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Beyond The Skin Barrier: How Transfersomes and Transethosomes are Revolutionizing Topical Therapies

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ABSTRACT

Introduction*: The fundamental challenge of effective skin permeation has long limited the therapeutic potential of topical drug delivery systems. Conventional formulations frequently fail to achieve adequate penetration through the skin barrier, necessitating innovative approaches to enhance drug bioavailability while maintaining targeted delivery to specific skin layers.* ***Aims****: This review evaluates the transformative impact of transfersomes and transethosomes as advanced nanovesicular systems designed to overcome traditional limitations in topical drug delivery.* ***Methods****: The review examines ultra-deformable nanovesicle technologies through comprehensive analysis of their operational mechanisms, including osmotic gradient exploitation in transfersomes and ethanol-facilitated lipid fluidization in transethosomes. Performance comparisons with conventional formulations across various therapeutic applications were conducted to assess clinical efficacy and delivery capabilities.* ***Result****: These nanovesicular systems demonstrate superior performance in delivering diverse therapeutic agents to targeted skin layers while effectively minimizing systemic absorption. The analysis reveals significant advantages over traditional formulations, with enhanced penetration capabilities that extend to macromolecular therapeutics and biologics when integrated with complementary technologies such as microneedle arrays and iontophoresis. Current research developments focus on addressing existing limitations through lyophilization techniques, hybrid polymer systems, and advanced manufacturing processes.* ***Conclusion****: Transfersomes and transethosomes represent a significant advancement in topical drug delivery technology, offering promising solutions to longstanding permeation challenges. The future trajectory toward personalized formulations and sustainable production methods using plant-derived components indicates their potential to fundamentally redefine treatment approaches in dermatology, oncology, and pain management, establishing minimally invasive yet highly effective therapeutic options as the standard in patient care.*

KEYWORDS*: Ultra-deformable nanovesicles, transfersomes, transethosomes, topical delivery, dermatology*

INTRODUCTION

The skin, the body's largest and most accessible organ, is a remarkably efficient barrier, protecting against pathogens, UV radiation, and dehydration. However, this same protective function complicates the delivery of therapeutic agents, rendering many conventional topical formulations, such as creams, gels, and ointments, ineffective for deep-tissue targeting (Bos & Meinardi, 2000). The stratum corneum, the outermost skin layer, acts as a selective gatekeeper, permitting only small, lipophilic molecules to passively diffuse through its tightly packed corneocytes and lipid matrix. This limitation has long plagued dermatological therapies, with studies showing that less than 5% of applied doses penetrate beyond this barrier, leading to suboptimal bioavailability and frequent treatment failures (Prausnitz & Langer, 2008).

The inefficacy of traditional systems is particularly evident in the delivery of macromolecules (e.g., peptides, siRNA) and hydrophobic drugs, which face additional hurdles due to their size and solubility. Patients with chronic conditions like psoriasis, eczema, or melanoma often endure repetitive dosing, systemic side effects, or invasive procedures, highlighting an unmet need for advanced delivery platforms (Sala et al., 2018). Advancements in nanotechnology have opened new frontiers in topical drug delivery, with transfersomes and transethosomes emerging as groundbreaking solutions. These ultra-deformable, lipid-based nanovesicles are engineered to navigate the skin's complex architecture, enabling precise delivery of therapeutics to deeper epidermal and dermal layers. By enhancing drug solubility, stability, and penetration, these systems hold transformative potential for treating chronic skin diseases (e.g., psoriasis, eczema), localized infections, and even skin cancer, while minimizing systemic toxicity. Their versatility extends beyond pharmaceuticals, with applications in cosmeceuticals for anti-aging and antioxidant delivery, further broadening their societal and commercial impact (Cevc & Blume, 1992; Touitou et al., 2000).

The urgency to adopt such innovations is underscored by the global rise in skin disorders. The World Health Organization estimates that 30% of people worldwide suffer from at least one dermatological condition, a burden exacerbated by aging populations and environmental factors (Michalek et al., 2016). Concurrently, patient preferences are shifting toward non-invasive, pain-free treatments, driving demand for transdermal systems that combine efficacy with convenience. Transfersomes and transethosomes answer this call, enabling the delivery of biologics,

antifungals, and chemotherapeutics across intact skin without needles or patches, a leap forward for precision medicine (Chowdary et al., 2023; Opatha et al., 2020; Vera Pérez et al., 2022). Recent advancements have further cemented their potential. Transfersomes, composed of phospholipids and edge activators like sodium cholate, deform in response to osmotic gradients to navigate the skin's tortuous pathways (Kadam et al., 2025; Majumdar et al., 2024). Transethosomes, enriched with ethanol, exhibit superior flexibility and lipid bilayer fluidity, achieving deeper penetration and higher drug-loading capacities (Marto et al., 2016). Cutting-edge research now explores hybrid systems integrating these vesicles with stimuli-responsive polymers or microneedle arrays, enabling on-demand drug release and real-time monitoring (AL-Japairai et al., 2024; Mukherjee et al., 2021; Negut & Bita, 2024; Yang et al., 2019). Pre-clinical studies for transethosome-based melanoma therapies and transfersomal anti-inflammatory agents highlight their transition from experimental tools to clinical mainstays, marking a new era in dermatological care (Abdellatif et al., 2023; Al-Ameri & Al-Gawhari, 2024; Khan et al., 2022; Motawea et al., 2024; Mwangi et al., 2021).

This review presents a comprehensive examination of the current research landscape surrounding transfersomes and transethosomes as transformative technologies in topical drug delivery systems. Our systematic analysis synthesizes the substantial body of evidence demonstrating their efficacy in both laboratory settings and biological models. We specifically evaluate their application as delivery platforms for conventional pharmaceutical compounds and complex biological therapeutics, providing an integrated perspective on their performance across diverse therapeutic contexts. The review deliberately identifies critical knowledge gaps that exist between the theoretical advantages of these ultra-deformable nanovesicular systems and their practical implementation in clinical settings. By highlighting these research deficiencies, we establish a clear roadmap for future investigations aimed at optimizing these promising technologies. Our work serves as both a definitive resource on the current state of transfersomal and transethosomal drug delivery and a strategic guide for advancing these systems toward clinical translation and commercialization.

TRANSFERSOME: A FLEXIBLE DELIVERY SYSTEMS

Transfersomes are elastic vesicles with a sophisticated molecular design, consisting of one or more phospholipid layers and a surfactant chain (edge activator), incorpo-

rating at least one aqueous compartment surrounded by phospholipid membranes (Bhasin & Londhe, 2018). These nanocarriers demonstrate remarkable size variability, ranging from 30 nm to several micrometers (Balata et al., 2020). Transfersomes represent a revolutionary drug delivery system that signifies a breakthrough in modern pharmacological science. This advanced technology is strategically designed to address systematic limitations of conventional treatment methods, particularly regarding drug penetration through biological barriers. The unique molecular construction of transfersomes consists of phospholipids and surfactants, enabling the formation of flexible vesicles with extraordinary mechanical and functional characteristics (Opatha et al., 2020).

The fundamental mechanism distinguishing transfersomes from traditional delivery systems lies in their remarkably high deformability. These vesicular structures can undergo significant shape transformations without compromising structural integrity, allowing them to traverse microscopic channels in the stratum corneum with unprecedented efficiency (Akombaetwa et al., 2023; Chaurasiya et al., 2019). Most notably, transfersomes possess two critical biomechanical properties. First, they can actively compress or "squeeze" themselves through narrow cellular pathways. Second, and perhaps more impressively, they can fully reshape and reconstruct their structural integrity after traversing extremely constricted skin channels or pores significantly smaller than their original vesicular dimensions (Onkar Nandraj et al., 2024). This process is guided by complex hydration gradients, where vesicles respond to moisture differences across various skin layers, facilitating spontaneous drug molecule transportation with minimal energy expenditure (Natsheh & Touitou, 2020). The technological advantages of transfersomes become evident in their extensive application spectrum. The system can transport drug molecules with both hydrophilic and lipophilic characteristics, providing flexibility previously unachievable in earlier delivery methods (R. S. Kumar & Pradhan, 2022). Developed clinical applications encompass diverse therapeutic categories, including dermatological treatments with corticosteroids, systemic antiviral therapies, and topical anti-inflammatory interventions (Matharoo et al., 2024). Each therapeutic category leverages the unique capability of transfersomes to penetrate skin barriers with exceptional precision and efficiency.

