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Lipid-Based Nanocarriers for Acne Treatment: Current Progress and Clinical Feasibility

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ABSTRACT

Acne vulgaris, a widespread inflammatory skin disorder, affects millions globally and is particularly common among teenagers and young adults. It is driven by genetic, hormonal, environmental, and microbial factors, presenting with lesions such as comedones, papules, and cysts in sebaceous gland rich areas. Conventional treatments including antibiotics, retinoids, and hormonal therapies are limited by side effects, antimicrobial resistance, and poor patient adherence. Nanotechnology has emerged as a novel approach to overcome these limitations. Among these, lipid-based nanocarriers (e.g., liposomes, nanoemulsions, and solid lipid nanoparticles) improve therapeutic outcomes through enhanced skin penetration, controlled release, and reduced irritation. This review highlights acne pathophysiology, evaluates current therapies, and explores advances in lipid-based nanocarriers, including recent and ongoing clinical trials, to support more effective and personalized treatment strategies using lipid nanoparticles.

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Introduction

Inflammatory skin conditions, like acne, seborrheic dermatitis, atopic dermatitis, and psoriasis affected 20-25% of the population, and are marked by recurring lesions and severe itching, greatly affecting quality of life.[1] These conditions frequently lead to physical or psychological distress, although their exact causes are not well understood. Multiple factors contribute to the development of inflammatory skin diseases, including genetics, environmental influences, immune system responses, epidermal barrier integrity, mental health issues, and infections.[2] In recent years, the skin microbiota has also been recognized as a crucial factor in the pathogenesis of these conditions.[3]

Acne, also known by its medical term acne vulgaris, is a widespread inflammatory skin condition affecting the pilosebaceous units. Over 80% of individuals experience this skin condition at some point in their lives. Acne is particularly prevalent among adolescents and young adults, affecting more than 85% of this demographic.[4] The prevalence of acne in boys ranges from 40% to 95%, while in girls it varies from 61% to 83% at different ages.[5] Recent research has emphasized the rising global impact of acne vulgaris. Between 1990 and 2021, the age-standardized prevalence rate among adolescents and young adults surged from 8,563.4 to 9,790.5 cases per 100,000 individuals.[6] This upward trend aligns with prior studies documenting increased prevalence, particularly among females in adolescent and adult populations.[7] Geographically, Western Europe maintains the highest prevalence rates, while North Africa and the Middle East have witnessed the most dramatic increases.[6] Acne predominantly develops in anatomical regions with elevated sebaceous gland density, particularly the face, neck, chest, and upper back[8,9], with its etiology arising from a multifactorial convergence of genetic susceptibility, environmental determinants, dietary influences, endocrine-driven sebum dysregulation, stress, smoking, comedogenic pharmacotherapies, microbial colonization, and pore-occluding cosmetic formulations.[10] Clinically, the condition presents with both inflammatory lesions (including papules, pustules, nodules, and cysts) and non-inflammatory lesions (both open and closed comedones), reflecting the spectrum of acne pathology.[11] Pathogenic mechanisms involve *Cutibacterium acnes (C. acnes;* formerly *Propionibacterium acnes [P. acnes])*–driven lipase activity, which converts sebum triglycerides into pro-inflammatory fatty acids, and reactive oxygen species (ROS)-mediated inflammation via tumor necrosis factor-α (TNF-α) (TNF-α) and Toll like receptor 2 (TLR2) pathways, exacerbating follicular rupture and scarring.[12,13] Conventional therapeutic approaches encompass the strategic application of topical/systemic pharmacological agents (antibiotics, retinoids), hormonal modulators (anti-androgens), phototherapeutic modalities, and chemical peels, with therapeutic selection guided by clinical evaluation of lesion phenotype, disease severity, systemic health parameters, and any potential adverse effects.[14] The management of acne is complicated by multiple factors such as individual patient differences, adverse effects of therapies, and growing antimicrobial resistance. Effective treatment strategies must account for personalized characteristics, geographical disparities in practice, and evolving clinical concerns to enhance therapeutic efficacy and address existing limitations. Traditional topical therapies frequently induce skin irritation and demonstrate suboptimal patient compliance.[15]

In this context, nanotechnology-driven drug delivery systems have shown potential as innovative solutions, enabling sustained active ingredient release, enhanced cutaneous absorption, and minimized dermal irritation compared to conventional approaches.[9] Various nanocarrier systems have demonstrated notable clinical effectiveness in combating acne.[16] These nano-technological approaches optimize therapeutic agent delivery by improving cutaneous permeation and achieving follicular localization, while simultaneously enabling modulated release kinetics of active pharmaceutical ingredients to maintain sustained pharmacological activity.[17] Lipid-based

nanocarriers (LNCs), with their intrinsic biocompatibility, biomimetic structural alignment with skin lipids, and reduced irritant potential, offer a transformative platform for advancing acne therapeutics.[18,19] This review examines the biological pathways and multifactorial etiology driving acne pathogenesis while critically assessing the limitations of current therapies, such as poor drug penetration and off-target effects. By integrating preclinical advances and clinical developments in LNCs, particularly in drug encapsulation efficiency and site-specific delivery, this review highlights their capacity to overcome therapeutic barriers, a technological approach that not only refines treatment efficacy but also accelerates the development of personalized skincare solutions aligned with emerging trends in precision dermatology.

Pathogenic Mechanisms and Clinical Variants of Acne

Factors contributing to acne vulgaris include genetics, exposome-related factors, such as environmental influences, diet, hormones, stress, smoking, comedogenic medications, *C. acnes*, and cosmetics,[10] all of which can trigger or worsen acne (Fig. 1). The pathogenesis of acne involves four main mechanisms: excessive sebum production, *C. acnes* proliferation, abnormal follicular keratinization, and inflammation (Fig. 1).[20] Excessive sebum secretion, influenced by hormones like testosterone and insulin-like growth factor 1 (IGF-1), directly correlates with acne intensity and recurrence.[21] In acne, abnormal keratinocyte proliferation leads to follicular obstruction, while *C. acnes* thrives in oxygen-poor, sebum-rich follicles. By breaking down sebum into free fatty acids, *C. acnes* contributes to both comedone formation and inflammation.[22] The immune response to *C. acnes* triggers inflammation, follicle rupture, and exacerbates lesion severity through reactive oxygen species (ROS) from neutrophils.[23,24] Environmental stressors induce epigenetic changes, influencing acne pathogenesis and offering new therapeutic targets.[25]

Acne presents in various subtypes, with non-inflammatory lesions (open/closed comedones) and inflammatory lesions (papules, pustules, nodules, cysts). Blackheads form when sebum and dead skin block follicles, while whiteheads form when these blockages are enclosed. Inflammatory lesions like papules and pustules arise from bacterial activity and excess oil Acne nodules, a severe inflammatory form, develop when bacterial-clogged pores (from oil and dead cells) penetrate deeper tissue, causing red, swollen bumps; larger than papules (5–10 mm), these persistent lesions, often on the jawline/chin, resist over-the-counter treatments and may last weeks to months.[11,26]

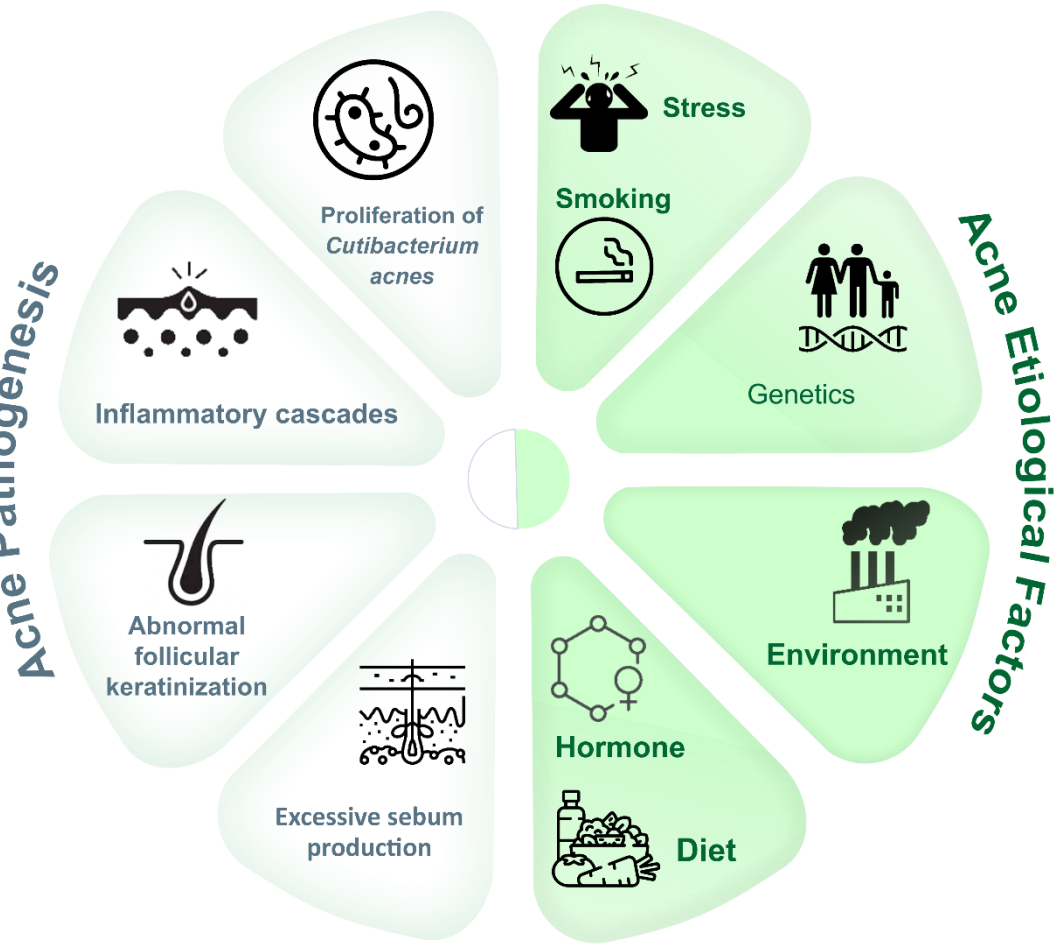

Fig. 1 Schematic Representation of acne pathogenesis and key acne etiological factors. Created by the authors using CorelDRAW.

