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Formulation And Evaluation of Clindamycin Phosphate-Loaded Nanoemulgel for Enhanced Topical Delivery in The Treatment of Acne Vulgaris

ASHUTOSH TRIPATHI[1], DR. AMRESH GUPTA[2], HAKIM SINGH RAJPUT[3], ARUN KUMAR[4], ASHISH VERMA[5]

[1]*Department of Pharmaceutics, Institute of Pharmaceutical Sciences & Research, Unnao*
[2]*Director, Institute of Pharmaceutical Sciences & Research, Unnao*
[3, 4, 5]*Assistant Professor, Institute of Pharmaceutical Sciences & Research, Unnao*

Abstract- ***Acne vulgaris is a chronic inflammatory disorder of the pilosebaceous unit affecting approximately 85% of adolescents and young adults worldwide. Topical clindamycin phosphate remains a first-line treatment for inflammatory acne; however, its clinical utility is significantly compromised by poor follicular penetration due to the drug's hydrophilic nature (log P ≈ -0.8) and the formidable lipophilic barrier of the stratum corneum. This review critically examines the development of nanoemulgel formulations as an advanced topical delivery system for clindamycin phosphate, with particular emphasis on the strategic incorporation of tea tree oil as a functional oil phase possessing intrinsic anti-Cutibacterium acnes activity. The nanoemulgel hybrid system combines the enhanced penetration capabilities of nanoemulsions (droplet size 20- 200 nm) with the rheological and aesthetic benefits of hydrogels. Key mechanisms of enhanced delivery include transfollicular targeting, surfactant-mediated lipid bilayer disruption, and penetration enhancement by natural oil constituents. The synergistic potential between clindamycin and tea tree oil components, with fractional inhibitory concentration indices of 0.3- 0.5, permits dose reduction of the antibiotic by 60-80% while maintaining antimicrobial efficacy. This review synthesizes current literature on formulation strategies, characterization techniques, stability studies, and clinical evidence, while identifying critical research gaps and future prospects for this green nanotechnology-enabled approach to acne therapy.***

Keywords: ***Acne Vulgaris, Clindamycin Phosphate, Nanoemulgel, Tea Tree Oil, Cutibacterium Acnes, Follicular Targeting, Antibiotic Resistance, Topical Delivery***

I. INTRODUCTION

Acne vulgaris represents one of the most prevalent chronic inflammatory dermatological conditions encountered in clinical practice worldwide, affecting nearly 85% of individuals between the ages of 12 and 25 years at some point during their lives, with the condition persisting into adulthood in 15-20% of cases. This high prevalence makes acne the eighth most common disease globally, transcending geographical, racial, and socioeconomic boundaries. Far from being a mere cosmetic inconvenience, severe or persistent acne exerts profound psychological sequelae on affected individuals, including depression, anxiety, social withdrawal, lowered self-esteem, and, in extreme cases, suicidal ideation. The Global Burden of Disease Study consistently ranks acne among the top ten causes of years lived with disability in adolescents across the globe.

The disease primarily targets the pilosebaceous unit, a complex anatomical structure comprising the hair follicle, the hair shaft, and the associated sebaceous gland. Four interdependent pathophysiological pillars collectively sustain the acne cascade: androgen-driven sebaceous hyperplasia and hyperseborrhoea, abnormal follicular keratinization (comedogenesis), colonisation by Cutibacterium acnes, and immune-mediated inflammation. The interplay of these four factors explains the polymorphic lesions characteristic of acne, ranging from open and closed comedones to papules, pustules, nodules, and cysts.

The rising prevalence of antibiotic-resistant C. acnes strains has emerged as a critical concern in contemporary dermatology. Global surveillance studies report resistance rates to clindamycin exceeding 50-60% in Europe, the United States, and parts of Asia. Resistance to erythromycin is even higher, and cross-resistance between clindamycin and erythromycin is common due to similar ribosomal binding sites.

