

IN VITRO, EX VIVO, AND IN VIVO EVALUATION OF A HERBAL NANOEMULSION GEL FOR THE MANAGEMENT OF PSORIASIS

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ABSTRACT

Psoriasis is a chronic inflammatory skin disorder marked by excessive keratinocyte proliferation and an overproduction of pro-inflammatory cytokines. In this work, we developed and fine-tuned a herbal nanoemulsion gel intended for topical psoriasis management, with the hope of improving drug delivery while balancing efficacy and safety. The optimized formulation—settled on after several less-than-ideal trial runs—yielded droplets averaging 96.4 ± 3.2 nm, a low polydispersity index (0.18 ± 0.01), and a zeta potential of -34.2 ± 1.5 mV. Drug encapsulation was consistently high (86–93%), and release profiles suggested a sustained delivery pattern (91–95% over 12 h), though whether this will fully translate in patient skin remains to be confirmed. Once incorporated into a gel base, the preparation retained its physicochemical stability and exhibited pseudoplastic flow. Spreadability measured 6.3 ± 0.4 cm and the pH hovered at 6.1 ± 0.2 —comfortably within the skin-friendly range.

Cytotoxicity testing on HaCaT cells indicated >85% viability at 100 $\mu\text{g/mL}$, and ELISA assays showed substantial reductions in TNF- α (70.37%), IL-6 (70.79%), and IL-17 (73.10%). Ex vivo skin permeation data pointed to a controlled release profile (82.2 ± 3.1 $\mu\text{g/cm}^2$ cumulative permeation, flux 11.3 ± 0.5 $\mu\text{g/cm}^2/\text{h}$). In a murine imiquimod-induced psoriasis model, PASI scores dropped from 3.2 to 2.0 by day 7, accompanied by histological improvements. No visible irritation, erythema, or edema was noted. While the results collectively suggest a stable, safe, and biologically active preparation, longer-term and broader-scale studies will be needed to verify its clinical relevance.

KEYWORDS: Psoriasis, Nanoemulsion gel, Cytokine inhibition, Skin permeation, PASI score

1. INTRODUCTION

Psoriasis is an immune-mediated skin disease with a complex pathophysiology, involving hyperproliferation of keratinocytes, infiltration of inflammatory cells, and a tangle of dysregulated immune signaling [1]. Clinically, it manifests as erythematous, scaly plaques that can be as psychologically taxing as they are physically uncomfortable. The global prevalence—around 2–3%—appears to be rising, likely due to a mix of genetic predisposition, environmental triggers, and lifestyle factors [2].

Current treatments, from corticosteroids to vitamin D analogs and systemic immunosuppressants, tend to address symptoms rather than the deeper immunological drivers [3]. Their benefits are often undermined by side effects, adherence issues, and high relapse rates—frustrations familiar to both patients and clinicians [4]. This has kept the search for gentler yet effective topical options very much alive.

Plant-derived bioactives have drawn attention for their multi-pronged actions—anti-inflammatory, antioxidant, immunomodulatory—and for the perception that they may carry fewer systemic risks [5]. Extracts from *Psoralea corylifolia* [6], *Azadirachta indica* [7], *Acacia catechu* [8], and *Pongamia pinnata* [9] have each been reported to dampen inflammatory cascades, mitigate oxidative stress, and slow keratinocyte overgrowth. Yet, as any formulator knows, translating these compounds from promising in vitro profiles to patient-ready products is not straightforward. Poor aqueous solubility, chemical instability, low bioavailability, and a stubborn stratum corneum often stand in the way [10].

Nanoemulsions—when prepared with care—offer a means of slipping past some of these barriers. Droplet sizes in the nanometer range can boost solubility and stability of hydrophobic actives, while promoting skin penetration without overly increasing systemic exposure [11]. Converting them into gel form adds the practical benefits of sustained release, better skin residence time, and a texture that spreads evenly without dripping. In theory, this makes them well-suited for delivering herbal bioactives into psoriatic lesions, where prolonged local action could temper inflammation and keratinocyte proliferation [12].

