JHWCR JOURNAL OF HEALTH, WELLNESS AND COMMUNITY RESEARCH 3007-0570

https://doi.org/10.61919/wwhra973

Original Article

Formulation Design, Response Surface Methodology-Based Optimization And Characterization Of Linseed Oil Emulgel for Skin Care

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"Cite this Article" Received: 06 April 2026; **Accepted**: 26 May 2026; **Published**: 09 June 2026

Author Contributions: Concept: HJ, SNHS; Design: HJ, SNHS; Data Collection: MIQ, HA, YT, SRNB, MM, MR; Analysis: HJ, SNHS; Drafting: AA. **Ethical Approval**: Bahauddin Zakariya University, Multan, Pakistan. **Informed Consent**: Written informed consent was obtained from all participants; **Conflict of Interest**: The authors declare no conflict of interest. **Funding**: No external funding; **Data Availability**: Available from the corresponding author on reasonable request; **Acknowledgments**: N/A.

ABSTRACT

Background: Linseed oil is a lipophilic natural oil with potential topical utility, but its poor aqueous solubility and formulation limitations require an appropriate semisolid delivery system. Emulgels provide a suitable platform for incorporating oil-based active ingredients while maintaining spreadability, consistency, and topical acceptability. Objective: This study aimed to formulate, optimize, and characterize linseed oil-loaded oil-in-water emulgels using response surface methodology, with rose oil and lemon oil evaluated as formulation variables. Methods: Thirteen emulgel formulations were prepared using Carbopol-940 as the gelling polymer, Tween 20 and Span 20 as surfactants, propylene glycol as a co-solvent, and varying concentrations of rose oil and lemon oil. Formulations were evaluated for physicochemical characteristics, pH, viscosity, spreadability, extrudability, drug yield, drug content, FTIR compatibility, thermal behavior, in-vitro release through a cellophane membrane, release kinetics, response surface model fit, in-vitro SPF, preliminary antimicrobial activity, skin-irritation observation, and accelerated stability. Results: All formulations were smooth, homogeneous, transparent, and free from visible phase separation, with pH values of 6.7–6.8 ± 0.1 and viscosity ranging from 640 × 10^3 to 671 × 10^3 cps. EG6, containing 0.75 g rose oil and 1.8 g lemon oil, showed the highest 24-hour cumulative release of 96.69 ± 0.01%. The RSM model was significant ($p = 0.0394$), and the quadratic effect of rose oil was significant ($p = 0.0321$), indicating a nonlinear release response. SPF values ranged from 14.56 ± 0.01 to 19.9 ± 0.01, and EG6 showed 85% antimicrobial inhibition with no visible irritation in ten volunteers over seven days. Conclusion: EG6 demonstrated the most favorable preliminary formulation performance within the tested design space, supporting further ex-vivo, microbiological, dermatological, and in-vivo evaluation of linseed oil emulgel. Keywords: Linseed oil; emulgel; response surface methodology; in-vitro release; Carbopol-940; sun protection factor; antimicrobial activity; topical formulation.

INTRODUCTION

Topical drug delivery is widely used for local dermatological and cosmeceutical applications because it allows direct application of active ingredients to the skin surface, minimizes unnecessary systemic exposure, and improves patient acceptability for long-term or repeated use. However, conventional topical preparations may show limited residence time, inadequate spreadability, poor retention at the application site, instability of lipophilic active ingredients, and variable release from the vehicle, all of which can compromise formulation performance (1,2). These limitations are particularly relevant for

natural oil-based active ingredients, which often require a suitable semisolid carrier to achieve uniform application, acceptable sensory properties, and controlled release behavior.

Emulgels have emerged as useful topical semisolid systems because they combine the solubilizing capacity of emulsions with the viscosity and application advantages of gels. In an oil-in-water emulgel, the internal oil phase can accommodate lipophilic ingredients, while the gel network enhances consistency, spreadability, skin residence, ease of removal, and physical stability (3,4). The use of polymers such as Carbopol-940, together with suitable surfactants and co-solvents, supports formation of a stable gelled emulsion by improving viscosity, reducing phase separation, and maintaining uniform dispersion of the active oil phase. These characteristics make emulgels suitable vehicles for the development of topical formulations intended for skin application, particularly when the active ingredient is poorly water soluble and requires a formulation strategy that supports both stability and release (5).

Linseed oil, also known as flaxseed oil, is a lipid-rich natural oil containing a high proportion of polyunsaturated fatty acids, particularly alpha-linolenic acid. Its fatty-acid composition has been associated with skin-conditioning, emollient, and inflammation-modulating properties, which has increased interest in its incorporation into topical and cosmeceutical systems (6–8). Despite this potential, linseed oil is lipophilic and poorly soluble in aqueous media, which limits its direct incorporation into simple aqueous topical vehicles. A structured emulgel system may therefore provide a more suitable approach for incorporating linseed oil into a stable, aesthetically acceptable semisolid formulation with measurable in-vitro release and handling properties.

