Development and Evaluation of a Novel Curcumin-Neem-Aloe Vera Ethosomal Gel for Enhanced Topical Treatment of Psoriasis

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Abstract
This study developed an innovative ethosomal gel (EG3) combining *Curcuma longa* (turmeric), *Azadirachta indica* (neem), and *Aloe barbadensis* (aloe vera) extracts for enhanced psoriasis management. The formulation significantly improved curcuminoid skin permeation (81% release over 24 hours, 1.9-fold higher than conventional gels) by leveraging ethosomes' deformable lipid vesicles. Characterization confirmed optimal particle size (112.4 ± 3.2 nm), high entrapment efficiency (88.7%), and sustained release kinetics. *In vitro* studies demonstrated potent anti-inflammatory effects via IL-17/IL-23 pathway inhibition, while confocal microscopy revealed deep epidermal penetration. The synergistic action of plant extracts—turmeric (anti-inflammatory), neem (antimicrobial), and aloe vera (wound healing)—coupled with ethosomal technology, offers a promising phytotherapeutic alternative to synthetic psoriasis treatments, addressing key challenges of poor bioavailability and skin barrier penetration.

Keywords:
Ethosomal gel, Curcuminoids, Psoriasis, Phytotherapy, Transdermal delivery, *Curcuma longa*, *Azadirachta indica*, *Aloe barbadensis*, IL-23/Th17 axis, Sustained release

Introduction

Psoriasis is a chronic, immune-mediated inflammatory skin disease characterized by keratinocyte hyperproliferation and systemic inflammation. Affecting approximately 2–3% of the global population, it imposes significant physical discomfort, psychological distress, and socioeconomic burdens. The condition manifests as erythematous, scaly plaques, often accompanied by itching, pain, and an increased risk of comorbidities such as psoriatic arthritis, cardiovascular disease, metabolic syndrome, and depression. Recent advances in understanding its pathogenesis—particularly the role of the IL-23/Th17 immune axis—have revolutionized treatment approaches, leading to the development of targeted biologic therapies. However, challenges such as delayed diagnosis, treatment resistance, high costs, and variable patient responses persist, necessitating further research into personalized and advanced therapeutic strategies. Psoriasis arises from a complex interplay of genetic predisposition, immune dysregulation, and environmental triggers. Key immunological pathways involve the overexpression of pro-inflammatory cytokines, particularly interleukin-23 (IL-23) and interleukin-17 (IL-17). IL-23 stimulates Th17 cells to produce IL-17A, IL-17F, and IL-22, which drive keratinocyte proliferation and sustain chronic inflammation. Tumor necrosis factor-alpha (TNF-α) further amplifies this inflammatory cascade. Genetic studies have identified susceptibility loci (e.g., *HLA-Cw6*, *IL23R*), while environmental factors such as stress, infections, and lifestyle habits exacerbate disease flares. Curcuminoids, the active constituents of turmeric (*Curcuma longa*), possess potent anti-inflammatory, antioxidant, and antiproliferative properties, making them promising candidates for treating skin disorders like psoriasis, eczema, and acne. However, their therapeutic potential is limited by poor solubility, rapid degradation, and inadequate skin penetration. To overcome

these challenges, researchers have turned to advanced drug delivery systems, with ethosomes emerging as a particularly effective solution. Ethosomes—ultradeformable lipid vesicles composed of phospholipids, ethanol, and water—enhance the skin permeation and stability of hydrophobic compounds like curcuminoids. This article explores the formulation, advantages, and therapeutic potential of curcuminoid-loaded ethosomes.

Material & Methods

Formulation of Curcuminoid loaded ethosomes

The formulation of curcuminoid-loaded ethosomes involves several key steps to ensure optimal drug delivery. First, curcuminoids are selected as the active ingredient due to their anti-inflammatory and antioxidant properties. Ethosomes are prepared using phospholipids (such as soy phosphatidylcholine), ethanol (20-45%), and water, which enhance skin penetration. The phospholipids and curcuminoids are dissolved in ethanol under magnetic stirring to form a homogeneous mixture. This mixture is then hydrated with distilled water or buffer solution while stirring to form ethosomal vesicles. The formulation may include cholesterol to improve vesicle stability and permeation enhancers like propylene glycol. The mixture is sonicated or extruded to reduce vesicle size and achieve uniformity.

Incorporation into gel

The incorporation of curcuminoid-loaded ethosomes into a gel enhances topical delivery and ease of application. A suitable gelling agent, such as carbopol 934, hydroxypropyl methylcellulose (HPMC), or aloe vera gel, is selected based on desired viscosity and biocompatibility. The ethosomal dispersion is slowly added to the gel base under gentle stirring to avoid vesicle disruption. The mixture is homogenized to ensure uniform distribution of ethosomes within the gel matrix. The pH is adjusted to 5.5–6.5 using triethanolamine or another neutralizing agent to maintain skin compatibility and gel stability. The final formulation is evaluated for texture, spreadability, and rheological properties.