Current acne treatments

When deciding on the best treatment approach, it is crucial to consider current acne treatment guidelines, as well as the treatment's efficacy, safety, tolerability, and patient preferences.[27] Emerging strategies for managing acne emphasize a comprehensive approach that includes topical and systemic treatments, procedural therapies, and dietary modifications (Fig. 2). Key topical agents include retinoids, benzoyl peroxide (BPO), antibiotics, and other specialized agents. Systemic options such as antibiotics, hormonal therapies, and retinoids offer significant therapeutic benefits, particularly for moderate to severe cases. Procedural interventions like laser devices, photodynamic therapy, chemical peels, and intralesional injections provide effective alternatives for reducing acne symptoms and scarring.[28]

Topical treatments are essential for acne management due to their direct action on the skin, minimal systemic side effects, and ease of use. Retinoids, such as tretinoin, adapalene, tazarotene, and trifarotene, work by binding to retinoic acid receptors (RARs) in the cell nucleus, regulating gene transcription and influencing cellular growth, differentiation, and inflammation.[29] BPO acts as an antimicrobial and mild comedolytic,[30] while topical antibiotics like clindamycin and erythromycin target inflammation and bacterial growth.[31] Other agents like azelaic acid, salicylic acid, dapsone, sulfur, and sodium sulfacetamide offer additional benefits. Clascoterone is a novel topical antiandrogen for reducing sebum production.[28]

Systemic treatment is essential, especially when scarring occurs. Antibiotics with anti-inflammatory properties, like tetracyclines (e.g., minocycline, doxycycline) and macrolides (e.g., erythromycin, azithromycin), are preferred for papulopustular acne, though resistance is increasing. Treatment typically lasts 8-12 weeks. For severe papulopustular and nodulocystic acne, the oral ITN is recommended. Hormonal treatments, such as estrogens with progestins or anti-androgens, are alternatives for severe forms of acne in females. Control of seborrhea and acne can be achieved after 3 months with hormonal treatments. Low-dose corticosteroids are used for adrenal hyperandrogenism or acne fulminans.[32]

In the realm of procedural therapies, recent studies indicate that laser and light devices, intralesional steroid injections, and chemical peels can alleviate acne symptoms and reduce scarring. Photodynamic therapy (PDT), LED (light-emitting diode), and IPL (intense pulsed light) treatments are effective, though personalized approaches are essential to minimize side effects.[33-36] Additionally, non-ablative fractionated radiofrequency microneedling combined with ITN shows potential in treating acne and scarring.[37]

Moreover, recent research highlights the impact of diet on acne, showing that certain dietary patterns, such as high dairy and high-glycemic-index carbohydrate intake, can exacerbate acne by influencing insulin and IGF-1 levels.[38] Adopting a diet that minimizes processed foods while emphasizing fresh vegetables, fruits, and omega-3-rich foods may help improve acne by promoting gut health and reducing inflammation.[39,40] Additionally, nutrients like vitamin D, zinc, and biotin play roles in acne management, with deficiencies potentially worsening acne symptoms.[41-43]

Due to the multifactorial nature of acne pathogenesisand the limitations of current treatments, several challenges hinder effective acne management. These include undesirable toxicities, growing concerns about antibiotic resistance, significant side effects from ITN therapy, and the lack of low-risk and effective treatments for pregnant women. Additionally, issues such as insufficient penetration through the stratum corneum, short retention time at the target site, and poor aqueous solubility of drugs further limit their medicinal applications.[44]

Emerging therapies are exploring novel biologics, probiotics, bacteriophages, and peptides, which present promising future selections for acne treatment.[28] Concurrently, recent advancements have focused on nanotechnology-based drug delivery systems to overcome the limitations of conventional formulations. These systems aim to enhance drug penetration, improve targeting, increase retention time, and provide sustained release.[44] LNCs such as liposomes, niosomes, microemulsions, and microspheres have recently demonstrated potential in improving anti-acne therapy by boosting drug efficacy and reducing side effects. These systems can enhance local tolerability and enable controlled drug release, even reaching the pilosebaceous unit.[17] These innovations seek to offer more effective and better-tolerated acne management options, potentially improving acne management outcomes.

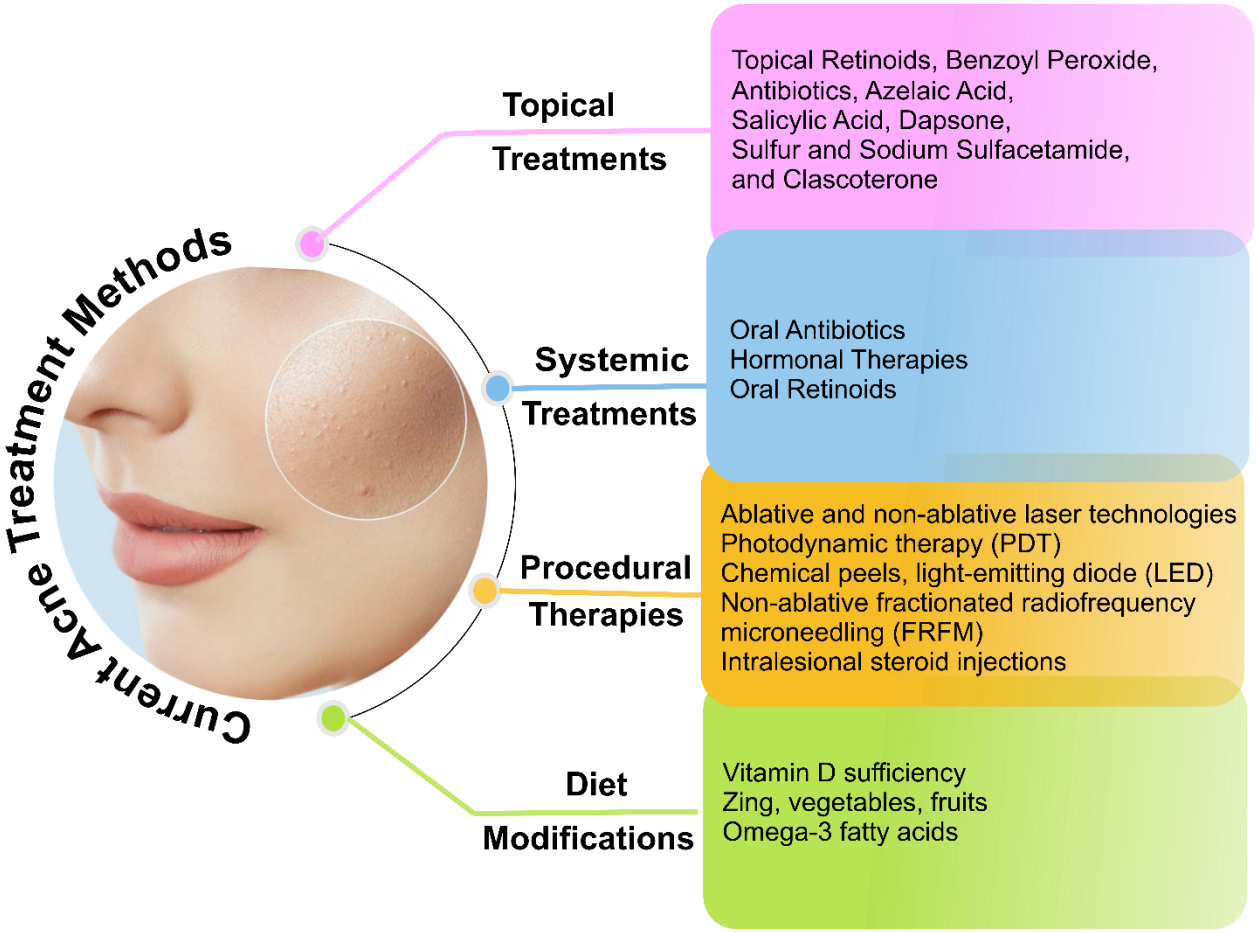

Fig. 2 Current acne management approaches involve topical/systemic treatments, clinical procedures, and diet modifications. Created by the authors using CorelDRAW.

LNCs-based treatments for acne

Nanotechnology-driven innovations in medical biology, especially for diagnostics and treatment, have become a major focus in modern research and clinical practice. These systems, developed from synthetic, natural, or biological materials such as polymers, metal ions, and lipids, rely on fabrication methods, physicochemical properties, drug loading efficiency, release behavior, and minimal toxicity for clinical success. Among them, LNCs offer distinct advantages due to their low toxicity and demonstrated progress in drug delivery,[45] particularly in dermatological pharmaceuticals where precision-engineered designs address complex therapeutic and hygiene-related needs.[46] LNCs derive structural integrity and stability from lipid composition while their biomimetic nature facilitates membrane penetration and intracellular delivery, followed by endosomal escape in acidic environments.[47] Key characteristics, including size, surface charge, morphology, stability, loading efficacy, and entrapment efficiency critically influence performance: smaller particles (<100 nm) enhance uptake and circulation, whereas larger ones (>100 nm) improve loading but reduce uptake;[48] zeta potential influences stability, with higher charge preventing aggregation;[49] and surface morphology modulates biological interactions, where smooth surfaces enhance stability and biodistribution while roughness may impair efficacy.[50] Stability, loading, and entrapment efficiency remain essential for consistent therapeutic outcomes.[51] LNCs are broadly classified into particulate-, vesicular-, and emulsion-based systems (Figs. 3,5,and6), each with distinct delivery advantages: vesicular carriers (i.e., liposomes, niosomes, transferosomes) enable encapsulation of diverse drugs with reduced systemic toxicity;[52] particulate systems such as SLNs and nanostructured lipid carriers (NLCs) provide improved stability, controlled release, and biocompatibility;[53] and emulsion-based delivery systems such

as nanoemulsions leverage surfactant-stabilized lipid droplets to increase solubility, bioavailability, and transdermal permeation of hydrophobic drugs, enhancing their therapeutic potential.[54]