Here, we report on the development and optimization of a multi-herbal nanoemulsion gel combining *P. corylifolia*, *A. indica*, *A. catechu*, and *P. pinnata* extracts. A factorial design was used to identify optimal surfactant/co-surfactant ratios and processing conditions, with characterization covering particle size, PDI, zeta potential, morphology, rheology, encapsulation efficiency, and release behavior. The formulation was then assessed through in vitro, ex vivo, and in vivo assays for skin penetration, anti-inflammatory potential, and therapeutic efficacy in a psoriasis model. While our data make a case for its potential, the question of how it will perform in diverse patient populations remains open—a reminder that formulation science is only one piece of the therapeutic puzzle.

2. MATERIALS AND METHODS

2.1 Formulation of the Gel

The gel base was prepared by dispersing Carbomer 940 in distilled water, allowing it to hydrate for approximately two hours—long enough to achieve complete swelling without introducing excessive air bubbles. Neutralization with triethanolamine was performed gradually, targeting a pH in the range of 6.0–6.5 to match skin compatibility while avoiding over-neutralization, which can compromise viscosity [13]. This yielded a clear, stable base.

The optimized herbal nanoemulsion—previously obtained via ultrasonication—was incorporated slowly into the gel under continuous stirring. This step required some patience; rapid addition tended to cause localized aggregation, so the dispersion was done in small increments. Glycerin, serving as a humectant, was included to maintain moisture content and improve textural consistency, resulting in a smooth, homogenous formulation suitable for topical application [14].

The gel was then examined for visual parameters such as clarity, color, and homogeneity, ensuring no evidence of phase separation. Physicochemical evaluation included pH measurement, conductivity assessment, and rheological profiling using a Brookfield viscometer at varying shear rates to determine flow characteristics [15]. Spreadability was quantified by the parallel plate method, while adhesion (“stickiness”) was evaluated using standard tactile assessment techniques. Drug content uniformity was confirmed by sampling multiple sites within the batch and quantifying bioactive components via HPLC or UV–Vis spectrophotometry.

Short-term stability was assessed by storing samples at 4°C, 25°C, and 40°C for 30 days. At predetermined intervals, appearance, pH, viscosity, and drug content were re-evaluated. While one month is too short to confirm long-term stability, it provided an early indication of the formulation’s resilience to typical storage conditions [16].

2.2 In Vitro Studies

Cell Line Selection – Human keratinocyte (HaCaT) cells were chosen for cytotoxicity and anti-inflammatory assays, as they closely resemble normal epidermal keratinocytes in terms of proliferation, differentiation, and inflammatory responses. Their established role in modeling psoriasis makes them a reasonable—though not perfect—stand-in for in vivo epidermal behavior. Cells were maintained in DMEM supplemented with 10% FBS and 1% penicillin–streptomycin, at 37°C in a humidified 5% CO₂ incubator [17].

MTT Assay – Cytotoxicity was assessed using the standard MTT protocol. HaCaT cells were seeded in 96-well plates (1 × 10⁴ cells/well) and allowed to attach overnight. Treatments consisted of nanoemulsion gel at concentrations between 10 and 200 µg/mL, incubated for 24 hours. After treatment, 20 µL of MTT solution (5 mg/mL in PBS) was added, and plates were incubated for four hours. Formazan crystals were dissolved in DMSO, and absorbance was read at 570 nm. Viability was calculated as a percentage of untreated controls, providing a measure of biocompatibility [18]. While MTT is widely used, it does not account for potential sublethal metabolic effects—an acknowledged limitation.

Cytokine Quantification (ELISA) – To assess anti-inflammatory activity, HaCaT cells were pretreated with the nanoemulsion gel for two hours before stimulation with TNF-α (10 ng/mL). After 24 hours, supernatants were collected, and TNF-α, IL-6, and IL-17 levels were quantified using commercial ELISA kits, following the manufacturer’s protocols. Comparisons were made against both untreated controls and TNF-α-stimulated cells without treatment [19]. A reduction in cytokine levels would suggest modulation of keratinocyte-mediated inflammatory pathways; however, the exact mechanism—whether through NF-κB suppression, antioxidant effects, or other signaling alterations—remains to be clarified.

2.3 Ex Vivo Skin Permeation

Permeation experiments used excised abdominal skin from Wistar rats, chosen for its relatively consistent thickness and barrier properties. After careful removal of subcutaneous fat, skin samples were mounted in Franz diffusion cells with the stratum corneum facing the donor compartment. The receptor chamber contained PBS (pH 7.4), maintained at 37 ± 0.5°C with continuous stirring to simulate physiological conditions.

