release observed in the formulation containing 5 mL of IPM may reflect differences in drug partitioning, matrix structure, and diffusion pathways through the gel. Conversely, a higher polymer concentration may increase the resistance to drug transport under certain compositional conditions. These explanations are plausible mechanisms of formulation, but the experimental data do not

independently establish the contribution of each mechanism.[26]

The reported response-surface equation was:

1hr Drug Release = 43.99 - 5.84125·A - 1.97125·B + 5.5525·C + 3.3825·AB + 9.35·AC - 8.055·BC + 10.48625·A² - 0.36375·B² + 2.65875·C²

The negative linear coefficients for Poloxamer 407 and lecithin indicate a decrease in predicted initial release with increasing coded levels of these factors. In contrast, the positive coefficient for IPM suggests the opposite trend. The positive AC interaction indicates that the combined effect of Poloxamer 407 and IPM differs from the sum of their individual linear effects.

3.3.2. Drug release at 5 h

At 5 h, the cumulative release varied from 40.16% to 79.07%. The maximum value was recorded for the formulation containing 10 g of Poloxamer 407, 3 g of lecithin, and 5 mL of IPM. This was the same formulation that exhibited the highest release at 1 h.

The persistence of relatively high release at both time points suggests that the initial release behavior was influenced by the combined formulation composition rather than by a single excipient. Differences in the amount of drug available for diffusion and in the gel's microstructure may have contributed to the observed release profiles.

The corresponding response-surface equation was:

5hr Drug Release = 51.85667 - 5.39625·A - 1.62375·B + 4.8225·C + 2.68·AB + 9.0725·AC - 7.0625·BC + 10.09167·A² - 0.06333·B² + 1.72917·C²

The coefficients show a pattern similar to that observed for the 1 h response, with negative linear coefficients for Poloxamer 407 and lecithin and a positive coefficient for IPM.[27] However, the response equations alone do not establish whether these effects are statistically significant. The ANOVA results and model diagnostics should be included in the final manuscript.

3.3.3. Drug release at 8 h

The cumulative drug release at 8 h ranged from 52.99% to 81.84%. The highest value was again observed for the formulation containing 10 g of Poloxamer 407, 3 g of lecithin, and 5 mL of IPM. This formulation, therefore, exhibited comparatively high release across the early and intermediate sampling periods.

The observed differences among formulations suggest that the relative proportions of polymer and lipid components influenced drug transport through the gel matrix. A more viscous polymer network may increase the diffusional path length or reduce molecular mobility, whereas the oil phase may alter drug solubilization and partitioning.[28] The net effect depends on the formulation's composition and cannot be predicted from polymer concentration alone.

The reported response-surface equation was:

8hr Drug Release = 64.8 - 4.31125·A - 1.02375·B + 2.775·C + 2.525·AB + 7.5675·AC - 6.1575·BC + 7.235·A² + 0.965·B² - 0.2775·C²

The decreasing magnitude of the negative linear coefficient for Poloxamer 407 across the 1, 5, and 8 h equations suggests that its modeled influence on release changed with sampling time. This may indicate a time-dependent response to formulation composition; however, this interpretation requires confirmation using the statistical model and the underlying experimental observations.

3.3.4. Drug release at 24 h

At 24 h, cumulative release ranged from 73.94% to 99.99%. The maximum value was reported for the formulation containing 10 g of Poloxamer 407, 3 g of lecithin, and 9 mL of IPM. In contrast, the minimum value was observed for the same polymer and lecithin quantities, using 9 mL of IPM, in another experimental run. Because these runs have the same nominal composition but different recorded responses, the underlying formulation records must be checked before attributing the difference to experimental variability.