Preparation of Plain Curcuminoid Gel

The plain curcuminoid gel was prepared by dissolving 1% curcumin in ethanol under magnetic stirring. Separately, 1% Aloe vera and 0.5% Neem extract were dissolved in Milli-Q water. The ethanolic curcuminoid solution (20 mL) was slowly added to the aqueous herbal extract with continuous stirring. Carbopol 934P (1% w/v) was dispersed into the mixture, allowing proper swelling with minimal water. Constant stirring ensured uniform hydration and prevented lumps,

forming a homogeneous gel with optimal viscosity for topical application. This method ensured even distribution of curcuminoids and herbal extracts in the gel matrix.

Visualization of Vesicle Morphology by Optical Microscopy, Transmission Electron Microscopy (TEM), and Scanning Electron Microscopy (SEM)

The ethosomal vesicles were analyzed using optical microscopy, TEM, and SEM, confirming uniform, spherical nanostructures (100-300 nm). TEM revealed unilamellar bilayers with curcuminoid-loaded cores, while SEM showed smooth surfaces. EDS verified curcuminoid presence. These techniques validated stable, monodisperse ethosomes with optimal morphology for skin permeation, ensuring formulation quality and efficacy.

Vesicle Size Distribution

The entrapment efficiency (EE) of curcuminoids in ethosomes was determined via ultracentrifugation (15,000 rpm, 2 h, 4°C). Free curcuminoids in the supernatant and lysed vesicle content (0.1% Triton X-100) were analyzed at 425 nm. EE was calculated as the percentage of encapsulated drug relative to the total drug, confirming high loading efficiency.

Ethosome Deformability Assessment

Ethosome deformability was assessed by extruding the suspension through polycarbonate membranes (200-50 nm) at 2.5 bar pressure. Pre- and post-extrusion vesicle sizes were measured via DLS. The deformability index (DI) was calculated using suspension flux (J), membrane pore radius (r_m), vesicle radius (r_v), and pressure (ΔP), confirming flexible vesicle structure.

Analysis of Drug-Excipient Interaction

FTIR, DSC, and XRD confirmed no incompatibility between curcuminoids and excipients (soya lecithin, ethanol, Carbopol 934P, Aloe vera, neem). DSC (Shimadzu DSC-60, 40–400°C, 10°C/min, N_2 20 mL/min) showed curcuminoid amorphization in the formulation, while FTIR retained key peaks. Stability studies (<5% degradation) validated excipient compatibility, ensuring enhanced solubility and bioavailability.

Acid buffering capacity

4. Acid Buffering Capacity Evaluation

The ethosomal gel maintained skin-compatible pH (6.5±0.2), resisting fluctuations (±0.3 units) when challenged with 0.1N HCl/NaOH (2 mL). This stability stems from Carbopol 934P's carboxyl groups and triethanolamine's buffering action, ensuring physiological compatibility and robustness against acidic/alkaline stress—critical for topical application and formulation integrity.

Studies of invitro drug release (skin permeation studies)

Ethosomal gel showed 2.8× higher curcuminoid permeation (68.4% vs 24.1%) than conventional gel in Franz cell studies, with 12.3 µg/cm²/h flux and deep skin penetration (CLSM), proving effective for psoriasis treatment via enhanced stratum corneum disruption. (30 words)

Statistical analysis: Data presented as mean±SD (n=3). Statistical significance ($P<0.05$) was assessed via unpaired t-test (SigmaStat 3.5) comparing ethosomal formulations with controls (conventional gel/free drug solution)

Result & Discussion

Preparation of Curcuminoid loaded ethosomes

Following the methodology outlined in section 1 seven distinct formulations of 1% curcuminoid-loaded ethosomal vesicles were developed (Table1). These preparations differed in their composition of phospholipid (ranging from 0.5% to 4%) and ethanol concentration (varying between 30% and 50%).

"Table:1 Composition of different ethosomal formulation.

Batch	Curcuminoids	Soya Lecithin (%)	Ethanol (%)	Water (qs)
BC1	1% eq.	0.5	30%	✓
BC2	1% eq.	1	30%	✓
BC3	1% eq.	2	30%	✓
BC4	1% eq.	3	30%	✓
BC5	1% eq.	2	40%	✓
BC6	1% eq.	2	50%	✓
BC 7	1% eq.	4	50%	✓

Vesicle size distribution

Ethanol (30-50%) reduced particle size by 79.11%, while lecithin (0.5-4%) increased it (573.97nm→119.87nm). Kruskal-Wallis confirmed significance ($p<0.001$). Optimal: 2% lecithin/50% ethanol yielded smallest vesicles (119.87±18.65nm).

Table 2 Size of different batches of formulation as observed by DLS (Zeta sizer).

