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Design, optimization, and characterization of curcumin-loaded proniosomal vesicular systems as a novel phytopharmaceutical delivery strategy for psoriasis management

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ABSTRACT: Herbal therapeutics such as curcumin have potent anti-inflammatory and antioxidant potential but face challenges of low solubility, poor bioavailability, and instability. Proniosomes, surfactant-coated dry vesicular carriers, offer enhanced stability, scalability, and bioavailability, making them suitable for delivering insoluble herbal actives through topical applications.This study was designed to develop and optimize curcumin-loaded Proniosomes using Box-Behnken Design (BBD) to improve physicochemical features for psoriasis management. Proniosomes were prepared by antisolvent precipitation using Span 80, soya lecithin, and cholesterol. A three-factor, three-level BBD was applied to evaluate the effect of Span (X_1), lecithin (X_2), and cholesterol (X_3) on critical quality attributes: particle size (Y_1), zeta potential (Y_2), and PDI (Y_3). Seventeen runs were performed and statistically analyzed using ANOVA, Pearson's correlation, and lack-of-fit testing. Entrapment efficiency and in vitro drug release were further measured.Formulations showed particle sizes of 143–366 nm, zeta potential of 14–32 mV, and PDI of 0.045–0.53. The optimized batch exhibited ~206 nm particle size, ~24 mV zeta potential, and 0.22 PDI. Entrapment efficiency reached ~84%, while drug release was sustained over 24 h, with ~96.64% cumulative release at 48 h compared to ~25.5% for pure curcumin. Enhanced release was attributed to the amphiphilic surfactants forming stable bilayered vesicles, and cholesterol providing structural integrity for controlled release.In conclusion, optimized curcumin Proniosomes established high stability, scalability, entrapment, and sustained release, providing a promising topical delivery platform for effective psoriasis management.

1. INTRODUCTION

Psoriasis is a chronic, immune-mediated inflammatory skin disorder characterized by keratinocyte hyperproliferation and immune cell infiltration, resulting in red, scaly plaques (Yamanaka, Yamamoto and Honda, 2021). Affecting 2–3% of the global population, psoriasis significantly impairs quality of life and is associated with systemic comorbidities such as psoriatic arthritis, metabolic syndrome, and cardiovascular disease (Michalek, Loring and John, 2017). Conventional

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treatments (topical corticosteroids, immunosuppressants, and phototherapy) often suffer from adverse effects, limited efficacy, and poor patient compliance (Sugumaran, Yong and Stanslas, 2024).

Because of their numerous mechanisms of action, safety profile, and biocompatibility, natural phytoconstituents have garnered increasing attention in recent years for use in dermatological treatments (Diotallevi et al., 2022). Among these, curcumin—the main bioactive ingredient in turmeric, or Curcuma longa—has shown promise in the treatment of psoriasis (Li et al., 2022). Curcumin, the principal bioactive constituent of Curcuma longa, has demonstrated potent anti-inflammatory, antioxidant, and antiproliferative effects relevant to psoriasis. These qualities specifically target the pathological characteristics of psoriasis (Sadeghi Ghadi et al., 2019). However, its clinical use is limited by poor solubility, low bioavailability, and rapid metabolism.

Novel drug delivery methods are being investigated in an effort to overcome these restrictions. Proniosomes, a dry, non-aqueous form of vesicles coated with surfactants, have drawn interest as a reliable and effective delivery system. They form niosomes upon hydration, which improves the stability and bioavailability of encapsulated medications, increases skin penetration, and prolongs drug release. In contrast to traditional vesicular systems, Proniosomes provide improved handling, scalability, and storage stability, making them appropriate for topical administration of poorly soluble herbal compounds such as curcumin (Monga et al., 2024).

The goal of this study is to create and refine proniosomal formulations loaded with curcumin as a new herbal-based topical treatment for psoriasis. Enhancing curcumin's solubility, skin retention, and therapeutic efficacy while reducing systemic side effects is the primary objective of the formulation approach (Thirumal et al., 2023). This work aims to establish the foundation for an alternative, patient-friendly herbal treatment for the long-term management of psoriasis through a methodical process that includes formulation design, characterization, and in vitro evaluation (Rakesh K. Sindhu, Sumitra Singh, 2025).