The higher cumulative release at 24 h than at earlier sampling times indicates continued drug release from the formulations throughout the study period. Several formulations approached complete release at the final sampling point, whereas others retained a larger fraction of the nominal drug content. These differences highlight the importance of optimizing the

formulation for the desired balance between early drug availability and sustained release.[29]

The reported quadratic equation for 24 h release was:

24 hr Drug Release = 85.84 − 1.1175A + 1.3588B + 2.7163C − 5.165AB + 0.63AC + 1.4225BC − 1.2188A² + 4.9288B² − 0.5763C²

Compared with the early-release models, the linear coefficients for lecithin and IPM were positive, while the magnitude of the Poloxamer 407 coefficient was smaller. This pattern suggests that the relationship between composition and release changed over time. Nevertheless, mechanistic conclusions require confirmation through the complete release dataset, appropriate statistical analysis, and validation of the analytical method.[30]

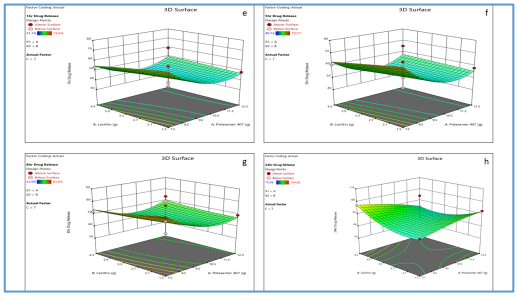


Figure 5: 3D graphs representing relationships between independent variables, for *in-vitro* release at e.1; f.5; g.8; and h.24 Hours

3.4. Optimization of the PLO Gel Using the Box–Behnken Design

Numerical optimization was performed using the reported response-surface models to identify a formulation with desirable physicochemical characteristics and drug-release behavior. The selected solution contained approximately 11.166 g of Poloxamer 407, 1.748 g of lecithin, and 5 mL of IPM. The experimental document reports a combined desirability value of approximately 0.7574 for this solution.[31]

3.4.1. Significance of the QbD-Based Optimization Approach

Discuss how the experimental design enables assessment of factor interactions, why multiple release time points are useful, and how physicochemical characteristics should be considered together. Use the response-surface plots and optimization data already included in the manuscript.[32] The reported optimized formulation and associated responses are summarized in Table 4. The detailed results and solutions provided by BBD are presented in Tables 5 and 6, respectively.

Table 4: Optimized dependent and independent variables of the study by BBD

Response	Reported value
Poloxamer 407	11.1661 g
Lecithin	1.74901 g
IPM	5 mL
Viscosity	129,800 cP
Thermoreversibility	36°C
pH	6.37
Spreadability	0.84
Drug release at 1 h	38.97%
Drug release at 5 h	75.59%
Drug release at 8 h	97.35%
Drug release at 24 h	98.76%
Combined desirability	0.7574

The optimized composition reflects a compromise among the formulation responses rather than maximizing a single parameter. Its reported pH and spreadability provide initial physicochemical information, while the release values indicate substantial drug release by the later sampling times.[33] Figure 6 shows a graphical representation of desirability. Maximum desirability is shown in the 2D contour graph in Figure 7.