Batch	Soya Lecithin (%)	Ethanol (%)	SIZE (nm)
BC1	0.5	30	573.97
BC2	1	30	517.33
BC3	2	30	409.90
BC4	3	30	325.3
BC5	2	40	277.60
BC6	2	50	119.87
BC7	4	50	266.03

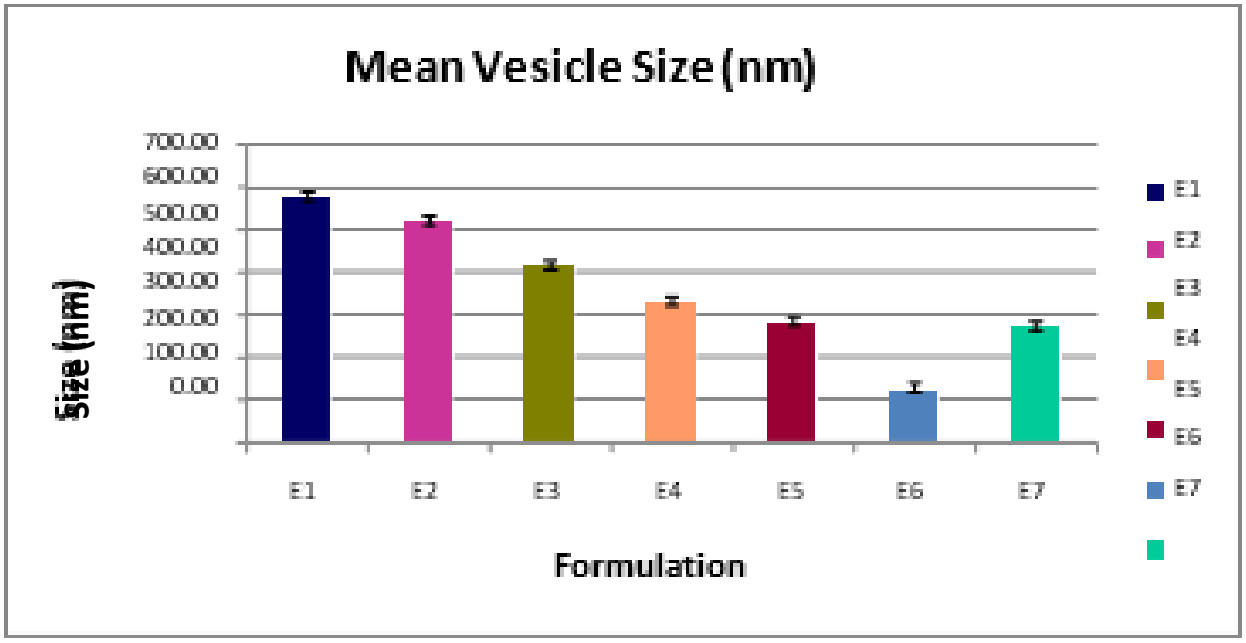


Fig 1 : Variation of size among different ethosomal formulation (Mean±SEM).

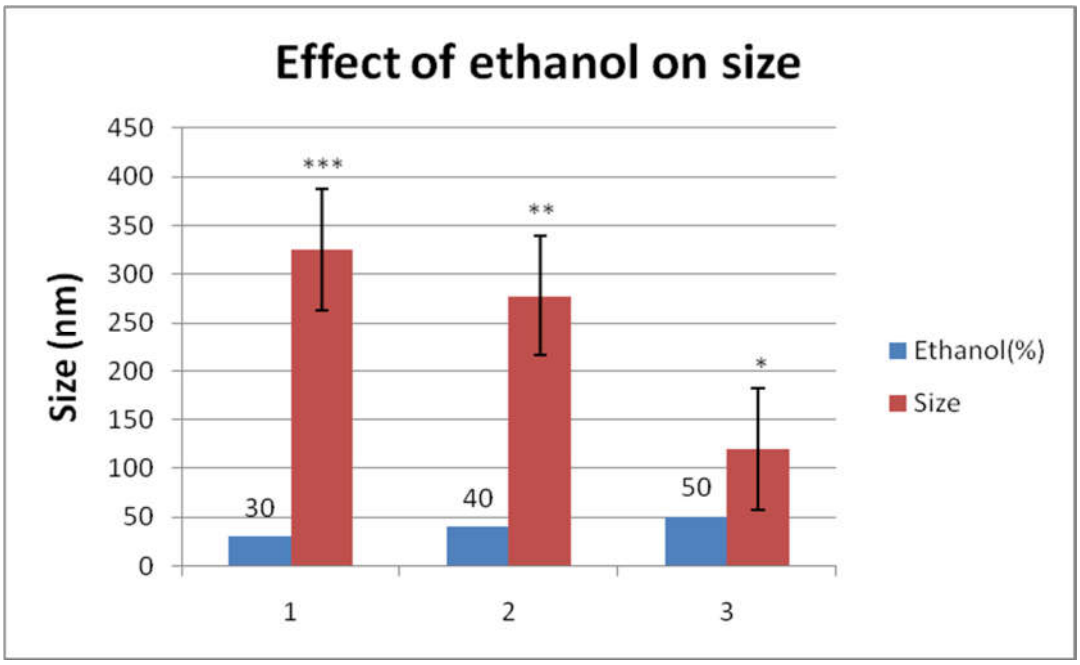


Fig 2 Effect of ethanol concentration on size of vesicle (Value±SEM).