The formulation of stable and efficient Proniosomes, however, requires careful optimization of critical formulation and process parameters (CMPs) to achieve desirable physicochemical characteristics such as particle size, polydispersity index (PDI), and entrapment efficiency. In this study, three key variables—the amount of Span (X_1), soya lecithin (X_2), and cholesterol (X_3)—were identified as influential components in determining the stability and performance of Proniosomes (Mohammad Rashid., 2014)(Chaudhari and Kuchekar, 2018).

To systematically evaluate and optimize these parameters, a nonlinear second-order Box-Behnken Design (BBD) was employed. This statistical design of experiments approach enables efficient exploration of interactions between multiple variables with a reduced number of experimental runs. A total of seventeen experimental trials were generated by the design matrix, each representing a unique combination of the selected factors at different levels (Sengel-Turk, Ozmen and Bakar-Ates, 2021)(Sultana et al., 2011). The resulting formulations were assessed for their key quality attributes, enabling the identification of optimal conditions for nanoparticle development.

2. MATERIALS AND METHODS

2.1. Materials

Curcumin (≥90% purity), soya lecithin, Span 80, and cholesterol were procured from Sigma-Aldrich, India. Analytical-grade solvents (ethanol, dichloromethane) were used. Milli-Q water was used throughout (Topuzoğlu et al., 2025).

2.2. Selection of solvent

The choice of solvent plays a critical role in the successful formulation of Proniosomes, particularly in terms of solubilizing both the polymeric carrier and the hydrophobic herbal bioactive compound. In this study, solvents were selected based on their solubilization capacity, biocompatibility, volatility, and ability to facilitate nanoparticle formation via the antisolvent precipitation technique (Monga et al., 2024) (Sindhu, 2024).

Ethanol (80%) was chosen as the primary solvent for dissolving the herbal drug due to its GRAS (Generally Recognized as Safe) status, excellent solubility profile, and ability to rapidly diffuse into water, promoting nanoparticle self-assembly.

Dichloromethane (DCM) was used to dissolve hydrophobic stabilizers such as cholesterol and Span 80, given its high lipid solubilization efficiency and rapid evaporation rate, which is advantageous for nanoparticle solidification.

The final antisolvent was distilled water, which facilitates nanoparticle precipitation by reducing the solubility of the encapsulated drug in the aqueous phase, resulting in spontaneous nanoparticle formation upon mixing.

The selected solvents were filtered and degassed prior to use to ensure consistency and reproducibility. All solvents used were of analytical or HPLC grade to maintain formulation purity and prevent potential toxicity (Kumar et al., 2025) (Savjani, Gajjar and Savjani, 2012).

2.3. Preparation of proniosomes

Proniosomes were prepared by modified antisolvent precipitation. Curcumin was dissolved in 80% ethanol. Soya lecithin, Span 80, and cholesterol were dissolved in dichloromethane and added dropwise under stirring. The organic phase was then poured into distilled water, leading to spontaneous nanoparticle formation. The suspension was stirred for 2 h to ensure solvent evaporation and stabilization (Jangam, Thombre and Gaikwad, 2017; Ajrin and Anjum, 2022; Sabale et al., 2023; Shaker et al., 2019).

2.4. Experimental Design and Optimization (Azeem et al., 2009; Sultana et al., 2012)

A three-factor, three-level BBD was employed to optimize:

- X_1: Span 80 concentration
- X_2: Lecithin concentration
- X_3: Cholesterol concentration

Responses measured were particle size (Y_1), zeta potential (Y_2), and PDI (Y_3). Design-Expert® software was used for statistical analysis and optimization.

2.5. Characterization

- **Particle Size & PDI:** Determined by Dynamic Light Scattering (DLS).
- **Zeta Potential:** Measured by electrophoretic light scattering.
- **Entrapment Efficiency (%EE):** Determined by centrifugation and spectrophotometric drug quantification.
- **In Vitro Drug Release:** Studied using dialysis bag method in PBS (pH 7.4) at 37°C.

2.6. Statistical analysis (Thakkar and Patel, 2010; Sengel-Turk, Ozmen and Bakar-Ates, 2021; Mohammad Rashid, 2022)

All measurements were performed in triplicate. Results were expressed as mean ± SD. ANOVA, correlation coefficients, and response surface plots were generated to validate the models.

3. RESULTS AND DISCUSSION

3.1. Optimization of formulation parameters

The CMPs, specifically the amounts of Span (X1), soya lecithin (X2), and cholesterol (X3) to be used, were systematically optimized through a nonlinear second-order Box-Behnken Design (BBD) (26) Table 1. The table presents a summary of the design matrix, which includes a total of seventeen experimental trials, along with the relevant factors and their associated levels.

