TRANSETHOSOMES IN PRECISION DERMATOLOGY: A NEW ERA OF TARGETED SKIN DRUG DELIVERY

Ms. Bushra Baig[1], Ms. Shrushti Bhagat[1], Dr. Ravikiran Wakade[2], Prof. Sudarshan Behere[3*], Dr. Pravin Kawtikwar[4]

1. Research student, M. Pharm (Pharmaceutics) Sudhakarrao Naik Instutute of Pharmacy, Pusad
2. Associate professor, Sudhakarrao Naik Instutute of Pharmacy, Pusad
3. Assistant professor, Sudhakarrao Naik Instutute of Pharmacy, Pusad
4. Principal, Sudhakarrao Naik Instutute of Pharmacy, Pusad

Corresponding author: Prof. Sudarshan Behere
sudarshanbehere22@gmail.com

Abstract

Effective topical and transdermal drug delivery systems are needed for dermatological disorders like psoriasis, acne, fungal infections, dermatitis and skin cancer to achieve better therapeutic outcomes. The barrier effect of the stratum corneum causes conventional topical preparations to have poor skin absorption, insufficient drug retention, frequent use and low bioavailability. To surmount these drawbacks, sophisticated vesicular nanocarriers have been created and transethosomes have proved to be very promising ultra-deformable ones. Transethosomes are hybrid vesicular systems consist of phospholipids, ethanol, and edge activators which are designed to benefit of ethosomes and transferosomes, with the potential of improving the permeation through the skin, high deformability, drug entrapment, and controlled drug release.

This review covers the composition, mechanism of penetration of skin barrier, preparation methods, characterization parameters, merits, drawbacks and recent developments in transethosomal drug delivery systems. Transethosomes have the potential to deliver locally and target specific areas of the skin, while minimizing systemic side effects, due to the synergistic effect of ethanol along with the edge activators. Recent research has shown their efficacy in anti-inflammatory, antifungal, anti-acne, anticancer and cosmeceutical therapies, showing improved therapeutic effectiveness and patient compliance. Moreover, there is a growing potential in precision dermatology with the emergence of smart stimulus responsive transethosomes, surface modified vesicles and multifunctional nanocarriers. While there have been great advances, issues of stability, large-scale manufacturing, reproducibility and clinical translation continue to exist. In general, transethosomes are a promising new generation nanovesicular system for advanced dermatological and transdermal drug delivery applications.

Keywords: Transethosomes; Ultra-deformable vesicles; Dermatological drug delivery; Transdermal drug delivery; Vesicular nanocarriers; Skin permeation; Ethosomes; Transferosomes; Controlled drug release; Precision dermatology.

INTRODUCTION

Dermatological drug delivery is important for treating skin disorders such as psoriasis, acne, fungal infections, dermatitis, and inflammation. Topical and transdermal delivery systems are preferred because they provide localized drug action, reduce systemic side effects, and improve patient compliance [1]. However, the stratum corneum acts as a strong barrier that limits the penetration of many drugs, making effective and controlled skin delivery a major challenge in dermatological therapy [2].

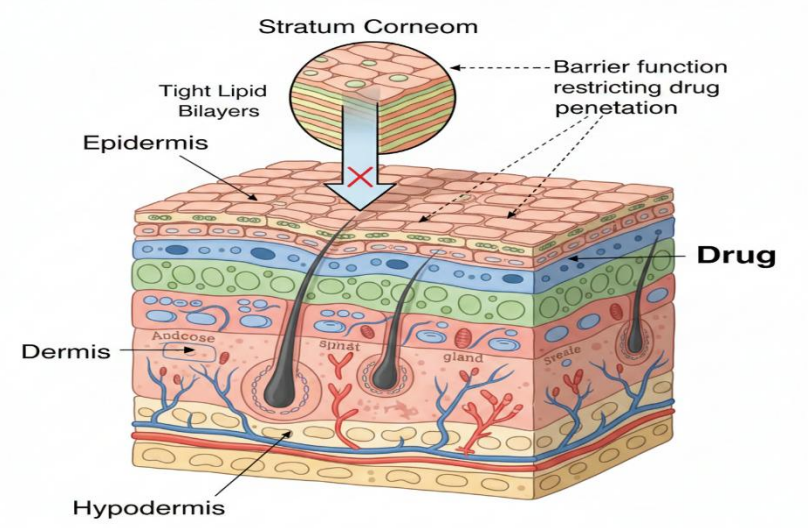


Figure 1. Structure of human skin highlighting the barrier role of the stratum corneum.

