https://doi.org/10.31925/farmacia.2026.4.1 **REVIEW**

ECO-FRIENDLY LIPID-BASED NANOVESICLES FOR ACNE TREATMENT: SUSTAINABLE APPROACHES IN DRUG DELIVERY

MONA MAHMOUD ABOUSAMRA

Pharmaceutical Technology Department, National Research Centre, 33 El-Buhouth Street, Dokki, Giza, 12622, Egypt

**corresponding author: mm.samra@nrc.sci.eg*

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Abstract

Acne vulgaris is a widespread inflammatory skin disorder that arises from a combination of hormonal activity, microbial proliferation, excessive sebum production, and follicular hyperkeratinization. While traditional treatments such as antibiotics and retinoids are commonly used, they often face challenges like skin irritation, resistance development, and limited efficacy. Lipid-based nanovesicles, especially liposomes and related vesicular systems, have gained attention for their potential to enhance drug penetration, improve targeting of pilosebaceous units, and reduce side effects. This review provides an overview of acne pathophysiology and treatment options, highlighting the role of lipid-based nanovesicles in acne management. A key focus is placed on the integration of eco-friendly strategies in lipid-based nanovesicle development, including the use of biodegradable lipids, renewable materials, green solvents, and sustainable manufacturing processes. These advancements support the creation of dermatological formulations that are not only effective but also aligned with environmental sustainability goals. The review discusses the potential of green nanotechnology in reshaping the future of acne treatment.

Rezumat

Acneea vulgară este o afecțiune inflamatorie cutanată, larg răspândită, care apare ca urmare a unei asocieri între activitatea hormonală, proliferarea microbiană, producția excesivă de sebum și hiperkeratinizarea foliculară. Deși tratamentele tradiționale, precum antibioticele și retinoizii sunt frecvent utilizate acestea pot provoca iritație cutanată, pot duce la dezvoltarea rezistenței și pot avea eficacitate limitată. Nanoveziculele lipidice, în special lipozomii și sistemele veziculare, au potențial de a îmbunătăți penetrarea medicamentelor, de a optimiza țintirea unităților pilosebacee și de a reduce efectele adverse. Acest studiu discută fiziopatologia acneei și optiunile terapeutice, evidențiind rolul nanoveziculelor lipidice în managementul acesteia. Este subliniată integrarea strategiilor ecologice în dezvoltarea nanoveziculelor lipidice, precum utilizarea lipidelor biodegradabile, a materialelor regenerabile, a solvenților verzi și a proceselor de fabricație sustenabile. Aceste progrese susțin crearea unor formulări dermatologice care nu doar sunt eficiente, ci și aliniate obiectivelor de sustenabilitate ecologică.

Keywords: acne vulgaris, nanocarriers, lipid-based systems, eco-friendly nanovesicles, sustainable drug delivery

Introduction

Acne vulgaris is a multifactorial chronic dermatological inflammatory disorder that arises from a complex interaction of genetic, hormonal, microbiological, and immunological factors affecting the pilosebaceous unit (1). Its pathogenesis involves hyperseborrhea driven by androgenic stimulation, follicular hyperkeratinization due to altered keratinocyte proliferation, microbial dysbiosis dominated by *Cutibacterium acnes*, and a cascade of innate immune responses triggering chronic inflammation (2). When these factors come together, they can dam-age the pilosebaceous unit, causing normal follicular canals to change into microcomedones and then proceed into inflammatory lesions (3). Moreover, the impact of diet, particularly high-glycemic foods and dairy, on insulin-like growth factor-1 (IGF-1) signalling has gained attention in acne pathophysiology (4).

Since this illness affects about 85% of teenagers globally, it has serious psychological effects and can undermine confidence and self-worth at a critical period in life (5).

Topical drugs (benzoyl peroxide and retinoids), topical antibiotics (clindamycin and erythromycin), and systemic treatments (oral retinoids, oral antibiotics, and hormone therapy) are commonly used to treat acne (6). The primary disadvantage of these treatments is that they may cause gastrointestinal distress (7), bacterial resistance (8), or irritant dermatitis (9). Although acne is still frequently treated with the afore-mentioned methods, safer and more efficient materials are desperately needed. Recent advancements in nanocarrier-based drug delivery systems have shown significant promise in enhancing the treatment of acne vulgaris. Lipid-based systems are among the most commonly used nanocarriers for acne management (10). They are commonly explored for their ability to improve drug stability, skin penetration, and controlled release (11). These innovative nanocarriers offer improved drug bioavailability and reduced side effects, contributing to the

development of more efficient and safer acne treatment (11).

This article gives a complete overview of the principles and applications of lipid-based nanovesicles in addressing acne vulgaris. We delve into the role and the mechanism of action of lipid-based systems in acne therapy. We study their targeting processes and address their potential therapeutic uses in acne management. Furthermore, the growing emphasis on sustainability has led to the exploration of eco-friendly approaches in the development of lipid-based nanovesicles, such as the use of biodegradable materials, renewable lipids, and green solvents. This review discusses these innovations, focusing on their potential to provide effective, environmentally responsible treatment options for acne vulgaris.

