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Review Article

Recent Advances in Bilosomes for the Treatment of Skin Diseases: A Review

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Skin diseases such as psoriasis, acne vulgaris, atopic dermatitis, fungal infections, and bacterial infections remain a major global health concern due to their chronic nature and the limitations of conventional topical therapies. The stratum corneum acts as a formidable barrier, restricting drug penetration and reducing therapeutic efficacy. Bilosomes, a novel class of bile salt stabilized lipid vesicles, have emerged as promising nanocarriers for topical and transdermal drug delivery. Incorporation of bile salts into lipid vesicles enhances membrane flexibility, improves drug encapsulation, increases skin permeation, and provides greater vesicular stability compared with conventional liposomes. Recent studies have demonstrated the successful application of bilosomes for delivering antifungal, antibacterial, anti-inflammatory, and anticancer agents to the skin. This review summarizes the composition, preparation methods, mechanisms of skin permeation, recent applications in skin diseases, advantages, limitations, and future perspectives of bilosomal drug delivery systems.

Keywords: Bilosomes, Skin diseases, Topical drug delivery, Nanovesicles, Bile salts, Transdermal delivery.

INTRODUCTION

Skin diseases affect approximately one third of the world's population and significantly impair quality of life. Common disorders including psoriasis, eczema, acne vulgaris, fungal infections, and skin cancer require prolonged treatment with topical formulations. However, conventional creams, gels, and ointments often exhibit poor skin penetration, limited drug retention, and frequent dosing requirements due to the barrier function of the stratum corneum [1, 2]. Nanotechnology based drug delivery systems have attracted considerable attention for improving topical therapy. Among these, bilosomes are flexible lipid vesicles composed of phospholipids, cholesterol, and bile salts that enhance drug penetration through the skin while protecting encapsulated drugs from degradation [3-4].

Bilosomes

Bilosomes are nanosized lipid vesicles containing phospholipids stabilized with bile salts such as sodium deoxycholate, sodium cholate, or sodium taurocholate. Originally developed for oral vaccine delivery, bilosomes have recently gained importance in topical and transdermal drug delivery because of their enhanced deformability and stability [5].

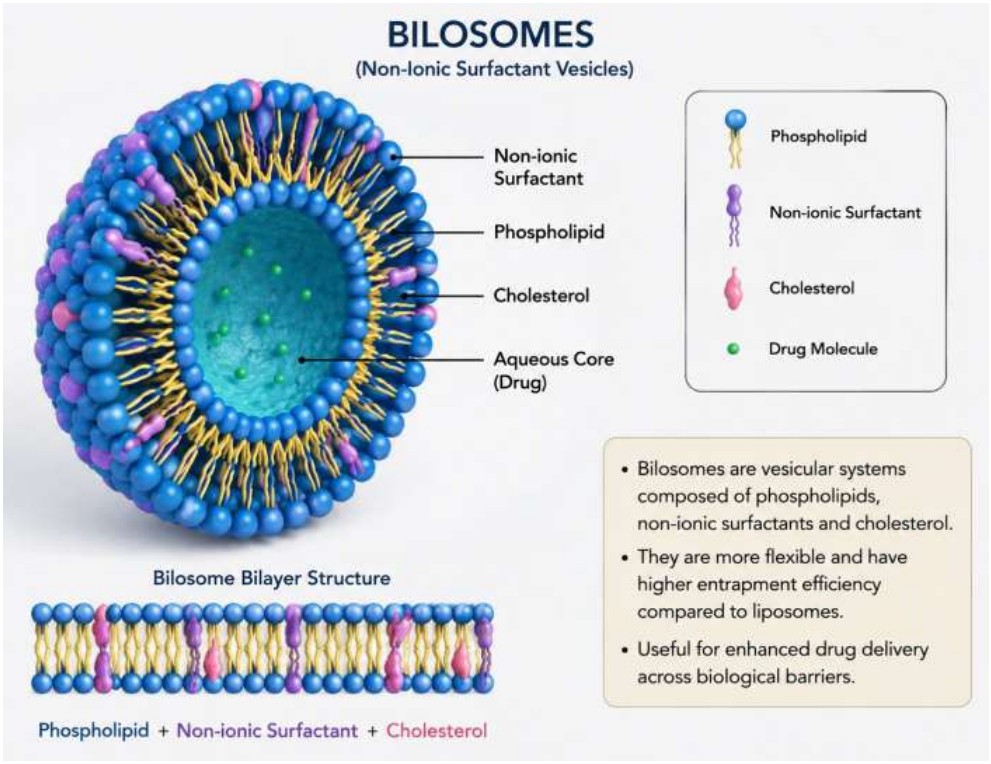

Figure 1 Structure of Bilosomes

The presence of bile salts increases membrane fluidity, enabling bilosomes to penetrate narrow intercellular spaces within the stratum corneum and deliver drugs into deeper skin layers.