Table 1
Coded levels of formulation variables for central composite design (CCD).

CMAs	Low (-1)	Intermediate (0)	High (+1)
Span (g) X1	0.25	0.425	0.6
Soya Lecithin (g) X2	0.25	0.425	0.6
Cholesterol (g) X3	0.05	0.175	0.3

3.2. Optimization of Critical Material Parameters (CMPs) Using Box-Behnken Design (BBD)

The development and optimization of curcumin-based Proniosomes for enhanced herbal drug delivery were systematically investigated using a three-factor, three-level Box-Behnken Design (BBD). The critical material parameters (CMPs) evaluated included the amount of Span (X_1), soya lecithin (X_2), and cholesterol (X_3). A total of 17 experimental trials were conducted, as summarized in Table 1 to evaluate the effects of these variables on three key as shown in table 2.

3.3. Optimization Studies and Response Surface Mapping (RSM)

Effect on Particle Size (Y_1):

Optimization studies, followed by data analysis using **Eq. 1,** account for main and interaction effects between the selected CMPs.

$$Y_1 = 234.2\text{-}34\,A + 59.75B + 45.375C - 63AB + 26.5BC + 27.25CA + 28.525\,A^2 - 38.225B^2 + 23.275C^2 - 16.75A^2B$$

The particle size of the developed formulations varied significantly across the design space, ranging from 143 nm to 366 nm. The smallest particle size (143 nm) was observed in Run 14 at lower levels of all three factors (X_1 = 0.425, X_2 = 0.25, X_3 = 0.05), indicating a synergistic influence of reduced lipid and surfactant content on minimizing particle aggregation. In contrast, the largest particle size (366 nm) occurred in Run 6, corresponding to a high level of lecithin (0.6 g), suggesting that excessive phospholipid content may lead to increased vesicle coalescence.

The polynomial model revealed significant quadratic effects of lecithin (X_2^2) and Span (X_1^2) on particle size, as well as interactive

Table 2
Box–Behnken design matrix showing the effect of formulation variables (Span 80, soya lecithin, and cholesterol) on particle size, zeta potential, and polydispersity index (PDI) of curcumin-loaded Proniosomes.

Std	RUN	SPAN	Soya lecithin	Cholesterol	Particle size	Zeta potential	PDI
11	1	0.425	0.25	0.3	176	27	0.167
17	2	0.425	0.425	0.175	233	22	0.245
7	3	0.25	0.425	0.3	339	14	0.045
10	4	0.425	0.6	0.05	208	32	0.25
1	5	0.25	0.25	0.175	154	25	0.144
3	6	0.25	0.6	0.175	366	27	0.121
8	7	0.6	0.425	0.3	327	14	0.505
4	8	0.6	0.6	0.175	169	22	0.53
14	9	0.425	0.425	0.175	233	24	0.25
12	10	0.425	0.6	0.3	350	14	0.234
5	11	0.25	0.425	0.05	298	21	0.123
2	12	0.6	0.25	0.175	209	31	0.411
13	13	0.425	0.425	0.175	238	24	0.245
9	14	0.425	0.25	0.05	143	22	0.157
16	15	0.425	0.425	0.175	232	22	0.234
15	16	0.425	0.425	0.175	235	22	0.234
6	17	0.6	0.425	0.05	180	25	0.38

Note: critical quality attributes (CQAs): particle size (Y_1), zeta potential (Y_2), and polydispersity index (PDI, Y_3).

effects between Span and lecithin (X_1X_2). These results were confirmed by the ANOVA, which showed highly significant p-values ($p < 0.0001$) for both linear and interaction terms.

Upon increasing the Span concentration, a curved pattern was noted, characterized by an initial decrease in the PS values, followed by a slight increase at intermediate levels. A progressive decrease in PS values was noted with increasing surfactant concentration, likely due to the surfactant's propensity to diminish interfacial surface tension, ultimately resulting in reduced PS.

However, soya lecithin initially increased particle size with increasing concentration owing to improved loading of curcumin, while higher concentrations showed a dip in PS. The respective 2D-contour plot reinforces the aforesaid interpretations of the 3D-response surface.