Nevertheless, this innovation is not without challenges requiring continuous

personalized therapeutic design. The

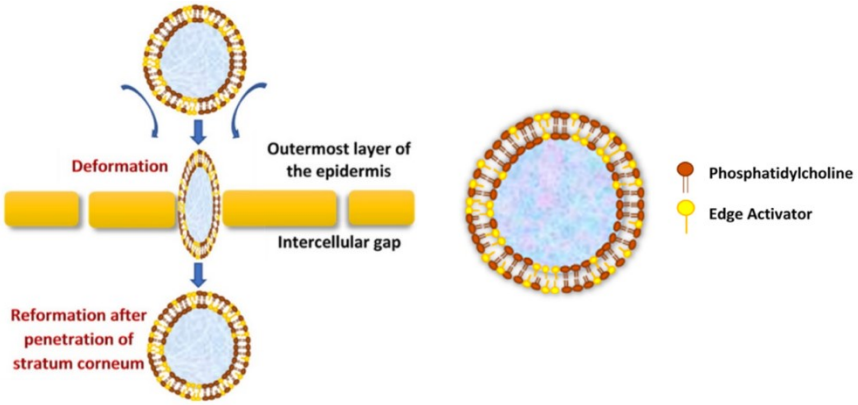

Figure 1. Schematic illustration of structure and mechanism of transfersomes crossing microscopic channels in the stratum corneum (reproduced from Ophata, 2020 under the term of CC-BY 4.0 License, copyright 2020 MDPI).

investigative efforts. Formulation complexity, relatively high production costs, and in vivo stability variability remain focal points for advanced research (Grit & Crommelin, 1993; Iskandarsyah et al., 2018; Pande, 2023). Researchers persistently optimize molecular compositions, evaluate long-term safety profiles, and develop comprehensive standardization protocols (Akombaetwa et al., 2023). This systematic approach aims to accelerate the transformative potential of transfersomes technology within modern treatment landscapes. Philosophically, transfersomes represent more than mere technological innovation; they reflect an evolution of pharmacological thinking that transcends conventional paradigms. By integrating advanced molecular engineering principles with profound understanding of biological barriers, this technology opens new possibilities for more precise, efficient, and future of medical treatment appears increasingly defined by innovative approaches like transfersomes, challenging traditional boundaries in drug delivery methodologies.

TRANSETHOSOMES: EVOLUTION FROM TRANSFERSOMES

Transethosomes emerge as a significant evolution of transfersomes technology, presenting a revolutionary approach to topical drug delivery systems. The unique molecular construction, comprising phospholipids, ethanol, and surfactants, creates a delivery platform with highly sophisticated functional characteristics (Seenivasan et al., 2025). The presence of ethanol as a key component distinctively differentiates transethosomes from previous delivery systems, introducing a more complex and efficient penetration mechanism (Raj et al., 2023).

The penetration mechanism of transethosomes is built upon a dynamic synergy between ethanol and vesicle deformability. Ethanol functions as an intelligent penetration enhancer, inducing structural modifications in skin cell membranes and increasing stratum corneum permeability (Chowdary et al., 2023). This process enables vesicles to penetrate biological barriers with unprecedented precision while maintaining the integrity of the drug molecules being transported (Song et al., 2012). The ability to reversibly modify membrane structure represents a fundamental technological advantage. The technological superiority of transethosomes becomes evident across three primary dimensions: stability, penetration, and drug payload capacity. Compared to conventional delivery systems, transethosomes demonstrate significantly superior chemical and physical stability (Bin Jardan et al., 2023; Hassan et al., 2023; Srifiana & Amalia, 2019). Enhanced penetration capabilities allow drug molecule delivery to deeper skin layers, unlocking therapeutic possibilities previously constrained (Güzel et al., 2022; Zi et al., 2024). The increased drug payload capacity enables optimal therapeutic concentrations with minimal active ingredient usage (Manpreet et al., 2025).

Transethosomes are typically formulated using the thin-layer hydration

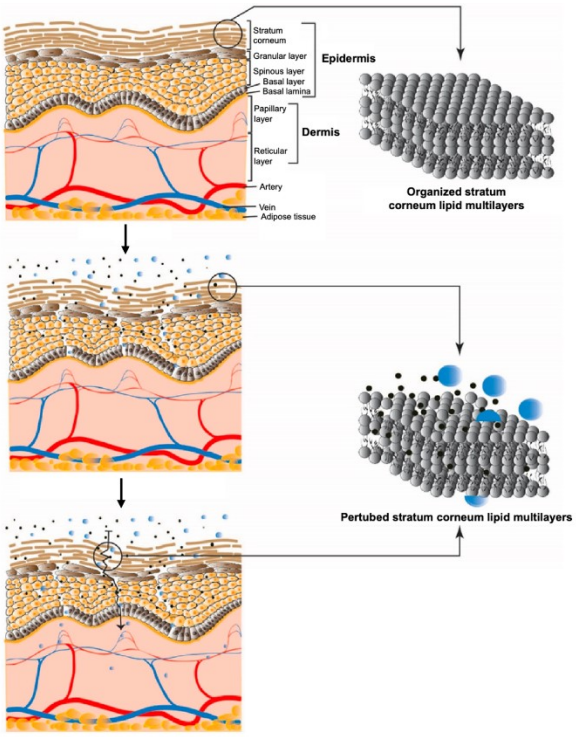

Figure 2. Schematic ilustration of penetration mechanism of transethosomes (reproduced from Abdulbaqi et al., 2016 under the term of CC-BY-NC 4.0 License, copyright 2016 Dovepress).

method, a technique that has proven remarkably effective in producing vesicles with precisely engineered characteristics. Research by Aprianti Aprianti et al. (2023) and Abdulbaqi et al. (2018) demonstrate that this approach consistently yields vesicles with optimal small size, high entrapment efficiency, and appropriate zeta potential. By carefully varying edge activator concentrations and organic solvent evaporation time, researchers can significantly influence vesicle characteristics, optimizing their performance for transdermal applications. The pharmaceutical potential of transethosomes is illustrated through compelling research outcomes. A study by Qureshi (Qureshi et al., 2023) involving

Ticonazole encapsulation revealed impressive performance metrics. The transethosomes demonstrated an entrapment efficiency ranging from 60.56% to 86.13%, with drug permeation percentages between 77.01% and 92.03%. The particle size range of 219.1-757.1 nm further underscores the technology's precision. Critically, the antifungal activity of transethosomes - encapsulated Ticonazole showed statistically significant superiority compared to the market-standard Canesten, highlighting the technology's transformative potential.

In the cosmetic domain, transethosomes have emerged as a groundbreaking delivery system. Anwar's (Anwar et al., 2018) research on green tea extract encapsulation revealed remarkable skin penetration capabilities, attributed to the synergistic interactions between ethanol and surfactants within the vesicle composition. This enhanced delivery mechanism substantially improves the bioavailability and efficacy of active ingredients, as confirmed by Sundar et al. (Sundar et al., 2020). The lipid layers of transethosomes provide critical protection for encapsulated substances, preventing environmental degradation and extending product effectiveness. Contemporary cosmetic applications of transethosomes span multiple product categories, including anti-aging creams, moisturizers, and sunscreens. Antioxidant-focused formulations demonstrate enhanced anti-aging treatments through improved skin penetration, as documented by Soradech et al. (Soradech et al., 2024) and Sguizzato et al. (Sguizzato et al., 2021). The technology's site-specific targeting capabilities offer significant advantages for addressing specific skin conditions and overall skin appearance, a point emphasized by Bajaj et al. (Bajaj et al., 2021). Notably, the controlled release mechanisms of transethosomes allow for sustained active ingredient delivery, potentially reducing application frequency and improving overall product performance.

The controlled release properties and superior penetration capabilities position transethosomes as a revolutionary approach in drug delivery and cosmetic technologies. By addressing traditional limitations in active ingredient delivery, these sophisticated vesicular systems open new frontiers in pharmaceutical and cosmetic formulations. Researchers continue to explore and expand the potential of transethosomes, promising further innovations in targeted, efficient, and effective therapeutic and cosmetic solutions. Nevertheless, research challenges persist. Formulation complexity, biological response variability, and the need for standardized testing protocols remain focal points of continuous investigation

(Dehaghani et al., 2021; Manpreet et al., 2025). Researchers continue to explore technological boundaries, optimize molecular compositions, and evaluate long-term safety profiles (Adnan et al., 2023; Aodah et al., 2023; Y. Wang et al., 2021). This systematic approach aims not only to accelerate transethosomes's potential but also to open new paradigms in more precise, personalized, and efficient molecular therapy design.

TRANSFERSOME VS TRANSETHOSOMES

Composition and Mechanistic Insights

The fundamental distinction between transfersomes and transethosomes lies in their innovative molecular architectures designed to overcome transdermal drug delivery challenges. Transfersomes leverage surfactants as edge activators, enabling remarkable membrane flexibility that allows deformation through stratum corneum pores (Cevc & Blume, 1992; Dehaghani et al., 2021). In contrast, transethosomes introduce ethanol (20-50%) as a dual-action agent, simultaneously dissolving skin lipids and enhancing vesicle membrane fluidity (Patil et al., 2024; Sudhakar et al., 2021). This unique composition grants transethosomes a distinct advantage in penetrating deeper skin layers. However, the volatile nature of ethanol presents a potential stability challenge, necessitating careful formulation with polymer binding agents to mitigate long-term degradation (Chowdary et al., 2025; Mhatre et al., 2024). The delicate balance between enhanced penetration and structural integrity becomes a critical consideration in advanced drug delivery systems.