Composition of Bilosomes

Table 1 Components of Bilosomes And Their Functions

Component	Examples	Function
Phospholipids	Soy lecithin, Phosphatidylcholine	Vesicle formation
Cholesterol	Cholesterol	Membrane stabilization
Bile salts	Sodium deoxycholate, Sodium cholate, Sodium taurocholate	Improve flexibility and penetration
Surfactants (optional)	Span 60, Tween 80	Improve stability
Hydration medium	PBS, distilled water	Vesicle hydration

Preparation Methods

The commonly employed techniques include:

- Thin-film hydration
- Ethanol injection
- Reverse-phase evaporation
- Solvent evaporation
- Micro fluidization
- High-pressure homogenization

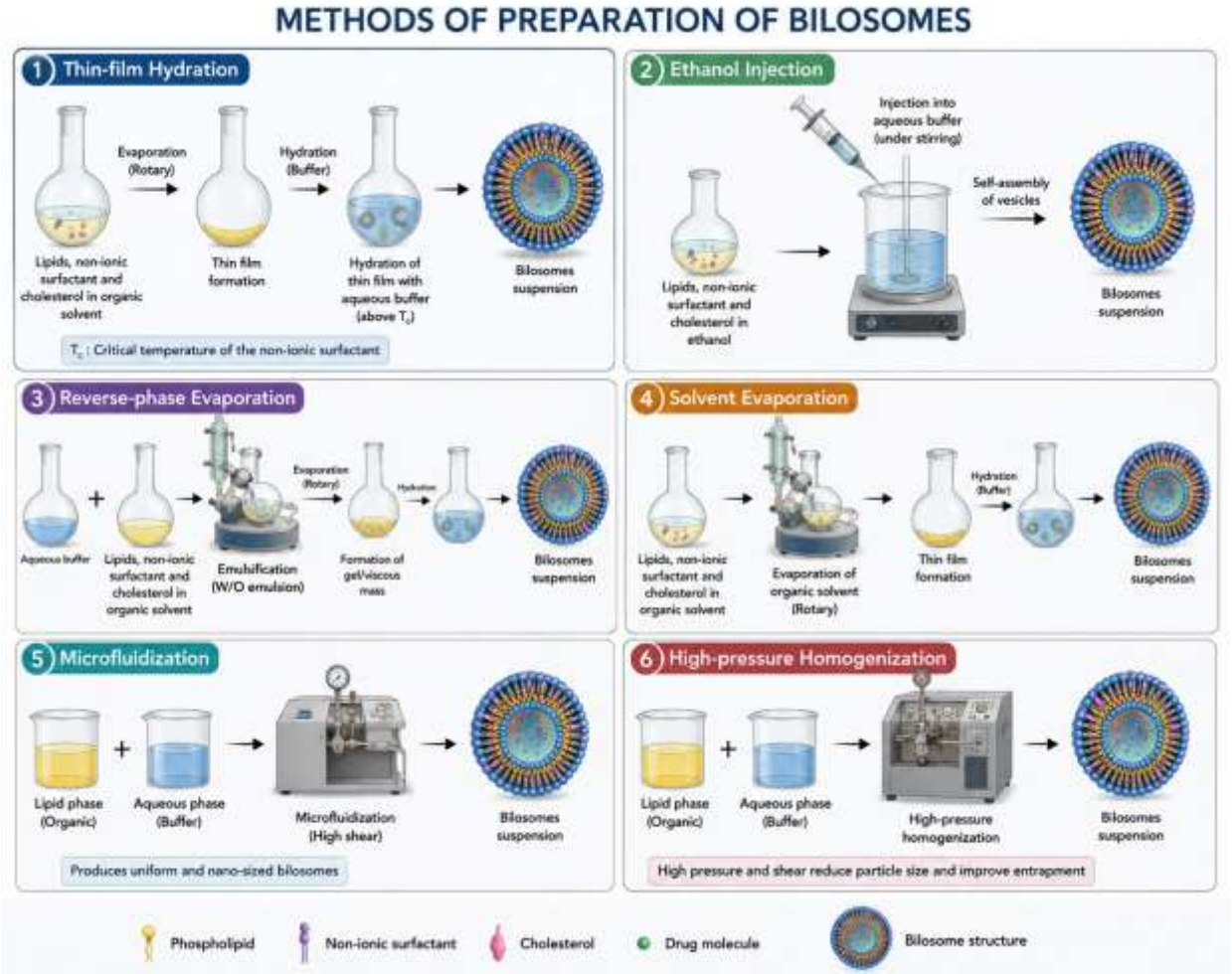

Figure 2 Methods of Preparation of Bilosomes

Thin-film hydration remains the most widely used laboratory method because of its simplicity and reproducibility [6].