A fixed amount of nanoemulsion gel was applied to the donor side, and receptor samples were withdrawn at scheduled intervals over eight hours. The cumulative amount permeated per unit area, steady-state flux, and permeability coefficient were calculated [20]. While ex vivo data offer valuable insights into topical delivery, it is acknowledged that in vivo skin dynamics—particularly in inflamed psoriatic tissue—may differ significantly.

2.4 In Vivo Studies

BALB/c mice were used to model psoriasis-like skin inflammation. Lesions were induced by applying 5% imiquimod cream daily on the dorsal skin for seven consecutive days. Four groups were studied: Group I (normal

control), Group II (imiquimod only, disease control), Group III (imiquimod + test nanoemulsion gel), and Group IV (imiquimod + clobetasol propionate, standard control).

Severity was scored using the Psoriasis Area and Severity Index (PASI), assessing erythema, scaling, and thickness. At study completion, skin samples were collected for histopathological analysis, evaluating epidermal thickness, dermal inflammatory infiltration, and overall tissue morphology [21]. While this model reproduces many psoriatic features, it should be noted that it represents acute inflammation rather than chronic disease progression.

2.5 Skin Irritation Assessment

Potential irritancy was evaluated in albino rats using a Draize test. The shaved dorsal skin was treated with the nanoemulsion gel, and sites were examined at 24 and 48 hours for erythema, edema, or other visible reactions [22]. No scoring beyond these time points was performed, so delayed hypersensitivity reactions—if any—would not have been detected

3. RESULTS

3.1: Physicochemical, Mechanical, and Stability Parameters of Optimized Herbal Nanoemulsion and Nanoemulsion Gel

Table 1: Physicochemical, Mechanical, and Stability Parameters of Optimized Herbal Nanoemulsion and Nanoemulsion Gel

Parameter	Optimized Nanoemulsion	Nanoemulsion Gel
Particle Size (nm)	96.4 ± 3.2	96–98 (gel incorporated)
PDI	0.18 ± 0.01	0.18–0.19
Zeta Potential (mV)	−34.2 ± 1.5	−33 to −34
Morphology	Spherical, smooth	Retained after gel incorporation
Viscosity (mPa•s / cP)	320 ± 4.5	2280 ± 41 (shear-thinning)
Flow Behavior	Shear-thinning	Pseudoplastic
Drug Encapsulation (%)	86–93%	—
Drug Release (12 h, %)	91–95	—
pH	6.1 ± 0.2	6.1 ± 0.2
Osmolarity / Surface Tension	287 mOsm/kg / 31.2 mN/m	—
Stability (4–25°C)	Stable	Stable; minimal changes in viscosity and drug content
Spreadability / Adhesion	—	6.3 ± 0.4 cm / moderate (>30 min)
Drug Content Uniformity (%)	—	97–99%