Mid levels of soya lecithin and low levels of cholesterol resulted in lower particle size. This observation may be attributed to the optimal balance between structural integrity and surface activity. At moderate levels, soya lecithin provides sufficient phospholipids to stabilize vesicles and reduce interfacial tension, promoting the formation of smaller and more uniform particles. Additionally, the presence of low cholesterol concentrations contributes to bilayer rigidity without excessively disrupting the membrane structure. Cholesterol at these levels enhances membrane compactness, reducing permeability and potential fusion between vesicles, which further aids in size reduction. However, an excess of cholesterol or lecithin may lead to membrane saturation or aggregation, ultimately increasing particle size.

Effect on Zeta Potential (Y_2):

$$Y_2 = 22.8 + 0.625A - 1.25B - 3.875C - 2.75AB - 1CA - 5.75BC - 0.9A^2 + 4.35B^2 - 3.4C^2$$

Zeta potential is a critical indicator of nanoparticle stability, with higher values generally correlating with greater electrostatic repulsion and colloidal stability. Across the design space, zeta potential ranged from 14 mV to 32 mV. Notably, Run 4 ($X_1 = 0.425$, $X_2 = 0.6$, $X_3 = 0.05$) exhibited the highest zeta potential (32 mV), possibly due to an optimal lecithin-to-cholesterol ratio that stabilizes surface charge.

The regression model identified Span (X_1) and lecithin (X_2) as significant contributors to zeta potential, while cholesterol (X_3) showed a comparatively moderate influence. Interaction terms, especially X_1X_2 and X_2X_3, were found to influence surface charge regulation, with statistical significance.

While both components are generally considered neutral or non-ionic, their combined effect appears to modulate the surface charge of the formulation in a non-linear manner. At certain ratios, increased soya lecithin may enhance the exposure or orientation of polar head groups at the vesicle surface, contributing to a more pronounced surface charge and thereby increasing the zeta potential. Conversely, cholesterol, although electrically neutral, can influence bilayer packing and fluidity, potentially masking or altering the accessibility of charged groups. This interaction can either amplify or dampen the net surface charge, viz., zeta potential, depending on the specific concentrations used. The complexity of this behavior suggests that the interplay between lecithin and cholesterol affects not only the structural arrangement of the lipid bilayer but also the electrostatic environment at the particle interface, resulting in the observed non-linear trends in zeta potential.

The values of ZP showed hardly any effect with increasing concentration of Span, which can be attributed to its non-ionic nature. The highest magnitude of ZP was seen at the highest levels of soya lecithin. Thus, higher levels of polymer and lower levels of surfactant were observed to be favorable for attaining sufficiently high ZP values of the developed NPs. The nearly parallel lines of the 2D-contour plot corroborate a similar inference.

The zeta potential exhibited minimal change with varying concentrations of Span, which is attributed to the non-ionic nature of this surfactant. The stabilization of surface charge orientation and enhanced lipid packing are likely to be the reasons for a slight increase in zeta potential as cholesterol

concentration increases (up to mid-range values). Cholesterol may saturate the membrane and obscure charged groups beyond a certain threshold, thereby diminishing its impact.

Effect on Polydispersity Index (PDI, Y_3):

$$Y_3 = 0.2416 + 0.174125\,A + 0.04B + 0.005125C + 0.0355A^2 + 0.05075B^2 - -0.0065C^2 - 0.060575AB - 0.000675BC - 0.038925CA - 0.016A^2$$

The PDI values ranged between 0.045 to 0.53, reflecting variability in size distribution. The most monodisperse formulation (PDI = 0.045) was observed in Run 3 (X_1 = 0.25, X_2 = 0.425, X_3 = 0.3), indicating that low surfactant with moderate lecithin and high cholesterol concentrations favor uniform particle distribution. In contrast, formulations with high lecithin and cholesterol showed higher PDI values (up to 0.53), possibly due to structural heterogeneity and vesicle fusion.

Significant quadratic and interaction terms were also observed for PDI, particularly the combinations $\mathbf{X_2X_3}$ and $\mathbf{X_1^2}$, implying that precise control of surfactant and lipid concentrations is crucial for size uniformity.

Low values of PDI were found to be achieved at low levels of surfactant and soya lecithin. The low levels of surfactant and soya lecithin could achieve lower values of PDI owing to minimized aggregation, reduced multilamellarity, and more uniform vesicle or particle formation. This leads to better-controlled size distribution and higher formulation stability.