This alarming trend has prompted dermatological societies worldwide to recommend antibiotic stewardship programs, including limiting antibiotic use to the shortest duration necessary, avoiding antibiotic monotherapy, combining antibiotics with benzoyl peroxide or retinoids, and developing novel delivery systems that enhance follicular targeting while reducing the required antibiotic dose.

II. CLINDAMYCIN PHOSPHATE AS A TOPICAL ANTI-ACNE AGENT

2.1. Mechanism of Action and Clinical Efficacy

Clindamycin phosphate is the 2-phosphate ester of clindamycin, a lincosamide antibiotic derived semi-synthetically from lincomycin. The phosphate ester confers water solubility and chemical stability, allowing formulation into aqueous gels, lotions, and solutions at 1-2% strength. Once applied to the skin, endogenous skin phosphatases rapidly hydrolyse the prodrug to release active clindamycin within the stratum corneum and follicular epithelium.

Clindamycin acts by inhibiting bacterial protein synthesis through reversible binding to the 50S ribosomal subunit at the peptidyl transferase centre, halting the elongation of the polypeptide chain. It exhibits exquisite potency against C. acnes, with minimum inhibitory concentrations (MIC_{90}) of ≤0.12 µg/mL for most strains. Beyond its bacteriostatic effects, clindamycin demonstrates direct anti-inflammatory properties, including suppression of neutrophil chemotaxis, inhibition of complement-derived chemotactic factors, and reduction of pro-inflammatory free fatty acids in sebum.

Multiple randomised controlled trials confirm that topical 1% clindamycin achieves 50-70% reduction in inflammatory lesion counts after 8-12 weeks of once- or twice-daily application. Combination with benzoyl peroxide or retinoids is now considered standard practice, as fixed- dose clindamycin-benzoyl peroxide preparations dramatically lower the emergence of resistant

C. acnes strains.

2.2. Limitations of Conventional Formulations

Despite proven efficacy, conventional topical clindamycin formulations suffer from significant limitations. The primary limitation is poor follicular penetration. Clindamycin phosphate is highly hydrophilic, with a log P value of approximately -0.8, whereas the pilosebaceous unit is lipophilic and shielded by the stratum corneum, a 10-20 micrometre thick hydrophobic barrier composed of corneocytes embedded in a lipid matrix enriched in ceramides, cholesterol, and free fatty acids.

Quantitative studies using skin biopsy and follicular extraction techniques demonstrate that less than 5-10% of the applied dose of a conventional clindamycin formulation typically reaches the infrainfundibulum, the deepest portion of the follicle where C. acnes resides. Consequently, high surface concentrations are required, leading to local irritation, dryness, erythema, and burning sensations. Prolonged sub-therapeutic exposure fosters selection of resistant C. acnes clones through mutations in the 23S rRNA gene and acquisition of erm(X) methylases.

III. NANOEMULGEL SYSTEMS FOR ENHANCED TOPICAL DELIVERY

3.1 Nanoemulsion Component

A nanoemulsion is defined as a transparent or translucent, kinetically stable dispersion of oil in water stabilised by surfactant and co-surfactant mixtures, with droplet diameters typically ranging from 20 to 200 nanometres. Unlike microemulsions, which form spontaneously, nanoemulsions require low-to-moderate energy input through high-pressure homogenisation or ultrasonication but offer superior kinetic stability against coalescence and Ostwald ripening. Several mechanisms contribute to enhanced skin penetration from nanoemulsions. The ultrafine droplet size provides an enormous interfacial area exceeding 200 m^2 per gram of oil for drug release.

Nano-droplets act as "virtual needles", exploiting the transfollicular route, which occupies only 0.1% of total skin surface area but offers 10 to 100-fold higher permeability than the interfollicular stratum corneum. Surfactants transiently disrupt intercellular lipid bilayers, fluidising ordered domains and increasing diffusivity. Surface charge characteristics influence

follicular targeting, with negatively charged nano-droplets (zeta potential < -30 mV) being electrostatically repelled from the negatively charged stratum corneum surface but attracted to positively charged follicular openings.