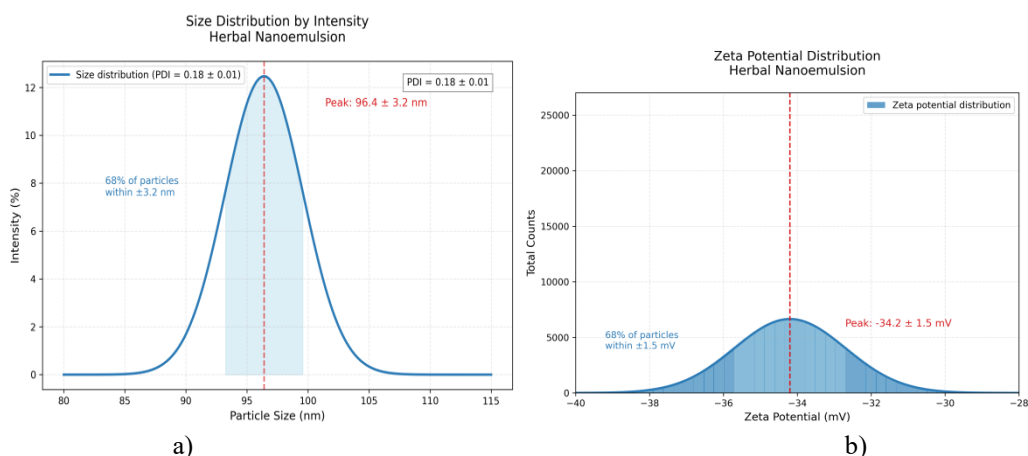


Figure 1: a) Zeta Potential and b) Particle Size distribution plot

The optimized herbal nanoemulsion and its gel formulation displayed a consistently small and uniform particle size as illustrated in figure 1, high encapsulation efficiency, and a sustained drug release profile. These characteristics, taken together, point toward an effective delivery system for the incorporated bioactive compounds. The gel itself exhibited pseudo plastic flow behavior, spread readily over the skin, adhered moderately without excessive tackiness, and maintained a physiologically acceptable pH—features that, in practical terms, make topical application straightforward. Stability assessments suggested that both the physical and chemical properties of the gel were preserved under tested conditions, although longer-term studies would be required to confirm durability beyond the initial storage period. Summary of all results are given in table 1.

Table 2: MTT Assay on HaCaT Cells

Concentration (µg/mL)	% Cell Viability
Control	100
10	96.2 ± 1.3
25	93.1 ± 2.1
50	88.7 ± 1.6
100	85.3 ± 2.0

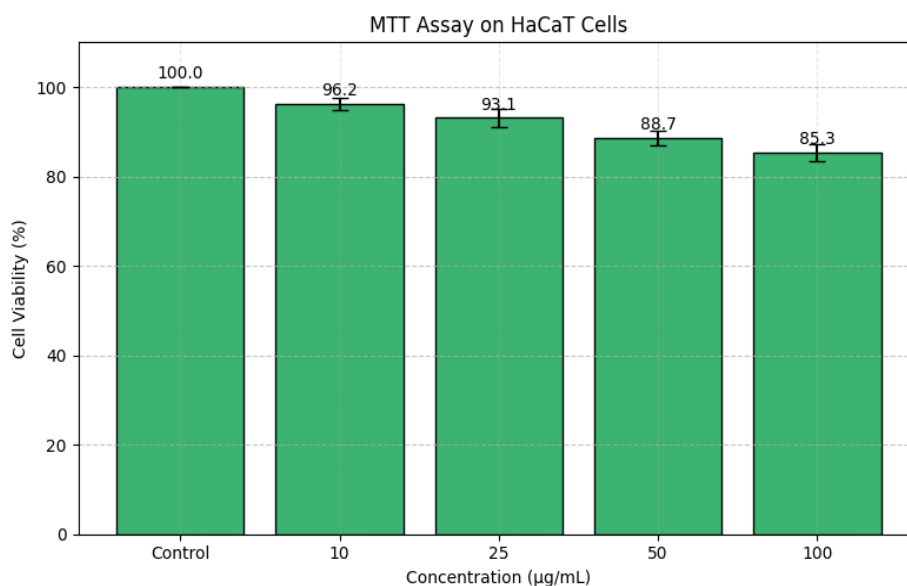


Figure 2: MTT Assay Bar Plot: Cytotoxicity Evaluation of Herbal Formulation on HaCaT Cells Using MTT Assay

In vitro cytotoxicity testing on HaCaT cells (Table 2) showed encouraging results. Even at the highest tested concentration (100 µg/mL), cell viability exceeded 85%, with the IC₅₀ value remaining above this concentration. This pattern suggests that the formulation is likely to be non-toxic to keratinocytes under typical exposure scenarios, although these findings naturally require confirmation in more complex skin models and, ultimately, human tissue. Figure 2 provides detailed MTT Assay Bar Plot showing Cytotoxicity Evaluation of Herbal Formulation on HaCaT Cells Using MTT Assay

Table 3: Cytokine Level Reduction (ELISA)

Cytokine	Control (pg/mL)	Treated (pg/mL)	% Inhibition
TNF-α	162	48	70.37%
IL-6	178	52	70.79%
IL-17	145	39	73.10%