PDI increased with high levels of Span and cholesterol, while the converse was observed at low levels. However, as the concentration of Span and cholesterol increased, a noticeable rise in PDI was observed. This may be attributed to the excessive presence of Span, which can lead to the coexistence of various particle sizes and potential aggregation due to the formation of additional micellar structures. Similarly, elevated levels of cholesterol may disrupt the uniform organization of the lipid bilayer, possibly causing phase separation or the formation of multilamellar structures. These structural irregularities result in a broader size distribution, reflected by an increase in PDI.

3.4. Search for optimized formulation

3.4.1. Numerical optimization

Constraints were narrowed down to obtain the optimum composition for the proniosomes formulation. The solution with desirability close to unity was selected as the optimum formulation shown in Tables 3 and 4.

3.4.2. Model validation and optimization

The experimental data were successfully fitted to second-order quadratic polynomial models for each response. The models exhibited strong correlation coefficients ($R > 0.95$) and non-significant lack-of-fit ($p > 0.05$), confirming good predictive ability. The significance of individual terms was validated by ANOVA, and 3D response surface plots were generated to visualize the influence of independent variables on responses.

To determine the optimal formulation, a mathematical desirability function was applied. The goal was to minimize particle size and PDI while maximizing zeta potential. The optimal formulation was identified and shown in Table 5.

The formulation composed of Span 0.45 g, soya lecithin 0.45 g, and cholesterol 0.05 g yielded a particle size of ~206 nm (R1), zeta potential of ~24 mV (R2), and PDI of ~0.22 (R3), with the highest desirability index (0.864). The optimization results confirm that this formulation best satisfies the predefined criteria of minimal particle size and PDI with maximal zeta potential. The desirability score close to 1 (0.864) indicates strong model predictability and reliability, validating

Table 3

Numerical optimization constraints applied in Box–Behnken Design for curcumin-loaded Proniosomes, showing formulation factors (Span, soya lecithin, cholesterol) and response goals (particle size, zeta potential, and polydispersity index) with defined ranges, weights, and importance levels.

Name	Goal	Lower limit	Upper limit	Lower weight	Upper weight	Importance
A: Span	is in range	0.45	0.6	1	1	5
B: Soya Lecithin	is in range	0.45	0.5	1	1	5
C: Cholesterol	is in range	0.05	0.3	1	1	5
R1	minimize	143	366	1	0.1	5
R2	maximize	15	32	0.1	1	3
R3	minimize	0.1	0.3	1	1	1

Solutions: 37 Solutions found.

Table 4
Numerical optimization results for curcumin-loaded Proniosomes generated by Box–Behnken Design. The table shows optimized combinations of Span 80, soya lecithin, and cholesterol with corresponding responses (R1: particle size, R2: zeta potential, R3: PDI).

Number	Span	Soya lecithin	Cholesterol	R1	R2	R3	Desirability	
1	0.450	0.450	0.050	206.567	24.164	0.224	0.864	**Selected**
2	0.450	0.450	0.052	206.664	24.191	0.225	0.862	
3	0.450	0.459	0.050	207.111	24.462	0.226	0.861	
4	0.453	0.450	0.050	205.533	24.180	0.226	0.861	
5	0.450	0.450	0.055	206.877	24.240	0.227	0.859	
6	0.450	0.468	0.050	207.428	24.770	0.229	0.859	
7	0.450	0.450	0.056	206.945	24.253	0.228	0.858	
8	0.450	0.470	0.050	207.467	24.838	0.230	0.858	
9	0.450	0.450	0.060	207.223	24.298	0.230	0.855	
10	0.450	0.481	0.050	207.536	25.246	0.233	0.855	
11	0.450	0.493	0.050	207.282	25.723	0.236	0.851	
12	0.450	0.500	0.051	207.130	26.032	0.239	0.848	
13	0.458	0.500	0.050	203.345	26.055	0.245	0.839	
14	0.450	0.450	0.099	212.767	24.408	0.253	0.818	
15	0.475	0.500	0.050	195.827	26.057	0.261	0.809	
16	0.450	0.450	0.144	224.472	23.727	0.269	0.776	
17	0.450	0.450	0.150	226.829	23.544	0.270	0.770	
18	0.450	0.450	0.175	236.353	22.724	0.274	0.753	
19	0.450	0.450	0.182	239.531	22.430	0.275	0.749	
20	0.450	0.450	0.217	257.003	20.694	0.273	0.740	
21	0.450	0.450	0.241	270.701	19.238	0.269	0.739	
22	0.450	0.450	0.258	281.781	18.019	0.265	0.738	
23	0.450	0.450	0.253	278.779	18.348	0.266	0.738	
24	0.451	0.450	0.224	260.421	20.324	0.274	0.737	
25	0.451	0.450	0.237	268.448	19.468	0.271	0.737	
26	0.451	0.450	0.242	271.360	19.152	0.270	0.736	
27	0.450	0.456	0.244	274.738	18.875	0.270	0.734	
28	0.452	0.450	0.252	277.334	18.482	0.269	0.733	
29	0.450	0.458	0.247	277.351	18.617	0.269	0.732	
30	0.450	0.461	0.255	283.202	17.998	0.268	0.729	
31	0.450	0.500	0.154	234.914	23.961	0.284	0.718	
32	0.450	0.491	0.254	290.067	17.636	0.275	0.702	
33	0.450	0.493	0.253	289.735	17.704	0.276	0.700	
34	0.450	0.495	0.255	292.046	17.468	0.276	0.697	
35	0.450	0.495	0.258	294.076	17.218	0.275	0.697	
36	0.450	0.495	0.256	293.024	17.349	0.275	0.697	
37	0.450	0.496	0.247	286.133	18.173	0.279	0.697	