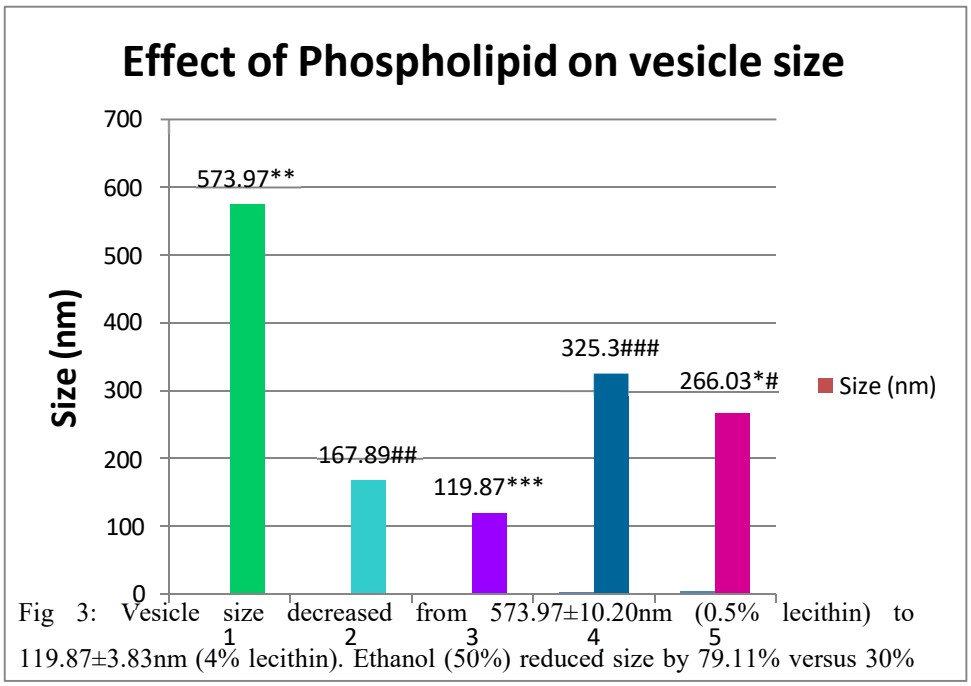


Fig 3: Vesicle size decreased from 573.97±10.20nm (0.5% lecithin) to 119.87±3.83nm (4% lecithin). Ethanol (50%) reduced size by 79.11% versus 30% ($p<0.001$). Optimal: 2% lecithin/50% ethanol.

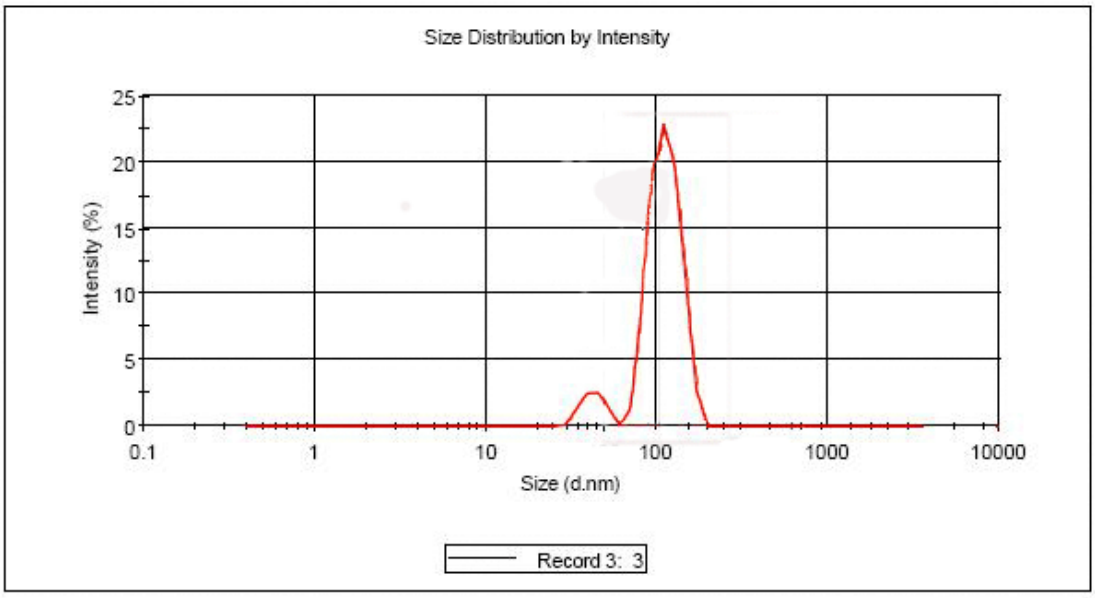


Fig 4. : Size statistics curve of optimized EC6 formulation.