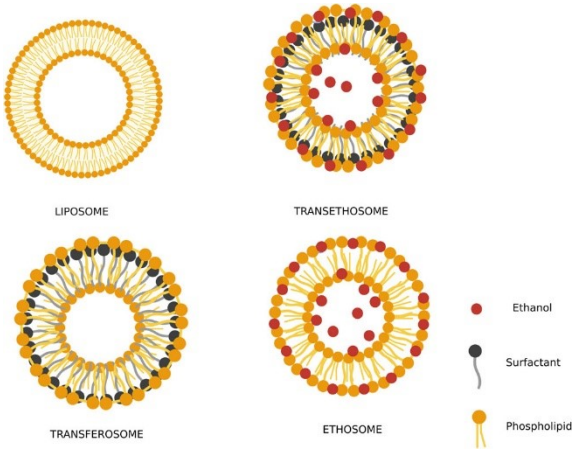

Figure 3. Schematic ilustration of the differences between transfersomes and transethosomes (reproduced from Chowdary et al., 2023 under the term of CC-BY 4.0 License, copyright 2023 Wiley).

Penetration Efficiency and Performance Dynamics

Empirical research provides compelling evidence of the divergent performance characteristics of these innovative delivery systems. In vivo studies on porcine skin reveal that transethosomes generate a vitamin E, caffein, and sinapic acid penetration flux 1.25-3-fold higher than traditional transfersomes (Ascenso et al., 2015; Malviya et al., 2023). The ethanol component strategically reduces stratum corneum lipid cohesion while maintaining the vesicle's ability to preserve drug integrity. Interestingly, the performance

Table 1. Comparison between transfersomes and transethosomes

Parameters	Transfersomes	Transethosomes
Compositions	Phospholipid + surfactant (e.g., sodium cholate as edge activator)	Phospholipid + ethanol (20-50%) + surfactant
Size range	100 – 300 nm	80 – 200 nm
Penetration mechanism	Osmotic deformation driven by hydration gradients	Synergy of ethanol (disrupting stratum corneum lipids) + vesicle deformability
Penetration efficiency	5-10 times higher than liposomes; reaches reticular dermis	2-3 times higher than transfersomes; reaches hypodermis and hair follicles
Stability	Prone to aggregation due to surfactants; requires lyophilization	Ethanol enhances colloidal stability, but ethanol volatility requires control
Drug loading capacity	Optimal for small molecules (<10 kDa; hydrophilic/lipophilic)	Suitable for macromolecules (peptides, siRNA) and hydrophobic drugs
Limitations	Reduced efficiency on dry skin; surfactant-induced irritation	Ethanol may irritate sensitive skin; complex formulation requirements

landscape shifts under varying physiological conditions. In scenarios involving low-hydration skin environments, such as psoriatic conditions, transfersomes demonstrate superior performance through their unique hydration-responsive gradient mechanism (Singh & Awasthi, 2023). This nuanced behavior underscores the complexity of transdermal drug delivery technologies.

Stability and Payload Capacity

Stability emerges as a critical parameter in evaluating these advanced drug delivery systems. Transethosomes exhibit enhanced stability during simulated storage conditions (4°C, three months), with ethanol effectively inhibiting phospholipid oxidation (Abdulbaqi et al., 2018). Nevertheless, the dual-edged impact of ethanol concentration on vesicular structures presents a critical balance. When ethanol levels exceed the optimal threshold, the bilayer's integrity becomes compromised, resulting in increased permeability and modest vesicle enlargement while significantly reducing entrapment efficiency. Further increases in ethanol concentration ultimately dissolve the vesicular structures completely. Research indicates two primary mechanisms for these effects: some studies demonstrate that elevated ethanol concentrations cause hydrocarbon chain infiltration, diminishing membrane thickness and consequently reducing vesicle dimensions. Alternative research suggests that ethanol alters the system's net charge, introducing a degree of steric stabilization that contributes to decreased mean vesicle size (Abdulbaqi et al., 2016; Bendas & Tadros, 2007; Zhou et al., 2010). Similarly, transfersomes demonstrate an excelent stability after six months evaluation in two enviromental condition

(4°C and 25°C) (Hadidi et al.,2018; Moqejwa et al., 2022). Payload capacity reveals another fascinating dimension, with transethosomes demonstrating superior encapsulation efficiency for hydrophobic compounds like curcumin, achieving 84.21-91.17% versus 56-82.8 % in transfersomes, attributed to ethanol's enhanced lipid core solubilization capabilities (Eleraky et al., 2023; Monga et al., 2024; Moqejwa et al., 2022; Vergara et al., 2023; Xiaoshan LI et al., 2021).

Clinical Applications and Case Studies

The landscape of topical drug delivery has been revolutionized by innovative vesicular systems that challenge traditional pharmaceutical limitations. At the forefront of this technological advancement are transfersomes and transethosomes, two sophisticated approaches that promise enhanced drug penetration and therapeutic efficacy. The groundbreaking study by Allam et al. (Allam et al., 2022) on minoxidil dermal delivery illuminates the remarkable capabilities of these systems. Focusing on hair growth treatment, they discovered that transethosomes demonstrated an extraordinary penetration depth by 3.36-fold within 24 hours, compared to a mere 2.84-fold achieved by transfersomes. This significant difference stems from the unique molecular architecture of transethosomes, which incorporate ethanol as a dual-action agent capable of dissolving skin lipids and enhancing membrane fluidity. The mechanism of drug delivery becomes particularly fascinating when examining cellular interactions. Transethosomes excel in navigating the complex terrain of skin layers, strategically disrupting lipid membranes and facilitating deeper drug penetration. Their ability to interact more effectively with cellular structures allows for more uniform drug distribution, a critical factor in therapeutic success.

In the realm of cancer therapy, Ferrara et al. (Ferrara et al., 2022) provided further compelling evidence of transethosomes' potential. Their melanoma study revealed that transethosomes reduce migration in 90% of HT-144 melanoma cells, compared to just 80% when using traditional transfersomes. This remarkable difference highlights the sophisticated mechanism by which ethanol-enhanced vesicles can improve drug internalization and cellular responsiveness. The molecular dynamics underlying these systems are intricate and nuanced. Transfersomes rely on surfactants as edge activators, creating ultraflexible vesicles capable of navigating through stratum corneum pores. Transethosomes, by contrast, leverage ethanol's unique properties to create a more dynamic and penetrative delivery system. The ethanol component not only reduces lipid cohesion but also enhances the overall fluidity of the drug carrier.

Table 2. The application of transfersomes and transethosomes in clinical field.

Application	Formulation	Study design	Key findings	References
Diabetic treatment	Insulin-loaded transfersomes	İn vivo	Significantly reduce glucose levels.	(Cevc, 2003; Cevc et al., 1998)
Anti-inflammatory therapy	Corticosteroids-loaded transfersomes	İn vivo	Improved pharmacological potency in low dose with prolonged effect.	(Cevc et al., 1997; Cevc & Blume, 2004)
Anti-inflammatory therapy	Triamcinolone/acetonide-loaded transfersomes	İn vivo	Reduce therapeutic dose by 10-fold and prolonged anti-inflammatory effect	(Cevc & Blume, 2003)
Anasthesia	Lidocain-loaded transfersomes	In vivo/Ex vivo	Increase anasthetic effect by elevating skin permeation	(Bnyan et al., 2019; Omar et al., 2019)
Antioxidant	Mangiferin-loaded transethosomes	İn vitro	Enchanced antioxidant activity by increasing magiferin to keratinocytes	(Sguizzato et al., 2021)
Muscolosceletal pain management	Naproxen sodium-loaded transethosomes	İn vivo	Significantly reduce rate of edema in mucolosceletal-related disorders	(Kaul et al., 2022)
Hypertensive treatment	Propanolol HCl-loaded transethosomes	In vitro/İn vivo	Avoid first-pass effect, reduce therapeutic dose and organ toxicity	(L. Kumar & Utreja, 2019)
Cosmetics	Niacinamide-loaded transethosomes	In vitro	Enhanced photoprotection effect, skin penetration and controlled drug release of niacinamide	(Basto et al., 2021)

CHALLANGES AND LIMITATIONS OF TRANSFERSOMES AND TRANSETHOSOMES

The realm of pharmaceutical nanotechnology presents remarkable opportunities and formidable challenges through transfersome and transethosome drug delivery systems. These innovative molecular carriers represent a sophisticated approach to enhancing topical drug administration, yet they remain constrained by complex scientific and economic limitations that demand comprehensive strategic resolution (Dehaghani et al., 2021; Opatha et al., 2020).