Causes and factors contributing to chronic acne

Acne vulgaris is the eighth most prevalent skin condition globally, with an estimated prevalence of 9.38% across all age categories, according to the Global Burden of Disease Study (12). However, its prevalence is substantially higher among adolescents, affecting more than 85% of teenagers, and it may persist into adulthood, particularly in women (13). The distinct lesions can be classified as either inflammatory or non-inflammatory, resulting in skin pigmentation or scarring that requires ongoing, intensive treatment (14). Many external and internal factors contribute to prolonged inflammation and dysfunction of the skin, leading to persistent or recurring acne (Figure 1).

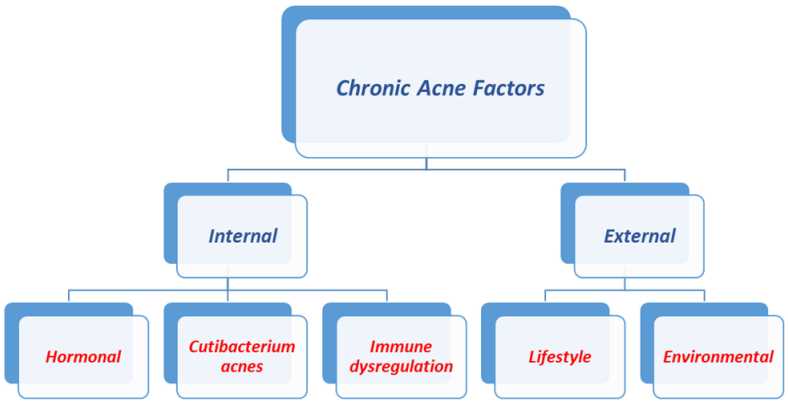

Figure 1.
Diagram representing an overview of key factors contributing to chronic acne formation

Hormonal imbalances

One of the main reasons acne develops is increased sebum production in the hair follicles. Sebum production and release are increased by elevated levels of androgen hormones, particularly testosterone and IGF-1 (15). Since there is a direct link between the severity and frequency of acne lesions and increased sebum production that clogs pores, leading to acne formation, hormonal imbalance is an important factor to take into account in patients with acne vulgaris (16).

Persistent Cutibacterium acnes colonization

Cutibacterium acnes, formerly known as *Propionibacterium acnes*, is a gram-positive, lipophilic, commensal, aerotolerant anaerobe that becomes opportunistically pathogenic and prefers to settle in sebaceous follicles due to high sebum production and the ideal anaerobic environment for bacterial growth (17). Chronic overgrowth of *C. acnes* can perpetuate inflammation and maintain the acne cycle through the release of the lipase enzyme, which breaks down sebum triglycerides into glycerol and fatty acids, leading to comedones and skin irritation (18).

Inflammatory and immune dysregulation

As a consequence of chronic *C. acnes* overgrowth, strong inflammation may release chemotactic factors that recruit neutrophils, macrophages, and lymphocytes. In addition, these conditions cause follicular damage, rupture, and release of germs, fatty acids, and lipids into the dermis. These mechanistic processes will cause inflammatory lesions (pustules, nodules, cysts, and papules) (1). Furthermore, it was found that neutrophils generate reactive oxygen species (ROS), which harm the follic-ular epithelium and fuel inflammation in acne. As a result, the follicular substances are released into the dermis, causing a range of inflammatory acne lesions (19).

Lifestyle factor

Numerous possible risk factors for acne vulgaris have been found in previous research, including dietary patterns, stress levels, and lifestyle habits like smoking and inactivity (20). For instance, consuming large amounts of milk or dairy products and following a diet high in glycemic load have been linked to an in-creased risk of acne due to their impact on insulin and androgen levels (21). Hyperinsulinemia

significant-ly increases circulating levels of IGF-1. IGF-1 is a hormone primarily synthesized in the liver that pro-motes sebaceous cell proliferation and lipogenesis in the sebaceous glands. IGF-1 also increases androgen levels and suppresses the production of the IGFBP-1 and IGFBP-3, while sex hormone-binding globulin (SHBG) suppression is primarily mediated by insulin, with IGF-1 also contributing to this effect. The inhi-bition of the production of these proteins implies increased availability of androgens and IGF-1, thereby exacerbating acne (22, 23). Moreover, stress can make acne worse, in part by triggering cortisol release, which consequently increases inflammatory reactions (24).

Environmental triggers

Many research (25, 26) and review articles (27, 28) have documented the skin alterations that occur after exposure to ambient air pollution, particularly the development of inflammatory acne (28). Exposure to high levels of outdoor pollution was found to trigger an oxidation stress response in human skin, followed by an increase in oxidized protein levels, a decrease in ATP levels, and a decrease in relevant antioxidants of the skin, such as vitamin E and squalene (27). Oxidation will produce inflammatory cytokines and hy-perproliferation of keratinocytes, ultimately causing acne to develop or worsen (25).

Another factor considered to be associated with the worsening of acne is the use of cosmetics applied directly to the skin. Generally, regularly used cosmetics are associated with the aggravation of acne (29).

From the above, acne vulgaris is a complex skin condition that arises from the dysfunction of the pilosebaceous unit, which includes the hair follicle and sebaceous gland. Multiple factors, such as increased sebum production, abnormal shedding of skin cells within the follicle, overgrowth of C. acnes, and subse-quent inflammation influence its development. Hormonal changes, genetics, and environmental influences often exacerbate these processes. C. acnes plays a pivotal role by triggering immune responses and releas-ing inflammatory mediators. A thorough understanding of these mechanisms provides a foundation for developing advanced, targeted treatments, including nanocarrier-based therapies, to address the specific drivers of acne.