Formulation performance in emulgels is influenced not only by the active oil but also by the type and concentration of excipients used to modify release, viscosity, spreadability, and interaction between the oil and aqueous phases. Propylene glycol is frequently used in topical formulations as a co-solvent and penetration-enhancing excipient, while essential oils such as rose oil and lemon oil may influence release behavior and formulation characteristics through their lipophilic composition and interaction with the emulsion matrix (9,10). However, the combined influence of rose oil and lemon oil concentrations on linseed oil emulgel performance has not been adequately established through systematic optimization. A one-factor-at-a-time formulation approach may fail to detect nonlinear effects or interactions between formulation variables, particularly when both excipients may contribute to the same response through different mechanisms.

Response surface methodology provides a rational statistical approach for formulation optimization because it evaluates the effects of independent variables, their interactions, and possible nonlinear relationships on selected formulation responses. In the present study, rose oil and lemon oil were selected as independent formulation variables, while cumulative in-vitro release of linseed oil in phosphate buffer at pH 6.8 was used as the principal optimization response. The study further characterized the prepared emulgels for physicochemical properties, spreadability, extrudability, drug content, FTIR compatibility, thermal behavior, release kinetics, in-vitro sun protection factor, preliminary antimicrobial activity, skin-irritation observation, and accelerated stability. This study aimed to formulate and optimize linseed oil-loaded oil-in-water emulgels using response surface methodology and to determine the influence of rose oil and lemon oil concentrations on in-vitro release and overall formulation performance.

MATERIALS AND METHODS

This study was designed as an experimental laboratory-based pharmaceutics formulation-development and in-vitro optimization study. Linseed oil-loaded oil-in-water emulgels were prepared using response surface methodology to evaluate the influence of rose oil and lemon oil concentrations on formulation performance. The study was conducted in the pharmaceutics laboratory using linseed oil as the active oil phase component, rose oil and lemon oil as formulation variables, Carbopol-940 as the gelling

polymer, propylene glycol as a co-solvent and permeation-enhancing excipient, Tween 20 and Span 20 as surfactants, triethanolamine as the pH-adjusting agent, chloroform water as preservative, and double-distilled water as the aqueous vehicle. Linseed oil, rose oil, and lemon oil were obtained from the local market, whereas propylene glycol, Carbopol-940, Tween 20, Span 20, triethanolamine, chloroform, methanol, and n-hexane were obtained from Merck, Germany. Double-distilled water was prepared using the distillation apparatus of the Pharmacy Department, Bahauddin Zakariya University, Multan.

Phosphate buffer solution at pH 6.8 was prepared using potassium dihydrogen phosphate and sodium hydroxide, followed by pH adjustment and confirmation with a calibrated pH meter. Quantification of linseed oil-associated absorbance was performed by UV spectrophotometry at 290 nm using a Perkin Elmer Lambda 25 UV spectrophotometer. Standard dilutions were prepared in the concentration range of 1–5 µg/mL and analyzed against a suitable blank. The calibration curve produced the regression equation $Y = 0.0219x + 0.1325$, with a regression coefficient of 0.999, where Y represented absorbance at 290 nm and X represented concentration in µg/mL. This equation was used to calculate linseed oil concentration during in-vitro release analysis after appropriate dilution.

The solubility of linseed oil was assessed in n-hexane, methanol, and phosphate buffer at pH 6.8. An excess quantity of linseed oil was added to 5 mL of each solvent and maintained under thermostatically controlled stirring at 37°C. After equilibration, the samples were centrifuged at 13,000 rpm for 10–15 minutes, and the clear supernatant was collected, diluted when required, and analyzed by UV spectrophotometry at 290 nm. Measurements were performed in triplicate at 25 ± 0.5°C and expressed as mean ± standard deviation. The octanol/water partition coefficient was determined by mixing linseed oil with distilled water and n-octanol in a separating funnel, shaking the mixture, allowing phase separation for 24 hours, centrifuging aliquots from each phase, and analyzing the diluted samples spectrophotometrically. The partition coefficient was calculated from the ratio of linseed oil concentration in the octanol phase to that in the aqueous phase.

Response surface methodology was applied using Design-Expert software, trial version 7.3, State-Ease Inc., Minneapolis, MN, USA. A central composite design was used to prepare thirteen formulations, coded EG1 to EG13. Rose oil and lemon oil were selected as independent variables and evaluated at five coded levels. The actual quantities used for each factor were 0.5, 0.75, 1.25, 1.8, and 2 g. The center-point formulation contained 1.25 g rose oil and 1.25 g lemon oil and was repeated to evaluate experimental variability. The principal dependent response for optimization was cumulative percentage release of linseed oil from the emulgel formulation in phosphate buffer at pH 6.8. Other formulation components were kept constant throughout the study so that the effects of rose oil and lemon oil could be evaluated systematically (11–16).