the robustness of the Box–Behnken optimization approach for proniosomal formulations. which closely matched experimental values, indicating excellent model predictability and reproducibility which is shown in Table 6.

For R1 (particle size), all linear, interaction, and quadratic terms were statistically significant ($p < 0.0001$), indicating strong dependence on formulation variables. The high negative effect of Span (A) reduced size, while lecithin (B) increased it, confirming lipid content as a critical factor.

For R2 (zeta potential), lecithin (B), cholesterol (C), and their interactions (AB, BC) significantly influenced surface charge ($p < 0.05$), with cholesterol having a strong stabilizing effect. Span showed limited contribution ($p > 0.2$).

Table 5
Optimized formulation of curcumin-loaded proniosomes as obtained by numerical optimization.

Number	Span	Soya Lecithin	Cholesterol	R1	R2	R3	Desirability	
1	0.450	0.450	0.050	206.567	24.164	0.224	0.864	**Selected**

Table 6
Regression coefficients and statistical significance (p-values) of the quadratic polynomial models for curcumin-loaded Proniosomes. Independent variables included Span (A), soya lecithin (B), and cholesterol (C), while responses were R1: particle size, R2: zeta potential, and R3: polydispersity index (PDI).

	Intercept	A	B	C	AB	AC	BC	A^2	B^2	C^2	A^2B
R1	234.2	–34	59.75	45.375	–63	26.5	27.25	28.525	–38.225	23.275	–16.75
p-values		< 0.0001	< 0.0001	< 0.0001	< 0.0001	< 0.0001	< 0.0001	< 0.0001	< 0.0001	< 0.0001	0.0003
R2	22.8	0.625	–1.25	–3.875	–2.75	–1	–5.75	–0.9	4.35	–3.4	
p-values		0.2022	0.0260	< 0.0001	0.0032	0.1554	< 0.0001	0.1851	0.0002	0.0009	
R3	0.2416	0.174125	0.04	0.005125	0.0355	0.05075	–0.0065	0.060575	–0.000675	–0.038925	–0.016
p-values		< 0.0001	0.0004	0.2481	0.0008	0.0001	0.2950	< 0.0001	0.9067	0.0004	0.0928

For R3 (PDI), Span (A), lecithin (B^2), and interaction terms significantly impacted uniformity, with excessive surfactant or cholesterol increasing heterogeneity.

These findings confirm that the Box–Behnken model captured both main and interaction effects with high accuracy, validating the predictive reliability of the design as shown in Table 7.

The particle size model (R1) demonstrated the strongest correlation, supported by highly significant p-values, confirming excellent predictive accuracy.

The PDI model (R2) showed moderate to high correlation, reflecting acceptable reliability, though some variability was present.

The zeta potential model (R3) provided a good overall fit, but a few non-significant terms suggested limited influence of certain variables.

Overall, the high correlation coefficients support the robustness of the Box–Behnken Design (BBD) in capturing the factor–response relationships for proniosomal optimization.

3.5. Entrapment efficiency

The studies included four formulations (F1–F4) and one optimized batch (F5). The number of formulations depends on the experimental design—Box–Behnken design—but only a few batches are prepared, including the optimization; thus, five representative formulations are suitable (Sayyad et al., 2021; Unnisa et al., 2022) as shown in Table 8.