Treatment strategies for acne vulgaris

The management of acne vulgaris involves a multifaceted approach targeting key pathophysiological mechanisms, including excessive sebum production, follicular hyperkeratinization, microbial colonization, and inflammation (30). Treatment selection depends on acne severity, lesion type, and individual patient factors. Topical therapies, such as retinoids, benzoyl peroxide, and antibiotics, are commonly used for mild to moderate cases, whereas systemic agents, including oral antibiotics, hormonal therapy, and isotretinoin, are reserved for more severe or resistant forms (31). Additionally, adjunctive therapies like chemical peels, laser treatments, and microbiome-targeted interventions are gaining interest for their po-tential to enhance treatment outcomes (30). A personalized approach that considers efficacy, safety, and patient adherence is essential for optimizing acne management and minimizing the risk of recurrence (32). Table I outlines the available treatment options for acne management based on acne severity, skin type, and individual response.

While conventional therapies for acne vulgaris have shown efficacy, challenges such as antibiotic resistance, systemic side effects, poor skin penetration, dryness, irritation, and patient adherence remain significant concerns.

Nanocarrier-based drug delivery systems have emerged as a promising strategy to enhance treatment outcomes by improving drug solubility, stability, and targeted delivery to sebaceous glands.

Role of lipid-based nanovesicles in acne therapy

Nanocarriers represent a promising innovation in the management of acne vulgaris, offering solutions to the challenges faced by conventional treatments. These advanced drug delivery systems are designed to enhance the stability, penetration, and targeted delivery of therapeutic agents. By targeting the sebaceous glands and hair follicles, the main sites involved in acne development, nanocarriers enhance treatment efficacy while minimizing systemic side effects.

Lipid-based nanovesicles, a class of nanocarriers, have gained attention for their ability to enhance the efficacy of topical treatment (45). These carriers, such as liposomes, niosomes, proniosomes, glycerosomes, and ethosomes, consist of lipid bilayers that closely resemble the natural lipids of the skin(46). This structural similarity allows them to encapsulate both hydrophilic and hydrophobic drugs, improving their stability and enhancing skin penetration (47). By interacting with the lipid matrix of the stratum corneum (SC), nanovesicles facilitate the therapeutic agents into deeper skin layers, including sebaceous glands and hair follicles (48).

Moreover, the flexibility of liposomes, niosomes, and other elastic and deformable vesicles is evidenced by their stability when incorporated into conventional formulations. The preparation of liposomal or transfersomal gels or creams for acne treatment combines the drug delivery capabilities of nanosystems with the technological attributes of traditional formulations, including spreadability, viscosity, and simplicity of application, thereby enhancing patient compliance (49).

Table I

Treatment options for acne management

Treatment category	Drugs/Approach	Mechanism of action	Indication	Considerations	References
Topical retinoids	Tretinoin, adapalene, tazarotene, trifarotene	Normalize keratinization, reduce inflammation, and prevent comedone formation	Mild to moderate acne	Initial irritation, erythema, exfoliation, peeling, pain, and sun sensitivity	(31, 33)
Topical antibiotics	Clindamycin, erythromycin, minocycline, dapsone	Reduce *C. acnes* colonization and reduce lesion inflammation	Mild to moderate acne	Risk of antibiotic resistance, which may be prevented by combination with benzoyl peroxide	(34, 35)
Topical benzoyl peroxide	2.5-10% formulations	Antimicrobial agent that releases free oxygen radicals and is mildly comedolytic, and prevents resistance	Mild to moderate acne	Dryness, irritation, pain, peeling, and burning sensation	(36, 37)
Topical azelaic acid	10-20% formulations	Comedolytic, antibacterial, and anti-inflammatory agent	Mild to moderate acne	Helpful for patients with sensitive skin or darker skin types due to its lightening effect on dyspigmentation	(38)
Topical salicylic acid	0.5-2% formulations	Reduce inflammatory lesions, reduce open comedones, showing no difference in closed comedones	Mild to moderate acne	Observed dryness with excessive use	(31)
Oral antibiotics	Doxycycline, minocycline, sarecycline	Anti-inflammatory and reduces *C. acnes*	Moderate to severe acne	Hyperpigmentation, lupus-like drug eruption, and hypersensitivity syndromes	(39)
Oral hormonal Therapy	Combined oral contraceptives (estrogen + progestin)	Reduce 5α-reductase activity and block the androgen receptor	Hormonal acne, moderate to severe acne	Not suitable for smokers or those at risk of thromboembolism	(40)
Oral antiandrogen	Spironolactone	Has antiandrogenic properties, reduces sebum production, and hyperkeratinization in acne-prone follicles	Hormonal and resistant acne	It is mainly prescribed for women because of its feminizing side effects if used by men	(32)
Oral isotretinoin	Isotretinoin	Reduces secretion of sebaceous glands, inhibits comedogenesis by normalizing keratinocyte keratinization	Severe nodular acne	Require strict monitoring, teratogenic	(41)
Physical treatments	Laser & light therapy	Target *C. acnes*	Moderate to severe acne	Expensive, no side effects recorded	(42)
Emerging therapies	Probiotics, microbiome modulation	Restore the imbalance of skin microbiota caused by *C. acnes*	Antibiotic-resistant and recurrent acne	Needs further research	(43)
	Topical clascoterone	Compete with dihydrotestosterone for androgen receptors	Hormonal acne	Promising alternative	(44)

However, we can say that there are few studies specifically focusing on nanovesicles loaded with anti-acne drugs for the treatment of acne vulgaris. While research on nanovesicles, such as liposomes, ethosomes, glycerosomes, and niosomes, is growing, their application in acne therapy remains relatively underexplored compared to other drug delivery systems.