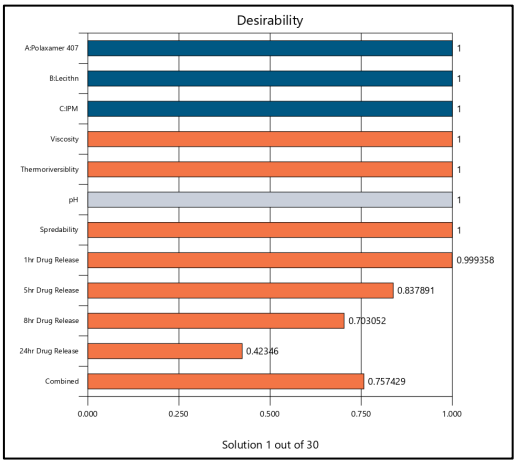


Figure 6: Bar Graph Showing Desirability

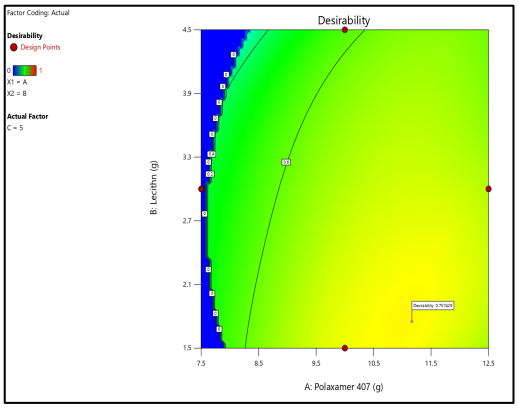


Figure 7: 2D-contour plots showing the maximum desirability of the optimized formulation of PLO Gel

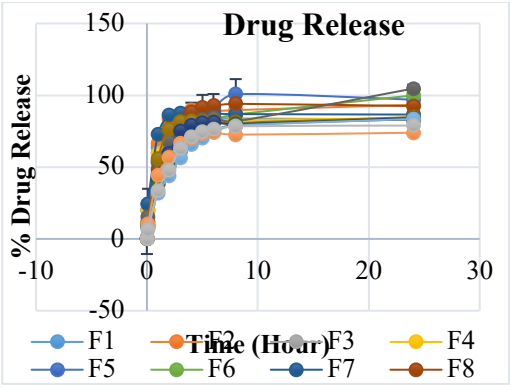


Figure 8: *In Vitro* Drug Release of PLO Gels

3.5. Comparative In Vitro Drug-Release Profiles

The comparative release plot in the uploaded document shows the release profiles of formulations F1–F15 over the 24 h study period. The profiles differ in their initial, intermediate, and final cumulative releases, indicating that changes in formulation composition altered the overall release pattern.

Several formulations exhibited relatively rapid initial drug release, while others showed a more gradual increase over the sampling period. At later time points, many profiles approached approximately 80–100% release, although the magnitude and timing of this increase differed among formulations. The overall trend is consistent with continued drug liberation from the semisolid matrix. However, the available plot does not independently establish whether the process was controlled predominantly by diffusion, matrix relaxation, or another mechanism.[34]

The comparison of release profiles also demonstrates why optimization based only on the final cumulative release may be inadequate. A formulation that releases a large proportion of its drug early may behave differently from one that produces a more gradual release profile, even if both show similar cumulative release at 24 h. Therefore, the response-surface approach provides a useful framework for considering multiple time points during formulation development. Comparative drug release is presented in Figure 8.

Table 5:- (A) Confirmation location one PLO DOE Parameter

Poloxamer 407 (g)	Lecithin (g)	IPM (ml)
11.166	1.748	5

(B) Response Data

Viscosity (cP)	Thermoreversibility (°C)	pH	Spreadability (g.cm/sec)	1hr Drug Release (%)	5hr Drug Release (%)	8hr Drug Release (%)	24hr Drug Release (%)
129800	36	6.37	0.84	38.97	75.59	97.35	98.76

(C) Confirmation location two

Confirmation Two-sided Confidence = 95%

Analysis	Predicted Mean	Predicted Median	Observed	Std Dev	n	SE Pred	95% PI Low	Data Mean	95 % PI High
Viscosity	126687	126687	128766.6	-	1	102006	-92093.8	199800	345467
Thermoreversibility	36.6024	36.6024	36	0.908295	1	1.17022	33.5942	36	39.6105
pH	6.33448	6.33448	6.3	0.390959	1	0.446334	5.35211	6.77	7.31686
Spreadability	0.357634	0.357634	0.494665	0.494665	1	0.620191	-1.07253	0.84	1.7878
1hr Drug Release	31.7789	31.7789	11.2524	11.2524	1	14.1078	-0.753869	38.97	64.3116
5hr Drug Release	73.7997	73.7997	64.1665	4.78334	1	6.16273	59.6511	75.59	85.9484
8hr Drug Release	80.9362	80.9362	86.53	4.32293	1	5.56955	66.6129	97.35	95.2532
24hr Drug Release	86.9578	86.9578	81.4691	11.4609	1	14.7659	49.0008	98.76	124.915