Long-term stability emerges as the most critical challenge confronting these advanced drug delivery systems. Phospholipid-based carriers demonstrate significant vulnerability to molecular degradation mechanisms, including oxidative processes, surfactant hydrolysis, and structural instability (Siriwardane et al., 2020). Moqejwa et al. (Moqejwa et al., 2022) documented dramatic structural transformations in transfersomes, with particle sizes expanding from 102 nm to 130 nanometers within three months of room-temperature storage due to phospholipid oxidation and surfactant degradation. Various studies have proposed multiple innovative stabilization strategies to address these fundamental challenges. Lyophilization techniques utilizing cryoprotectants like trehalose and sucrose offer promising avenues for extending

system stability up to six months (Lu et al., 2024). In addition, another proposed alternative approaches involving hybrid formulation technologies, such as combining transethosomes with stimuli-responsive polymers can be used for mitigating physical degradation processes (Cunha et al., 2025; De Leo et al., 2021; Soomherun et al., 2024).

Economic constraints further complicate transfersome and transethosome development. The production requires pharmaceutical-grade surfactants and edge activators with extraordinary purity levels, dramatically increasing raw material costs (Yadav et al., 2017). Kumar and Rajeshwarrao (G. P. Kumar & Rajeshwarrao, 2011) noted that sodium deoxycholate and specialized phospholipids can be two to three times more expensive than conventional surfactant alternatives. Transethosome formulations introduce additional economic complexity, with pharmaceutical-grade ethanol increasing production expenses by 30–40% compared to traditional liposomal systems. Additionally, manufacturing processes present equally intricate challenges. Precise membrane extrusion through ultra-fine polycarbonate membranes demands technological sophistication. Jain et al. (Jain et al., 2015) highlighted the necessity of maintaining narrow deviation margins during particle size uniformization, requiring advanced microfluidic technologies to reduce material waste. Furthermore, Regulatory frameworks present another substantial obstacle. Current FDA/EMA guidelines lack specific provisions for nano-drug delivery systems, creating commercialization barriers.

FUTURE PROSPECTIVES AND OPPORTUNITIES

Integration with other delivery technologies

The convergence of transfersome and transethosome technologies with cutting-edge delivery methods presents revolutionary opportunities in transdermal drug administration. Microneedle and iontophoresis technologies offer particularly promising synergistic potential for enhancing drug delivery mechanisms. Microneedle technologies create micropores in the stratum corneum, facilitating the penetration of nano-vesicles into deeper skin layers. A groundbreaking study on telmisartan delivery demonstrated that combining transethosome with iontophoresis dramatically improved drug bioavailability, increasing it by 1.85 times compared to oral routes while reducing peak concentration time by 50% (Teaima et al., 2021). Iontophoresis leverages low-level electrical currents to propel charged molecules through the skin, while microneedles addr-

ess traditional vesicle size limitations. Experimental research using recombinant human growth hormone (rhGH) in mouse models confirmed that the combination of microneedle technology and iontophoresis could enhance drug flux up to 10 times compared to passive delivery methods (Noh et al., 2018). This innovative approach not only expands the range of deliverable drugs, including macromolecules exceeding 500 Dalton, but also enables more precise dosage control through closed-loop systems (Gujjar & Banga, 2014; G. Wang et al., 2025).

Personalized Therapy and Biological Drug Potential

Transfersome and transethosome technologies offer an ideal platform for personalized therapeutic interventions, particularly in treating skin cancer, autoimmune diseases, and metabolic disorders. By modifying vesicle composition, such as phospholipid-surfactant ratios or ethanol concentrations, these systems can be tailored to individual patient profiles based on specific skin biomarkers like pH, sebum levels, and stratum corneum thickness (Chowdary et al., 2023). For instance, quercetin-loaded transethosome formulations targeting melanoma demonstrated a remarkable 90% increase in cancer cell apoptosis compared to conventional transfersome systems (Ferrara et al., 2022). This enhanced efficacy stems from ethanol's unique ability to dissolve target cell membrane lipids. Biological drugs, including proteins (insulin, monoclonal antibodies) and nucleic acids (siRNA, mRNA), have shown particular promise. Successful trials have demonstrated the delivery of anti-diabetic insulin to the dermis, effectively reducing blood glucose levels without enzymatic degradation (Nabila et al., 2024; Padma Prashanthini et al., 2023). Transethosome technologies have demonstrated the capacity to transport high-molecular-weight peptides (>20 kDa), such as recombinant human growth hormone, with no toxicity against fibroblast cells (Azimi et al., 2019). This approach holds significant potential for topical gene therapy and immunotherapy with minimal systemic effects.

Material Innovation: Natural and Biodegradable Approaches

The emerging trend toward natural and biocompatible materials represents a critical innovation in transfersome and transethosome development. Researchers are exploring plant-based phospholipids like soybean lecithin and biocompatible surfactants derived from coconut oil to reduce dependence on synthetic materials. Soybean lecithin-based transethosome for-

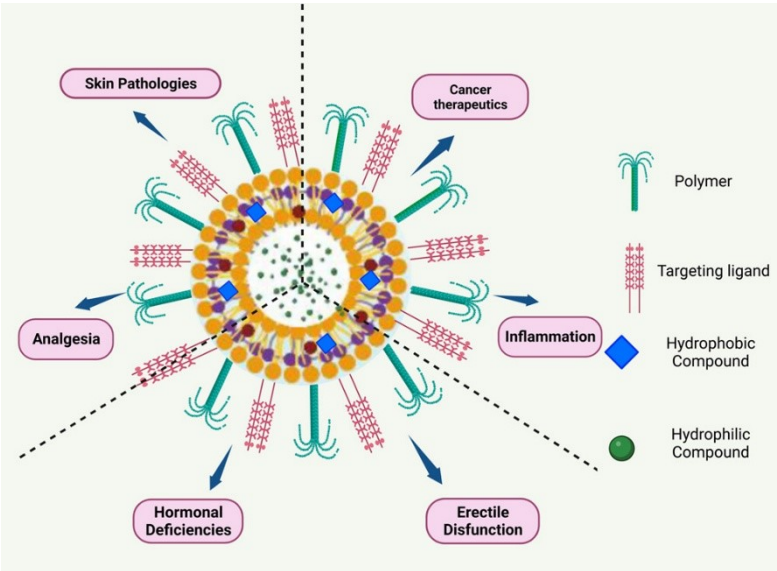

Figure 4. Schematic ilustration of personalized application design of transfersomes/transethosomes by surface functionalization (reproduced from Chowdary et al., 2023 under the term of CC-BY 4.0 License, copyright 2023 Wiley).

mulations for human growth hormon have demonstrated remarkable stability, maintaining chemical integrity for four weeks at room temperature with maximum delivery amount of 489.54 ng/cm2 (Kateh Shamshiri et al., 2019). Additionally, biodegradable polymers such as poly (lactic-co-glycolic acid) (PLGA) and chitosan are being integrated into vesicle structures to enhance drug release control. Innovative stimulus-responsive materials are emerging as another exciting development (Estupiñán et al., 2021; Nojoki et al., 2022). Transethosome systems incorporating marine collagen can now release drugs "on-demand" when exposed to body temperature, significantly reducing premature drug leakage. This approach is particularly relevant for skin areas with temperature variations or inflammatory conditions (Han et al., 2021).

CONCLUSION

Transfersomes and transethosomes represent a paradigm shift in topical drug delivery, offering unprecedented solutions to the long-standing challenge of bypassing the skin's formidable barrier. These nanovesicles, with their unique deformability and penetration-enhancing properties, have demonstrated remarkable efficacy in delivering both hydrophilic and hydrophobic therapeutics to deeper skin layers, outperforming conventional formulations like creams and gels. By exploiting osmotic gradients (transfersomes) or ethanol-mediated lipid disruption (transethosomes), they achieve targeted delivery while minimizing systemic exposure, a critical advantage for chronic conditions. Despite their promise, challenges such as long-term stability, production costs, and limited clinical valid-

ation remain significant hurdles. For instance, phospholipid degradation in transfersomes and ethanol volatility in transethosomes necessitate innovative stabilization strategies, including lyophilization and hybrid formulations with biodegradable polymers. However, emerging technologies like microneedle integration and iontophoresis are poised to amplify their potential, enabling deeper penetration of biologics such as siRNA and monoclonal antibodies. The future of these systems lies in personalization and sustainability. Biomarker-driven formulations tailored to individual skin profiles and eco-friendly materials like plant-derived phospholipids could democratize access while reducing costs. In essence, transfersomes and transethosomes are not merely incremental improvements but revolutionary tools redefining topical therapy. As research bridges existing gaps, these systems could transform dermatology, oncology, and pain management, ushering in an era of precision medicine where effective, minimally invasive treatments become the norm rather than the exception.