This section will explore various studies that demonstrate the potential of lipid-based nanovesicles in the management of acne.

Liposomes

Liposomes are spherical vesicles distinguished by the amphiphilic lipid molecules that form their bilayer structure. The structure of the amphiphilic lipid consists of a hydrophilic head and a hydrophobic tail. This enables liposomes to self-assemble in water, exposing their hydrophilic head groups while shielding the hydrophobic tails within the bilayer. Drugs with varying degrees of hydrophobicity can be loaded into liposomes due to the formation of this bilayer structure (50). Some research has examined the use of lipo-somes as carriers for anti-acne drugs.

Eroglu et al. developed a topical carbopol-based gel incorporating liposomes loaded with tetracycline HCl and tretinoin to target acne vulgaris (51). The liposomes prepared using the thin film hydration method showed high encapsulation efficiencies exceeding 80% for both active ingredients. The study primarily evaluated the effects of this combination therapy using *in vitro* studies. Cytotoxicity tests were conducted on the L929 mouse fibroblast cell line to ensure the safety of the formulation. Additionally, the antibacterial activity of the tested liposomal formulation was assessed against *Staphylococcus epidermidis* and *Staphylococcus aureus*, two bacteria commonly associated with acne-related infections. The authors succeeded in introducing a novel product that combines two active components with bacteriostatic and comedolytic properties into a single, stable, and safe liposome formulation.

Another study focused on improving acne treatment was conducted by Asma *et al*. Authors developed a liposome-based gel containing adapalene, a third-generation retinoid with proven effectiveness against acne vulgaris (52). Liposomes were created using a spontaneous phase transition method, exhibiting adapalene encapsulation efficiency of 89.69%. *In vitro* release studies showed sustained drug release of 79% over 24 hours, while *ex vivo* permeation tests indicated effective skin retention, with 28.27% adapalene remaining in the epidermis. The *in vivo* study conducted on a testosterone-induced acne model in mice revealed a significant reduction in acne lesions. Although the testosterone-induced mouse model provides valuable preclinical insights, its translational relevance to human acne is limited because rodents do not fully recapitulate the pilosebaceous biology and pathophysiology of human acne.

Niosomes

The success of liposomes as nanocarriers is largely attributed to phospholipids, which are constituents of cell membranes, thereby forming a biocompatible system. On the other hand, disadvantages related to their production cost and stability under certain conditions led to the development of niosomes by replacing phospholipids with non-ionic surfactants (53). Because of their greater chemical stability, simplicity of manufacture, lower cost, and wide range of surfactant options, they are favored over conventional lipo-somes. Lipophilic moieties are captured by partitioning into the lipophilic part of the bilayers, while hy-drophilic drugs can be encapsulated in the aqueous core (54).

A study by Ghasemiyeh *et al*. emphasized the combined effect of tretinoin and bicalutamide in treating acne vulgaris due to their complementary actions (55). The authors developed niosomes co-loaded with these drugs to enhance follicular targeting. The niosomal encapsulation efficiencies for tretinoin and bicalutamide, measured indirectly by the centrifugation ultrafiltration technique, were 99% and 94.63%, respectively. The *in vivo* assessments using rhodamine B-loaded niosomes demonstrated significant accumulation within hair follicles, suggesting effective targeting. Authors explained the rationale for using this combined treatment, which returned to the enhancement of tretinoin-mediated skin turnover, preventing the formation of comedones and improving skin texture. Bicalutamide, as an antiandrogen, reduces sebum production by blocking androgen activity.

Photodynamic therapy (PDT), a relatively modern method for treating acne, gained attention in the late 20th century (56). It is a newly developed treatment approach for acne that uses a photosensitizing agent activated by a specific light source to generate reactive oxygen species (ROS). These ROS target and de-stroy C. acnes, reduce inflammation, and may reduce sebaceous gland activity (57). El-Mahdy *et al*. developed a niosomal hydrogel formulation of methylene blue specifically designed for photodynamic therapy using the reversed-phase evaporation method (58). The clinical evaluation conducted by the authors demonstrated that the niosomal formulation significantly reduced inflammation in acne patients compared to intense pulsed light treatment, highlighting its potential as an effective PDT approach for acne management.

Proniosomes

Proniosomes are vesicular particle drug delivery vehicles that readily transform into niosomes upon hydration (59). Proniosomes are superior to niosomes in a number of ways, including reducing physical sta-bility issues (aggregation, fusion, and leakage) and offering greater convenience in dosage, storage, and transportation (60). Due to their superior percutaneous absorption and simplicity of application, pronio-somal gels are gaining popularity in the field of semisolid dosage forms. They are regarded as gel prepara-tions because they can regulate drug release, conform to the shape of the treated area, and withstand the physiological stress caused by skin flexion and mucociliary movement (61). Vesicle systems were able to promote skin penetration of drug through several mechanisms, including (a) the free drug mechanism, (b) the penetration-enhancing process of the vesicle components, (c) vesicle adsorption to and/or fusion with the SC, and (d) the proposed penetration of intact vesicle into and through the intact skin, although this mechanism remains controversial (62).