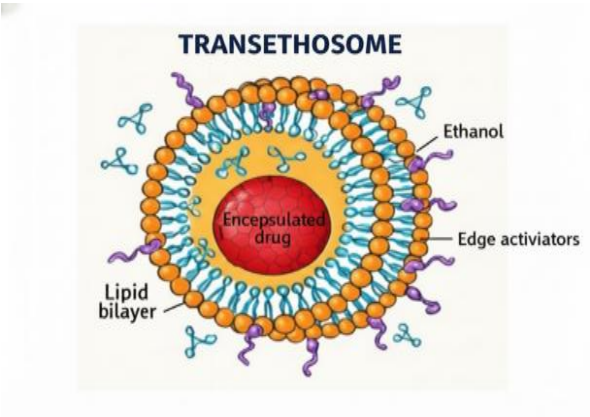
The conventional topical formulations include topical creams, gels and ointments which have poor penetration, low retention, require frequent application and lack consistency of effect [3]. Another limitation of the traditional transdermal systems is that the stratum corneum also acts as a barrier which limits the efficacy of the treatment [4].

In order to overcome these limitations, these vesicular carriers such as liposomes, niosomes, transfersomes, and ethosomes are developed to enhance the skin delivery. [5] The stability, deformability and drug loading problems remain, however. [6]

Advanced ultra deformable vesicular (nano) carriers called transethosomes are made of phospholipids, ethanol and edge activators. Their properties are superior skin permeation, higher entrapment of drug and controlled drug release. [7][8] These compounds have been proved as effective carriers for the delivery of anti-inflammatory, antifungal, analgesic and anticancer drugs with improved therapeutic efficacy and decreased systemic toxicity in the recent studies. [9,10]

TRANSETHOSOMES

Transethosomes are advanced, ultra-deformable vesicular nanocarriers composed of phospholipids, a high concentration of ethanol, and edge activators (surfactants). They represent a hybrid vesicular system that integrates the key features of ethosomes and transfersomes to achieve superior skin penetration and enhanced drug deliveryperformance [25]. The presence of ethanol disrupts the lipid organization of the stratum corneum, while edge activators impart high flexibility to the vesicular membrane, allowing transethosomes to squeeze through narrow intercellular pathways of the skin [26]. Due to these unique characteristics, transethosomes are considered smart vesicular nanocarriers capable of delivering both hydrophilic and lipophilic



drugs in a controlled and targeted manner for dermatological applications [27].

Figure 2. Structure of Transethosome

RATIONALE BEHIND THE DEVELOPMENT OF TRANSETHOSOMES

Transethosomes were developed to overcome the limitations of earlier vesicular carriers such as liposomes, ethosomes, and transfersomes [28][29]. Ethosomes provide enhanced skin permeation due to ethanol but lack sufficient vesicle flexibility, while transfersomes possess high deformability but limited ability to disrupt stratum corneum lipids.

To combine the advantages of both systems, transethosomes were designed with phospholipids, ethanol, and edge activators. This synergistic composition improves vesicle deformability, enhances skin penetration, increases drug entrapment efficiency, and provides controlled drug release [30]. As a result, transethosomes have emerged as promising carriers for precision-driven dermatological drug delivery with improved therapeutic efficacy and reduced side effects [31].

COMPARISON BETWEEN LIPOSOMES, NIOSOMES, ETHOSOMES, TRANSFEROSOMES AND TRANSETHOSOMES

Vesicular drug delivery systems are nano-sized carriers made of amphiphilic molecules that can encapsulate both hydrophilic and lipophilic drugs. They improve drug stability, skin penetration, controlled release, and reduce systemic side effects in dermatological therapy [11]. Various vesicular systems such as liposomes, niosomes, ethosomes, and transfersomes have been developed for topical and transdermal delivery, but their limitations led to the development of advanced hybrid carriers like transethosomes [12][13].