Table 6:- Solutions: 25 Solutions found; 10 solutions are listed out of 25

SNo.	Poloxamer 407	Lecithin	IPM	Viscosity	Thermoreversibility	pH	Spreadability	1hr Drug Release	5hr Drug Release	8hr Drug Release	24hr Drug Release	Desirability	Remark
1	11.1661	1.7485	5.00000	12666.67	36.6016	6.33445	0.3576	31.7762	73.8018	80.9404	86.9613	0.7574	Selected

2	11.1482	1.7550	5.000000	1266686.67	36.6180	6.3334	0.3620	31.9378	73.7579	80.8279	86.9053	0.7574	
3	11.1414	1.7353	5.000000	1266686.67	36.5900	6.3318	0.3602	31.8871	73.8367	80.9707	87.0410	0.7574	
4	11.1283	1.7533	5.000000	1266686.67	36.6224	6.3318	0.3656	32.0730	73.7476	80.7774	86.9057	0.7574	
5	11.1125	1.7449	5.000000	1266686.67	36.6146	6.3301	0.3674	32.1446	73.7698	80.7963	86.9554	0.7574	
6	11.1434	1.7131	5.000000	1266686.67	36.5542	6.3307	0.3563	31.7598	73.9365	81.1666	87.2025	0.7574	
7	11.1022	1.7432	5.000	1266686.67	36.6152	6.32	0.3691	32.2096	73.7688	80.7783	86.9618	0.7574	
			00			92							
8	11.1256	1.7800	5.000000	1266686.67	36.6639	6.3330	0.3704	32.2276	73.6329	80.5488	86.7174	0.7573	
9	11.1215	1.6825	5.000000	1266686.67	36.5125	6.3273	0.3557	31.7634	74.0538	81.3581	87.4115	0.7572	
10	11.0369	1.7469	5.000000	1266686.67	36.6393	6.3242	0.3823	32.6996	73.7013	80.5432	86.8954	0.7571	

3.6. Drug-Release Kinetic Analysis

The release data for the optimized PLO gel were fitted to zero-order, first-order, Higuchi, and Korsmeyer–Peppas models. The reported regression equations and coefficients of determination are summarized in Table 7 and Figure 9.

Table 7. Reported regression parameters for drug-release kinetic models

Kinetic model	**Reported regression equation**	**(R^2)**
Zero-order	(y=4.1829x+1.9441)	0.9797
First-order	(y=0.05757x+0.72251)	0.9347
Higuchi	(y=21.3300x-16.1889)	0.9179
Korsmeyer–Peppas	(y=1.3698x+0.3245)	0.9094

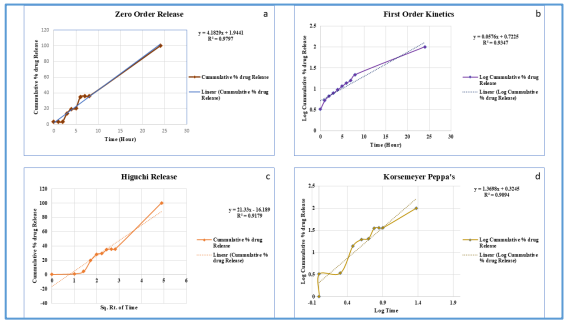


Figure 9: Graphs of release kinetics for *in-vitro* release a: Zero; b: First; c: Higuchi; d: Korsmeyer–Peppas kinetics

3.6.1. Zero-order kinetics

The zero-order model exhibited the highest reported coefficient of determination (R^2=0.9797) among the four kinetic models. This indicates that the cumulative drug-release data plotted showed the strongest linear association with time in the reported analysis.

Zero-order behavior is characterized by a constant release rate over time. The relatively high (R^2) suggests that the zero-order model may provide a useful empirical description of the plotted profile. However, a high coefficient of determination alone does not prove that the formulation releases the drug at a truly constant rate. The underlying release values, sampling corrections, and regression procedure should be checked to ensure that the model has been fitted appropriately.