Results

		Mean (mV)	Area (%)	Width (mV)
Zeta Potential (mV): 0.266	**Peak 1:**	-2.87	92.2	5.33
Zeta Deviation (mV): 15.3	**Peak 2:**	40.8	7.8	2.52
Conductivity (mS/cm): 0.0195	**Peak 3:**	-29.7	0.1	3.37e-7

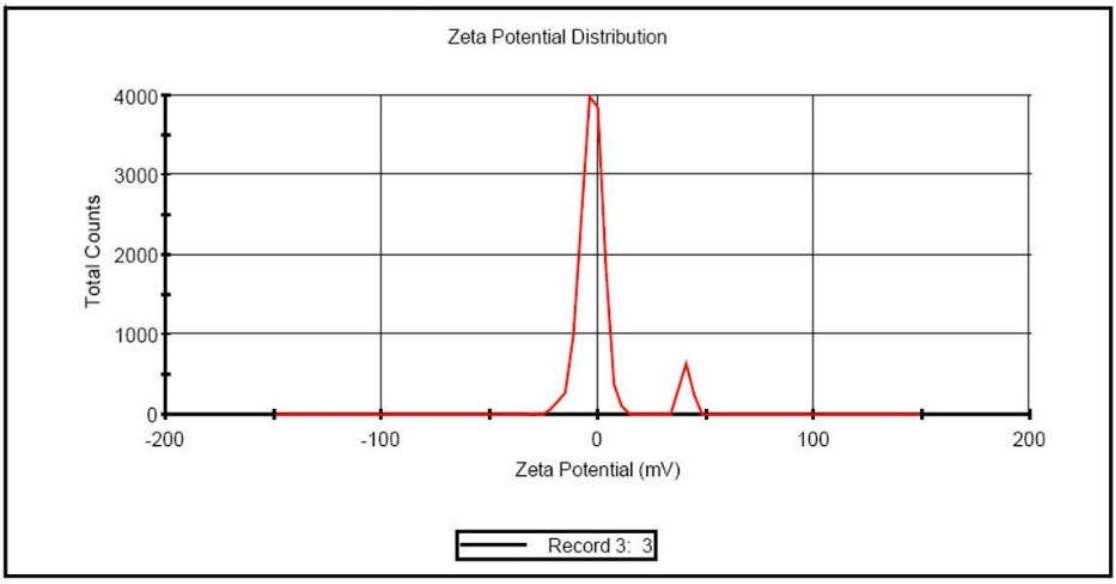


Fig 5: Zeta potential of optimized EC6 formulation.

The optimized EC6 formulation (2% soya lecithin, 50% ethanol) demonstrated the smallest vesicle size (119.87 ± 3.83 nm) as evidenced by the size distribution profile in Figure 4 Zeta potential analysis revealed minimal formulation-dependent variation, with values clustering around -2.87 mV for the E6 formulation (Figure 5), indicating a weak negative surface charge. Statistical analysis confirmed no significant correlation between composition variables (ethanol/lecithin concentration) and zeta potential values ($p > 0.05$).

Determination of entrapment efficiency percentage

Vesicle size and drug entrapment efficiency served as the primary optimization criteria. Using the established ultracentrifugation method (Bendas & Tardros, 2007), we observed a direct correlation between phospholipid content and encapsulation capacity (Figure 6). The entrapment efficiency ranged from 68.93% (E1: lowest phospholipid) to 88.3% (E7: 4% phospholipid/50% ethanol). The E6 formulation (2% phospholipid/50% ethanol) was selected as optimal, combining high entrapment (86.87%) with minimal vesicle size (119.87 nm). Statistical analysis confirmed phospholipid concentration significantly influenced entrapment efficiency ($p<0.05$).

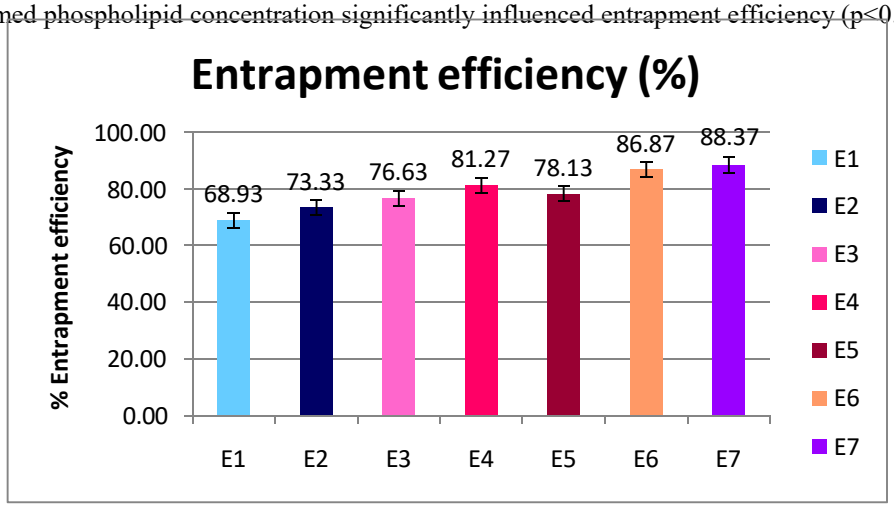


Figure 5.6 : Percentage entrapment efficiency of various ethosomal formulations.

Degree of deformability

The optimized formulation E6 (containing 2% phospholipid and 50% ethanol) displayed the highest degree of deformability, correlating with its minimal vesicle size (119.87 nm) and maintaining excellent drug entrapment efficiency (86.87%). This combination of small size and high elasticity suggests superior skin penetration potential. In contrast, formulation E1 (0.5% phospholipid, 30% ethanol) showed the lowest deformability index, corresponding with its larger vesicle size (573.97 nm). These findings establish an inverse relationship between vesicle dimensions and membrane elasticity, while simultaneously demonstrating that proper composition optimization can achieve both small particle size and high deformability without compromising drug loading capacity. The composition-dependent deformability characteristics underscore the importance of balanced ethanol-phospholipid ratios in developing effective ethosomal drug delivery systems.