Mechanism of Skin Penetration

Bilosomes improve topical drug delivery through several mechanisms:

- Increased membrane flexibility
- Disruption of stratum corneum lipids
- Enhanced drug partitioning into skin
- Improved hydration of the epidermis
- Controlled and sustained drug release
- Increased residence time within skin layers

These mechanisms contribute to enhanced drug deposition while minimizing systemic absorption [7].

Applications in Skin Diseases

Acne vulgaris

Bilosomal formulations of adapalene, clindamycin, and doxycycline have demonstrated improved skin penetration and reduced irritation compared with conventional gels [8].

Psoriasis

Methotrexate and curcumin-loaded bilosomes have shown enhanced dermal deposition and significant reduction in inflammatory cytokines in experimental psoriasis models [9].

Atopic dermatitis

Tacrolimus and corticosteroid-loaded bilosomes improve skin retention, reduce transepidermal water loss, and decrease inflammation while minimizing systemic exposure [10].

Fungal skin infections

Itraconazole, terbinafine, fluconazole, and Luliconazole loaded bilosomes exhibit improved antifungal activity against *Candida albicans* and dermatophytes because of increased drug penetration into infected tissues [11].

Bacterial infections

Bilosomal delivery of mupirocin and fusidic acid enhances antibacterial activity against resistant *Staphylococcus aureus* strains and improves wound healing [12].

Skin cancer

Topical bilosomes loaded with 5-fluorouracil or natural compounds such as curcumin and resveratrol have demonstrated enhanced skin localization and antitumor activity in preclinical studies [13].

Recent Studies on Bilosomes for Skin Diseases

Table 2 Selected recent bilosomal formulations for topical treatment

Drug	Disease	Major findings	References
Curcumin	Psoriasis	Improved skin deposition and anti-inflammatory activity	[9]
Methotrexate	Psoriasis	Enhanced therapeutic efficacy with reduced toxicity	[9]
Itraconazole	Fungal infections	Higher antifungal activity and prolonged release	[11]
Terbinafine	Dermatophytosis	Increased skin permeation	[11]
Tacrolimus	Atopic dermatitis	Improved skin retention	[10]
Adapalene	Acne	Reduced irritation and enhanced penetration	[8]
Mupirocin	Bacterial infection	Better antibacterial efficacy	[12]

Advantages of Bilosomes

- High drug encapsulation efficiency
- Improved stability compared with liposomes
- Enhanced skin permeation
- Controlled drug release
- Reduced dosing frequency
- Better patient compliance
- Suitable for hydrophilic and lipophilic drugs
- Potential for targeted topical therapy

LIMITATIONS

Despite promising results, several limitations remain:

- Limited clinical studies
- Large-scale manufacturing challenges
- Long-term stability concerns
- High production cost
- Regulatory uncertainties for nanomedicines

Further clinical investigations are needed before widespread commercialization [14].

Recent Patents and Intellectual Property Trends in Bilosomal Drug Delivery

Although research on bilosomes has expanded rapidly during the last five years, the number of granted patents specifically claiming bilosomal formulations for skin diseases remains relatively limited. Most intellectual property (IP) protection has focused on bilosomal composition, manufacturing methods, topical gels, hydrogel systems, PEGylated bilosomes, and combination nanovesicular platforms rather than disease specific claims. Recent patent activity indicates growing industrial interest in bilosomal formulations for psoriasis, fungal infections, melanoma, wound healing, and transdermal drug delivery. Recent reviews also highlight increasing

patent filings as bilosomes transition from laboratory-scale research toward commercialization.

Table 3 Representative Recent Patents and Patent Applications Related to Bilosomal Drug Delivery

Year	Patent/Patent Application*	Innovation	Therapeutic Area	Significance	Ref.
2020	Lipid vesicular drug delivery systems containing bile salts	Stable bilosomal composition for enhanced topical drug delivery	Dermal delivery	Improved vesicle stability and skin permeation	[15, 16]
2021	Nano-vesicular topical formulations comprising bilosomes	Bilosomal gel technology for localized drug delivery	Skin diseases	Enhanced dermal deposition with sustained release	[17]
2022	PEGylated bilosomal nanocarriers	Surface-modified bilosomes with prolonged skin residence	Fungal infections	Improved stability and penetration	[16, 17]
2023	Bilosomal hydrogel compositions	Hydrogel-integrated bilosomes for controlled drug release	Psoriasis and wound healing	Better patient compliance and prolonged release	[15, 17]
2024	Bilosomal transdermal delivery platform	Flexible bile salt vesicles for enhanced transdermal permeation	Chronic inflammatory diseases	Improved drug bioavailability	[16]
2025–2026	Edge-activated bilosomes (Limobilosomes)	Combination of bile salts and terpene penetration enhancers	Melanoma	Increased intradermal drug deposition and anticancer efficacy	[18]