Vesicular-Based Systems

Vesicular nanocarriers (such as liposomes, niosomes, transferosomes, and ethosomes), despite variations in composition and structural organization, generally exhibit similar mechanisms of action. These carriers are based on amphiphilic architectures that enable the incorporation of both hydrophilic and lipophilic therapeutic agents. Composed of biocompatible and biodegradable materials, they can spontaneously self-assemble in aqueous environments into vesicular structures with diverse physicochemical properties and biological behaviors. Compared with conventional nanostructures, their key advantage lies in this amphiphilic nature, which allows efficient encapsulation and delivery of drugs with varying solubility profiles.[55] The following section provides a detailed explanation of these nanovesicles, and a summary of studies conducted on their application in acne therapy is presented in **Supplementary Table 1.**

Liposomes are spherical vesicles made of one or more lipid bilayers surrounding a hydrophilic core, and are classified based on size and structure into multilamellar and unilamellar types.[56] They are primarily composed of phospholipids such as phosphatidylethanolamine, phosphatidylserine, and phosphatidylcholine, with cholesterol often added to improve structural stability. Due to their amphipathic nature, liposomes can encapsulate both hydrophilic and hydrophobic drugs simultaneously. These nanocarriers offer advantages like improved drug delivery, enhanced efficacy at target sites, and reduced toxicity. However, limitations include short half-life, high production costs, and low solubility. Liposomes are widely used in dermal and transdermal drug delivery to enhance skin penetration, achieve localized therapeutic effects, and limit systemic absorption.[57,58] Their biocompatibility and biodegradability make them suitable for delivering acne treatments, including antibiotics (e.g., erythromycin, clindamycin) and other agents such as benzoyl peroxide and retinoids (e.g., tretinoin, adapalene).[59,60] Topical tretinoin is widely used for acne due to its strong comedolytic effects, but its poor solubility, instability, and tendency to cause irritation limit its effectiveness.[61] Liposomal encapsulation helps overcome these issues by improving stability, enhancing skin retention, and reducing irritation.[62] Notably, negatively charged liposomes show superior performance in increasing hydration and drug accumulation in the skin compared to conventional formulations.[63] Liposomal tretinoin gels also demonstrate better tolerability and clinical outcomes than commercial products.[64] Adapalene, although more tolerable than other retinoids, can still cause irritation.[59] Liposomal formulations enhance its penetration into hair follicles and reduce side effects, making it more effective for targeted acne therapy.[65] BPO, a non-resistance-inducing antimicrobial agent, shows improved skin bioavailability and efficacy when co-encapsulated with adapalene in liposomes.[30,66] Recent advances include multifunctional liposomal nano-vesicles carrying agents such as retinoic acid and proteinase K, which effectively reduce *C. acnes*, inhibit biofilms, and decrease inflammation while improving skin tolerance. These findings highlight liposomes as promising carriers for enhancing acne treatment outcomes.[67]

Terpenes

Ethosomes represent a modified form of liposomes containing high concentrations of ethanol (20–45%), which disrupts the lipid organization of the stratum corneum and significantly enhances drug penetration. This characteristic makes them particularly effective for deeper skin delivery. Numerous studies have demonstrated the effectiveness of ethosomes in aiding acne recovery.[68] Ethosomal formulations incorporating diverse anti-acne agents such as cryptotanshinone (CPT),[69] azelaic acid (AZA),[70] spironolactone,[71] and tazarotene[72] consistently

demonstrate improved transdermal flux, enhanced skin deposition, and superior therapeutic efficacy compared to conventional topical formulations. CPT, a bioactive compound from *Salvia miltiorrhiza* with anti-inflammatory and protective effects,[73] suffers from poor water solubility. When formulated into an ethosomal Carbomer 974 gel, it achieved 2.1-fold higher skin deposition than conventional gels and showed superior *in vivo* anti-acne activity with minimal irritation, highlighting its potential as an advanced topical delivery system.[69] Similarly, tazarotene-loaded ethosomal gels exhibited better drug release and comparable improvements in penetration and anti-acne efficacy versus transfersomal gels, with ethosomes showing superior release performance overall.[72]

Binary ethosomal systems have also been explored to improve drug limitations. For example, chloramphenicol-loaded binary ethosomal hydrogel enhanced skin penetration, reduced systemic toxicity, and improved antibacterial and anti-inflammatory effects, demonstrating its promise for acne therapy.[74] Other bioactive-loaded ethosomes, such as karanjin formulations, showed increased transdermal flux (1.9-fold) and skin deposition (2.4-fold), along with antibacterial and anti-inflammatory benefits and reduction in sebaceous gland size in preclinical models.[75] Retinyl palmitate-loaded ethosomal hydrogels were developed as a safer alternative to tretinoin, achieving significant clinical reduction in acne lesions with minimal irritation, thus improving patient tolerability and compliance.[76] These findings establish ethosomes as an effective vesicular carrier system for topical anti-acne therapy, capable of enhancing drug delivery, efficacy, and safety across a wide range of active compounds.

Niosomes, composed of non-ionic surfactants, offer a more stable and cost-effective alternative to liposomes while maintaining similar drug delivery capabilities. Their enhanced stability and scalability make them attractive for pharmaceutical development.[77] Clinical studies highlight niosomes as effective carriers for acne treatment, improving drug delivery, efficacy, and safety. Niosomal formulations of agents such as dapsone showed significant clinical improvement in mild-to-moderate acne after 8 weeks [78]. Methylene blue-loaded niosomal hydrogels demonstrated superior reduction of inflammatory lesions compared to intense pulsed light therapy in moderate-to-severe acne, supporting their use in photodynamic therapy.[79] Similarly, doxycycline-loaded niosomes enhanced skin deposition (~3-fold), reduced systemic exposure, and improved antibacterial activity, offering a safer alternative to oral antibiotics.[80] Natural-product-based systems, such as mangosteen peel extract-loaded niosomes, provided anti-inflammatory and antimicrobial effects while improving skin hydration and barrier function, suggesting a multifunctional, plant-based therapeutic option.[81] Advanced approaches include 3D-printed niosomal hydrogels containing cryptotanshinone, enabling personalized dosing with enhanced penetration and strong in vivo anti-acne efficacy without irritation.[82] Combination therapies using niosomes such as adapalene with BPO or co-encapsulation of BPO and clindamycin demonstrated controlled release, improved permeation, sustained action, and reduced irritation.[83,84] These findings highlight niosomes as a practical balance between efficacy, stability, and cost.

Invasomes are advanced vesicular drug delivery systems that enhance skin penetration and retention of therapeutic agents, making them particularly useful in dermatological treatments such as acne. Composed of phosphatidylcholine, ethanol, and terpenes, they exhibit greater flexibility and permeability than conventional liposomes.[85] Research highlights their effectiveness in delivering both synthetic and natural anti-acne agents. For example, dapsone-loaded invasomes prepared via the thin film hydration method showed significantly improved skin deposition about 2.5 times higher than conventional drug solutions in Wistar rats, demonstrating enhanced retention and therapeutic potential.[86] Invasomes have also been explored for natural compounds like *Ocimum basilicum*, leveraging its antimicrobial and antioxidant properties. Studies suggest that combining invasomes with micro-emulsion systems could further improve efficacy, stability, and targeted delivery in acne treatment.[87] Additionally, tazarotene-loaded invasomes have shown promise for transdermal delivery. Optimization studies

revealed vesicle sizes ranging from approximately 220 to 346 nm, with higher phosphatidylcholine content improving drug entrapment. Charged invasomes exhibited better stability, while *in vitro* release studies confirmed sustained drug delivery, addressing key challenges in topical acne therapy.[88] These findings suggest that terpene-containing systems can significantly enhance drug permeation and retention in the skin. Despite its benefits, the main safety concern relates to elevated ethanol levels; nevertheless, at lower concentrations (1–5%) any irritation is minimal and involves reversible effects on the lipids of the stratum corneum.[89]

Cubosomes are nanostructured carriers derived from bicontinuous cubic phases, composed of lipid bilayers forming a 3D honeycomb-like structure with interconnected aqueous channels.[90] This architecture enables encapsulation of hydrophilic, hydrophobic, and amphiphilic drugs, while offering protection from degradation, controlled drug release, enhanced bioavailability, and improved patient compliance. They are non-toxic, non-irritant, and suitable for both local and systemic delivery.[91] In acne therapy, cubosomes loaded with drugs such as tretinoin and erythromycin have shown enhanced skin retention and sustained effects compared to conventional formulations.[91,92] Erythromycin-loaded cubosomal gels demonstrated superior antibacterial activity and therapeutic efficacy over plain gels, supporting their potential for localized acne treatment.[92] Similarly, tretinoin-loaded cubosomes exhibited high entrapment efficiency, improved stability, controlled release, and reduced side effects, with evidence of rapid onset and sustained epidermal drug deposition.[93] Therefore, cubosomes represent an effective and innovative topical delivery system for acne, offering improved efficacy and better patient compliance compared to traditional formulations. Despite their advantages, cubosomes are associated with higher formulation complexity and viscosity-related challenges.[94]