Rahman *et al*. developed a proniosomal formulation loaded with tretinoin as a useful approach to address drawbacks such as redness, peeling, swelling, and blistering associated with the use of tretinoin for the treatment of acne (62). The developed formulation exhibited high entrapment efficiency and a high percentage of medication released after five hours. The

clinical research conducted on 12 human volunteers with acne vulgaris lesions on the face showed superiority of the tested proniosomal formulation over the market product during the study period with respect to improvement of individual lesions. An improvement in the patients' lesions was reported when treated with a tretinoin-loaded proniosomes formula. Authors explain that these findings could be attributed to the small vesicle size and enhanced penetration of the tretinoin across the SC and targeting the dermis as well as the epidermis and deep dermis, thereby enhancing trans-follicular drug absorption.

Ethosomes

Ethosomes are soft phospholipid nanovesicles used for dermal and transdermal drug delivery. They contain a high ethanol concentration, which increases skin permeation by acting as a penetration enhancer. It penetrates intercellular lipids, increases lipid fluidity, and decreases the density of the lipid multilayer of the cell membrane, thereby increasing skin permeability. For this reason, they readily permeate the deep skin layers and combine with skin lipids, resulting in drug release within them (63). These properties char-acterizing ethosomes make them a good candidate and a promising alternative to conventional acne treatment.

To avoid the negative effects of traditional retinoids and enhance drug penetration and localization in deep skin layers, Salem *et al*. conducted a study to develop an ethosomal gel of retinyl palmitate (RP) (64). In comparison with tretinoin cream, a clinical assessment of the effectiveness and tolerance of treatment in volunteers with mild to moderate facial acne vulgaris was conducted over 6 weeks. Results demonstrated that the RP ethosomal hydrogel had equivalent efficacy to conventional tretinoin formulations, with a significant improvement over the commercial tretinoin formulation in reducing non-inflammatory acne lesions. Furthermore, it was found to have superior tolerability, with few or no local treatment-related skin responses, such as erythema, peeling, burning, and itching, in treated volunteers compared with the traditional cream.

A study on spironolactone-loaded ethosomes explored their potential for topical acne treatment by enhancing drug penetration and retention in the skin, conducted by Verma *et al*. (65). The formulated ethosomes exhibited a small vesicle size, ensuring better permeability, with a high drug encapsulation efficiency. When incorporated into carbomer 974 gel, it demonstrated a 2.5-fold increase in transdermal flux and a 2.1-fold enhancement in skin deposition compared to conventional hydroethanolic gels. Although an increase in transdermal flux was observed, the enhanced skin deposition is more relevant to topical acne treatment, where localized drug delivery, rather than systemic permeation, is the primary therapeutic objective. Additionally, the ethosomal formulation showed superior anti-acne effects with minimal skin irritation, suggesting its potential as an effective alternative for localized spironolactone delivery in acne management.

Glycerosomes

Glycerosomes are a newer generation of vesicular structures. They contain significant quantities of glyc-erol, phospholipids, and cholesterol. Glycerol is a rapidly absorbed, safe excipient used in pharmaceutical technology (66). Furthermore, glycerol has anti-inflammatory and anti-irritant properties in a dose-dependent manner (67). In cutaneous medication administration, using glycerol can increase drug penetra-tion by hydrating biological membranes (68, 69). Together, these three components form a lipid bilayer structure similar to that of biomembranes. Such similarities are used to ensure safe topical and transdermal administration of natural and synthetic compounds (70-74). Glycerosomes have well-documented deform-ability and flexibility, which are mostly due to the high concentration of glycerol. Glycerol significantly influences the fluidity of their bilayers, resulting in improved vesicular characteristics and enhanced lo-calized drug absorption by squeezing into skin layers (70). All these properties make glycerosomes highly effective for delivering anti-acne agents. Compared to conventional therapies, glycerosomes offer en-hanced drug retention and controlled release, making them a promising approach for improving the thera-peutic efficacy of topical acne treatments (48). Few studies have explored the potential of glycerosomes in acne treatment, evaluating their ability to en-hance drug delivery, improve skin penetration, and yield better therapeutic outcomes than traditional for-mulations.

AbouSamra *et al*. introduced an innovative approach to acne treatment by developing glycerosomes co-loaded with lincomycin and lauric acid, thereby enhancing both antibacterial efficacy and skin penetration (47). The optimized vesicular system showed remarkable encapsulation efficiencies of 90% and 97% for lincomycin and lauric acid, respectively. Notably, the skin deposition study confirmed a two-fold increase in lincomycin delivery compared to lincomycin gel, indicating superior drug retention and penetration. The results for the *in vivo*-performed experiment on the acne mouse model demonstrated significant reductions in inflammation and bacterial load, underscoring the formulation's potential as an effective topical therapy for acne vulagaris. In addition to the previously discussed lipid nanovesicles, other formulations used for acne treatment are listed in Table II.