REFERENCES

Abdellatif, A. A. H., Aldosari, B. N., Al-Subaiyel, A., Alhaddad, A., Samman, W. A., Eleraky, N. E., Elnaggar, M. G., Barakat, H., & Tawfeek, H. M. (2023). Transethosomal Gel for the Topical Delivery of Celecoxib: Formulation and Estimation of Skin Cancer Progression. Pharmaceutics, 15(1), 22. https://doi.org/10.3390/pharmaceutics15010022

Abdulbaqi, I. M., Darwis, Y., Assi, R. A., & Khan, N. A. K. (2018). Transethosomal Gels as Carriers for the Transdermal Delivery Of Colchicine: Statistical Optimization, Characterization, and Ex Vivo Evaluation. Drug Design, Development and Therapy, 12, 795–813. https://doi.org/10.2147/DDDT.S158018

Abdulbaqi, I. M., Darwis, Y., Khan, N. A. K., Assi, R. A., & Khan, A. A. (2016). Ethosomal Nanocarriers: The Impact of Constituents and Formulation Techniques on Ethosomal Properties, In Vivo Studies, and Clinical Trials. International Journal of Nanomedicine, 11, 2279–2304. https://doi.org/10.2147/IJN.S105016

Adnan, M., Afzal, O., S. A. Altamimi, A., Alamri, M. A., Haider, T., & Faheem Haider, Md. (2023). Development And Optimization of Transethosomal Gel of Apigenin for Topical Delivery: In-Vitro, Ex-Vivo and Cell Line Assessment. International Journal of Pharmaceutics, 631, 122506. https://doi.org/https://doi.org/10.1016/j.ijpharm.2022.122506

Akombaetwa, N., Ilangala, A. B., Thom, L., Memvanga, P. B., Witika, B. A., & Buya, A. B. (2023). Current Advances in Lipid Nanosystems Intended for Topical and Transdermal Drug Delivery Applications. Pharmaceutics, 15(2), 656. https://doi.org/10.3390/pharmaceutics15020656

Al-Ameri, A. A. F., & Al-Gawhari, F. J. (2024). Formulation Development of Meloxicam Binary Ethosomal Hydrogel for Topical Delivery: In Vitro and In Vivo Assessment. Pharmaceutics, 16(7), 898. https://doi.org/10.3390/pharmaceutics16070898

AL-Japairai, K., Almurisi, S. H., Abdul-Halim, N., & Mahmood, S. (2024). Dissolving Microneedle Integrated with Benidipine Loaded Ethosomes for Transdermal Delivery. Surfaces and Interfaces, 52, 104903. https://doi.org/https://doi.org/10.1016/j.surfin.2024.104903

Allam, A. A., Fathalla, D., Safwat, M. A., & Soliman, G. M. (2022). Transferosomes Versus Transethosomes for the Dermal Delivery For Minoxidil: Preparation and In Vitro/Ex Vivo Appraisal. Journal of Drug Delivery Science and Technology, 76, 103790. https://doi.org/https://doi.org/10.1016/j.jddst.2022.103790

Anwar, E., Ramadon, D., & Ardi, G. D. (2018). Novel Transethosome Containing Green Tea (Camellia sinensis L. Kuntze) Leaf Extract for Enhanced Skin Delivery of Epigallocatechin Gallate: Formulation and In Vitro Penetration Test. International Journal of Applied Pharmaceutics, 10(1), 299–302. https://doi.org/10.22159/ijap.2018.v10s1.66

Aodah, A. H., Hashmi, S., Akhtar, N., Ullah, Z., Zafar, A., Zaki, R. M., Khan, S., Ansari, M. J., Jawaid, T., Alam, A., & Ali, M. S. (2023). Formulation Development, Optimization by Box–Behnken Design, and In Vitro and Ex Vivo Characterization of Hexatriacontane-Loaded Transethosomal Gel for Antimicrobial Treatment for Skin Infections. Gels, 9(4), 322. https://doi.org/10.3390/gels9040322

Aprianti, I., Iskandarsyah, & Setiawan, H. (2023). Diflunisal Transethosomes for Transdermal Delivery: Formulation and Characterization. International Journal of Applied Pharmaceutics, 15(3), 61–66. https://doi.org/10.22159/ijap.2023v15i3.47691

Ascenso, A., Raposo, S., Batista, C., Cardoso, P., Mendes, T., Praça, F. G., Bentley, M. V. L. B., & Simões, S. (2015). Development, Characterization, and Skin Delivery Studies of Related Ultradeformable Vesicles: Transfersomes, Ethosomes, and Transethosomes. International Journal of Nanomedicine, 10, 5837–5851. https://doi.org/10.2147/IJN.S86186

Azimi, M., Khodabandeh, M., Deezagi, A., & Rahimi, F. (2019). Impact of the Transfersome Delivered Human Growth Hormone on the Dermal Fibroblast Cells. Current Pharmaceutical Biotechnology, 20(14), 1194–1202. https://doi.org/10.2174/1389201020666190809120333

Bajaj, K. J., Parab, B. S., & Shidhaye, S. S. (2021). Nano-Transethosomes: A Novel Tool for Drug Delivery Through Skin. Indian Journal of Pharmaceutical Education and Research, 55(1), s1–s10. https://doi.org/10.5530/ijper.55.1s.33

Balata, G. F., Faisal, M. M., Elghamry, H. A., & Sabry, S. A. (2020). Preparation and Characterization of Ivabradine HCl Transfersomes for Enhanced Transdermal Delivery. Journal of Drug Delivery Science and Technology, 60, 101921. https://doi.org/https://doi.org/10.1016/j.jddst.2020.101921

Basto, R., Andrade, R., Nunes, C., Lima, S. A. C., & Reis, S. (2021). Topical Delivery of Niacinamide to Skin Using Hybrid Nanogels Enhances Photoprotection Effect. Pharmaceutics, 13(11), 1968. https://doi.org/10.3390/pharmaceutics

Bendas, E. R., & Tadros, M. I. (2007). Enhanced Transdermal Delivery of Salbutamol Sulfate Via Ethosomes. AAPS PharmSciTech, 8(4), 107. https://doi.org/10.1208/pt0804107

Bhasin, B., & Londhe, V. Y. (2018). An Overview of Transfersomal Drug Delivery. International Journal of Pharmaceutical Sciences and Research, 9(6), 2175. https://doi.org/10.13040/IJPSR.0975-8232.9(6).2175-84

Bin Jardan, Y. A., Ahad, A., Raish, M., & Al-Jenoobi, F. I. (2023). Preparation and

Characterization of Transethosome Formulation for the Enhanced Delivery of Sinapic Acid. Pharmaceutics, 15(10), 2391. https://doi.org/10.3390/pharmaceutics15102391

Bnyan, R., Khan, I., Ehtezazi, T., Saleem, I., Gordon, S., O'Neill, F., & Roberts, M. (2019). Formulation And Optimisation of Novel Transfersomes for Sustained Release of Local Anaesthetic. Journal of Pharmacy and Pharmacology, 71(10), 1508–1519. https://doi.org/10.1111/jphp.13149

Bos, J. D., & Meinardi, M. M. H. M. (2000). The 500 Dalton Rule for the Skin Penetration of Chemical Compounds and Drugs. Experimental Dermatology, 9(3), 165–169. https://doi.org/10.1034/j.1600-0625.2000.009003165.x

Cevc, G. (2003). Transdermal Drug Delivery of Insulin with Ultradeformable Carriers. Clinical Pharmacokinetics, 42(5), 461–474. https://doi.org/10.2165/00003088-200342050-00004

Cevc, G., & Blume, G. (1992). Lipid Vesicles Penetrate into Intact Skin Owing to the Transdermal Osmotic Gradients and Hydration Force. Biochimica et Biophysica Acta (BBA) - Biomembranes, 1104(1), 226–232. https://doi.org/https://doi.org/10.1016/0005-2736(92)90154-E

Cevc, G., & Blume, G. (2003). Biological Activity and Characteristics of Triamcinolone-Acetonide Formulated with The Self-Regulating Drug Carriers, Transfersomes®. Biochimica et Biophysica Acta (BBA) - Biomembranes, 1614(2), 156–164. https://doi.org/https://doi.org/10.1016/S0005-2736(03)00172-X

Cevc, G., & Blume, G. (2004). Hydrocortisone and Dexamethasone in Very Deformable Drug Carriers Have Increased Biological Potency, Prolonged Effect, and Reduced Therapeutic Dosage. Biochimica et Biophysica Acta (BBA) - Biomembranes, 1663(1), 61–73. https://doi.org/https://doi.org/10.1016/j.bbamem.2004.01.006