Sr. No.	Vesicular system	Composition	Entrapment efficiency	Flux rate	Skin permeation
1	Liposomes[14, 15]	Phospholipids, Cholesterol, Aqueous phase	Modern to high	Low	Limited penetration; mainly acts as a drug reservoir on stratum corneum
2	Niosomes [16, 17]	Non ionic surfactant, Cholesterol	High	Low to moderate	Better penetration than liposomes due to surfactant interaction with skin lipids
3	Ethosomes [18, 19]	Phospholipids, High ethanol content (20-45%), Water	Moderate	Higher than liposomes and niosomes	Ethanol fluidizes stratum corneum lipids, enhancing permeation
4	Transferosomes [20, 21]	Phospholipids, Edge activators (Tween/Span),Water	High	High	Highly deformable vesicles penetrate through narrow skin pores
5	Transethosomes [22, 23, 24]	Phospholipids, Ethanol,Edge activators, Water	Highest	Highest	Combined effect of ethanol-induced lipid disruption and vesicle deformability

Table 1. Table adapted from[32,33,34,35,36]

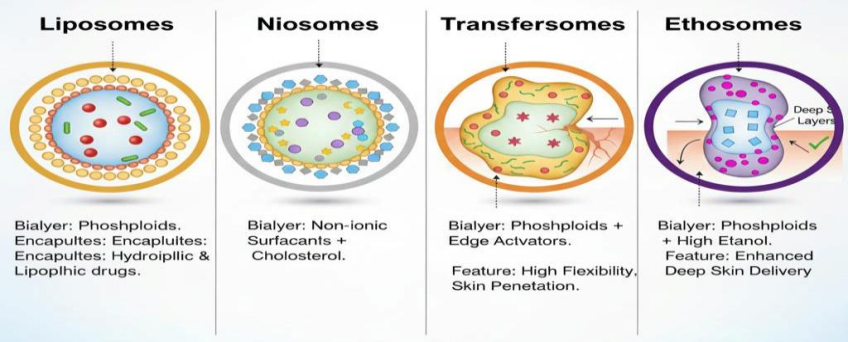


Figure 3. Comparative illustration of conventional and advanced vesicular nanocarriers

COMPOSITION OF TRANSETHOSOMES

Transethosomes are ultra-deformable vesicular nanocarriers which are primarily composed of phospholipids, ethanol and edge activators. All these components act to improve the flexibility of vesicles, permeation through skin, entrapment of drug molecules and controlled drug release.[36][37]

Phospholipids: They are used to create the bilayer structure of vesicles and to encapsulate both hydrophobic and hydrophilic drugs. [38, 39]

Ethanol: Increases the permeability of the skin by fluidizing the lipids of stratum corneum and decreasing the vesicle size, which leads to an increase in drug penetration and solubility [40][41].

Edge Activators: Transethosomes are transferred through narrow pores of the skin without rupturing by increasing the elasticity of the vesicles, for that purpose, some surfactants like Tween 80 and Span 80 are used. [42] [43]

Aqueous Phase (Water): Hydration medium that stabilizes vesicles. [44]

Optional components include cholesterol for membrane stability, active drug (API), penetration enhancers or stabilizers that improve the formulation performance. [45][46]

Composition	**Role**
Phospholipids	Form vesicle bilayer
Ethanol (20-45%)	Increase penetration and flexibility
Edge activators (Tween/Span/Cholate)	Enhances deformiblity
Water	Hydration medium
Optional: Cholesterol, Drug, Stabilizer	Stability or functionality

Table 2. Composition of Transethosomes

MECHANISM OF SKIN PENETRATION OF TRANSETHOSOMES

Transethosomes exhibit enhanced skin penetration due to the synergistic action of ethanol, phospholipids, and edge activators, which collectively help overcome the barrier properties of the stratum corneum [47][48]. Their ultra-deformable nature allows efficient delivery of drugs into deeper skin layers, making them highly suitable for advanced dermatological therapy.

Ethanol plays an important role by fluidizing and disrupting the lipid matrix of the stratum corneum, thereby increasing skin permeability [49]. It also improves the flexibility of the vesicular membrane, enabling transethosomes to penetrate more effectively than conventional vesicular systems. [50]

Edge activators further enhance vesicle deformability and elasticity, allowing transethosomes to squeeze through narrow intercellular pores without rupture [51]. This elastic transport mechanism facilitates deeper drug penetration and localized drug deposition within the skin layers [52].