The gel phase was prepared by dispersing the required quantity of Carbopol-940 in distilled water under continuous magnetic stirring until a uniform, lump-free gel base was obtained. The oil phase was prepared by mixing Span 20 with the oil phase vehicle, followed by addition of rose oil and lemon oil according to the formulation design. Linseed oil was separately dissolved in methanol and incorporated into the oil phase under continuous stirring. The aqueous phase was prepared by dissolving Tween 20 in distilled water, followed by incorporation of propylene glycol and chloroform water. The oil and aqueous phases were heated separately at 70–80°C for 5–8 minutes and then cooled to room temperature. The oil phase was gradually added to the aqueous phase with continuous stirring to form an oil-in-water emulsion with an HLB value of approximately 8.7–8.8. The resulting emulsion was incorporated into the Carbopol gel phase under continuous magnetic stirring, and the pH was adjusted to approximately 6.8 by dropwise addition of triethanolamine. The final weight was adjusted with distilled water, and the prepared emulgels were packed in aluminum collapsible tubes for evaluation.

The prepared formulations were evaluated for appearance, homogeneity, transparency, texture, phase separation, pH, viscosity, percentage yield, drug-content uniformity, spreadability, and extrudability. Visual inspection was used to assess color, uniformity, smoothness, aggregate formation, and phase

separation. The pH of each formulation was measured at 25 ± 0.5°C using a calibrated pH meter. Viscosity was determined using a Brookfield digital viscometer with spindle 63 at room temperature. Percentage yield was calculated by comparing the practical mass obtained after formulation preparation with the theoretical formulation mass. Drug-content uniformity was determined by dispersing 1 g of each formulation in phosphate buffer at pH 6.8, shaking, filtering, diluting the filtrate when required, and analyzing the sample at 290 nm. Drug content was expressed as the measured amount of linseed oil relative to the theoretical amount incorporated into the formulation, multiplied by 100. Spreadability was determined by placing approximately 1 g of formulation between two glass slides, applying a 5 g weight for 5 minutes, measuring the spread diameter, and calculating spreadability using $S = M \times L / T$, where S represents spreadability, M represents applied mass, L represents spread length, and T represents time. Extrudability was assessed by filling 20 g of each formulation into aluminum collapsible tubes, applying a 1 kg weight for 30 seconds at the closed end, and recording the quantity of emulgel extruded from the tube (17–22).

Fourier-transform infrared spectroscopy was performed to evaluate possible interactions among linseed oil, Carbopol-940, rose oil, lemon oil, and the optimized linseed oil emulgel. Samples were analyzed using the potassium bromide disc method, and spectra were compared to assess the retention, disappearance, broadening, or shifting of major functional group peaks. Thermal behavior of the optimized formulation was evaluated by thermogravimetric analysis. Approximately 190 mg of optimized emulgel was placed in an aluminum pan under nitrogen flow at 20 mL/min, equilibrated at 40°C for 1 minute, and heated from 40°C to 400°C at a rate of 10°C/min using a Perkin-Elmer thermal analyzer. The resulting thermogram was examined to assess the thermal behavior and stability of the optimized formulation.

In-vitro release of linseed oil from each emulgel formulation was assessed using a USP type-II dissolution apparatus. One gram of formulation was placed in a cellophane membrane, tied securely to the paddle assembly, and immersed in 500 mL of phosphate buffer at pH 6.8. The release medium was maintained at 37 ± 2°C and stirred at 100 rpm. Samples were withdrawn at predetermined intervals up to 24 hours and replaced with an equal volume of fresh release medium to maintain sink volume conditions. Withdrawn samples were analyzed by UV spectrophotometry at 290 nm, and cumulative percentage release was calculated using the calibration equation. Each experiment was performed in triplicate, and results were expressed as mean ± standard deviation. The release profiles were fitted to zero-order, first-order, Higuchi, Hixson–Crowell, and Korsmeyer–Peppas kinetic models using DDSolver version 1.0. Model fit was assessed using the coefficient of determination and Akaike information criterion, with higher R^2 and lower AIC values indicating better fit (23,24).

Statistical analysis was performed using Microsoft Excel 2013 and Design-Expert software. Descriptive data were summarized as mean ± standard deviation. Regression analysis, analysis of variance, and multiple linear regression analysis were used to evaluate the effects of rose oil and lemon oil on cumulative linseed oil release. A polynomial model containing linear, interaction, and quadratic terms was fitted for the release response. Positive coefficients were interpreted as increasing effects on the response, while negative coefficients were interpreted as reducing or antagonistic effects. Statistical significance was assessed at $p < 0.05$. Contour plots and three-dimensional response-surface plots were generated to visualize the relationship between formulation variables and cumulative linseed oil release. The optimized formulation was selected based on the combined assessment of release performance, model output, and formulation characteristics (25).

The in-vitro sun protection factor of each formulation was determined by UV spectrophotometry. One gram of emulgel was dispersed in ethanol, sonicated for 10 minutes, filtered, and serially diluted. Absorbance was recorded from 290 to 320 nm at 5 nm intervals using ethanol as the blank. SPF was calculated using the equation $SPF = CF \times \Sigma EE(\lambda) \times I(\lambda) \times Abs(\lambda)$, where CF represents the correction factor, $EE(\lambda)$ represents the erythemal effect spectrum, $I(\lambda)$ represents the solar intensity spectrum, and

Abs(λ) represents the absorbance of the formulation at each wavelength. Standard EE × I values were applied across the 290–320 nm range (26–28).