3.2 Gel Matrix Component

Incorporation of drug-loaded nanoemulsion into a hydrophilic polymer network yields the final nanoemulgel . Suitable polymers include Carbopol grades (934, 940, 980), hydroxypropyl methylcellulose, sodium alginate, and xanthan gum. The three-dimensional polymeric network confers pseudoplastic rheology (shear-thinning behaviour ideal for spreading), bioadhesion via hydrogen bonding and van der Waals interactions, controlled drug release through diffusion and erosion mechanisms, occlusive moisturising effects, and aesthetic elegance with non-greasy, transparent appearance.

Clinical studies of nanoemulgel systems for anti-acne agents demonstrate 3 to 8-fold higher follicular drug deposition, faster onset of action (2-4 weeks versus 6-8 weeks for conventional gels), and superior tolerability with reduced erythema, peeling, and burning.

IV. STRATEGIC UTILIZATION OF NATURAL OILS

4.1 Tea Tree Oil

Tea tree oil (Melaleuca alternifolia) is one of the most extensively studied essential oils for acne treatment, containing more than 100 distinct chemical constituents, with terpinen-4-ol (30-48%) being the primary contributor to its antimicrobial activity. Terpinen-4-ol exhibits MIC against C. acnes of 0.05-0.25% v/v, comparable to benzoyl peroxide but with less irritation. Its mechanism involves disrupting bacterial cell membranes, increasing membrane fluidity, disrupting the proton motive force, and causing leakage of intracellular ions.

Randomised clinical trials have shown that 5% tea tree oil gel is comparable to 5% benzoyl peroxide in reducing inflammatory and non-inflammatory lesion counts, with significantly fewer adverse effects including less erythema, dryness, and peeling . Tea tree oil also exhibits anti- inflammatory activity independent of its antimicrobial effects, suppressing histamine release and inhibiting LPS-induced TNF-α production.

4.2 Synergistic Potential with Clindamycin

Fractional inhibitory concentration studies reveal strong synergism between tea tree oil components and clindamycin, with FIC indices of 0.31-0.45 for combinations against C. acnes, indicating true synergy (FIC ≤ 0.5). This synergy allows dose reduction of the antibiotic by 60- 80% while maintaining or enhancing antimicrobial efficacy. The mechanism involves enhanced membrane permeabilization by terpinen-4-ol, allowing increased intracellular accumulation of clindamycin and interference with efflux pump function.

4.3 Other Natural Oils

Neem oil (Azadirachta indica) exhibits MIC against C. acnes of 0.015-0.06 mg/mL, with nimbidin reducing sebum secretion in animal models by 40-60%. Oregano oil, rich in carvacrol and thymol, exhibits bactericidal activity against resistant C. acnes strains and inhibits bacterial efflux pumps, potentially reversing multidrug resistance.

Other essential oils including lavender, manuka, rosemary, eucalyptus, and clove oils have also demonstrated MIC values
≤0.5% v/v against C. acnes.

V. FORMULATION AND OPTIMIZATION STRATEGIES

5.1. Excipient Screening and Phase Diagram Studies

Screening of excipients through solubility studies is the first critical step in nanoemulsion development. The saturation solubility of clindamycin phosphate is determined in various oils (tea tree oil, isopropyl myristate, oleic acid), surfactants (Tween 80, Span 80, Labrasol), and co- surfactants (PEG 400, propylene glycol, Transcutol P).

Pseudo-ternary phase diagrams are constructed using the aqueous titration method to identify the nanoemulsion region. Smix (surfactant:co-surfactant) is prepared in different weight ratios (1:1, 2:1, 3:1, and 4:1), mixed with oil, and titrated dropwise with

distilled water. The formation of clear, transparent, low-viscosity mixtures is marked as the nanoemulsion region.

5.2. Quality by Design Optimization

Modern studies employ Quality by Design approaches to systematically optimize formulation parameters. Box-Behnken and Central Composite Designs are routinely used to optimise droplet size, zeta potential, and drug release. Independent variables typically include oil concentration (5-15% w/w), Smix ratio (1:1 to 4:1), and Smix concentration (20-40% w/w). Dependent variables include globule size (target <100 nm), polydispersity index (target <0.3), and percentage drug release at 8 hours (target >80%).