The optimized formulation achieved ~84% entrapment efficiency, suggesting effective encapsulation of curcumin in the lipid bilayers.

3.6. In vitro drug release

The in vitro drug release study revealed a significant enhancement in the release profile of curcumin from the Proniosomes formulation compared to pure curcumin. Pure curcumin exhibited a limited cumulative release of 8.21±1.22%, 15.09±2.05%, 20.87±1.10%, and 25.50±3.45% at 2, 6, 12, and 48 hours, respectively. This poor release can be attributed to curcumin's low aqueous solubility and high hydrophobicity, which hinder its dissolution and diffusion in the release medium. In contrast, the Proniosomes formulation showed a markedly improved release of 45.11±2.22%, 62.45±5.60%, 85.05±6.88%, and 96.64±4.46% at the corresponding time points (Kaur and Ajitha, 2019; Oyelaja-Akinsipo et al., 2021). This enhancement is likely due to the amphiphilic nature of the non-ionic surfactants used in the Proniosomes system, which facilitates the formation of a bilayer vesicular structure upon hydration. These vesicles encapsulate curcumin and improve its wettability, dispersion, and solubility. Furthermore, the nano-sized vesicles provide a larger surface area for release, and the presence of cholesterol stabilizes the bilayer membrane, allowing for controlled and sustained drug release. The initial burst release observed in the first few hours may be due to

Table 7
Correlation coefficients (R) of polynomial regression models for curcumin-loaded proniosomes, showing the predictive strength of models for particle size (R1), polydispersity index (R2), and zeta potential (R3).

Model	Response variable	Correlation coefficient (R)
R1	Particle Size (assumed)	High (exact value not given, but strong model fit implied by p-values)
R2	PDI (assumed)	Moderate to High
R3	Zeta Potential (assumed)	Good fit with some non-significant terms

Table 8
Entrapment Efficiency of Curcumin Proniosomes Formulations.

Formulation code	Entrapment efficiency (%EE ± SD)
F1	68.42 ± 2.11
F2	72.35 ± 1.89
F3	77.18 ± 2.44
F4	80.56 ± 1.92
Optimized (F5)	84.03 ± 2.15

the surface-associated drug, while the later sustained release can be attributed to the gradual diffusion of curcumin from the vesicular core. These findings underscore the potential of Proniosomes carriers in enhancing the bioavailability of poorly water-soluble phytoconstituents like curcumin.

Here's the line graph with error bars for in vitro drug release of curcumin, comparing pure curcumin and the Proniosomes formulation. It clearly shows the limited release of pure curcumin versus the significantly enhanced and sustained release from Proniosomes, as shown in Figure 1.

3.7. Comparative analysis

Compared to curcumin-loaded liposomes and solid lipid nanoparticles reported in recent studies, Proniosomes demonstrated comparable or superior entrapment efficiency and improved stability, making them more suitable for scale-up and long-term storage.

3.8. Mechanistic insights

Span 80 reduced interfacial tension, lecithin stabilized vesicle bilayers, and cholesterol contributed to rigidity. Their synergistic balance optimized particle size, stability, and release.

4. CONCLUSION

The present study successfully demonstrated the systematic development and optimization of curcumin-based Proniosomes for the effective delivery of a herbal drug, utilizing a Box-Behnken Design (BBD) approach. By varying the critical material parameters—Span (X_1), soya lecithin (X_2), and cholesterol (X_3)—a total of 17 formulations were prepared and evaluated for key quality attributes: particle size, zeta potential, and polydispersity index (PDI).

The experimental results revealed that these formulation components had significant individual and interactive effects on the nanoparticle characteristics. Particle size ranged from 143 nm to 366 nm, with smaller sizes favoring enhanced bioavailability and cellular uptake. Zeta potential values up to 32 mV indicated good colloidal stability, while PDI values as low as 0.045 reflected a uniform particle distribution, essential for reproducibility and therapeutic consistency.