Transferosomes are a specialized class of highly deformable LNCs that have gained significant attention in dermatology, particularly for acne management, due to their superior transdermal delivery capabilities.[95] Structurally, they are composed of a phospholipid bilayer commonly phosphatidylcholine, combined with edge activators (10–25% w/w), such as ionic or non-ionic surfactants. These edge activators destabilize the lipid bilayer in a controlled manner, imparting remarkable elasticity and allowing the vesicles to squeeze through narrow intercellular spaces in the stratum corneum without losing integrity.[96] This unique deformability distinguishes transferosomes from conventional liposomes and enables deeper penetration into skin layers, including the epidermis and hair follicles, which are key targets in acne therapy. Extensive research supports their effectiveness in acne treatment. For example, clindamycin-loaded transferosomes demonstrated enhanced cutaneous retention, faster resolution of lesions, reduced side effects, and shorter treatment duration compared to conventional formulations.[97] Building on this, a chitosan-based transferosomal gel co-loaded with clindamycin (1%) and benzoyl peroxide (2.5%) showed high entrapment efficiency (81%) and significantly improved skin permeation in experimental models. *In vivo* studies revealed marked reductions in acne lesion size ($p < 0.0001$) after 20 days, outperforming both untreated controls and a marketed formulation, while causing no detectable skin irritation.[98] Advanced formulations further illustrate the multifunctional potential of transferosomes. A transferosomal gel combining adapalene with vitamin C (ascorbyl-6-palmitate) demonstrated enhanced deformability, sustained drug release, and additional antioxidant activity. This dual-action system not only improved drug penetration but also addressed oxidative stress associated with acne pathogenesis. In testosterone-induced acne models, this formulation showed superior efficacy in reducing lesions compared to commercial products, highlighting its therapeutic advantage.[99] Clinical evidence reinforces these findings. Linoleic acid-based transferosomes encapsulating syringic acid achieved a 79.5% reduction in acne lesions, demonstrating strong anti-inflammatory activity while maintaining an irritation-free profile, which is critical for patient adherence in long-term therapy.[100]

Transethosomes are multilamellar lipid vesicles of phospholipids combined with ethanol and surfactant that confer a highly deformable structure. These can be used to encapsulate various drugs, allowing delivery through skin layers. These systems are a combination of formulation attributes of transferosomes and ethosomes, providing a solution to the limitations of using either one alone.[101,102] Patil et al. developed a transethosomal gel to improve the topical delivery of nadifloxacin for acne treatment. When formulated into Carbopol 934 (1%) gel, the transethosomal system demonstrated superior *in vitro* drug release and *ex vivo* skin permeation compared to marketed nadifloxacin formulation. In *in vivo* studies on *C. acnes*-infected Wistar rats, the transethosomal gel showed enhanced anti-acne activity and antimicrobial efficacy against the pathogen, outperforming the commercial product. The study concludes that transethosomal technology significantly enhances nadifloxacin delivery to deeper skin layers, offering a promising strategy to overcome solubility and penetration limitations in topical acne therapy.[103]

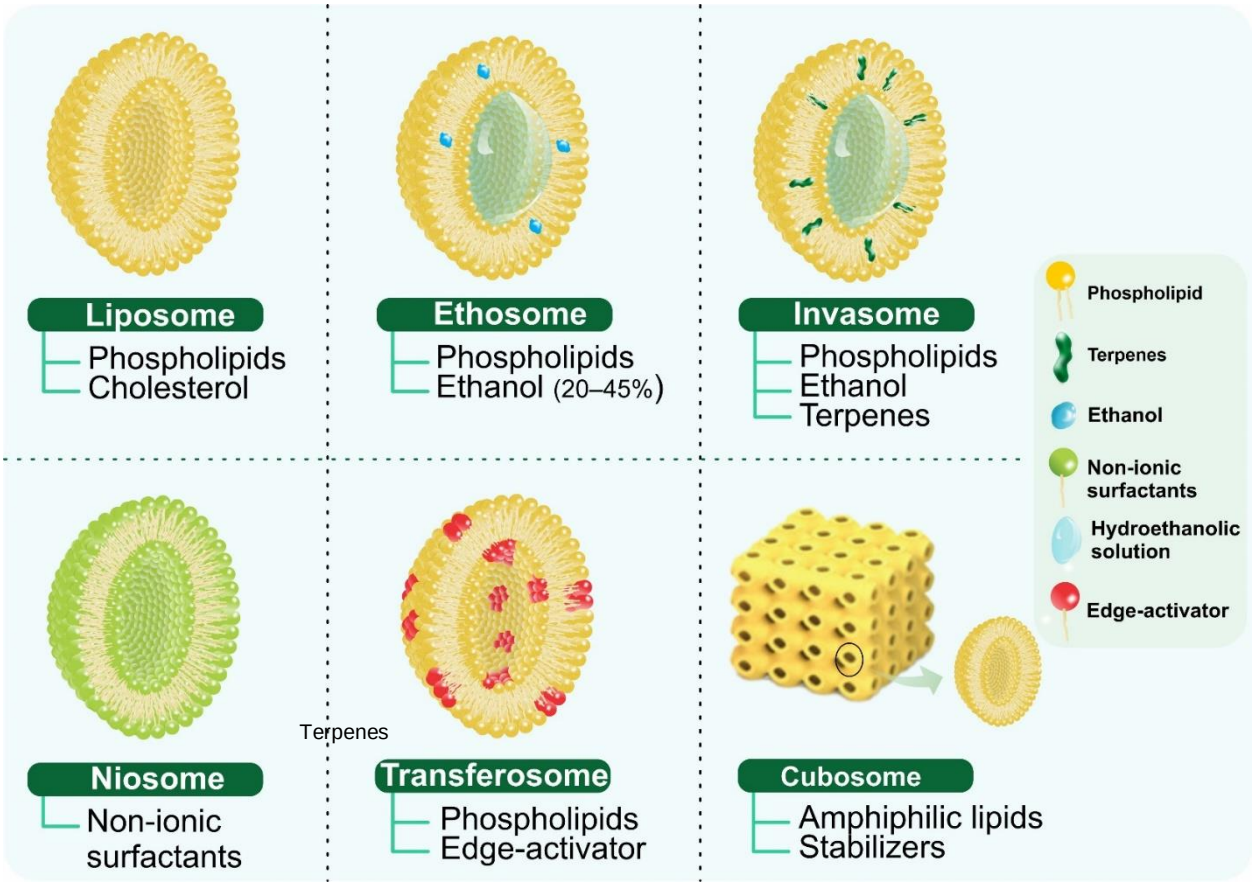

Fig. 3 Schematic illustration of several vesicular based nanocarriers for drug delivery in acne treatment. Created by the authors using CorelDRAW.

Particulate-Based Systems

Particulate-based LNCs are distinguished by a core structure that is either solid or semi-solid. The most prevalent types are SLNs and NLCs. The following section provides a detailed explanation of these nanoparticles, and a summary of studies conducted on their application in acne therapy is presented in **Supplementary Table 2.**

SLNs were developed as an alternative to liposomes and represent the first generation of lipid-based nanosystems with a solid matrix structure on the nanometer scale. These nanoparticles consist of biodegradable lipid cores forming aqueous colloidal dispersions. Common preparation techniques include high-pressure homogenization and solvent diffusion methods. Key advantages encompass controlled drug release mechanisms, enhanced

bioavailability, and effective protection of sensitive molecules such as peptides and oxidation-prone compounds like retinol. Additional benefits involve cost-efficient excipient materials, improved drug encapsulation efficiency, and versatile therapeutic applications. SLNs demonstrate administration flexibility through multiple routes, including oral delivery, injectable formulations, and respiratory system targeting.[104]

SLNs have emerged as a promising transdermal delivery platform, enabling both localized therapeutic action and systemic targeting capabilities.[105] Encapsulating therapeutic agents in SLNs enhance their localized retention in cutaneous layers while modulating drug release kinetics and minimizing systemic uptake.[106] Topical SLN gels exhibit distinctive rheological characteristics and demonstrate molecular interaction with epidermal lipid structures, potentially facilitating transdermal permeation through biomembrane fluidity modulation.[106] Such formulations have demonstrated favorable stability profiles, excellent cutaneous compatibility, and improved therapeutic outcomes in dermatological applications, including acne management.[107] The integration of retinoids and antimicrobials presents a novel strategy for acne management. Lauric acid, a saturated fatty acid, exhibits potent antimicrobial effects against *C. acnes*, while retinoic acid though effective, often causes skin irritation upon topical application. To address this, Silva et al.[108] formulated SLNs co-encapsulating both retinoic acid and lauric acid. The inclusion of stearylamine, a lipophilic additive, was found critical for maintaining encapsulation stability. *In vitro* assessments revealed that the dual-loaded SLNs significantly inhibited the growth of *C. acnes*, *Staphylococcus aureus (S. aureus)*, and *Staphylococcus epidermidis (S. epidermidis)*, demonstrating their potential as a topical therapeutic alternative for acne vulgaris with reduced adverse effects.

The topical gel formulation combining ITN and α-tocopherol acetate encapsulated in SLNs also demonstrated promising efficacy as a non-irritating therapeutic option for acne management. In this study a novel topical gel formulation combining ITN and α-tocopherol acetate (α-TA) encapsulated within SLNs, with the dual objectives of minimizing skin irritation while amplifying therapeutic outcomes in acne management. Preclinical evaluations revealed that the ITN and α-TA-loaded SLN (AE-SLN) gel exhibited complete absence of skin irritation markers such as erythema and edema in rabbit models, alongside marked therapeutic efficacy in reducing acne lesions in rat studies. These findings suggest that the AE-SLN gel emerged as a promising candidate for a non-irritating, topically administered acne treatment, offering a novel approach to acne therapy that prioritizes both safety and effectiveness.[109] In another study, Ghangas et al. conducted a study to enhance the oral bioavailability of ITN, by developing SLNs and comparing them with commercial formulations. Using Central Composite Design (CCD) for optimization, the researchers formulated SLNs with Compritol 888 ATO (lipid), poloxamer 188 (surfactant), and soy lecithin (stabilizer). They concluded that optimizing the drug-oil ratio and increasing homogenization speed critically enhanced SLN performance, suggesting a promising strategy to improve ITN oral bioavailability.[110]

SLNs loaded with BPO can reduce side effects and improve delivery for acne treatment. BPO has remained a widely utilized agent in acne management for decades, yet its application is often limited by common dermatological reactions like skin irritation and redness. Pokharkar et al. established an efficient preparation technique for BPO-loaded SLNs, demonstrating both enhanced formulation stability and preserved antibacterial efficacy against acne-causing bacteria. The SLN-based system achieved sustained drug release profiles, effectively lowering peak drug concentrations in the skin and associated irritation.[4] This innovation represents a strategic balance between therapeutic effectiveness and improved patient tolerance in acne therapy.