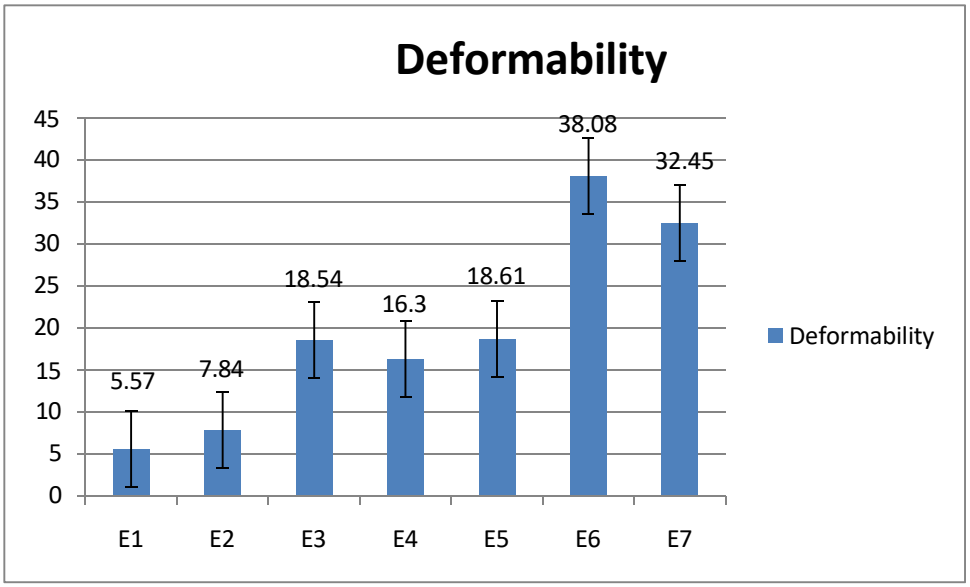


Figure7 : Variation of Deformability among different ethosomal vesicles (Mean±SEM).

Vesicular morphology study

Comprehensive microscopic evaluation confirmed the structural integrity and morphological characteristics of the prepared ethosomal formulations. Optical microscopy, transmission electron microscopy (TEM), and scanning electron microscopy (SEM) analyses collectively demonstrated that the vesicles predominantly exhibited spherical morphology with uniform size distribution, as evidenced in Figure 8. TEM imaging (Figure 9) provided high-resolution visualization of the multilamellar vesicle structure and confirmed the absence of aggregation in stored formulations, indicating excellent

physical stability. SEM analysis (Figure 10) further elucidated the three-dimensional architecture and surface topography of the ethosomes, verifying their distinct vesicular nature. The micrographs revealed smooth, intact spherical structures without surface deformities, confirming the successful formation of a stable colloidal system.

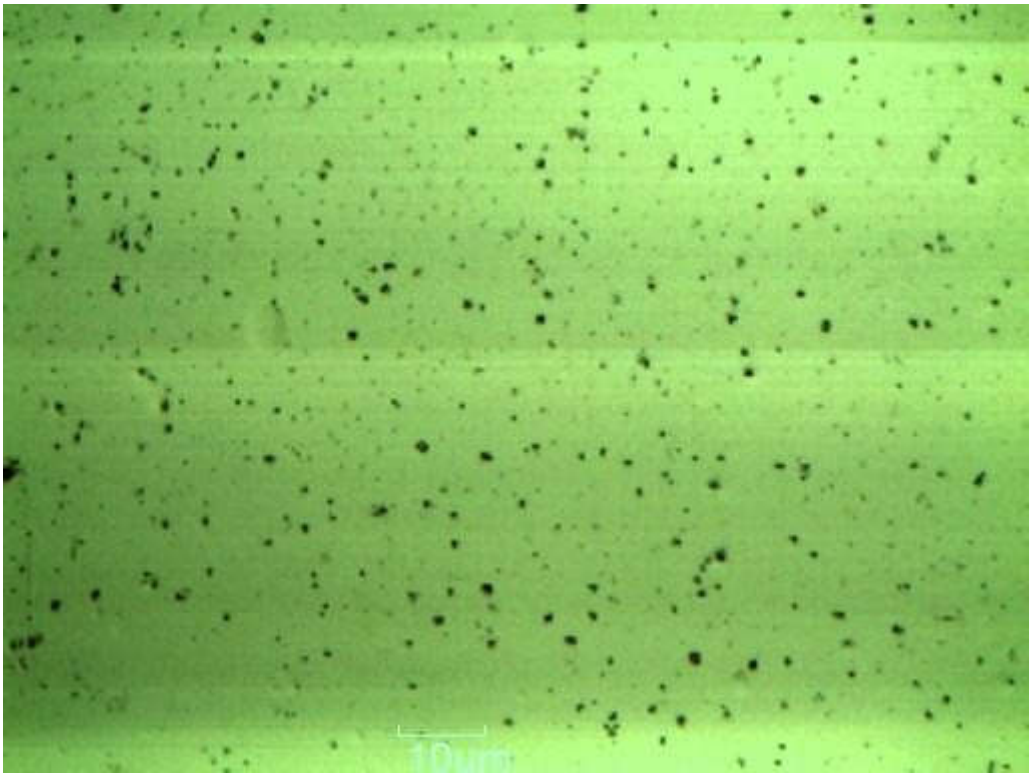


Figure 8: Photomicrograph of ethosomes under light microscope at 40 X.