Cevc, G., Blume, G., & Schätzlein, A. (1997). Transfersomes-Mediated Transepidermal Delivery Improves the Regio-Specificity and Biological Activity of Corticosteroids In Vivo. Journal of Controlled Release, 45(3), 211–226. https://doi.org/https://doi.org/10.1016/S0168-3659(96)01566-0

Cevc, G., Gebauer, D., Stieber, J., Schätzlein, A., & Blume, G. (1998). Ultraflexible Vesicles, Transfersomes, Have An Extremely Low Pore Penetration Resistance and Transport Therapeutic Amounts of Insulin Across the Intact Mammalian Skin. Biochimica et Biophysica Acta (BBA) - Biomembranes, 1368(2), 201–215. https://doi.org/https://doi.org/10.1016/S0005-2736(97)00177-6

Chaurasiya, P., Ganju, E., Upmanyu, N., Ray, S. K., & Jain, P. (2019). Transfersomes: A Novel Technique for Transdermal Drug Delivery. Journal of Drug Delivery and Therapeutics, 9(1), 279–285. https://doi.org/10.22270/jddt.v9i1.2198

Chowdary, P., Padmakumar, A., & Rengan, A. K. (2023). Exploring the Potential of Transethosomes in Therapeutic Delivery: A Comprehensive Review. MedComm – Biomaterials and Applications, 2(4), e59. https://doi.org/https://doi.org/10.1002/mba2.59

Chowdary, P., Puppala, E. R., Putta, C. L., Maddila, J. R., Pulavarthy, V., Prasad, V. V. S. R., & Rengan, A. K. (2025). Hyaluronic-Acid-Functionalized Tofacitinib Loaded Transethosomes for Targeted Drug Delivery in Rheumatoid Arthritis. ACS Applied Bio Materials, 8(2), 1594–1606. https://doi.org/10.1021/acsabm.4c01743

Cunha, J., Latocheski, E., Fidalgo, A. C. D., Gerola, A. P., Marin, C. F. de F., & Ribeiro, A. J. (2025). Core-Shell Hybrid Liposomes: Transforming Imaging

Diagnostics and Therapeutic Strategies. Colloids and Surfaces B: Biointerfaces, 251, 114597. https://doi.org/https://doi.org/10.1016/j.colsurfb.2025.114597

De Leo, V., Milano, F., Agostiano, A., & Catucci, L. (2021). Recent Advancements in Polymer/Liposome Assembly for Drug Delivery: From Surface Modifications to Hybrid Vesicles. Polymers, 13(7), 1027. https://doi.org/10.3390/polym13071027

Dehaghani, M. Z., Mahapatra, D., & Joseph, T. M. (2021). Transethosomes: Novel Technology for Skin Delivery of Drugs. International Journal of Medical & Pharmaceutical Sciences, 11(08), 1-5. https://doi.org/10.31782/ijmps.2021.11801

Eleraky, N. E., El-Badry, M., Omar, M. M., El-Koussi, W. M., Mohamed, N. G., Abdel-Lateef, M. A., & Hassan, A. S. (2023). Curcumin Transferosome-Loaded Thermosensitive Intranasal in situ Gel as Prospective Antiviral Therapy for SARS-Cov-2. International Journal of Nanomedicine, 18, 5831–5869. https://doi.org/10.2147/IJN.S423251

Estupiñán, Ó., Rendueles, C., Suárez, P., Rey, V., Murillo, D., Morís, F., Gutiérrez, G., Blanco-López, M. D. C., Matos, M., & Rodríguez, R. (2021). Nano-Encapsulation of Mithramycin in Transfersomes and Polymeric Micelles for the Treatment of Sarcomas. Journal of Clinical Medicine, 10(7), 1358. https://doi.org/10.3390/jcm10071358

Ferrara, F., Benedusi, M., Sguizzato, M., Cortesi, R., Baldisserotto, A., Buzzi, R., Valacchi, G., & Esposito, E. (2022). Ethosomes and Transethosomes as Cutaneous Delivery Systems for Quercetin: A Preliminary Study on Melanoma Cells. Pharmaceutics, 14(5), 1038. https://doi.org/10.3390/pharmaceutics14051038

Grit, M., & Crommelin, D. J. A. (1993). Chemical Stability of Liposomes: Implications for Their Physical Stability. Chemistry and Physics of Lipids, 64(1), 3–18. https://doi.org/https://doi.org/10.1016/0009-3084(93)90053-6

Gujjar, M., & Banga, A. K. (2014). Iontophoretic and Microneedle Mediated Transdermal Delivery of Glycopyrrolate. Pharmaceutics, 6(4), 663–671. https://doi.org/10.3390/pharmaceutics6040663

Güzel, İ. E., Güngör, S., & Erdal, M. S. (2022). Improved Skin Penetration and Deposition of Naftifine from Transethosomes and Transethosomal Gel Formulations. Farmacia, 70(3), 514–521. https://doi.org/10.31925/farmacia.2022.3.18

Hadidi, N., Saffari, M., & Faizi, M. (2018). Optimized Transferosomal Bovine Lactoferrin (BLF) as a Promising Novel Non-Invasive Topical Treatment for Genital Warts Caused by Human Papiluma Virus (HPV). Iranian Journal of Pharmaceutical Research, 17(l2),12-23.

Han, S.-B., Won, B., Yang, S., & Kim, D.-H. (2021). Asterias Pectinifera Derived Collagen Peptide-Encapsulating Elastic Nanoliposomes for The Cosmetic Application. Journal of Industrial and Engineering Chemistry, 98, 289–297. https://doi.org/https://doi.org/10.1016/j.jiec.2021.03.039

Hassan, A. S., Hofni, A., Abourehab, M. A. S., & Abdel-Rahman, I. A. M. (2023). Ginger Extract–Loaded Transethosomes for Effective Transdermal Permeation and Anti-Inflammation in Rat Model. International Journal of Nanomedicine, 18, 1259–1280. https://doi.org/10.2147/IJN.S400604

Iskandarsyah, Rahmi, A. D., & Pangesti, D. M. (2018). Comparison of the Characteristics of Transfersomes and Protransfersomes Containing Azelaic Acid. Journal of Young Pharmacists, 10(2), s11–s15. https://doi.org/10.5530/jyp.2018.2s.3

Jain, S., Niketkumar, P., Parshotam, M., & and Lin, S. (2015). Quality By Design Approach for Formulation, Evaluation and Statistical Optimization of Diclofenac-Loaded Ethosomes Via Transdermal Route. Pharmaceutical Development and Technology, 20(4), 473–489. https://doi.org/10.3109/10837450.2014.882939

Kadam, R., Hosmanii, A. H., Potdar, S. V, Savakhande, R. M., & Patil, S. G. (2025). Transfersomes: Pioneering Nanocarriers for Enhanced Drug Delivery. International Journal of Pharmaceutical Science, 3(3), 1–17. https://doi.org/10.5281/zenodo.14950131

Kateh Shamshiri, M., Momtazi-Borojeni, A. A., Khodabandeh Shahraky, M., & Rahimi, F. (2019). Lecithin Soybean Phospholipid Nano-Transfersomes as Potential Carriers for Transdermal Delivery of the Human Growth Hormone. Journal of Cellular Biochemistry, 120(6), 9023–9033. https://doi.org/https://doi.org/10.1002/jcb.28176

Kaul, S., Jain, N., & Nagaich, U. (2022). Ultra Deformable Vesicles for Boosting Transdermal Delivery of 2-Arylpropionic Acid Class Drug for Management of Musculoskeletal Pain. Journal of Pharmaceutical Investigation, 52(2), 217–231. https://doi.org/10.1007/s40005-021-00555-7

Khan, M. I., Yaqoob, S., Madni, A., Akhtar, M. F., Sohail, M. F., Saleem, A., Tahir, N., Khan, K. ur R., & Qureshi, O. S. (2022). Development and In Vitro / Ex Vivo Evaluation of Lecithin-Based Deformable Transfersomes and Transfersome-Based Gels for Combined Dermal Delivery of Meloxicam and Dexamethasone. BioMed Research International, 2022, 8170318. https://doi.org/10.1155/2022/8170318

Kumar, G. P., & Rajeshwarrao, P. (2011). Nonionic Surfactant Vesicular Systems for Effective Drug Delivery—An Overview. Acta Pharmaceutica Sinica B, 1(4), 208–219. https://doi.org/https://doi.org/10.1016/j.apsb.2011.09.002

Kumar, L., & Utreja, P. (2019). Formulation and Characterization of Transethosomes for Enhanced Transdermal Delivery of Propranolol Hydrochloride. Micro and Nanosystems, 12(1), 38–47. https://doi.org/10.2174/1876402911666190603093550