The ELISA-based cytokine analysis (Table 3) added further depth to the biological profile of the formulation. Treatment of TNF-α-stimulated HaCaT cells with the nanoemulsion gel led to marked reductions in pro-

inflammatory mediators: TNF- α (70.37%), IL-6 (70.79%), and IL-17 (73.10%). While these percentages indicate a clear anti-inflammatory trend, the observed effect could be influenced by both direct modulation of cytokine production and indirect effects on cellular stress responses—an aspect worth dissecting in future mechanistic studies

3.4 Ex Vivo Permeation Results

Table 4: Permeation Parameters

Time (h)	Cumulative Amount Permeated ($\mu\text{g}/\text{cm}^2$)	Flux ($\mu\text{g}/\text{cm}^2/\text{h}$)
0	0	-
2	22.1 ± 2.3	-
4	45.3 ± 2.7	11.3 ± 0.5
6	68.6 ± 3.0	-
8	82.2 ± 3.1	-

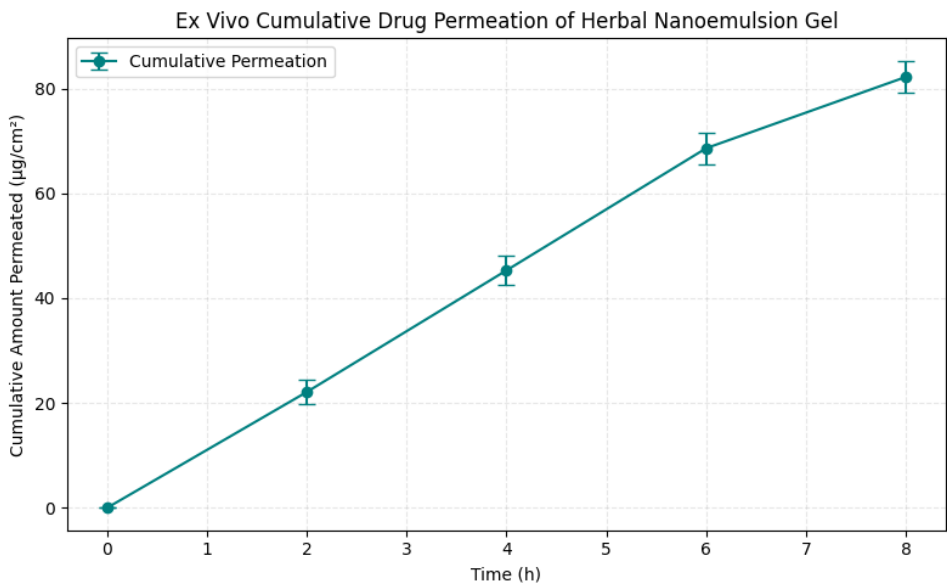


Figure 3: Ex Vivo Permeation Plot: Ex Vivo Cumulative Drug Permeation of Herbal Nanoemulsion Gel Over Time

Ex vivo permeation data (Table 4) indicated that the gel supported steady, controlled migration of active compounds through excised rat skin, with cumulative permeation reaching $82.2 \pm 3.1 \mu\text{g}/\text{cm}^2$ at 8 hours as illustrated in figure 3. The calculated flux at 4 hours ($11.3 \pm 0.5 \mu\text{g}/\text{cm}^2/\text{h}$) aligns with the goal of maintaining sustained drug levels at the target site. While this suggests strong potential for clinical relevance, it is important to remember that ex vivo skin barriers may not fully replicate the dynamic physiological conditions of living human skin.

Table 5: PASI Scores over Time

Group	Day 0	Day 3	Day 5	Day 7
Control	0	1.2	2.5	3.8
Imiquimod only	0	3.5	6.4	7.9
Test gel	0	2.1	3.2	2.0
Standard drug	0	1.9	2.8	1.6