Table II

Other loaded nanovesicles for acne management

Nanoformulations	Loaded drugs	Advantages	Limitations	References
Transferosomes	Clindamycin & benzoyl peroxide	Superior skin permeation compared with the marketed formulation and no skin irritation in mice, indicating its efficacy and safety.	Chemically unstable due to their tendency to undergo oxidative degradation, they require special storage conditions.	(75)
Cubosomes	Azelaic acid	Enhancement of skin penetration, retention, sustained release, and bioadhesiveness	Complex preparation, stability issues, and higher production costs.	(76)
Phytosomes	Bergamot Essential Oil & Spironolactone	Increase skin absorption and bioavailability, have remarkably high drug encapsulation, and reveal a better stability profile	Quick removal of phytoconstituents from the Phytosome, and pH-sensitivity	(77)
Bilosomes	Dapsone	More flexibility, absorption, and permeation due to the presence of bile salts.	They can be sensitive to preparation conditions and difficult to scale up. Additionally, the choice of phospholipids and bile salts can affect bilosome properties, such as size and stability.	(78)
Aquasomes	Cephalothin	The crystal core increases particle stability, and the carbohydrate layer provides an appropriate surface for the active substance to be adsorbed.	A potential challenge of aquasome-based drug delivery could be toxicity due to burst release of drugs if poorly absorbed on the carbohydrate coat, and they could be expensive to formulate.	(79)

Mechanism of action of lipid-based nanovesicles in acne management

Antibacterial and anti-inflammatory medications are used in conventional acne treatment. As recorded, unwanted toxicities are linked to the systemic usage of these medications. Therefore, topical use of anti-acne medications is preferred. However, the drug's limited water solubility and limited penetration across the skin make topical distribution difficult. Lipid-based nanovesicles emerged as promising delivery systems for acne treatment. Their small particle size, high surface area, and unique physicochemical properties improve drug solubility, stability, and therapeutic efficacy.

Along with liposomes' special benefits, there are drawbacks to employing them to transport medications to the skin. These primarily relate to issues with fluidity, stability, penetration, and entrapment efficacy. Liposomes accumulate on the outermost layer of skin because they cannot pass through the SC. Rigid conventional liposomes function as a depot formulation on the skin's surface because they cannot pass through the layers of the skin (80). The liposomes may directly interact with the skin and exchange the drug, or they may release the free drug, which can penetrate through the skin. As a result, modifications were made to their structure and composition to enhance their skin penetration, resulting in the creation of elastic novel lipid-based nanovesicles that are now often employed in drug delivery (46).

Advanced liposomes such as transferosomes, proniosomes, cubosomes, glycerosomes, and other flexible nanovesicles can induce structural changes in the SC, thereby facilitating drug absorption (81). They are extremely malleable, biocompatible, and biodegradable nanovesicles that can readily penetrate subcuta-neous tissue. When applied to intact skin, they can penetrate deeply and cross the intercellular spaces between epidermal cells. They move through the intercellular gap of the SC by undergoing self-deformation.

Regarding the other types of nanovesicles that contain a high percentage of ethanol, such as ethosomes and transethosomes, they easily navigate through small intercellular channels (82). Because of their elastic nature and the presence of ethanol and edge activators, these vesicles are characterized by high penetra-tion efficacy and flexibility, allowing them to squeeze through narrow intercellular spaces (83). Ethanol makes the SC intercellular lipids more fluid, reducing lipid layer thickness and increasing the flexibility of the vesicular structure. Ethanol thereby facilitates the drug's deeper penetration of the epidermis (84). They can also shield the drug from rapid clearance, thereby increasing circulation and bioavailability (85).

Challenges and unmet needs in using lipid-based nanovesicles for acne treatment

The use of nanocarriers in acne treatment presents several challenges and unmet needs that must be addressed to enhance their clinical applicability. One of the primary concerns is the stability of lipid-based formulations, as issues such as aggregation, drug leakage, and degradation can compromise their effective-ness. The stability of nanocarriers varies depending on their type and composition. Lipid-based systems, such as liposomes, often face stability challenges due to aggregation, fusion, or drug leakage (86). Fur-thermore, the high cost of production and stringent regulatory requirements make commercialization diffi-cult, necessitating extensive safety and efficacy evaluations (50). Variability in skin physiology among individuals can also influence the effectiveness of nanocarrier penetration and drug release, leading to inconsistent therapeutic outcomes. Moreover, while many lipid components are biocompatible, their inter-action with inflamed or sensitive acne-prone skin requires careful evaluation to prevent irritation or aller-gic reactions. Regulatory uncertainties surrounding nanomedicine further complicate the pathway to clini-cal translation. These challenges underscore the need for continued research to optimize formulation sta-bility, enhance scalability, and ensure safety, particularly when integrating environmentally sustainable practices into nanocarrier design.

Eco-friendly aspects of lipid-based nanocarriers

In recent years, the development of advanced drug delivery systems has increasingly prioritized not only therapeutic performance but also environmental responsibility. Among these systems, lipid-based nanocarriers have gained attention for their ability to enhance drug solubility, stability, and targeted delivery, particularly in dermatological applications such as acne treatment. As research expands in this area, there is growing interest in aligning nanocarrier formulation practices with sustainable, eco-conscious principles. Traditional preparation methods often involve hazardous solvents, synthetic excipients, and energy-intensive processes, which may contribute to environmental burdens. Consequently, incorporating eco-friendly strategies, such as using biodegradable lipids, renewable resources, and green synthesis techniques, has become a crucial focus (87). This section explores how lipid-based nanovesicles can be developed and optimized through sustainable approaches, highlighting their potential to provide effective acne treatment while reducing ecological impact.