Bendas et al. conducted a study to investigate the potential of SLNs in enhancing the therapeutic effectiveness of ternary metal complexes of copper (II) and zinc (II) for acne treatment. The researchers synthesized ternary complexes using glycine as the primary ligand and hydroxy acids:salicylic acid (L1), lactic acid (L2), or glycolic

acid (L3) as secondary ligands. These complexes were encapsulated into SLNs and evaluated for particle size (115–210 nm), zeta potential (-41.33 to -47.32 mV), entrapment efficiency (79–83%), and *in vitro* release, which demonstrated sustained drug delivery. Clinical trials in acne patients revealed that SLNs loaded with zinc-based complexes with glycine, (Zn (L1) (Gly)), achieved greater acne spot reduction and higher patient satisfaction compared to copper-based complexes also containing glycine (Cu (L1) (Gly)). The study concluded that SLN-encapsulated ternary metal complexes, especially zinc formulations, offer a promising therapeutic strategy for acne due to their stability, controlled release, and superior clinical efficacy.[111] Spironolactone (SPN), traditionally administered orally for over two decades to treat skin conditions, faces limitations due to endocrine side effects linked to its unpredictable absorption. Topical delivery emerges as a promising alternative, minimizing systemic exposure while enhancing patient compliance. Kelidari et al. developed and evaluated SLNs for enhancing the dermal delivery of SP to treat skin disorders like acne. Using an emulsion-solvent evaporation method followed by ultrasonication, SPN-loaded SLNs (SPN-SLNs) were characterized via photon correlation spectroscopy (mean diameter: 88.9 nm), zeta potential (-23.9 mV), differential scanning calorimetry (revealing amorphous SPN in SLNs), and FT-IR (showing hydrogen bonding between SPN and SLN components). The entrapment efficiency was 59.86%, and drug release from SPN-SLNs was 4.9 times faster than pure SP within 30 minutes. *In vitro* permeation studies demonstrated that SP-SLNs doubled cumulative skin penetration compared to pure SP over 24 hours, with enhanced skin retention and a biphasic release pattern. The authors concluded that SLNs significantly improve SPN's topical delivery, offering rapid and sustained release, making them a promising carrier for acne treatment.[112]

Despite their advantages, SLNs are hindered by critical limitations in topical drug delivery systems, including low drug encapsulation capacity, gel formation tendencies, nanoparticle aggregation, and instability during storage, leading to active ingredient leakage. This has encouraged the development of next-generation LNCs such as NLCs.

To address SLNs-related constraints, NLCs have emerged as advanced second-generation lipid nanoparticles.[113] Currently, over 40 NLC-based cosmetic products are commercially available, demonstrating their industrial viability.[113] NLCs offer enhanced pharmaceutical performance through superior drug encapsulation, biodegradable composition, reduced active ingredient expulsion, elimination of organic solvent use in manufacturing, and compatibility with existing large-scale production technologies. While sharing similar preparation methods and components with SLNs, NLCs differentiate through their composite matrix–blending liquid lipids (oils) with solid lipids to create nanocapsules with either liquid lipid phases dispersed within the solid matrix or concentrated at particle surfaces.[114]

NLCs have demonstrated significant potential as delivery systems for anti-acne agents, particularly through their ability to optimize therapeutic outcomes. In a pivotal study by Jain et al., adapalene-loaded NLCs synergized with vitamin C exhibited enhanced cutaneous bioavailability by achieving precise epidermal targeting while concurrently suppressing systemic absorption. This dual mechanism not only improved localized drug deposition but also minimized potential systemic side effects, establishing a foundation for safer topical therapies. These integrated findings position NLCs as transformative carriers for dermatological actives, with combinatorial formulations offering multifunctional therapeutic advantages through material science innovation and biochemical cooperation. Thymol, a natural compound with antioxidant, antimicrobial, and anti-inflammatory properties, enhances skin elasticity and porosity to prevent acne scarring.[115-117] To target acne-causing bacteria in deep skin layers, thymol-loaded NLCs were developed, enabling sustained release and improved follicular penetration. Optimized NLC-gel formulations, particularly carbomer-based systems, showed superior skin

retention in epidermal/dermal layers. While thymol-NLC gels demonstrated prolonged antimicrobial efficacy against *C. acnes*, they preserved *S. epidermidis* (healthy microbiome) compared to free thymol, balancing pathogen eradication with microbiome protection. This selective action positions thymol-NLC gels as promising topical therapeutics for acne vulgaris (Fig. 5).[118]

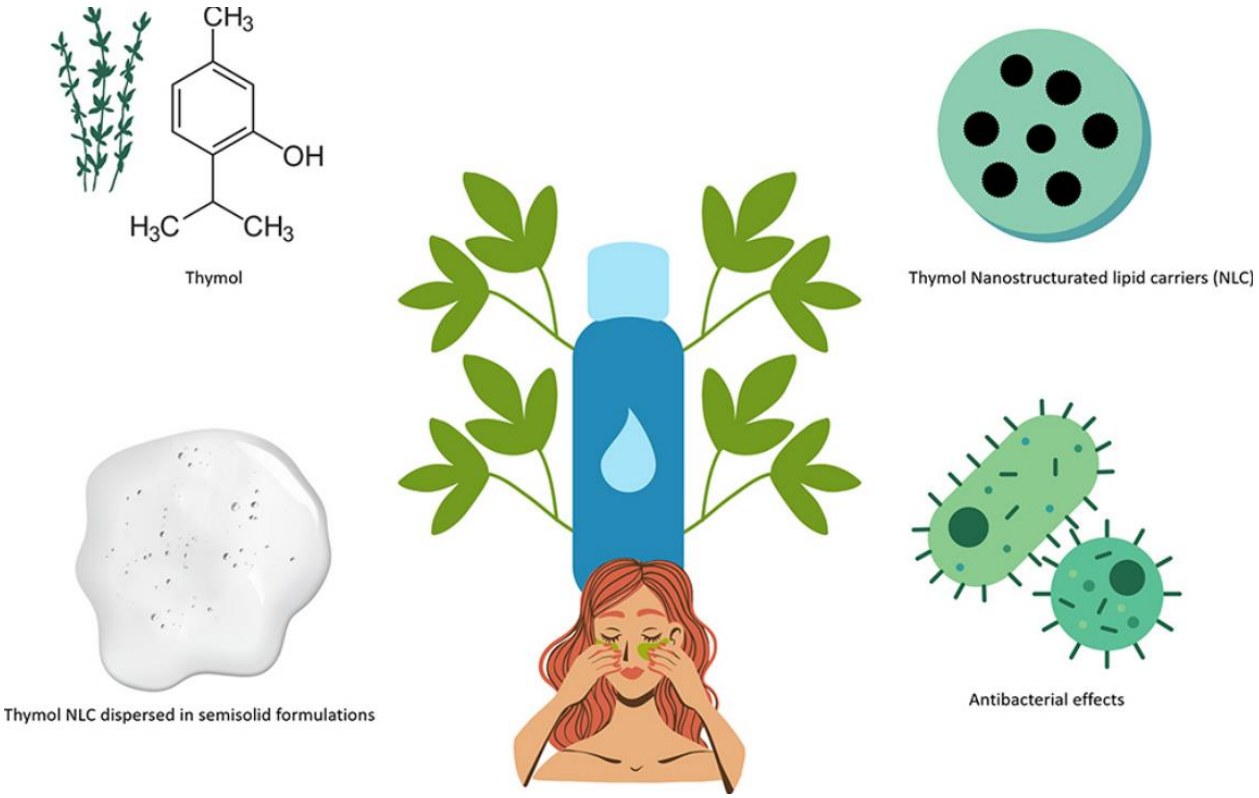

Fig. 4 Schematic illustration of gel-dispersed thymol-loaded nanostructured lipid carriers (NLCs) designed for topical acne treatment.[118] Reprinted from [Folle et al., 2024], [International Journal of Nanomedicine], [DOI: 10.2147/IJN.S433686]. This open access work is licensed under a Creative Commons Attribution-Non-Commercial (CC BY-NC) license. (https://pubmed.ncbi.nlm.nih.gov/38348173/).

Monensin (MON), a natural ionophore antibiotic derived from *Streptomyces cinnamonensis*, demonstrates anticoccidial and antimicrobial activity, including activity against gram-positive acne-associated bacteria (*S. aureus* and *S. epidermidis*). Abid et al. investigated the potential of MON, an antibiotic, encapsulated in NLCs as a targeted topical therapy against antimicrobial-resistant acne pathogens (*C. acnes*, *S. aureus*, *S. epidermidis*). MON-NLCs, formulated using stearic acid, oleic acid, and Tween® 80, exhibited optimized properties: 96.65 nm particle size, PDI of 0.13, and -36.5 mV zeta potential. *Ex vivo* studies on porcine skin revealed that MON-NLCs and their gel formulation deposited 4219.86 ± 388.32 ng/cm² and 8180.73 ± 482.37 ng/cm² in the epidermis, respectively, with no dermal permeation, ensuring localized action. MON demonstrated potent antibacterial activity, enhanced by NLC encapsulation, while cytotoxicity assays confirmed safety at therapeutic concentrations. The study highlights MON-NLCs as a promising epidermal-targeted strategy to combat resistant acne pathogens, minimizing systemic exposure.[119] The violacein (VIO) extract, derived from *Chromobacterium violaceum* ATCC 12472, exhibited potent antibacterial activity, particularly against *C. acnes*. VIO, a natural purple pigment, exhibits potent antimicrobial activity, making it a promising candidate for anti-acne formulations. Leelaudomlipi et al. investigated the antimicrobial efficacy of violacein extract-loaded NLCs (VIO-NLCs) against