Preliminary antimicrobial activity of the optimized emulgel was evaluated using the ditch plate technique. Nutrient agar medium was prepared, sterilized, poured into petri dishes, and allowed to solidify. A skin-pus sample was streaked on the agar surface using a sterile loop and incubated for 24 hours at 25 ± 0.5°C. The optimized formulation was then applied to the agar plate, followed by further incubation for 24 hours at 25 ± 0.5°C. Microbial growth was examined after crystal violet staining, and the length of inhibition was measured. Percentage inhibition was calculated as the total length of inhibition divided by the total length of streaked culture, multiplied by 100 (29).

Skin-irritation observation was performed for the optimized formulation in ten human volunteers after approval from the ethical committee of the Faculty of Pharmacy. Approximately 1 g of optimized emulgel was applied to a small area on the forearm, and the application site was observed daily for seven days for visible signs of rash, abrasion, itching, burning, allergy, or local irritation. Accelerated stability testing was performed by storing all formulations in a stability chamber at 40 ± 0.5°C and 75 ± 1% relative humidity for six months. Physical appearance, pH, drug content, viscosity, homogeneity, and spreadability were evaluated after one week, two weeks, one month, three months, and six months using the same procedures applied at baseline. Reproducibility and data integrity were supported by use of a predefined experimental design, constant formulation variables except the selected independent factors, triplicate measurements where applicable, controlled testing temperatures, blank correction during spectrophotometric analysis, and repeated center-point formulations within the response surface design.

RESULTS

Thirteen linseed oil-loaded emulgel formulations were prepared according to the response surface methodology design, with rose oil and lemon oil used as the independent formulation variables. The actual quantities of rose oil and lemon oil ranged from 0.5 g to 2.0 g. The center-point composition contained 1.25 g rose oil and 1.25 g lemon oil and was repeated in EG1 and EG10–EG13 to support model estimation and assessment of formulation variability. EG6 contained 0.75 g rose oil and 1.8 g lemon oil and was subsequently identified as the optimized formulation based on its terminal in-vitro release and overall formulation performance.

Table 1. Experimental Design Matrix for Linseed Oil Emulgel Formulations

Formulation Code	Coded Rose Oil Level	Coded Lemon Oil Level	Rose Oil (g)	Lemon Oil (g)
EG1	0	0	1.25	1.25
EG2	2	2	2.00	2.00
EG3	1	1	1.80	1.80
EG4	1	2	1.80	2.00
EG5	1	-1	1.80	0.75
EG6	-1	1	0.75	1.80
EG7	2	1	2.00	1.80
EG8	-2	1	0.50	1.80
EG9	1	-2	1.80	0.50
EG10	0	0	1.25	1.25
EG11	0	0	1.25	1.25
EG12	0	0	1.25	1.25
EG13	0	0	1.25	1.25

The solubility assessment showed that linseed oil had greater solubility in n-hexane than in methanol and phosphate buffer at pH 6.8. The reported solubility values were 0.00407 ± 0.25 mg/mL in n-hexane, 0.00185 ± 0.45 mg/mL in methanol, and 0.00084 ± 0.67 mg/mL in phosphate buffer. The octanol/water partition coefficient was 3.6, indicating lipophilic behavior and supporting the selection of an emulgel system for topical incorporation of linseed oil.

All emulgel formulations showed acceptable preliminary physicochemical and handling characteristics. The formulations were smooth, transparent, homogeneous, and free from visible lumps or phase separation. The pH values remained within 6.7–6.8 ± 0.1, which is compatible with topical application. Viscosity ranged from 640 × 10^3 to 671 × 10^3 cps, indicating adequate semisolid consistency. Spreadability values ranged from 0.034 ± 0.1 to 0.046 ± 0.1 g·cm/s, while extrudability ranged from 0.95 ± 0.01 to 1.31 ± 0.01 g/cm. Percentage yield ranged from 95.5 ± 0.2% to 99.6 ± 0.1%, and drug content ranged from 94.8 ± 0.1% to 99.6 ± 0.1%, indicating acceptable formulation recovery and content uniformity across the prepared batches.

Table 2. Solubility and Partition Characteristics of Linseed Oil

Parameter	Medium / System	Result
Solubility	n-Hexane	0.00407 ± 0.25 mg/mL
Solubility	Methanol	0.00185 ± 0.45 mg/mL
Solubility	Phosphate buffer, pH 6.8	0.00084 ± 0.67 mg/mL
Partition coefficient	Octanol/water	3.6

Table 3. Physicochemical and Handling Characteristics of Linseed Oil Emulgels

Parameter	Observed Result Across Formulations
Appearance	Smooth, transparent, homogeneous, lump-free
Phase separation	Not observed
pH	6.7–6.8 ± 0.1
Viscosity	640–671 × 10^3 cps
Spreadability	0.034 ± 0.1 to 0.046 ± 0.1 g·cm/s
Extrudability	0.95 ± 0.01 to 1.31 ± 0.01 g/cm
Percentage yield	95.5 ± 0.2% to 99.6 ± 0.1%
Drug content	94.8 ± 0.1% to 99.6 ± 0.1%

The terminal 24-hour in-vitro release of linseed oil varied across the thirteen formulations. EG6 produced the highest cumulative release at 96.69 ± 0.01%, followed by EG7 at 94.41 ± 0.01% and EG5 at 93.72 ± 0.01%. EG9 produced the lowest terminal release at 88.24 ± 0.01%. The difference between the highest and lowest 24-hour release values was 8.45 percentage points. The optimized formulation, EG6, contained 0.75 g rose oil and 1.8 g lemon oil, showing that the most favorable release was achieved with lower rose oil and higher lemon oil rather than with the highest concentration of both enhancers.