3.6.2. First-order kinetics

The first-order model yielded an (R^2) value of 0.9347, which was lower than that of the zero-order model. Under the conventional first-order interpretation, the release rate depends on the amount of drug remaining in the formulation.

The lower reported linear-fit statistic suggests that the first-order transformation described the plotted data less closely than the zero-order transformation. Nevertheless, this comparison should be considered provisional until the first-order plot is confirmed to use the logarithm of the percentage of drug remaining rather than the logarithm of cumulative drug release.

3.6.3. Higuchi model

The Higuchi model produced an (R^2) value of 0.9179. This model is commonly used to examine diffusion-based drug release from matrices under its underlying assumptions.

The observed fit suggests that the Higuchi model may capture some aspects of the release behavior but provides a weaker linear association than the zero-order model in the reported analysis. Consequently, diffusion may contribute to drug release, but the current data do not establish it as the dominant mechanism.

3.6.4. Korsmeyer–Peppas model

The Korsmeyer–Peppas model yielded an (R^2) value of 0.9094, the lowest among the four reported models. The slope of the plotted regression line was 1.3698.

The Korsmeyer–Peppas release exponent (n) is used to interpret release behavior in relation to the geometry of the delivery system and the model's assumptions. If the reported slope corresponds to (n), its value exceeds 1. However, this value should not be used to assign a release mechanism until the logarithmic transformation, fraction of drug released, fitting interval, and the model's applicability to the specific geometry have been verified. The model is generally applied to the initial portion of the release profile rather than automatically to the entire 24 h dataset.

3.6.5. Overall interpretation of the kinetic models

Based on the reported (R^2) values, the order of fit was:

Zero-order>First-order>Higuchi>Korsmeyer–Peppas

The zero-order model, therefore, provided the highest reported linear-fit statistic for the analyzed dataset. This finding supports describing zero-order kinetics as the best-fitting empirical model among those reported, rather than concluding that a zero-order mechanism has been conclusively established.[35]

3.7. Overall Discussion

The present study investigated the formulation and optimization of a BD-loaded PLO gel using a Box–Behnken design. The experimental results demonstrate that the formulation composition was associated with substantial variation in viscosity, spreadability, thermoreversibility, pH, and cumulative drug release. The response-surface equations provide a framework for examining the relationships among Poloxamer 407, lecithin, IPM, and the measured responses.[36]

The viscosity results indicate that the formulations differed markedly in consistency, while the spreadability results demonstrate that ease of application varied across the experimental design. The observed transition temperatures further indicate differences in temperature-dependent flow behavior. Together, these findings support the need to evaluate multiple physicochemical properties when selecting a topical organogel formulation.[37]

The in vitro release data showed continued drug release over 24 h, with substantial differences among the experimental formulations. The comparatively high cumulative release reported at later sampling times suggests that the developed system enabled extensive drug release under the experimental conditions.[38] However, in vitro release through a dialysis membrane should not be interpreted as direct evidence of transdermal permeation or improved therapeutic activity.[39] The kinetic analysis identified the zero-order model as the best-fitting model among the four models reported, based on the available R^2 values.[40]

Overall, the results provide a preliminary experimental basis for further development of BD-loaded PLO gel. Before publication, verification of the drug identity in the FTIR data, reconciliation of the formulation and optimization records, and reanalysis of the kinetic data are essential to ensure that the conclusions accurately reflect the experiments performed.

4. SUMMARY AND CONCLUSION

4.1. Summary

The present study focused on the formulation, optimization, and evaluation of BD-loaded Pluronic Lecithin Organogel (PLO) as a potential topical drug delivery system for the management of atopic dermatitis (AD). Atopic dermatitis is a chronic inflammatory skin disorder characterized by pruritus, dryness, erythema, and eczematous lesions, requiring effective and sustained topical therapy. The development of an appropriate topical formulation is essential for improving local drug delivery while minimizing unnecessary systemic exposure.