acne pathogens (*C. acnes*, *S. aureus*, and *S. epidermidis*). Using a melt-emulsification technique, NLCs were optimized by varying the ratio of lipid (oleic acid and Compritol® 888 ATO = 3:1) with surfactant (Tween 20: 1.5% (w/w)), and sonication time (10 minutes). The resulting NLCs (F8 formulation) showed a particle size of 213.7 ± 2.42 nm, polydispersity index (0.239), and zeta potential (-26.6 mV). When loaded with 2% VIO (VIO-NLCs), the formulation demonstrated sustained antimicrobial effects: inhibition of *C. acnes* for 60 days and *S. aureus* and *S. epidermidis* for 30 days during storage. The study highlights VIO-NLCs as a promising anti-acne therapy, combining targeted delivery, stability, and prolonged efficacy against resistant pathogens.[120] Shettigar et al. developed clarithromycin-loaded NLCs to overcome the antibiotic's poor solubility and enhance its topical delivery for acne treatment. Using glycerol monostearate, oleic acid, and poloxamer 188, the NLCs were optimized via the Quality by Design approach, yielding spherical nanoparticles with 164.8 nm particle size, -39.2 mV zeta potential, and 88.16% entrapment efficiency. Sustained drug release was achieved through lipid matrix diffusion, while *ex vivo* permeation studies on goat skin demonstrated superior permeation (89.5%) compared to a marketed gel (65%). The NLCs, formulated into a carbopol-based gel, exhibited optimal pH, spreadability, and stability under accelerated conditions. The authors concluded that this NLC system offers a promising strategy for sustained clarithromycin delivery, enhancing efficacy in acne management.[121] In another study, Malik et al. developed AZA-loaded NLCs to enhance acne treatment efficacy while minimizing dose-related side effects. The optimized NLCs, formulated into an aloe vera-based nanogel, demonstrated superior skin retention via confocal microscopy, with fluorescence concentrated at the epidermal-dermal junction, outperforming a marketed AZA preparation. Skin compatibility tests (Draize patch) showed no irritation (redness, edema), and cytotoxicity assays using *Saccharomyces cerevisiae* revealed negligible cell death (<10%), confirming biocompatibility. In *P. acnes*-infected mice, the NLCs gel exhibited potent anti-inflammatory and antimicrobial effects. The study concluded that AZA-NLCs enhance targeted delivery and therapeutic efficacy without compromising safety, offering a promising alternative for acne management.[122] Overall, according to the represented results, NLCs demonstrate significant potential as a targeted drug delivery strategy for acne treatment, enabling precise localization of therapeutics to affected areas, enhancing efficacy, and reducing off-target effects associated with conventional therapies.

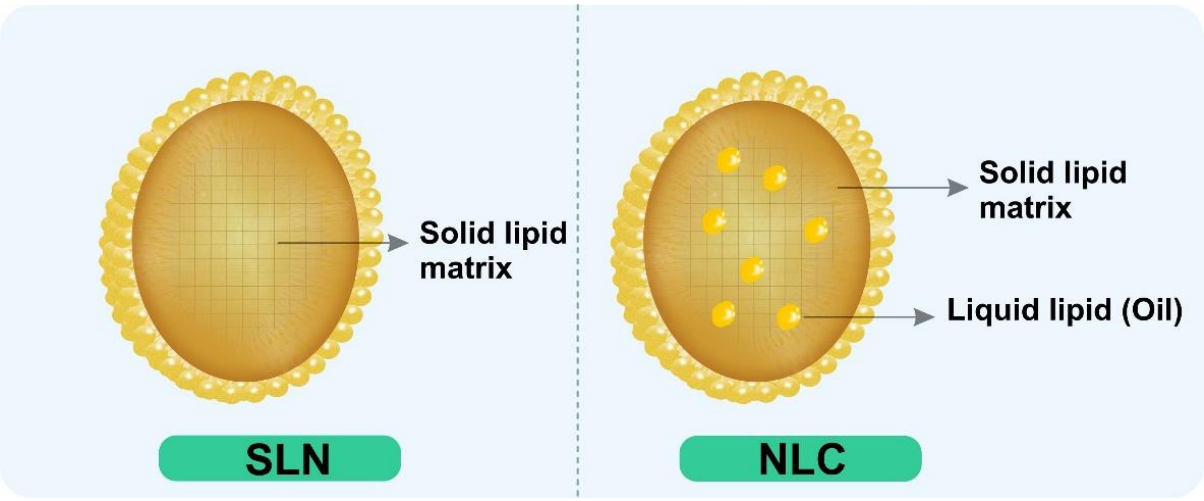

Fig. 5 Schematic illustration of particulate-based systems for drug delivery in acne treatment. NLC: Nanostructured Lipid Carriers, SLN: Solid Lipid Nanoparticles. Created by the authors using CorelDRAW.

Nanoemulsions

Nanoemulsions are submicron-sized colloidal systems with droplets typically ranging from 20-200 nm, composed of immiscible liquids stabilized by surfactants.[123] These systems offer numerous advantages, including improved solubility, bioavailability, and controlled delivery of drugs and bioactive compounds.[124] Nanoemulsions have diverse applications in pharmaceuticals, cosmetics, food, and pesticide formulations due to their unique properties such as high surface area, good physical stability, and rapid digestibility.[125] They can be administered through various routes, including oral, intravenous, topical, and nasal, with each route demonstrating distinct pharmacokinetic and pharmacodynamic features.[126] Their notable properties, including enhanced drug efficacy, simplified manufacturing requirements, formulation versatility across product types, and superior loading capacity for oil-soluble medications, collectively establish these systems as optimal delivery vehicles for dermatological acne treatments.[127] Hosny et al.[128] developed a self-nanoemulsion combining ITN with quercetin, refining the formula to improve drug dissolution, boost skin penetration, and ensure safer acne therapy. In another study,[129] a minocycline-loaded nanoemulgel was formulated and optimized for improved drug delivery and treating acne rosacea. In this study, various oil-in-water nanoemulsions were created using eucalyptus oil, Tween 20, and Transcutol HP, and their characteristics and stability were analyzed. The final nanoemulgel showed sustained-release behavior and is expected to treat acne rosacea effectively. Abdelhamed et al. investigated natural antimicrobials as alternatives to conventional antibiotics in acne treatment, addressing concerns over rising antibiotic resistance. Among five essential oils (EOs) tested (tea tree, clove, thyme, mentha, basil), thyme EO demonstrated the strongest antimicrobial and antibiofilm activity against *C. acnes* and *S. epidermidis*, attributed to its phenolic and terpenoid constituents. Mechanistic studies revealed thyme EO disrupts bacterial membrane integrity, inducing leakage of intracellular ions and nucleic acids, with Transmission Electron Microscopy (TEM) confirming cellular damage. Formulated as a nanoemulsion, thyme EO reduced bacterial load, suppressed inflammatory responses, and improved histopathological features in an *in vivo* acne model, outperforming standard antibiotics. The findings position thyme EO nanoemulsion as a promising natural therapeutic alternative, combining potent antimicrobial and anti-inflammatory actions to mitigate acne progression while circumventing antibiotic resistance.[130] In another study, Shakeel et al. developed a nanoemulsion delivery system for niaouli essential oil (NEO) to enhance its efficacy in treating acne vulgaris. The nanoemulsions were optimized using varying ratios of NEO (10% v/v), Kolliphor EL (9.25% (v/v)), Carbitol (27.75% (v/v)), and water (53% (v/v)) identified as the most promising based on droplet size, rheological properties, surface charge, and stability. *In vitro* studies demonstrated potent antimicrobial activity of all formulations against *C. acnes* and *S. epidermidis*. *Ex vivo* permeation assays revealed significantly enhanced skin penetration and steady-state flux ($p < 0.05$) compared to pure NEO. The study concludes that nanoemulsification markedly improves NEO's bioavailability and antimicrobial performance, positioning it as a viable topical strategy for acne management.[131] Recent studies have explored the potential of *Ananas comosus L. Merr* (pineapple) in treating acne. Chabib et al. developed a nanoemulsion gel from pineapple extract to enhance its antioxidant and anti-acne properties. The extract, obtained via maceration, was formulated using Tween 20, propylene glycol, and Kollisolv PYR as the oil phase. Antioxidant testing revealed very strong activity (IC50 = 0.1 μg/mL) with radical scavenging activity (%RSA) ranging from 17.70% to 70.32%. In anti-acne assays, the gel showed strong antibacterial efficacy against acne-causing bacteria, with an average inhibition zone of 10.5 mm ± 0.1. The study concludes that pineapple extract nanoemulsion gel is a promising dual-functional formulation, combining potent antioxidant and anti-acne effects for topical applications.[132] Similarly, pineapple peel extract gel showed significant inhibitory activity against *C. acnes*, with higher concentrations exhibiting stronger effects. Latu et al. evaluated the anti-acne potential of

ethanol extract from pineapple peel formulated into gel preparations. The peel, rich in flavonoids, tannins, phenolics, and bromelain, was tested against *C. acnes*. Gel formulations with extract concentrations of 2%, 3%, and 5% were prepared and assessed for physical stability and antibacterial activity using the agar well method. Stability tests revealed significant changes post-cycling but maintained usability across all parameters. Antibacterial results showed dose-dependent inhibition zones: the 5% gel exhibited the strongest activity (12.7 mm inhibition zone, categorized as "strong"), while the 3% (11.03 mm) and 2% (8.8 mm) formulations fell into the "moderate" category. The study concludes that pineapple peel extract gel, particularly at 5% concentration, holds promise as a natural anti-acne agent, leveraging its phytochemical composition to inhibit bacterial growth effectively.[133] Clinical trials have indicated that nanoemulsion formulations of anti-acne medications such as tretinoin, clindamycin, and adapalene are more efficient than standard formulations in decreasing the number and severity of acne lesions.[134,135] For example, in comparative clinical evaluations, a 1% clindamycin nanoemulsion gel formulation demonstrated statistically superior performance in decreasing inflammatory acne lesions, non-inflammatory comedones, and overall acne severity scores relative to conventional clindamycin gel formulations, with the enhanced bioavailability of the nanoemulsion delivery system likely contributing to its therapeutic advantages.[135] This highlights the potential of nanoemulsion technologies to enhance the effectiveness of topical acne treatments. As a scalable and adaptable platform, nanoemulsion technology not only elevates the performance of existing therapies but also paves the way for personalized, precision-based dermatological solutions. A summary of studies examining the use of nanoemulsions in acne treatment is provided in **Supplementary Table 3.**