The optimized nanoemulsion is incorporated into a gel base (e.g., Carbopol 934 at 1% w/w) with neutralization using triethanolamine to pH 5.5-6.0.

VI. CHARACTERIZATION TECHNIQUES

6.1. Nanoemulsion Characterization

Globule size and polydispersity index are determined using dynamic light scattering with a Zetasizer, with samples diluted 100-fold with distilled water and analyzed at 25°C with a 90° scattering angle. Zeta potential is measured using electrophoretic light scattering, with values preferably below -30 mV or above +30 mV for electrostatic stability. Transmission electron microscopy with negative staining (1% phosphotungstic acid) visualizes droplet morphology and confirms spherical shape and absence of aggregation.

6.2. Nanoemulgel Characterization

The nanoemulgel is characterized for physical appearance, pH, viscosity (using Brookfield viscometer), drug content (by UV-Vis spectroscopy at 210 nm after extraction), spreadability (parallel plate method), and extrudability from collapsible tubes. Rheological studies confirm pseudoplastic or thixotropic flow behaviour, with viscosity typically ranging from 10,000-50,000 cP at low shear rates.

6.3. In-Vitro and Ex-Vivo Studies

In-vitro drug release is assessed using Franz diffusion cells across synthetic membranes (MWCO 12,000 Da) with phosphate buffer saline pH 5.5 as receptor medium maintained at 37°C ± 0.5°C. Data are fitted to zero-order, first-order, Higuchi, and Korsmeyer-Peppas kinetic models to determine release mechanisms.

Ex-vivo skin permeation and retention studies use excised rat abdominal skin mounted on Franz diffusion cells. After 8 hours, receptor fluid is analyzed for permeated drug, and skin layers are separated by heating at 60°C for 2 minutes, homogenized, and analyzed for retained drug content.

VII. STABILITY AND SAFETY STUDIES

7.1 Stability Studies

Accelerated stability studies conducted according to ICH guidelines (40°C ± 2°C / 75% RH ± 5% for 3 months) show that optimized nanoemulgels retain droplet size, drug content exceeding 95%, and antimicrobial activity. Under long-term conditions (25°C ± 2°C / 60% RH ± 5% for 6 months), nanoemulgels demonstrate no significant changes in pH, viscosity, droplet size, or drug content. Stress testing involving freeze-thaw cycles and centrifugation is used to assess physical stability.

7.2 Safety Studies

HET-CAM (Hen's Egg Test-Chorioallantoic Membrane) and Draize skin irritation tests confirm non-irritancy of well-formulated nanoemulgels. Formulations with surfactant concentrations below 10% w/w and pH between 5.0-6.5 produce no significant irritation (irritation score < 1.0 on a 0-5 scale). Long-term photostability is improved by natural antioxidants present in essential oils, including tocopherols, flavonoids, and phenolic terpenes, which protect both the oil phase and the drug from oxidative degradation.

VIII. ANTIMICROBIAL EFFICACY STUDIES

8.1 Agar Well Diffusion Method

The agar well diffusion method is used against C. acnes (MTCC No. 1951). Molten Reinforced Clostridial Agar is inoculated with standardized C. acnes suspension (0.5 McFarland standard, 1.5×10^8 CFU/mL). Wells (8 mm diameter) are bored into solidified agar, and test samples (100 µL) are added. Plates are incubated anaerobically at 37°C for 72 hours, and zones of inhibition are measured.

8.2 Minimum Inhibitory Concentration and Synergy Testing

MIC is determined using the broth microdilution method as per CLSI guidelines. Serial two- fold dilutions of formulations are prepared in RCA broth in 96-well microtiter plates, inoculated with C. acnes (5×10^5 CFU/mL), and incubated anaerobically at 37°C for 48 hours. The fractional inhibitory concentration index is calculated as FIC = (MIC of clindamycin in combination / MIC of clindamycin alone) + (MIC of TTO in combination / MIC of TTO alone). Synergy is defined as FIC ≤ 0.5.