Table 4. Terminal 24-Hour In-Vitro Release and Release Ranking of Linseed Oil Emulgel Formulations

Formulation	Rose Oil (g)	Lemon Oil (g)	24-Hour Cumulative Release (%)	Release Rank
EG6	0.75	1.80	96.69 ± 0.01	1
EG7	2.00	1.80	94.41 ± 0.01	2
EG5	1.80	0.75	93.72 ± 0.01	3
EG1	1.25	1.25	93.26 ± 0.01	4
EG8	0.50	1.80	93.26 ± 0.01	4
EG10	1.25	1.25	93.26 ± 0.01	4
EG11	1.25	1.25	93.26 ± 0.01	4
EG12	1.25	1.25	93.26 ± 0.01	4
EG13	1.25	1.25	93.26 ± 0.01	4
EG3	1.80	1.80	91.67 ± 0.01	10
EG2	2.00	2.00	90.98 ± 0.01	11
EG4	1.80	2.00	90.52 ± 0.01	12
EG9	1.80	0.50	88.24 ± 0.01	13

Release-kinetic analysis indicated that the reported release profiles were best represented by the Korsmeyer–Peppas model among the model outputs available in the manuscript. The release exponent ranged from 0.240 to 0.278, while R^2 values ranged from 0.883 to 0.917. EG9 showed the highest R^2 value of 0.917 and the lowest AIC value of 101.3, although it had the lowest 24-hour cumulative release. EG6 showed a Korsmeyer–Peppas constant of 15.85, release exponent of 0.270, R^2 of 0.894, and AIC of 109.2. These findings indicate that formulation optimization was primarily based on terminal release performance and overall formulation acceptability rather than on kinetic-model fit alone.

Table 5. Korsmeyer–Peppas Kinetic Parameters for Linseed Oil Emulgel Formulations

Formulation	kKP	n	R^2	AIC
EG1	15.42	0.269	0.888	108.90
EG2	18.03	0.246	0.886	108.60
EG3	18.19	0.246	0.883	109.30
EG4	18.73	0.240	0.895	107.60
EG5	14.92	0.275	0.887	109.90
EG6	15.85	0.270	0.894	109.20
EG7	15.20	0.273	0.895	108.50
EG8	14.77	0.276	0.884	110.10
EG9	13.18	0.278	0.917	101.30
EG10	15.42	0.269	0.888	108.97
EG11	15.42	0.269	0.888	108.97
EG12	15.42	0.269	0.888	108.97
EG13	15.42	0.269	0.888	108.97

The response surface model for cumulative linseed oil release was statistically significant. The overall model had an F-value of 4.40 and p = 0.0394. Among the model terms, the quadratic effect of rose oil was significant, with F = 7.12 and p = 0.0321. The linear effect of rose oil, linear effect of lemon oil, interaction between rose oil and lemon oil, and quadratic effect of lemon oil were not statistically significant. The model had an R^2 value of 0.75, coefficient of variation of 17.33%, and mean response of 86.29 ± 14.95, indicating moderate explanatory performance.

Table 6. Analysis of Variance for the RSM Model of Cumulative Linseed Oil Release

Source	Sum of Squares	df	Mean Square	F-Value	p-Value
Model	4913.44	5	982.69	4.40	0.0394
A: Rose oil	721.87	1	721.87	3.23	0.1154
B: Lemon oil	342.00	1	342.00	1.53	0.2560
AB	240.26	1	240.26	1.07	0.3344
A^2	1591.28	1	1591.28	7.12	0.0321
B^2	28.04	1	28.04	0.13	0.7337
Residual	1565.02	7	223.57	—	—
Lack of fit	1565.02	3	521.67	—	—
Pure error	0.000	4	0.000	—	—

The coded polynomial equation for the release response was $Y = 96.75 + 38.28A + 26.35B - 20.79AB - 30.68A^2 - 4.07B^2$, where A represented rose oil and B represented lemon oil. The positive coefficients for the linear terms of rose oil and lemon oil indicated increasing effects on the response within the tested design space, whereas the negative AB coefficient indicated an antagonistic combined effect. The significant negative quadratic coefficient for rose oil indicated a nonlinear response, suggesting that increasing rose oil did not produce a simple proportional increase in cumulative release. This model behavior was consistent with the observed performance of EG6, which produced the highest terminal release at 0.75 g rose oil and 1.8 g lemon oil.