Use of biodegradable and renewable lipid sources

The choice of lipid type plays a crucial role in determining the biocompatibility and environmental footprint of lipid-based nanocarriers. For acne treatment, biodegradable and renewable lipid sources, such as natural phospholipids, are widely favored for their natural origin and minimal toxicity. These lipids not only enhance the safety profile of nanovesicles but also ensure their biodegradability (11), thereby reducing the risk of skin irritation and environmental accumulation. Additionally, naturally sourced cholesterol or plant sterols are often used to stabilize vesicle membranes, replacing synthetic or petroleum-derived alternatives. Recent advances in nanovesicle design have explored incorporating plant-derived lipids and sterols to enhance the biocompatibility and sustainability of formulations for acne management. Studies have shown that liposomes prepared using soybean-derived phosphatidylcholine and lanolin-derived cholesterol can effectively encapsulate antibacterial agents such as rhodomyrtone, demonstrating significant activity against acne-causing bacteria such as *Cutibacterium acnes* while maintaining structural stability and skin compatibility (88). Similarly, lauric acid, a naturally occurring fatty acid in coconut oil, has been incorporated into lipid-based vesicles for its potent antimicrobial properties and ability to disrupt bacterial membranes, offering a promising approach to the treatment of acne vulgaris (89). These studies highlight the potential of biodegradable, renewable lipid sources to develop eco-friendly, effective, and skin-safe nanocarriers tailored for acne therapy, aligning with the principles of green nanomedicine.

Green solvents and sustainable preparation techniques

The growing importance of environmental sustainability has prompted a shift toward greener methodologies in the development of lipid-based nanocarriers. Traditional preparation techniques often involve organic solvents such as chloroform or methanol, which pose environmental and health hazards. In contrast, green solvents such as ethanol, supercritical fluids (*e.g.*, supercritical CO_2), and natural deep eutectic solvents (NADES) offer eco-friendly alternatives that reduce toxicity and environmental burden. NADES, a third category of natural liquids, because of their solubilizing and stabilizing qualities, as well as their low toxicity and biodegradability, NADES exhibit potential as drug carriers in dermal formulations (90). Compared to traditional solvents such as ionic liquids (ILs) and organic solvents, eutec-tic solvents are considered less hazardous, less expensive, more environmentally safe, more biodegradable, and less volatile (91). A study conducted by Wu *et al*. successfully utilized deep eutectic solvents combined with paeonol and lauric acid as active pharmaceutical ingredients, creating a therapeutic deep eutectic solvent (THEDES) (92). The resulting liposomes demonstrated enhanced solubility and stability of paeonol, along with improved bioavailability

and reduced cytotoxicity. This approach highlights the potential of eutectic solvents as green, sustainable alternatives for liposome preparation, offering benefits for drug delivery applications. Another recent study explored the incorporation of African essential oils (*Argania spinosa*, *Passiflora edulis*) encapsulated within nanoliposomes, which were then incorporated into hydrogels to enhance transdermal drug delivery (93). The inclusion of eutectic solvents, composed of betaine and phytic acid, in the formulation aimed to stabilize the essential oils and improve their permeation through the skin. This innovative approach combines the therapeutic properties of African essential oils with the advantage of eutectic solvents and liposomal delivery systems to create effective transdermal patches. These patches offer a natural, well-tolerated approach to acne management by reducing sebum and promoting healing, making them ideal candidates for inclusion in sustainable and skin-friendly anti-acne formulations.

Another eutectic system composed of choline chloride, malonic acid, and PEG 400 was developed for topical delivery of azelaic acid (AzA) in acne treatment (94). This eutectic solvent-based formulation exhibited enhanced solubility and increased skin penetration of AzA, along with synergistic antibacterial activity against acne-causing bacteria. The optimized formulation showed favorable rheological properties and stability, indicating its potential as an effective topical treatment for acne vulgaris.

Additionally, sustainable techniques such as supercritical fluid (SCF) methods are being developed as effective alternatives to conventional liposome production methods (95, 96). Using SCFs in liposome for-mulation eliminates the need for water, high operating temperatures, and mechanical stresses that can de-grade labile substances such as vitamins, enzymes, essential oils, and flavors. It also enables the formula-tion of liposomes as dry powders without extensive use of organic solvents, which pose health risks due to their toxicity. By adjusting crucial parameters (such as temperature and pressure), this green technology may create micro- and nanosized liposomes with a restricted size distribution (96). SCF liposome formula-tion techniques enable high drug entrapment efficiency by producing uniform vesicles with controlled size and reduced solvent residues (97).