IX. CLINICAL AND IN VIVO EVIDENCE

9.1. Clinical Trial Evidence

A randomised controlled trial of clindamycin-tea tree oil nanoemulgel (1% clindamycin + 5% tea tree oil) in 120 patients with moderate acne vulgaris demonstrated 68% reduction in inflammatory lesions at week 12 compared to 52% for commercial clindamycin-benzoyl peroxide gel ($p < 0.05$) . Resistance emergence was negligible in the nanoemulgel group (2% of patients) compared to the comparator group (15% of patients, $p < 0.05$). Patient satisfaction scores were significantly higher for the nanoemulgel group, citing less irritation, better spreadability, and pleasant odour.

9.2. In Vivo Studies

In vivo studies using testosterone-induced acne models in rats show that clindamycin nanoemulgel reduces sebum production by 45%, inflammatory lesion count by 72%, and histological inflammation score by 65% compared to control. Sebaceous gland area is reduced by 40%, indicating direct anti-seborrhoeic effects possibly mediated by the nanoemulgel components.

X. GAPS IN EXISTING LITERATURE

Despite significant progress, several important research gaps persist. First, few studies have used natural oils as the primary oil phase in clindamycin nanoemulsions; most rely on synthetic oils lacking intrinsic anti-acne activity. Second, limited long-term clinical trials beyond 12 weeks have compared natural oil-based nanoemulgels with benchmark products. Third, scant data exist on the anti-biofilm activity of combined clindamycin-essential oil nanoformulations against resistant C. acnes strains. Fourth, inadequate exploration of synergistic combinations of multiple essential oils in a single formulation has been conducted. Fifth, lack of pharmacokinetic-pharmacodynamic modelling for follicular targeting represents a significant gap. Sixth, limited evaluation of sebum-suppressive effects of natural oil-based nanoemulgels has been performed . Seventh, insufficient data on formulation stability beyond 6 months, particularly for essential oil- containing systems, are available.

XI. FUTURE PROSPECTS

Based on current gaps, several future directions are proposed. Synthesis and testing of second- generation libraries with refined substitution patterns for VEGFR2-selective, EGFR-selective, and CDK2-selective compounds should be pursued. In vitro biological evaluation of lead compounds in biochemical kinase assays and cell-based assays is required. Co-crystallization studies to validate predicted binding modes would provide definitive information about binding mechanisms. In vivo efficacy studies in mouse xenograft models and pharmacokinetic studies should determine oral bioavailability, half-life, clearance, and toxicity profiles. Medicinal chemistry optimization using iterative design-make-test-analyze cycles with computational tools such as free energy perturbation should be integrated. Exploration of other kinase targets including BTK, JAK, and ALK could expand the therapeutic applications of pyrimidine-based inhibitors. Investigation of drug resistance mechanisms and formulation studies for solubility and bioavailability enhancement are also warranted.

XII. CONCLUSION

The development of clindamycin phosphate-loaded nanoemulgels using tea tree oil as a functional oil phase represents a significant advancement in topical anti-acne therapy. This green nanotechnology-enabled approach addresses the core limitations of conventional formulations by achieving superior follicular targeting, dual antimicrobial action, reduced resistance risk, and improved patient compliance. The nanoemulgel formulation is expected to achieve

globule size below 100 nm, polydispersity index below 0.3, zeta potential greater than |30| mV, sustained drug release (~85% over 8 hours), significantly higher skin retention (~45 µg/cm² vs ~19 µg/cm² for conventional gel), and enhanced antimicrobial activity (zone of inhibition ~28 mm vs ~21 mm). The synergistic action of tea tree oil permits reduction of the antibiotic concentration while maintaining or improving efficacy, thereby mitigating resistance development.

The successful development of this formulation could redefine topical anti-acne therapy in an era of rising antibiotic resistance. The parallel targeting of multiple pathophysiological pathways— antibacterial, anti-inflammatory, anti-comedonal, and sebum-regulating—offers a rational approach to overcoming the limitations of conventional monotherapy. With continued optimization and validation, this nanoemulgel platform may provide a clinically viable treatment option for patients with acne vulgaris.

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