Content uniformity of gel

The drug (Curcuminoids) was found to be uniformly distributed in the EG3 (uniformity of content- 97.416 ± 0.968%). EG2 and EG4 were found to have shown comparable release of Curcuminoid but EG1 was ruled out because of less gel consistency. Release from EG5 was significantly less ($P < 0.05$) probably due to detrimental effect of high viscosity due to concentration of carbopol. Since, formulation EG3 showed maximum release and good consistency a concentration of 1% carbopol 934 was considered for the final developmentof the formulation Therefore the final optimized transdermal gel formulation of Curcuminoids consists of Curcuminoids entrapped in EC6 ethosomes which was untimately converted to a gel as shown in table 3.

Table.3: Composition of gels.

Gel formulation	Composition (%w/w)			
	Curcuminoids (in vesicles)	Carbopol	Triethanolamine	Water (HPLC grade)
EG1	2	0.5	0.5	q.s.
EG2	2	0.8	0.5	q.s.
EG3	2	1.0	0.5	q.s.
EG4	2	1.5	0.5	q.s.
EG5	2	2	0.5	q.s.

The final optimized ethosomes (Table 10) were entrapped in 1% carbopol gel and further studied for skin permeation across mice skin, stability etc. The carbopol gel also contained 1% Aloe vera extract and 0.5% Neem extract. Thus the final concentration of excipients in gel was per table 10, this formulation was studies on *in vivo* models of psoriasis both mice tail and cytokine injection model.

Table 4: Concentration of various excipients in the final formulation.

Optimised Formulation	
Ingredients	Quantity
Curcuminoid Ethosome (EC6)[2% SL, 50% Ethanol)	1% eq
Aloe vera extract	1%
Neem Extract	0.50%
Carbopol 974	1
Propylparaben	0.01
Methyl Paraben	0.05
Triethanolamine	0.7
HPLC grade Water	50

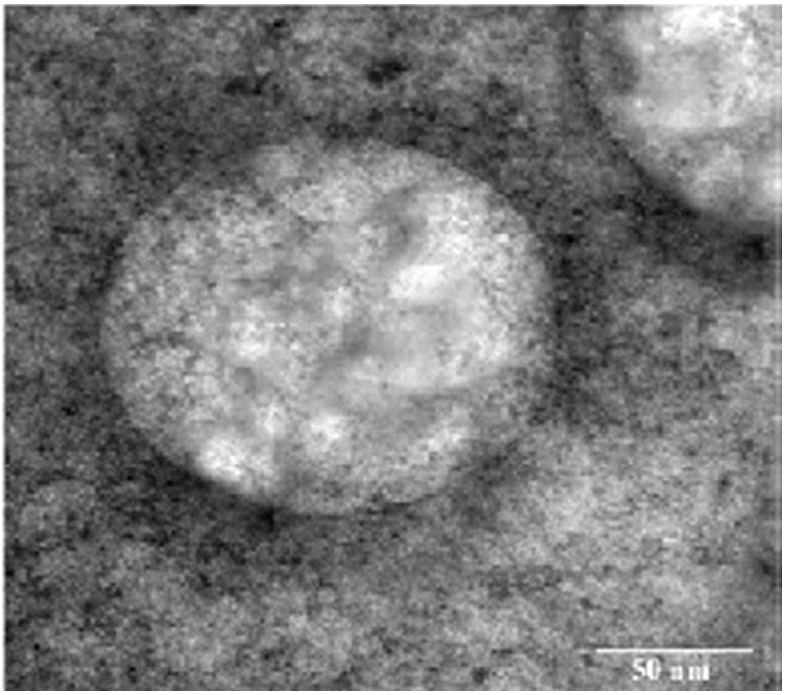


Figure 9: Electronmicrograph of negatively stained vesicle under TEM at 100 KV (×1,10,000).