Use of natural excipients and stabilizers

The incorporation of natural excipients and stabilizers into lipid-based nanocarriers has garnered increas-ing attention for their biocompatibility, biodegradability, and reduced toxicity risk. In the context of acne treatment, these naturally derived components not only enhance the structural stability of nanocarriers but also confer therapeutic benefits, including anti-inflammatory and antimicrobial activity. Commonly used natural excipients include phospholipids from soy or egg lecithin, which form the backbone of vesicular systems (11). Natural polymers such as chitosan, alginate, and pectin are frequently employed as coating agents or stabilizers to improve colloidal stability, prolong shelf life, and modulate drug release (98). Ad-ditionally, plant-derived antioxidants such as tocopherols and polyphenols can be incorporated to prevent lipid oxidation and enhance skin compatibility (99). The use of these eco-friendly and skin-compatible materials supports the development of sustainable, effective, and patient-friendly nanocarrier systems for the targeted treatment of acne vulgaris.

To increase stability and skin permeability, a study developed a novel delivery strategy for retinal (RAL) using flexible liposomes (FLPs) loaded with α-tocopherol succinate (α-TS). Pressure-sensitive adhesive (PSA) hydrogels were used to embed the RAL-FLPs, resulting in a delivery platform that facilitates effec-tive RAL penetration and extended skin residency. According to the authors' results, adding α-TS en-hanced RAL chemical and liposomal stability. Furthermore, research using skin permeation and fluores-cence microscopy revealed that adding α-TS increased RAL's skin permeability through hair follicles (100).

Another study sought to explore the use of both the liposomal system and a coating approach involving chitosan and alginate polysaccharides applied to nanoliposomes after encapsulating the phenolic extract of S. tenerrimum algae. The extracts from nanoliposomes were tested for minimum bactericidal concentrations (MBCs) and minimum inhibitory concentrations (MICs) against acne-causing microorganisms. The findings showed that the nanoliposomes' and coated nanoliposomes' MIC and MBC activity declined with time. According to the findings, nanoliposomes are a viable strategy for enhanced antibacterial activity against *Cutibacterium acnes* and an efficient carrier system for phenolic compounds (101).

Packaging and environmental footprint of final products

In developing eco-friendly liposomal formulations for acne treatment, the packaging and the final product's environmental footprint play a crucial role in ensuring overall sustainability. Eco-conscious formulations must be complemented by biodegradable, recyclable, or reusable packaging materials, such as glass containers, bioplastics, or post-consumer recycled (PCR) plastics, to reduce the product's ecological impact. Traditional plastic packaging, commonly used in pharmaceuticals and cosmetics, contributes significantly to microplastic pollution and landfill waste (102). Recently, the cosmetics sector has placed greater focus on sustainable packaging, with many busi-nesses opting for eco-friendly materials and processes (103). Additionally, the production

process for liposomes can be optimized to lower environmental burden by using solvent-free or low-energy methods, thus minimizing emissions and chemical waste. Several commercial anti-acne products have emerged that incorporate liposomal technology with an emphasis on natural ingredients and sustainable practices, as shown in Table III. When both formulation and packaging adhere to eco-friendly standards, the final product may potentially contribute to a reduced environmental impact. However, these benefits are rela-tive and depend on the manufacturing process, packaging, and distribution. As no quantitative life cycle assessment (LCA) data are available, these products should be considered potentially greener alternatives rather than definitively environmentally friendly.

Table III

Some Marketed eco-friendly liposomal products for acne

Brand/Product name	Eco-friendly features	Target function	References
Sesderma Azelac RU Liposomal Serum	Paraben-free, biodegradable components such as soy lecithin and xanthan gum	Anti-acne and used for hyperpigmentation	(104)
Herbivore Lapis Facial Oil	Free from synthetic additives, packaged in recyclable glass	Used for acne-prone skin as an anti-inflammatory	(105)
SkinCeuticals Phyto Corrective Gel	Free from synthetic dyes and formulated with botanical extracts	Anti-inflammatory and antiseptic effects used for acne-prone skin	(106)

Future perspectives in sustainable liposomal therapies for acne

The future of eco-friendly liposomal formulations for acne treatment lies in the convergence of sustainable materials science and advanced drug delivery technologies. Ongoing research is expected to emphasize the use of naturally derived, biodegradable lipids that not only support skin compatibility but also reduce environmental impact. Innovations in green manufacturing, such as solvent-free techniques and energy-efficient processes, are anticipated to become standard in liposome formulation. Furthermore, the incorporation of plant-based ingredients with anti-acne properties, including essential oils, flavonoids, and herbal extracts, offers a promising alternative to conventional synthetic agents. These developments are likely to be complemented by a shift toward environmentally responsible packaging solutions, including recyclable glass, bioplastics, and refill systems. As consumer demand for sustainable skincare grows, future products will need to meet not only therapeutic efficacy standards but also align with broader ecological values, potentially guided by emerging regulatory frameworks and eco-certifications.

Conclusions

Eco-friendly liposomal formulations offer a compelling alternative to conventional acne therapies by addressing both therapeutic and environmental concerns. Throughout this review, we highlighted how liposomes enhance drug stability, skin penetration, and targeted delivery while also offering opportunities for cleaner, greener formulation strategies. The integration of biodegradable lipids and plant-derived actives into nanocarrier systems not only improves treatment outcomes but also supports the growing demand for sustainable skincare solutions. However, despite promising advances in research and some movement in the commercial space, fully eco-conscious liposomal products for acne remain limited. A deeper understanding of formulation challenges, regulatory frameworks, and lifecycle impacts is essential for translating laboratory innovations into truly sustainable clinical and cosmetic applications.

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The authors declare no conflict of interest

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