Patent Landscape

The intellectual property landscape of bilosomes has evolved from oral vaccine delivery toward topical and transdermal therapeutics. Early patents primarily protected bile salt-containing lipid vesicles designed to improve vesicle stability. More recent inventions focus on surface engineering (PEGylation), edge activation, hydrogel incorporation, and hybrid nanovesicular systems that enhance skin penetration and prolong drug retention. These technologies are particularly attractive for chronic dermatological disorders because they reduce dosing frequency while minimizing systemic drug exposure. Recent innovations have introduced PEGylated bilosomes, which exhibit prolonged residence time within the skin and improved physicochemical stability. Similarly, edge-activated bilosomes (limobilosomes) incorporating terpenes such as limonene have demonstrated markedly improved intradermal deposition and therapeutic efficacy against melanoma in preclinical investigations, representing a promising direction for future patent development. Commercial translation of bilosomes remains in its early stages. The relatively small number of granted patents suggests that substantial opportunities remain for protecting innovations involving drug combinations, stimuli-responsive bilosomes, targeted dermatological therapies, microneedle assisted bilosomal delivery, and hydrogel based sustained release systems.

FUTURE PERSPECTIVES

Future research on bilosomal drug delivery systems for skin diseases should prioritize well designed clinical trials to establish their long term safety, therapeutic efficacy, patient compliance, and superiority over conventional topical formulations in the management of chronic dermatological conditions such as psoriasis, eczema, acne vulgaris, fungal infections, and skin cancer. Although numerous preclinical studies have demonstrated promising outcomes, successful clinical translation requires robust evidence from multicenter human studies. Simultaneously, there is a pressing need to develop scalable, cost-effective, and reproducible

manufacturing processes that ensure batch to batch consistency, high encapsulation efficiency, and long term stability while meeting regulatory and industrial standards for commercialization. Future investigations should also explore combination therapies in which bilosomes co-deliver multiple therapeutic agents, including conventional drugs, phytochemicals, peptides, nucleic acids, or immunomodulators, to achieve synergistic therapeutic effects, minimize drug resistance, and reduce treatment related adverse effects. Another promising direction involves the development of surface functionalized bilosomes by incorporating ligands, antibodies, peptides, or polymers that enable targeted delivery to specific skin cells, hair follicles, inflamed tissues, or tumor microenvironments, thereby improving therapeutic precision and minimizing off target effects. Furthermore, the design of stimuli-responsive bilosomal systems capable of releasing their drug payload in response to physiological or external triggers such as pH, temperature, enzymes, reactive oxygen species, light, ultrasound, or magnetic fields represents an innovative strategy for achieving controlled and site specific drug delivery. Finally, integrating bilosomal formulations with advanced drug delivery platforms, including hydrogels, dissolving microneedles, nanofiber mats, wound dressings and three-dimensional (3D)-printed topical dosage forms, has the potential to enhance skin penetration, prolong drug residence time, improve patient adherence, and facilitate personalized treatment approaches. Collectively, these research directions are expected to accelerate the clinical translation of bilosomal technology and establish it as a versatile, effective, and commercially viable platform for the treatment of a wide range of skin diseases. These advances may facilitate the translation of bilosomal formulations into clinically approved therapies.

CONCLUSION

Bilosomes represent an advanced lipid based nanocarrier with significant potential for improving topical drug delivery in various skin diseases. Their enhanced flexibility, stability, and ability to penetrate the stratum corneum make them superior to conventional liposomes for dermal applications. Preclinical studies have demonstrated encouraging results in psoriasis, acne, fungal infections, bacterial skin diseases, atopic dermatitis, and skin cancer. Furthermore, the growing number of patents related to bilosomal formulations, novel lipid compositions, bile salt incorporation, targeted delivery approaches, and sustained release topical systems reflects increasing industrial interest and commercial potential. These patent developments provide valuable intellectual property protection and are expected to accelerate the translation of bilosomes based technologies into clinically viable dermatological products. However, additional clinical studies, standardized manufacturing methods, and clear regulatory guidance are essential to support their successful translation into routine dermatological practice.

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