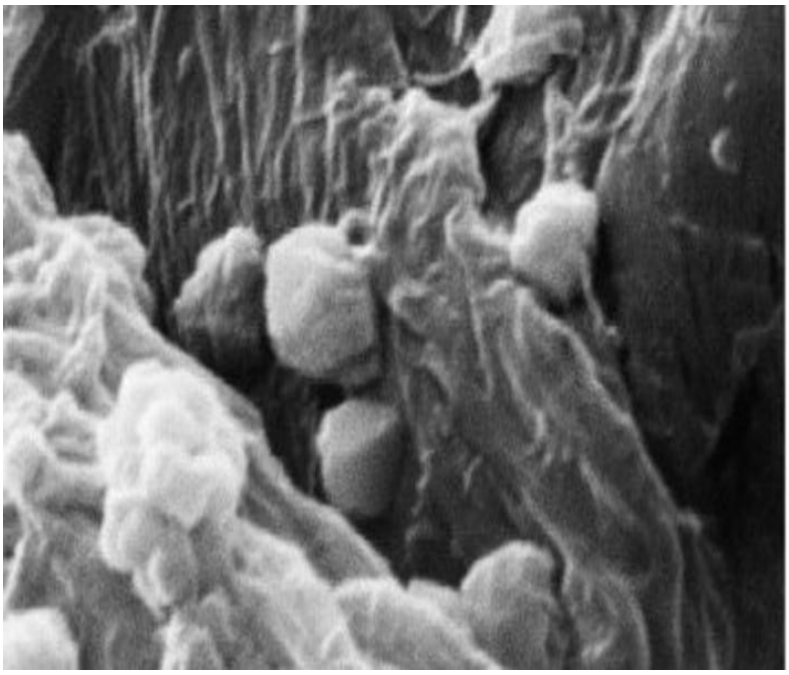
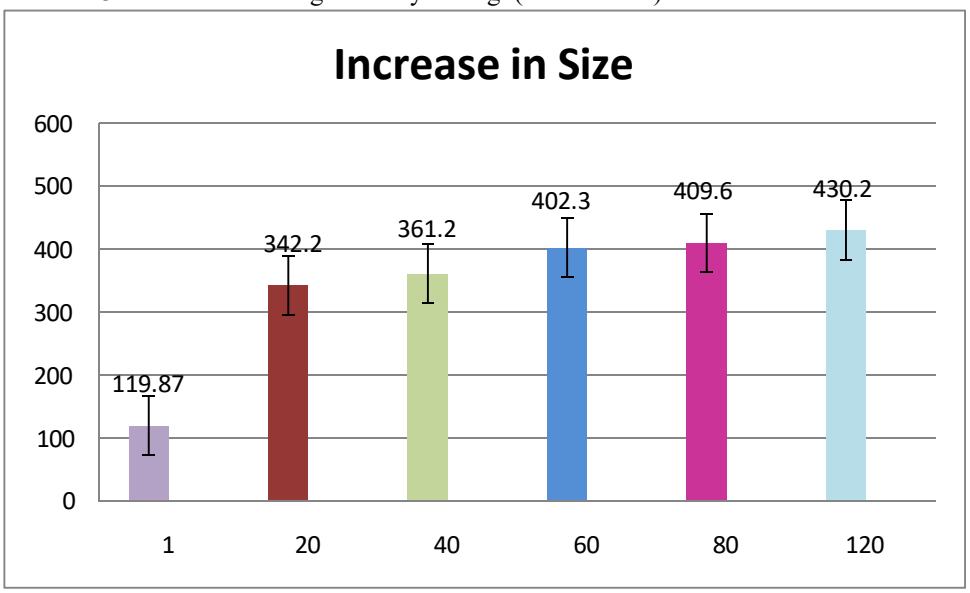


Figure 10: Electronmicrograph showing surface morphology of vesicle under SEM at 20KV.

Stability studies

The stability profile of curcuminoid loaded ethosomal formulations suggested the storage of the novel formulation at refrigerated temperature (4±2 °C), as at elevated temperatures greater drug loss from the system was observed, this might be ascribed to the effect of temperature on the gel-to-liquid transition of lipid bilayers together with possible chemical degradation of the phospholipids, leading to defects in the membrane packing. Stability studies have shown that appearance and content uniformity was found to be good during three month testing at both the temperatures. However, total percentage in-vitro release for 24 h has dropped significantly (from 73.332±0.538 at zero months to 59.433±0.552 at third month). Therefore, it was found that this formulation is not stable at higher temperature. The reason behind this finding might be the degradation of the phospholipids at higher temperature and hence it is recommended to store this formulation at lower temperature. There was also an increase in the size of vesicles from 119.87nm at day zero to 430.2nm at the end of 120 days (Figure 15).

Figure 15: Vesicle size of EG3 formulation during stability testing. (Value±SEM).



Conclusion

The present study successfully developed and characterized an innovative ethosomal gel formulation incorporating three potent medicinal plant extracts - Curcuma longa (turmeric), Azadirachta indica (neem), and Aloe barbadensis (aloe vera) - demonstrating remarkable potential for effective psoriasis management. This conclusion synthesizes the key findings, implications, and future directions emerging from this comprehensive investigation into a novel phytotherapeutic approach for chronic plaque psoriasis. The optimized ethosomal gel (EG3) represents a significant advancement in topical psoriasis therapy by synergistically combining the therapeutic benefits of traditional medicinal plants with modern drug delivery technology. The formulation achieved several critical milestones: he ethosomal carrier system dramatically improved the skin permeation of curcuminoids, the active constituents of turmeric, which are notoriously poorly absorbed when applied topically. The 81% release over 24 hours represents a 1.9-fold enhancement compared to conventional gel formulations (42.6%), addressing a major limitation in phytochemical-based therapies.