FTIR analysis was performed to assess compatibility among linseed oil, Carbopol-940, rose oil, lemon oil, and the optimized formulation. The spectra showed retention of major peaks without marked disappearance of characteristic bands, supporting the absence of obvious incompatibility between linseed oil and the emulgel excipients under the tested conditions. Thermal analysis of the optimized formulation showed a single sharp thermal event reported at -23°C, and the thermogram was used to support the thermal stability assessment of EG6.

The in-vitro SPF values of the prepared formulations ranged from 14.56 ± 0.01 to 19.9 ± 0.01, indicating measurable UV absorbance within the tested wavelength range. The optimized formulation EG6 showed 85% antimicrobial inhibition in the preliminary ditch plate assay. In the skin-irritation observation, none of the ten volunteers showed visible rash, abrasion, itching, burning, allergy, or local irritation during the seven-day observation period. During accelerated stability testing at 40 ± 0.5°C and 75 ± 1% relative humidity for six months, the formulations showed no major reported changes in pH, consistency, drug

content, or homogeneity. A slight color change was observed in some formulations, but this was not accompanied by reported deterioration in the principal physical stability parameters.

Table 7. Secondary Performance Outcomes of Linseed Oil Emulgel Formulations

Outcome Domain	Parameter	Empirical / Numerical Data
Sun protection performance	In-vitro SPF	14.56 ± 0.01 to 19.90 ± 0.01
Antimicrobial screening	Percentage inhibition	85%
Skin tolerability observation	Visible irritation response	0/10 volunteers
Stability testing	Duration	6 months
Stability testing	Storage condition	40 ± 0.5°C; 75 ± 1% RH
Stability testing	Physicochemical stability	Not reported as formulation-wise numeric values
Stability testing	Physical appearance	Not quantified

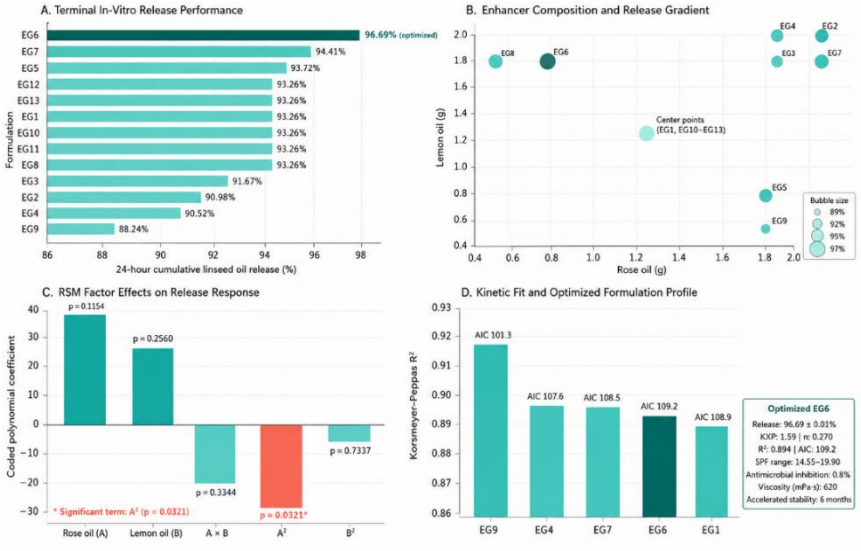

Figure 1 Integrated optimization profile of linseed oil emulgel formulations. Panel A ranks formulations by terminal 24-hour cumulative in-vitro release, identifying EG6 as the highest-releasing formulation at 96.69 ± 0.01%. Panel B maps rose oil and lemon oil concentrations against release magnitude, showing that the best release response occurred with lower rose oil and higher lemon oil rather than simultaneous high concentrations of both enhancers. Panel C summarizes the coded RSM polynomial coefficients and corresponding p-values, indicating a statistically significant quadratic effect of rose oil. Panel D shows the highest Korsmeyer–Peppas R² values with AIC labels and summarizes the optimized EG6 performance profile.

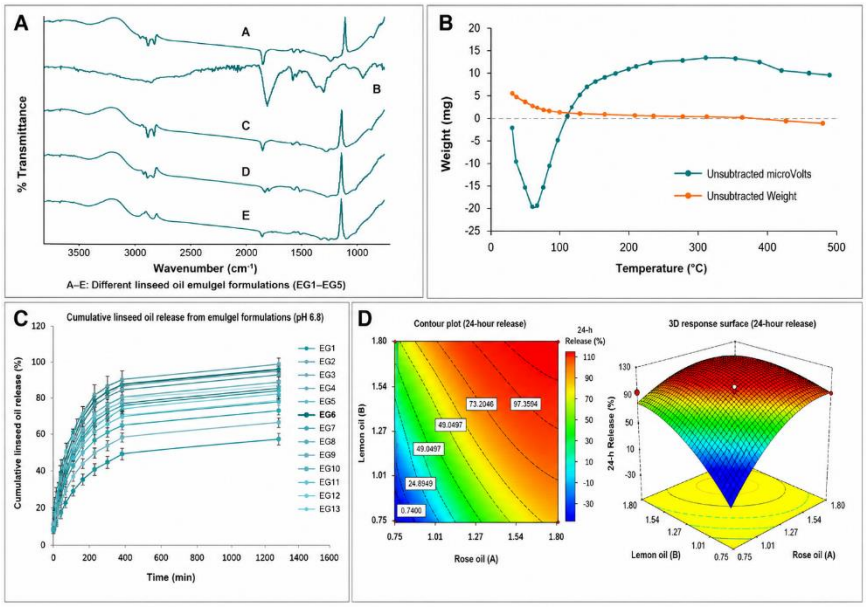

Figure 2 Comprehensive characterization and optimization profile of linseed oil emulgel formulations.