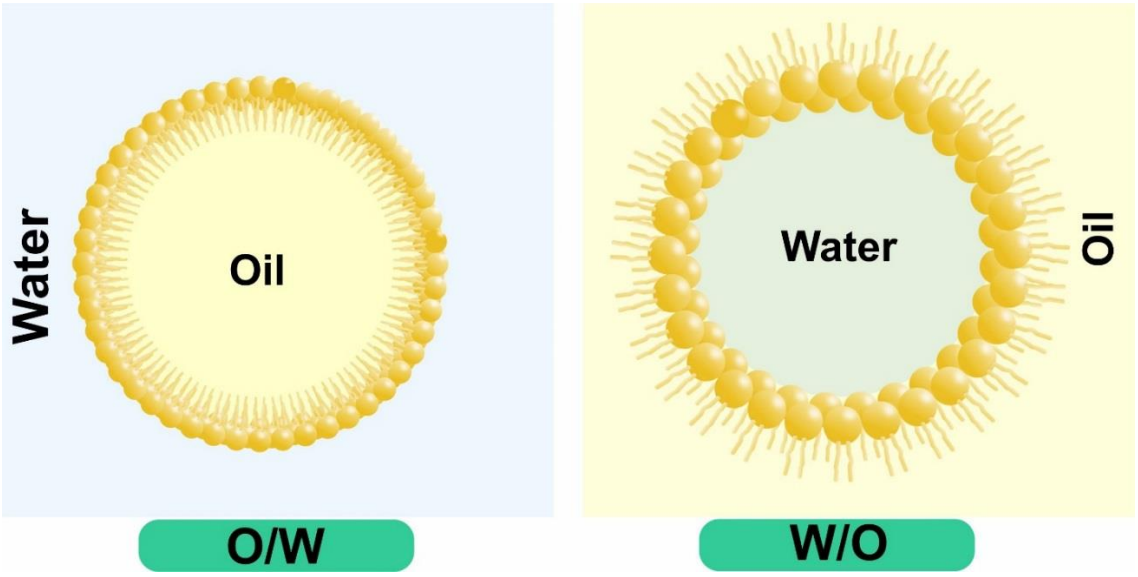

Fig. 6 Schematic illustration of Nanoemulsions for drug delivery in acne treatment. Created by the authors using CorelDRAW.

Clinical translation and Trials

Lipid-based vesicular and particulate systems are highly promising due to their structural similarity to the skin, which enables more effective delivery of active ingredients. These LNCs offer significant advantages in acne treatment by addressing the shortcomings of traditional therapies. They enhance the therapeutic efficacy and skin tolerance of anti-acne drugs such as retinoids, antibiotics, and BPO.[59] Composed of biocompatible materials, lipid nanoparticles reduce toxicity, improve physical stability, and protect encapsulated drugs from degradation.[18] These innovative delivery systems can mitigate common side effects like dryness, erythema, and scaling while maintaining drug efficacy through controlled release and enhanced penetration into the pilosebaceous unit.[136]

Recent clinical studies have shown that LNCs can significantly reduce acne lesion counts and improve skin condition with fewer side effects compared to conventional treatments. Table 1 outlines a summary of clinical trials assessing the performance of LNCs in acne management. These advancements highlight the potential of LNCs as a promising approach for managing acne.

SPN, known for its anti-androgenic properties, has shown effectiveness in treating acne. In a double-blind randomized clinical trial, Saeedi et al. aimed to improve the delivery of SPN to the skin for acne treatment by developing a chitosan-coated NLC through ultrasonication. Various hydrophilic-lipophilic balance (HLB) values were explored to optimize the SPN-NLCs. In the double-blind trial, a gel containing chitosan-coated SPN-NLC effectively treated mild to moderate acne vulgaris, leading to improved healing and reduced lesion count after 8 weeks of therapy compared to the placebo. It successfully addressed both non-inflammatory and inflammatory lesions without adverse effects on the skin.[137]

Topical retinoids are commonly used as the first-line treatment for acne vulgaris, but they frequently cause skin irritation. To address this issue, a randomized, single-blind, parallel-group study was conducted involving 40 patients, who were divided into two groups. The treatment regimen included the once-nightly topical application of ITN-loaded SLN (ITN-SLN) along with twice-daily topical application of clindamycin 2% solution for a duration of 8 weeks. The main objective of this study was to develop and assess the effectiveness of ITN-SLN in treating mild to moderate acne. The study aimed to reduce the adverse effects typically associated with the commercial product, Isotrex®, by utilizing nanotechnology to improve the delivery and efficacy of ITN while minimizing skin irritation. The findings revealed that IT-SLN demonstrated notably superior treatment results compared to Isotrex® for both non-inflammatory and inflammatory lesions, attaining higher global assessment scores by the end of the 8-week treatment period.[107]

In 2018, a study was conducted to synthesize and assess the impact of dapsone niosomes. This research focused on evaluating the topical application of dapsone niosomes, particularly in terms of drug release duration and control, as well as enhancing skin penetration. The niosomes were developed as a novel formulation for treating mild to moderate acne. Fifteen acne patients were treated with dapsone niosomes, and clinical evaluations were conducted before the treatment, at 2 weeks, and after 8 weeks of treatment. Niosomes formulated with Span 60 exhibited sustained drug release over 24 hours and superior entrapment efficiency relative to alternative formulations. Clinical improvements became evident within two weeks of use, with a marked reduction in acne lesions observed after an 8-week treatment period (Fig. 7). The results indicate that dapsone-loaded niosomes represent a well-tolerated and efficient delivery system, offering therapeutic benefits with negligible adverse effects.[78]

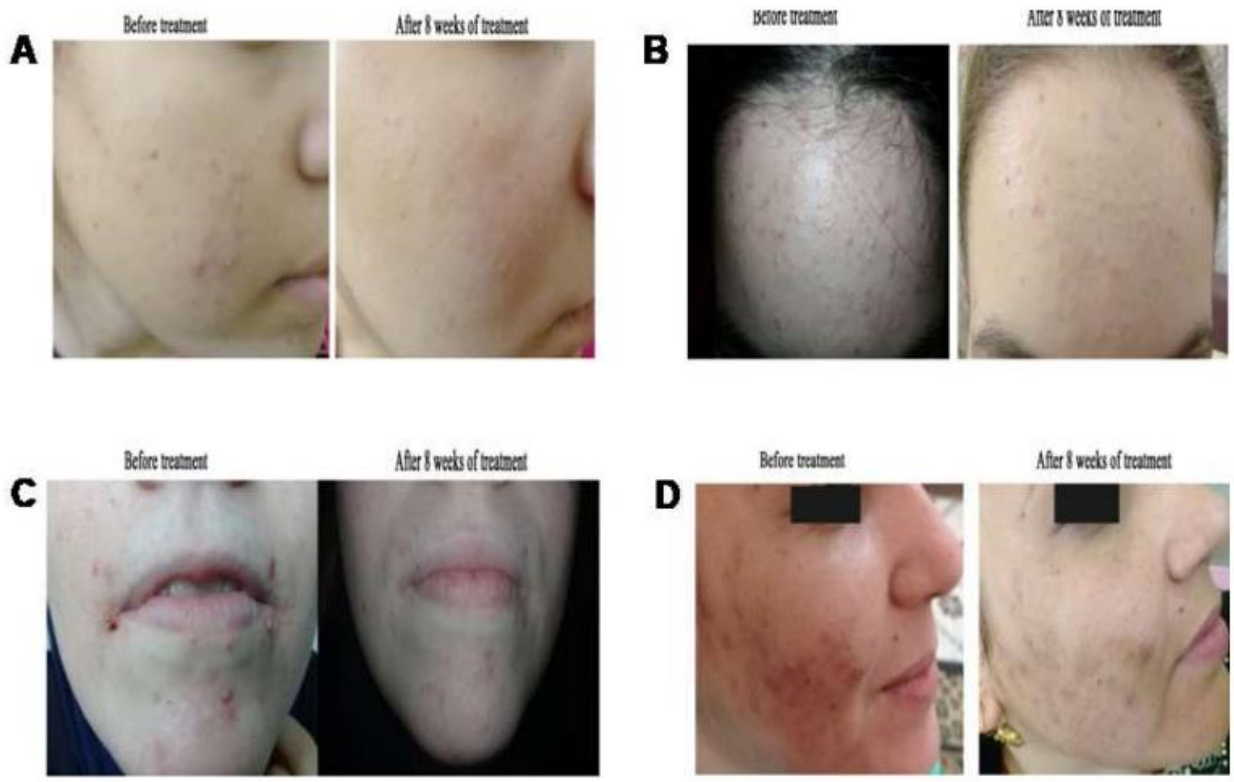

Fig 7 Clinical outcomes of dapsone niosome treatment across four acne vulgaris cases: (A) a 15-year-old female with mild acne on the right cheek; (B) a 20-year-old female presenting non-inflammatory (comedonal) acne on the forehead; (C) a 23-year-old female with inflammatory (papulo-pustular) acne in the lower facial region; and (D) a patient exhibiting inflammatory acne accompanied by residual post-inflammatory hyperpigmentation. Pre- and post-treatment images (after 8 weeks of therapy).[78] Reprinted from [Al Sabaa et al., 2018], [African Journal of Pharmacy and Pharmacology], [DOI: 10.5897/AJPP2018.4925]. This open access work is published under the terms of the Creative Commons Attribution License 4.0. (https://academicjournals.org/journal/AJPP/article-full-text/268F28757229).