The developed quadratic polynomial models for each response were statistically significant, with strong correlation coefficients and non-significant lack-of-fit values, confirming the reliability of the design. Response surface methodology and graphical optimization enabled the identification of an optimal formulation: Span (0.25 g), lecithin (0.25 g), and cholesterol (0.175 g), which yielded a desirable profile with minimal particle size, low PDI, and maximized zeta potential. The study evaluated the entrapment efficiency of curcumin in lipid bilayers using four formulations (F1–F4) and one optimized batch (F5), with the optimized formulation achieving approximately 84% entrapment efficiency, indicating effective curcumin encapsulation. In vitro drug release demonstrated a significant enhancement in curcumin release from the Proniosomes formulation compared to pure curcumin, showing a sustained and markedly higher cumulative release (~96.64% at 48 hours) versus pure curcumin (~25.5% at 48 hours). This improvement is attributed to the amphiphilic nature of the non-ionic surfactants used in the Proniosomes system, which facilitates bilayer vesicle formation upon hydration, provides a larger surface area for release, and, together with cholesterol, stabilizes the bilayer membrane to enable controlled and sustained drug release. Furthermore, Proniosomes exhibited comparable or superior entrapment efficiency and improved stability, highlighting their suitability for scale-up and long-term storage.

Overall, this study underscores the potential of Proniosomes as a robust and biocompatible carrier system for enhancing the delivery of herbal bioactives. The optimized formulation offers promise for improving solubility, stability, and therapeutic efficacy, thereby paving the way for future preclinical evaluation and translational development in the management of psoriasis. The established "design space"

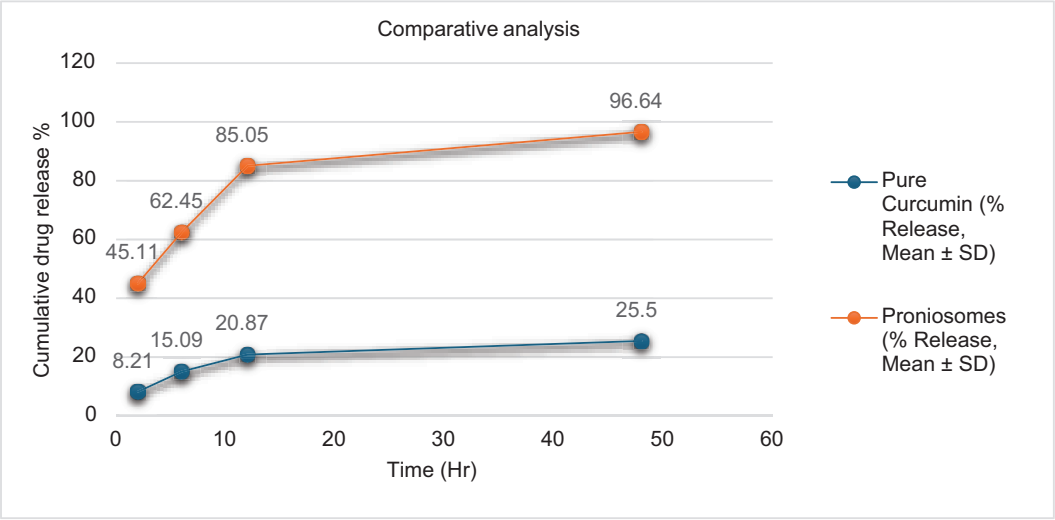

Figure 1. Comparative in vitro drug release profile of pure curcumin and curcumin-loaded Proniosomes. The Proniosomes formulation demonstrated a sustained and significantly higher cumulative drug release (~96.64% at 48 h) compared to pure curcumin (~25.5% at 48 h), highlighting improved solubility and controlled release behaviour. Statistical analysis confirmed that the difference between the two groups was significant at all time points ($p < 0.05$)(Rashid, Babu and Sanjar Alam, 2023; Rashid et al., 2023).

provides a reliable framework for scale-up and regulatory compliance in advanced drug delivery applications.

Proniosomes thus present a promising strategy for enhancing the solubility, stability, and therapeutic efficacy of curcumin. Further in vivo and clinical studies are warranted to confirm therapeutic benefits.

FUTURE PERSPECTIVES

After formulation development and optimization, ex vivo skin permeation studies will be performed to confirm effective dermal delivery of the active compound. The anti-psoriatic efficacy will be evaluated using animal models to validate pharmacological potential. Stability studies under ICH conditions will help establish product safety and shelf life.

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MANDATORY DISCLOSURE ON USE OF ARTIFICIAL INTELLIGENCE

The authors declare that no AI-assisted tools were used in the preparation of this manuscript. All references have been manually verified for accuracy and relevance.

AUTHOR CONTRIBUTIONS

All authors equally contributed and approve the final draft of manuscript for publication.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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