The panelled figure summarizes key formulation evidence: FTIR spectra show comparative functional-group profiles of formulations/components without obvious major incompatibility; thermal analysis presents weight/signal changes across increasing temperature; the release profile demonstrates progressive cumulative linseed oil release over 24 hours with EG6 showing comparatively higher release; and the contour plus 3D response-surface plots illustrate the combined influence of rose oil and lemon oil on 24-hour release response at pH 6.8.

Overall, EG6 was selected as the optimized linseed oil emulgel formulation because it achieved the highest 24-hour in-vitro cumulative release of 96.69 ± 0.01%, maintained acceptable physicochemical and handling characteristics, showed measurable SPF, demonstrated 85% antimicrobial inhibition in the preliminary assay, produced no visible irritation in ten volunteers over seven days, and remained physically stable under accelerated storage conditions. The RSM model supported a nonlinear influence of rose oil on cumulative release, with the rose oil quadratic term reaching statistical significance, while the combination of lower rose oil and higher lemon oil produced the most favorable release outcome within the tested formulation design.

DISCUSSION

The present study developed and optimized linseed oil-loaded oil-in-water emulgels using response surface methodology, with rose oil and lemon oil evaluated as formulation variables. The principal finding was that formulation EG6, containing 0.75 g rose oil and 1.8 g lemon oil, produced the highest terminal 24-hour in-vitro release of linseed oil, reaching 96.69 ± 0.01%. This result indicates that the most favorable release performance was not achieved by simultaneously increasing both enhancers to their highest levels, but rather by using a lower amount of rose oil with a higher amount of lemon oil. The finding is important from a formulation-development perspective because it supports the value of systematic optimization over a conventional one-factor-at-a-time approach, particularly when excipients may have nonlinear or interacting effects on release behavior.

The physicochemical findings supported the suitability of the emulgel platform for incorporating linseed oil into a semisolid topical vehicle. All formulations were reported to be smooth, homogeneous, transparent, and free from visible phase separation, while the pH remained within 6.7–6.8 ± 0.1. This pH range is compatible with topical application and suggests that the prepared formulations were unlikely to cause pH-related irritation under the limited observational conditions used in the study. The viscosity range of 640–671 × 10^3 cps indicated adequate semisolid consistency, while the spreadability and extrudability results suggested acceptable handling properties for application from collapsible tubes. These findings are consistent with the broader rationale for emulgels as topical vehicles that combine the lipophilic incorporation capacity of emulsions with the residence time, consistency, and application advantages of gels (1–5).

Linseed oil is a lipophilic natural oil rich in polyunsaturated fatty acids, particularly alpha-linolenic acid, and its incorporation into an emulgel matrix is pharmaceutically reasonable because direct aqueous formulation is limited by poor water solubility (7,8). In the present study, solubility was highest in n-hexane, followed by methanol and phosphate buffer at pH 6.8, while the octanol/water partition coefficient was reported as 3.6. These results support the lipophilic nature of linseed oil and justify the use of an oil-in-water emulgel rather than a purely aqueous vehicle. However, the reported solubility standard deviations appear disproportionately large relative to the mean values, and these values should be verified from the raw analytical data before final publication.

The in-vitro release findings demonstrated formulation-dependent variation across the experimental design. EG6 showed the highest terminal release, followed by EG7 and EG5, whereas EG9 showed the lowest terminal release. This pattern suggests that lemon oil may have contributed positively to release performance when used with lower rose oil concentration, but the RSM findings indicate that the response was not purely linear. The polynomial model showed positive linear coefficients for rose oil

and lemon oil but a negative interaction coefficient and a statistically significant negative quadratic effect for rose oil. This indicates a nonlinear formulation response in which increasing rose oil beyond an optimal range may reduce rather than improve release. Such behavior is plausible in semisolid emulgel systems, where changes in oil-phase composition, surfactant balance, viscosity, and matrix structure can modify diffusion pathways and active release from the formulation.

The RSM model was statistically significant, with $p = 0.0394$ for the overall model, and the quadratic rose oil term was significant, with $p = 0.0321$. The linear effects of rose oil and lemon oil, the interaction term, and the quadratic lemon oil term were not statistically significant. The model R^2 value of 0.75 and coefficient of variation of 17.33% indicate moderate explanatory strength rather than a highly predictive optimization model. Therefore, the optimization should be interpreted cautiously as identifying the best-performing formulation within the tested experimental design rather than establishing a definitive universal optimum. The repeated center-point formulations were useful for design estimation, but the reported cumulative-release values for the center-point batches require verification because several intermediate time-point values in the original release table appear non-monotonic, which is not expected for cumulative release data.