Kumar, R. S., & Pradhan, M. (2022). Transferosomes: Vesicular Carrier for both Hydrophilic and Lipophilic Drugs. Journal of Pharmaceutical Research International, 34(2B), 106–120. https://doi.org/10.9734/jpri/2022/v34i27b36013

Lu, Y., Cheng, B., Shan, Y., Zhou, S., Xu, C., Fei, Y., Pan, J., Piao, J., Li, F., Zhu, Z., & Zheng, H. (2024). Lyophilization Enhances the Stability of Panax Notoginseng Total Saponins-Loaded Transfersomes without Adverse Effects on Ex Vivo/In Vivo Skin Permeation. International Journal of Pharmaceutics, 649, 123668. https://doi.org/https://doi.org/10.1016/j.ijpharm.2023.123668

Majumdar, S., Mahanti, B., Kar, A. K., Parya, H., Ghosh, A., & Kar, B. (2024). Nanoliposome: As A Smart Nanocarrier in Transdermal Drug Delivery System. Intelligent Pharmacy, 2(6), 768-776. https://doi.org/10.1016/j.ipha.2024.04.004

Malviya, N., A, P., & Alexander, A. (2023). Comparative Study on Ethosomes and Transferosomes for Enhancing Skin Permeability of Sinapic Acid. Journal of Molecular Liquids, 383, 122098. https://doi.org/https://doi.org/10.1016/j.molliq.2023.122098

Manpreet, D., Sachdeva, S., Kaur, H., & Singh, J. (2025). Ethosomes: A Revolutionary Approach in Advanced Drug Delivery Systems. Journal of Drug Delivery and Therapeutics, 15(2), 186–192. https://doi.org/10.22270/jddt.v15i2.6993

Marto, J., Vitor, C., Guerreiro, A., Severino, C., Eleutério, C., Ascenso, A., & Simões, S. (2016). Ethosomes for Enhanced Skin Delivery of Griseofulvin. Colloids and Surfaces B: Biointerfaces, 146, 616–623. https://doi.org/https://doi.org/10.1016/j.colsurfb.2016.07.021

Matharoo, N., Mohd, H., & Michniak-Kohn, B. (2024). Transferosomes As A Transdermal Drug Delivery System: Dermal Kinetics and Recent Developments. WIREs Nanomedicine and Nanobiotechnology, 16(1), e1918. https://doi.org/https://doi.org/10.1002/wnan.1918

Mhatre, N., Rane, B., Padave, A., & Jain, A. (2024). Bilastine-Loaded Transethosome Based Nanogel for the Treatment of Allergic Reactions: An In vitro Characterization. Micro and Nanosystems, 16(4), 219 - 233. https://doi.org/10.2174/1118764029327886240724103121

Michalek, I. Maria., Loring, Belinda., & John, S. Malte. (2016). Global Report on Psoriasis. World Health Organization.

Monga, G., Kumar, S., & Kumar, R. (2024). Transethosomal Carrier of Curcumin for Improved Topical Delivery to Treat Psoriasis: Optimization, In-Vitro, In-Vivo and Stability Assessment. AfricanJournalofBiological Sciences Gorav MONGA / Afr.J.Bio.Sc, 6(5), 2663–2187. https://doi.org/10.33472/AFJBS.6.5.2024

Moqejwa, T., Marimuthu, T., Kondiah, P. P. D., & Choonara, Y. E. (2022). Development of Stable Nano-Sized Transfersomes as a Rectal Colloid for Enhanced Delivery of Cannabidiol. Pharmaceutics, 14(4), 703. https://doi.org/10.3390/pharmaceutics14040703

Motawea, A., Maria, S. N., Maria, D. N., Jablonski, M. M., & Ibrahim, M. M. (2024). Genistein Transfersome-Embedded Topical Delivery System for Skin Melanoma Treatment: In Vitro and Ex Vivo Evaluations. Drug Delivery, 31(1), 2372277. https://doi.org/10.1080/10717544.2024.2372277

Mukherjee, P., Khademhosseini, A., Seaberg, J., Montazerian, H., Hossen, M. N., & Bhattacharya, R. (2021). Hybrid Nanosystems for Biomedical Applications. ACS Nano,15(2) 2099–2142. https://doi.org/10.1021/acsnano.0c09382

Mwangi, A. N., Njogu, P. M., Maru, S. M., Njuguna, N. M., Njaria, P. M., Kiriiri, G. K., & Mathenge, A. W. (2021). Meloxicam Emulgels for Topical Management of Rheumatism: Formulation Development, In Vitro and In Vivo Characterization. Saudi Pharmaceutical Journal, 29(4), 351–360. https://doi.org/10.1016/j.jsps.2021.03.005

Nabila, F. H., Islam, R., Shimul, I. M., Moniruzzaman, M., Wakabayashi, R., Kamiya, N., & Goto, M. (2024). Ionic Liquid-Mediated Ethosome for Transdermal Delivery of Insulin. Chem. Commun., 60(30), 4036–4039. https://doi.org/10.1039/D3CC06130B

Natsheh, H., & Touitou, E. (2020). Phospholipid Vesicles for Dermal/Transdermal and Nasal Administration of Active Molecules: The Effect of Surfactants and Alcohols on the Fluidity of their Lipid Bilayers and Penetration Enhancement Properties. Molecules, 25(13), 2959. https://doi.org/10.3390/molecules25132959

Negut, I., & Bita, B. (2024). Polymersomes as Innovative, Stimuli-Responsive Platforms for Cancer Therapy. Pharmaceutics, 16(4), 463. https://doi.org/10.3390/pharmaceutics16040463

Noh, G., Keum, T., Seo, J. E., Bashyal, S., Eum, N. S., Kweon, M. J., Lee, S., Sohn, D. H., & Lee, S. (2018). Iontophoretic Transdermal Delivery of Human Growth Hormone (hGH) and the Combination Effect of a New Type Microneedle, Tappy Tok Tok®.

Pharmaceutics, 10(3), 153. https://doi.org/10.3390/pharmaceutics10030153

Nojoki, F., Ebrahimi-Hosseinzadeh, B., Hatamian-Zarmi, A., Khodagholi, F., & Khezri, K. (2022). Design and Development of Chitosan-Insulin-Transfersomes (Transfersulin) As Effective Intranasal Nanovesicles for the Treatment of Alzheimer's Disease: In Vitro, In Vivo, and Ex Vivo Evaluations. Biomedicine and Pharmacotherapy, 153. https://doi.org/10.1016/j.biopha.2022.113450

Omar, M. M., Hasan, O. A., & El Sisi, A. M. (2019). Preparation and Optimization of Lidocaine Transferosomal Gel Containing Permeation Enhancers: A Promising Approach for Enhancement of Skin Permeation. International Journal of Nanomedicine, 14, 1551–1562. https://doi.org/10.2147/IJN.S201356

Onkar Nandraj, J., Gajanan, K. A., & Karande, Dr. K. M. (2024). A Concise Review on Contemporary and Novel Treatments Addressing the Prevention and Control of Hyperpigmentation. Asian Journal of Pharmaceutical Research and Development, 12(2), 19–27. https://doi.org/10.22270/ajprd.v12i2.1363

Opatha, S. A. T., Titapiwatanakun, V., & Chutoprapat, R. (2020). Transfersomes: A Promising Nanoencapsulation Technique for Transdermal Drug Delivery. Pharmaceutic, 12(9), 1–23. https://doi.org/10.3390/pharmaceutics12090855

Padma Prashanthini, V., Sivaraman, S., Kathirvelu, P., Shanmugasundaram, J., Subramanian, V., Ramesh, S. S., Karthikeyan, E., & Cheriyan, B. V. (2023). Transferosomal Gel for Transdermal Delivery of Insulin: Formulation Development and Ex Vivo Permeation Study. Intelligent Pharmacy, 1(4), 212–216. https://doi.org/https://doi.org/10.1016/j.ipha.2023.07.001

Pande, S. (2023). Liposomes for Drug Delivery: Review of Vesicular Composition, Factors Affecting Drug Release and Drug Loading in Liposomes. Artificial Cells, Nanomedicine and Biotechnology, 51(1), 428–440. https://doi.org/10.1080/21691401.2023.2247036

Patil, S. R., Dharashive, V., Shafi, S., Rudrurkar, M. N., Kazi, A. J., Ritthe, P. V, Sante, R. U., & Shaikh, I. (2024). Transethosome Technology: Revolutionizing Transdermal Drug Delivery. Asian Journal of Pharmaceutical Research and Development, 12(3), 102–109. https://doi.org/10.22270/ajprd.v12i3.1402

Prausnitz, M. R., & Langer, R. (2008). Transdermal Drug Delivery. Nature Biotechnology, 6(11), 1261–1268. https://doi.org/10.1038/nbt.1504

Qureshi, M. I., Jamil, Q. A., Usman, F., Wani, T. A., Farooq, M., Shah, H. S., Ahmad, H., Khalil, R., Sajjad, M., Zargar, S., & Kausar, S. (2023). Tioconazole-Loaded Transethosomal Gel Using Box–Behnken Design for Topical Applications: In Vitro, In Vivo, and Molecular Docking Approaches. Gels, 9(9), 767. https://doi.org/10.3390/gels9090767

Raj, A., Dua, K., Nair, R. S., Sarath Chandran, C., & Alex, A. T. (2023). Transethosome: An ultra-Deformable Ethanolic Vesicle for Enhanced Transdermal Drug Delivery. Chemistry and Physics of Lipids, 255, 105315. https://doi.org/https://doi.org/10.1016/j.chemphyslip.2023.105315

Sala, M., Diab, R., Elaissari, A., & Fessi, H. (2018). Lipid Nanocarriers as Skin Drug Delivery Systems: Properties, Mechanisms of Skin Interactions and Medical Applications. International Journal of Pharmaceutics, 535(1), 1–17. https://doi.org/https://doi.org/10.1016/j.ijpharm.2017.10.046

Seenivasan, R., Halagali, P., Nayak, D., & Tippavajhala, V. K. (2025).