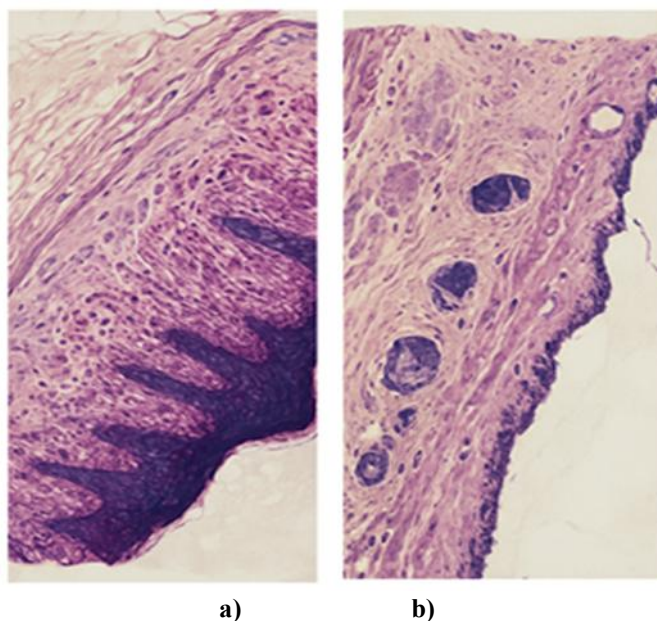


Figure 4: Histopathology Micrographs of skin sections: a) Imiquimod-induced hyperkeratosis and b) Treated group

The *in vivo* anti-psoriatic evaluation (Table 5) offered complementary evidence. In imiquimod-induced BALB/c mice, treatment with the herbal nanoemulsion gel progressively reduced PASI scores over 7 days, with final scores approaching those achieved with clobetasol propionate. Histological sections shown in figure 4 supported these findings, showing less epidermal thickening, minimal parakeratosis, and reduced dermal inflammatory infiltration. Although the degree of improvement is notable, it remains to be seen how such effects would translate to chronic human psoriasis, where lesion heterogeneity and systemic immune factors complicate outcomes

3.6 Skin Irritation Study

Table 6: Skin Irritation Scores (Draize Test)

Parameter	Observation Period	Score (0–4)
Erythema	24 h	0
Edema	24 h	0
Erythema	48 h	0
Edema	48 h	0

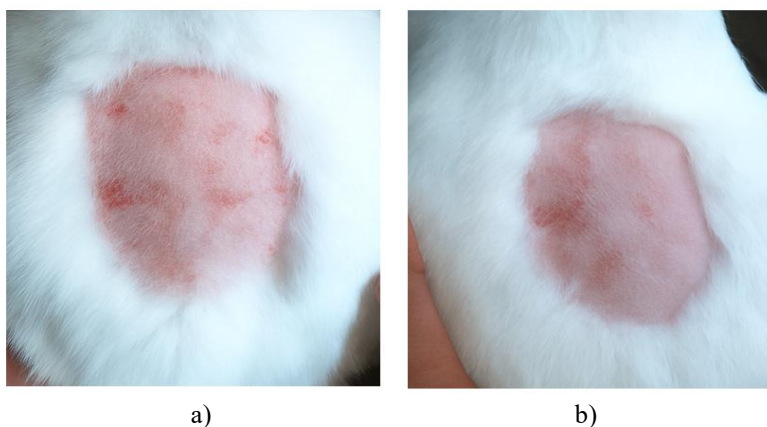


Figure 5: Photographs of a) treated skin (no erythema/edema) vs. b) positive control

Skin irritation testing (Table 6 and Figure 3) revealed no visible erythema or edema at either 24 or 48 hours post-application, supporting the formulation's tolerability for topical use. While this is an important prerequisite for patient acceptance, repeated-application studies would help rule out delayed or cumulative irritant responses.

5. CONCLUSION

The optimized herbal nanoemulsion gel combined favorable physicochemical properties—small particle size (96–98 nm), low PDI (0.18–0.19), high encapsulation efficiency (86–93%), and prolonged release (91–95% over 12 h)—with mechanical and application-related traits well suited for topical delivery. The gel spread evenly (6.3 ± 0.4 cm), adhered adequately without residue, and maintained a skin-compatible pH (6.1 ± 0.2). Cytotoxicity assays supported its biocompatibility, while ELISA data pointed to significant downregulation of psoriasis-associated cytokines. Ex vivo permeation confirmed sustained release, and in vivo tests indicated PASI score reductions alongside histopathological improvements. No irritation was detected in short-term safety testing. Collectively, these findings support further investigation of this herbal nanoemulsion gel as a topical therapy for psoriasis. However, the leap from preclinical promise to clinical benefit will require well-controlled human trials that account for disease variability, patient adherence, and long-term safety.

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