Release-kinetic analysis showed that the Korsmeyer–Peppas model was reported as the best-fitting model for the emulgel formulations, with R^2 values ranging from 0.883 to 0.917 and release exponent values ranging from 0.240 to 0.278. These values suggest that the release pattern was compatible with a diffusion-controlled or quasi-Fickian release process from a semisolid matrix, although the interpretation should remain cautious because the manuscript reports only the Korsmeyer–Peppas outputs and not the full comparative results for zero-order, first-order, Higuchi, and Hixson–Crowell models. A complete kinetic-model comparison using R^2, adjusted R^2 where appropriate, AIC, and residual diagnostics would strengthen the mechanistic interpretation and improve transparency (24).

The FTIR results suggested no obvious incompatibility among linseed oil, Carbopol-940, rose oil, lemon oil, and the optimized emulgel under the tested conditions. The thermal analysis of EG6 was also used to support formulation stability at the molecular or matrix level. However, the discussion of FTIR peak assignments should be chemically precise, as broad peak regions should not be overinterpreted without careful functional-group attribution. Similarly, thermal behavior should be reported with accurate event type, temperature, and interpretation, particularly because the reported sharp event at -23°C requires clear explanation in relation to the formulation matrix and linseed oil behavior.

The in-vitro SPF findings showed values ranging from 14.56 ± 0.01 to 19.9 ± 0.01 across formulations, suggesting measurable UV absorbance within the tested wavelength range. These values support preliminary sun-protection potential under spectrophotometric conditions, but they should not be interpreted as equivalent to in-vivo sunscreen efficacy. The optimized formulation also showed 85% antimicrobial inhibition in the ditch plate assay. This finding indicates preliminary antimicrobial activity, but the method requires cautious interpretation because the organism source, identification procedure, inoculum standardization, positive control, negative control, and replicate testing require fuller reporting. For a stronger antimicrobial claim, future work should use validated microbial strains or properly identified clinical isolates with standardized susceptibility methods (29).

The skin-irritation observation showed no visible rash, abrasion, itching, burning, allergy, or local irritation in ten volunteers over seven days. This supports preliminary local tolerability under the specific conditions tested, but it does not establish definitive dermatological safety. The small volunteer number, limited observation period, absence of a standardized irritation scoring scale, and incomplete ethics and consent reporting limit the strength of the safety conclusion. Accelerated stability testing at 40 ± 0.5°C and 75 ± 1% relative humidity for six months showed no major reported changes in pH, consistency, drug content, or homogeneity, although slight color change was observed in some formulations. These findings support preliminary physical stability but should be accompanied by formulation-wise stability data and clear acceptance criteria.

The major strength of this study is its systematic formulation-optimization approach, which combines RSM, physicochemical evaluation, in-vitro release, kinetic modeling, SPF estimation, preliminary antimicrobial testing, irritation observation, and accelerated stability assessment. The main limitations are the use of a cellophane membrane release system rather than excised skin, incomplete validation details for the UV analytical method, possible inconsistencies in the cumulative-release table, limited reporting of full kinetic-model comparisons, preliminary and non-standardized antimicrobial testing, and small-scale irritation observation. Because cellophane membrane release does not represent true skin permeation, future studies should include ex-vivo permeation through animal or human cadaver skin where ethically feasible, skin-retention analysis, standardized antimicrobial assays, expanded dermatological irritation testing, and in-vivo or clinical evaluation before therapeutic or cosmeceutical efficacy claims are made.

Overall, the findings suggest that linseed oil can be incorporated into an emulgel system with acceptable preliminary physicochemical and performance characteristics. EG6 emerged as the optimized formulation within the tested design space because it achieved the highest terminal in-vitro release and maintained favorable handling, SPF, antimicrobial-screening, irritation-observation, and stability findings. The results support further development of linseed oil emulgel as a topical formulation platform, but additional validated permeation, microbiological, safety, and efficacy studies are required before clinical or commercial claims can be justified.

CONCLUSION

Linseed oil-loaded oil-in-water emulgels were successfully formulated and optimized using response surface methodology, with rose oil and lemon oil evaluated as formulation variables. Among the thirteen prepared formulations, EG6, containing 0.75 g rose oil and 1.8 g lemon oil, showed the highest 24-hour in-vitro cumulative release of 96.69 ± 0.01% and demonstrated acceptable preliminary physicochemical properties, content uniformity, spreadability, extrudability, SPF response, antimicrobial inhibition, irritation-observation findings, and accelerated stability. The significant quadratic effect of rose oil indicated a nonlinear influence of enhancer concentration on release behavior, supporting the need for systematic formulation optimization. These findings support EG6 as the best-performing formulation within the tested experimental design, although further ex-vivo permeation, standardized antimicrobial testing, expanded dermatological safety evaluation, and in-vivo or clinical studies are required before definitive claims regarding transdermal delivery, therapeutic efficacy, or skin safety can be made.

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