Transethosomes: A Comprehensive Review of Ultra-Deformable Vesicular Systems for Enhanced Transdermal Drug Delivery. AAPS PharmSciTech, 26(1), 41. https://doi.org/10.1208/s12249-024-03035-x

Sguizzato, M., Ferrara, F., Hallan, S. S., Baldisserotto, A., Drechsler, M., Malatesta, M., Costanzo, M., Cortesi, R., Puglia, C., Valacchi, G., & Esposito, E. (2021). Ethosomes and Transethosomes for Mangiferin Transdermal Delivery. Antioxidants, 10(5), 768. https://doi.org/10.3390/antiox10050768

Singh, S., & Awasthi, R. (2023). Breakthroughs and Bottlenecks of Psoriasis Therapy: Emerging Trends and Advances in Lipid Based Nano-Drug Delivery Platforms for Dermal and Transdermal Drug Delivery. Journal of Drug Delivery Science and Technology, 84, 104548. https://doi.org/https://doi.org/10.1016/j.jddst.2023.104548

Siriwardane, D. A., Wang, C., Jiang, W., & Mudalige, T. (2020). Quantification of Phospholipid Degradation Products in Liposomal Pharmaceutical Formulations by Ultra Performance Liquid Chromatography-Mass Spectrometry (UPLC-MS). International Journal of Pharmaceutics, 578, 119077. https://doi.org/https://doi.org/10.1016/j.ijpharm.2020.119077

Song, C. K., Balakrishnan, P., Shim, C.-K., Chung, S.-J., Chong, S., & Kim, D.-D. (2012). A Novel Vesicular Carrier, Transethosome, For Enhanced Skin Delivery of Voriconazole: Characterization and In Vitro/In Vivo Evaluation. Colloids and Surfaces B: Biointerfaces, 92, 299–304. https://doi.org/https://doi.org/10.1016/j.colsurfb.2011.12.004

Soomherun, N., Kreua-ongarjnukool, N., Niyomthai, S. T., & Chumnanvej, S. (2024). Lipid-Polymer Hybrid Nanoparticles Synthesized via Lipid-Based Surface Engineering for a robust drug delivery platform. Colloids and Surfaces B: Biointerfaces, 237, 113858. https://doi.org/https://doi.org/10.1016/j.colsurfb.2024.113858

Soradech, S., Tiatragoon, W., Phanphothong, P., Ouamkan, K., Kengkwasingh, P., Ruengsomwong, S., Intawong, S., & Muangman, T. (2024). Development of Transethosomes Loaded with Fruit Extract from Carissa carandas L. as a Brightening and Anti-Aging Cosmeceutical Ingredient. Cosmetics, 11(6), 199. https://doi.org/10.3390/cosmetics11060199

Srifiana, Y., & Amalia, A. (2019). Stabilitas Fisik Transethosome Kurkumin yang Menggunakan Kombinasi Surfaktan Tween 60 dan Span 60. Jurnal Ilmu Kefarmasian Indonesia, 18(2), 184–191.

Sudhakar, K., Mishra, V., Jain, S., Rompicherla, N. C., Malviya, N., & Tambuwala, M. M. (2021). Development and Evaluation of the Effect of Ethanol and Surfactant in Vesicular Carriers on Lamivudine Permeation Through the Skin. International Journal of Pharmaceutics, 610, 121226. https://doi.org/https://doi.org/10.1016/j.ijpharm.2021.121226

Sundar, V. D., Divya, P., & Dhanaraju, M. D. (2020). Design Development and Characterisation of Tramadol Hydrochloride Loaded Transethosomal Gel Formulation for Effective Pain Management. Indian Journal of Pharmaceutical Education and Research, 54(2), S88–S97. https://doi.org/10.5530/ijper.54.2s.65

Teaima, M., Abdelmonem, R., Adel, Y. A., El-Nabarawi, M. A., & El-Nawawy, T. M. (2021). Transdermal Delivery of Telmisartan: Formulation, In Vitro, Ex Vivo, Iontophoretic Permeation Enhancement and Comparative Pharmacokinetic Study in Rats. Drug Design, Development and Therapy, 15,

4603–4614. https://doi.org/10.2147/DDDT.S327860

Touitou, E., Dayan, N., Bergelson, L., Godin, B., & Eliaz, M. (2000). Ethosomes — Novel Vesicular Carriers for Enhanced Delivery: Characterization and Skin Penetration Properties. Journal of Controlled Release, 65(3), 403–418. https://doi.org/https://doi.org/10.1016/S0168-3659(99)00222-9

Vera Pérez, J., Martínez Cortés, D. M., & Gómez y Gómez, Y. (2022). Potential Use of Transethosomes as A Transdermal Delivery System for Metabolites from Chenopodium murale. Materials Today Communications, 30, 103165. https://doi.org/https://doi.org/10.1016/j.mtcomm.2022.103165

Vergara, D., López, O., Sanhueza, C., Chávez-Aravena, C., Villagra, J., Bustamante, M., & Acevedo, F. (2023). Co-Encapsulation of Curcumin and α-Tocopherol in Bicosome Systems: Physicochemical Properties and Biological Activity. Pharmaceutics, 15(7), 1912. https://doi.org/10.3390/pharmaceutics15071912

Wang, G., Moriyama, N., Tottori, S., & Nishizawa, M. (2025). Recent Advances in Iontophoresis-Assisted Microneedle Devices for Transdermal Biosensing and Drug Delivery. Materials Today Bio, 31, 101504. https://doi.org/10.1016/j.mtbio.2025.101504

Wang, Y., Wang, R., Qi, X., Li, W., Guan, Q., Wang, R., Li, X., Li, Y., Yang, Z., & Feng, Y. (2021). Novel Transethosomes for the Delivery of Brucine and Strychnine: Formulation Optimization, Characterization and In Vitro Evaluation in Hepatoma Cells. Journal of Drug Delivery Science and Technology, 64, 102425. https://doi.org/https://doi.org/10.1016/j.jddst.2021.102425

Xiaoshan LI, Kaitong LI, Sandi JIN, & Qiaohong HU. (2021). Optimization of the Formulation of Curcumin Transethosomes. China Pharmacy, 12, 2383–2387.

Yadav, D., Sandeep, K., Pandey, D., & Dutta, R. K. (2017). Liposomes for Drug Delivery. Journal of Biotechnology & Biomaterials, 7(4), 1-8. https://doi.org/10.4172/2155-952x.1000276

Yang, H., Wu, X., Zhou, Z., Chen, X., & Kong, M. (2019). Enhanced Transdermal Lymphatic Delivery of Doxorubicin via Hyaluronic Acid Based Transfersomes/Microneedle Complex for Tumor Metastasis Therapy. International Journal of Biological Macromolecules, 125, 9–16. https://doi.org/https://doi.org/10.1016/j.ijbiomac.2018.11.230

Zhou, Y., Wei, Y.-H., Zhang, G.-Q., & Wu, X.-A. (2010). Synergistic Penetration of Ethosomes and Lipophilic Prodrug on the Transdermal Delivery of Acyclovir. Archives of Pharmacal Research, 33(4), 567–574. https://doi.org/10.1007/s12272-010-0411-2

Zi, M., Ke, J., Jiang, S., Cui, X., Zhang, J., Yuan, S., Huang, S., Wang, J., Liu, H., Zhang, J., & Peng, C. (2024). Colchicine-Loaded Transethosomes Enhances Transdermal Permeability and Therapeutic Effects of Acute Gouty Arthritis via Vesicle Extrusion and Lipid Perturbation. Colloids and Surfaces A: Physicochemical and Engineering Aspects, 687, 133582. https://doi.org/https://doi.org/10.1016/j.colsurfa.2024.133582