In 2014, a prospective clinical study was carried out to assess the efficacy and safety of a clindamycin nanoemulsion gel formulation compared to its conventional formulation for treating acne. The study involved treating acne patients with either the nanoemulsion gel formulation or the conventional gel formulation of clindamycin phosphate 1%, applied topically twice daily for 12 weeks. Monthly evaluations were conducted to assess the reduction in acne lesions (inflammatory, non-inflammatory, and total) and to grade the severity of the lesions. Each group consisted of 200 patients. The results indicated a significant reduction in inflammatory acne lesions (73.4% vs. 60.6%; $p<0.005$) and non-inflammatory acne lesions (65.1% vs. 43.7%; $p<0.001$) in the nanoemulsion gel formulation group compared to the conventional gel formulation group (Fig. 8). The clindamycin nanoemulsion gel formulation proved to be more effective in treating acne and demonstrated a better safety profile based on the study results.[135]

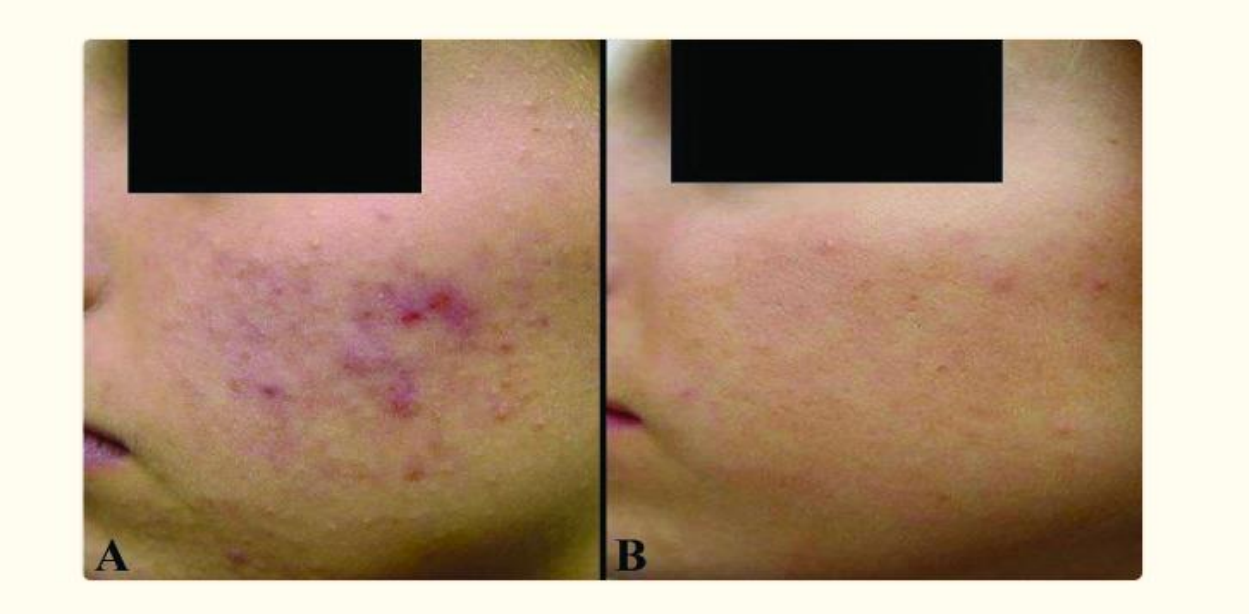

Fig 8. The Effect of clindamycin nanoemulsion gel on acne lesions. (A - baseline and B - 12 weeks).[135] Reprinted from [Bhavik Bhavsar et al., 2014], [Journal of Clinical and Diagnostic Researc], [DOI: 10.7860/JCDR/2014/9111.4769]. This open access work is licensed under a Creative Commons. (https://pmc.ncbi.nlm.nih.gov/articles/PMC4190779/).

In another clinical study, researchers examined the effectiveness of a combination therapy that included RA (0.025%) and BPO (2.5%) encapsulated in a liposomal gel for treating acne. The results showed that this formulation led to the clearance of skin lesions within 10 weeks, proving to be more effective than a gel containing the same drugs in their free form.[138]

Table 1. Summary of trials evaluating LNCs for topical acne treatment.

Type of Study	Formulation	Experimental Setup	Control/Comparator	Strengths & Limitations	Key Findings	Refs
Randomized Double-Blind Clinical Trial	SPN Loaded Chitosan-Coated Nano Lipid Carrier	40 patients within the age range of 8 to 65 years (22 ± 5.76)	placebo (chitosan-coated nanostructured lipid carrier gel + clindamycin 2% solution)	Strengths: Low bias (randomized double-blind); adequate short-term (8 weeks) assessment Limitations: Short follow-up (no long-term/recurrence data); active (non-true) placebo (clindamycin 2%)	Nano formulation improved healing and reduced lesion count after 8 weeks compared to placebo.	137
Double-blind clinical study	Clindamycin-loaded liposomes	73 patients	Conventional 1% clindamycin solution	Strengths: Double-blind design reduces bias Limitations: no long-term outcomes	1% clindamycin-loaded liposomes and 1% clindamycin solution was compared for treating acne vulgaris. The liposomal formulation was more effective and reported no side effects.	139
A randomized, double-blind,	SPN loaded nanostructured lipid carrier gel	76 patients, aged 8 years or older. 8 weeks	Spironolactone alcoholic gels	Strengths: Low bias (randomized double-blind); adequate short-	Demonstrated a more significant improvement in the acne severity	140

prospective trial		treatment duration		term (8 weeks) assessment Limitations: Short follow-up (no long-term/recurrence data)	index and a greater reduction in inflammatory lesion counts compared to the placebo gel	
Double-blind clinical study	Liposomal tretinoin	20 patients aged 18-31 years. patients received, once daily for 10 weeks	Conventional tretinoin gel (0.025% or 0.05%)	Strengths: Double-blind design reduces bias, adequate short-term (10 weeks) assessment Limitations: Very small sample (n=20), Male-only population	Patients reported that liposome-encapsulated tretinoin caused less burning and erythema than the 0.025% and 0.05% gels. Additionally, the investigator found it to be better tolerated.	[141]
Double-blind clinical study	Liposomal tretinoin	30 volunteers aged 16–28 Years. 3-month treatment duration	Plain (conventional) Tretinoin gel	Strengths: Double-blind comparison; improved efficacy Limitations: Small sample (n=30); short duration (3 months)	Tretinoin-liposomal gel was 1.5 times more effective than conventional gel, especially for comedones (62.36% to 94.17% lesion reduction). It also reduced side effects like erythema and irritation.	[142]
Double-blind clinical study	Liposomal tretinoin	10 subjects aged from 23 to 40 years. 4 weeks treatment duration	Marketed (conventional) Tretinoin product	Strengths: Randomized double-blind design; within-subject control (each patient serves as own control); weekly follow-up Limitations: Short follow-up (4 weeks); no long-term safety/recurrence data	Liposomal tretinoin gel was significantly more effective and caused less erythema than the marketed product, improving skin tolerability and patient compliance.	[64]
Single-blinded clinical trial	Benzoyl peroxide loaded liposomes	20 patients with average age 23 years. 2 weeks twice per day	Commercial and pharmacopoeial benzoyl peroxide	Strengths: comparative testing vs standard and commercial products Limitations: Small sample size (n=20); single-blinded design (not double-blind); short duration (2 weeks)	Liposomes improved Benzoyl peroxide's antibacterial action against *Propionibacteria* and *Micrococcaceae* compared to other formulations.	[143]
Uncontrolled, open-label clinical study	Myoinositol and trehalose-loaded liposomes	40 patients 27.3 ±4.1 years. 60-day-uncontrolled pilot study	No control group (uncontrolled, open-label pre–post study)	Strengths: multiple clinical outcomes (lesion count, sebum, GAGS) Limitations: No control group; open-label design (high risk of bias); short duration (60 days); limited ability to attribute effects solely to treatment; no blinding or comparator treatment	A peel-off facial mask with myoinositol and trehalose-loaded liposomes enhanced cosmetic appearance by lowering skin androgen levels and boosting autophagy.	[144]

A randomized controlled trial	Niosomal clindamycin phosphate	100 acne patients between 12 to 33 years	Conventional topical Clindamycin 1%	Strengths: Double-blind randomized clinical trial; adequate sample size (n=100); direct comparison with standard treatment Limitations: Conducted in a single center (Kerman, Iran), which may limit generalizability to other populations and clinical settings	Niosomal clindamycin significantly reduced acne lesions and improved acne grades according to the Global Acne Grading System, with no increased adverse effects.	145

Conclusion

Acne vulgaris, a globally prevalent inflammatory skin disorder with particularly high incidence among adolescents, presents major treatment challenges due to its intricate interplay of hormonal, genetic, microbial, and environmental drivers. Established treatments like antibiotics and retinoids continue to struggle with adverse reactions, resistance development, and inconsistent patient adherence. Innovations in LNCs, represent a breakthrough in acne management by enabling superior drug delivery via enhanced skin penetration, precise follicular targeting, and controlled release mechanisms. These advancements reduce treatment-related irritation, maximize therapeutic outcomes, and circumvent drawbacks of conventional methods. Future research should focus on optimizing nanoparticle design, clinical validation of long-term safety, and integration with biomarkers to refine acne management. Integrating cutting-edge scientific breakthroughs with clinical requirements, lipid nanotechnology is set to revolutionize acne management strategies, offering enhanced safety and efficacy in treatments across the globe. Critically, recent clinical trials underscore the translational potential of these nanocarriers. Trials also highlight enhanced patient compliance due to reduced dosing frequency and prolonged drug retention in pilosebaceous units. However, challenges such as standardization of nanoparticle characterization, scalability of production, and long-term safety monitoring remain critical hurdles for clinical adoption. Future research must prioritize large-scale, multicenter clinical trials to validate long-term biocompatibility and cost-effectiveness, particularly for combination therapies integrating antimicrobials and anti-inflammatories. By bridging cutting-edge nanotechnology with rigorous clinical validation, lipid-based delivery systems hold transformative potential to revolutionize acne management globally, offering safer, targeted, and patient-centric therapeutic strategies. Collaborative efforts among researchers, clinicians, and regulators will be essential to translate these innovations into mainstream dermatological practice.

Ethical Approval

Not applicable.

Authorship contribution statement

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All authors approved the final version of submitted manuscript and agreed to be accountable for all aspects of the work.

Competing interests

The authors have no relevant financial or non-financial interests to disclose.

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