Pluronic Lecithin Organogel was selected as the delivery system because its combination of lecithin and Poloxamer 407 provides a structured, semisolid matrix with potentially useful rheological and drug-release properties. Isopropyl myristate (IPM) was incorporated as an oil-phase component to facilitate formulation development and influence drug partitioning and release characteristics.

Formulation and Optimization

Different PLO formulations were prepared by varying the quantities of Poloxamer 407, lecithin, and IPM. A three-factor, three-level Box–Behnken design was employed to investigate the influence of these formulation variables on the physicochemical characteristics and drug-release behavior. The formulations were evaluated for viscosity, spreadability, pH, thermoreversibility, and cumulative drug release at 1, 5, 8, and 24 h.

FTIR spectroscopy was used to examine the characteristic functional groups of the drug and formulation components. UV spectrophotometry was used to quantify the drug during the in vitro release study. The release profiles were subsequently analyzed using zero-order, first-order, Higuchi, and Korsmeyer–Peppas kinetic models.

Key Findings

The numerical optimization procedure identified a candidate formulation containing approximately 11.16 g of Poloxamer 407, 1.748 g of lecithin, and 5 mL of IPM. The reported characteristics of this formulation were:

- **Viscosity:** 129,800 cP.
- **pH:** 6.37.
- **Spreadability:** 0.84, as reported in the experimental dataset.

- **Thermoreversibility:** 36°C, as reported in the optimization results.
- **Cumulative drug release:** 98.76% at 24 h, according to the reported optimized formulation table.

The in vitro release study demonstrated substantial drug release over the 24-h observation period, although the release profiles varied among the formulations. The physicochemical evaluation indicated that the formulation composition influenced its consistency, spreading characteristics, temperature-dependent behavior, and drug-release performance.

Among the evaluated kinetic models, the zero-order model exhibited the highest reported coefficient of determination (R^2=0.9797), followed by the first-order model (R^2=0.9347), Higuchi model (R^2=0.9179), and Korsmeyer–Peppas model (R^2=0.9094). Thus, the zero-order model provided the best linear fit among the models reported, subject to verification of the underlying release data and calculations.

4.2. Conclusion

The present study demonstrates the potential of Pluronic Lecithin Organogel as a topical formulation platform for BD. The application of a Box–Behnken experimental design enabled systematic investigation of the influence of formulation variables on physicochemical characteristics and in vitro drug release. The optimized candidate formulation exhibited a reported viscosity of 199,800 cP, a pH of 6.67, and cumulative drug release of 98.76% at 24 h.

The findings indicate that appropriate selection of Poloxamer 407, lecithin, and IPM concentrations can influence the performance of the developed organogel. The release study further demonstrated that substantial drug release was maintained over the investigated period. However, the reported results establish in vitro release behavior rather than enhanced skin permeation or sustained therapeutic efficacy.

The developed BD-loaded PLO formulation may therefore be considered a promising candidate for further investigation as a topical delivery system for inflammatory skin conditions, including atopic dermatitis. Further studies involving validated skin permeation experiments, formulation stability assessment, skin irritation and compatibility testing, and appropriate preclinical or clinical evaluation are required to establish its suitability and therapeutic benefits for the intended application.

The principal contribution of this work is the application of a Quality by Design-based formulation optimization strategy to the development of betamethasone dipropionate-loaded Pluronic Lecithin Organogel. By investigating the effects of Poloxamer 407, lecithin, and isopropyl myristate on physicochemical characteristics and in vitro drug release, the study provides a preliminary framework for rational selection of the formulation composition. Further validation of the optimized formulation, including reproducibility, stability, ex vivo skin permeation, skin compatibility, and comparative performance, is required before its potential therapeutic advantages in atopic dermatitis can be established.

Overall, this work provides a formulation-development and optimization framework for BD-loaded PLO gel and supports further research into its potential for topical corticosteroid delivery.

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