The combined effect of ethanol-induced lipid disruption and surfactant-mediated vesicle flexibility results in increased drug flux, prolonged skin retention, targeted delivery, and reduced systemic exposure, ultimately improving therapeutic efficacy in dermatological applications [53, 54]

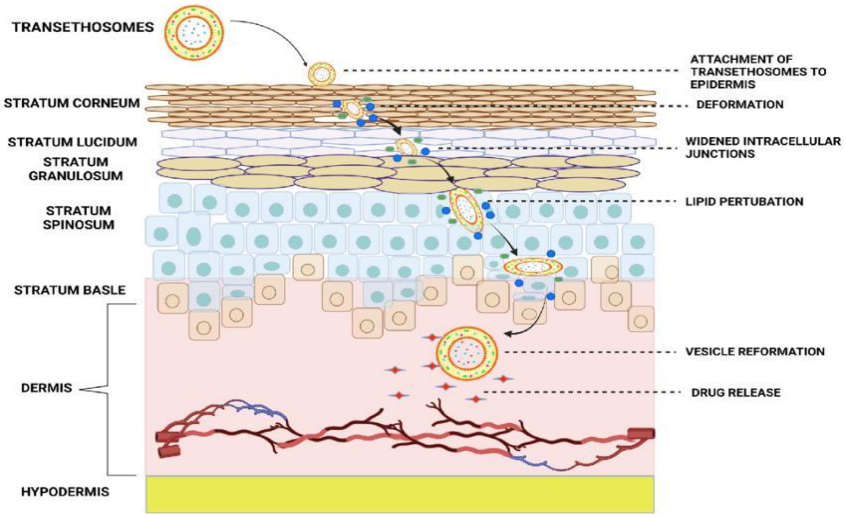


Figure 4 . Mechanism of transethosome- mediated skin penetration

METHODS OF PREPARATION OF TRANSETHOSOMES

Transethosomes are hybrid vesicular nanocarriers composed of phospholipids, ethanol, and edge activators, developed to enhance skin penetration and drug localization. The method of preparation plays a critical role in determining vesicle size, entrapment efficiency, deformability, and stability, which ultimately influence dermatological performance [55].

1.Cold Method

The cold method is the most commonly employed technique for preparing transethosomes due to its simplicity and suitability for thermolabile drugs. In this method, phospholipids and edge activators are dissolved in ethanol at room temperature under continuous stirring. The aqueous phase containing the drug is slowly added to the ethanolic phase, followed by sonication or extrusion to obtain nanosized vesicles with uniform distribution [56]. This method offers high entrapment efficiency and preserves drug stability, making it ideal for dermatological formulations [57].

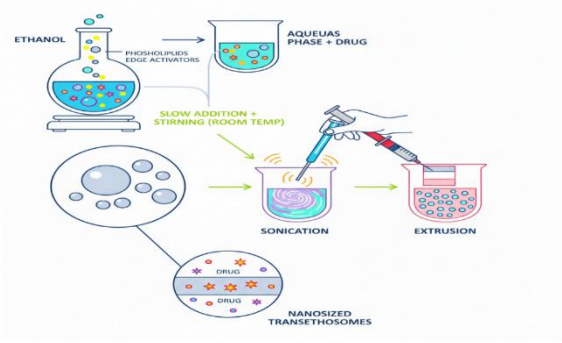


Figure 5. Cold method

2. Hot Method

In hot method, phospholipids and edge activators are dispersed in water and heated above their transition temperature. Ethanol, preheated to the same temperature, is added to the aqueous phase under continuous stirring. After cooling, vesicles are formed and downsized if required. This method is effective but less preferred for heat-sensitive drugs [58].

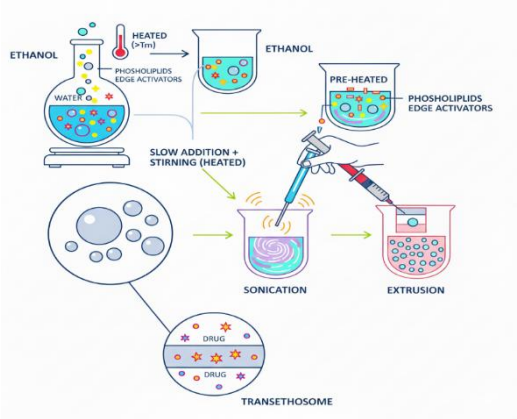


Figure 6. Hot method

3. Ethanol Injection Method

In this method, an ethanolic solution containing phospholipids, edge activators, and drug is rapidly injected into an aqueous phase under stirring, resulting in spontaneous vesicle formation

due to ethanol diffusion. Although it produces vesicles with narrow size distribution, issues related to ethanol removal and scalability limit its application [59].

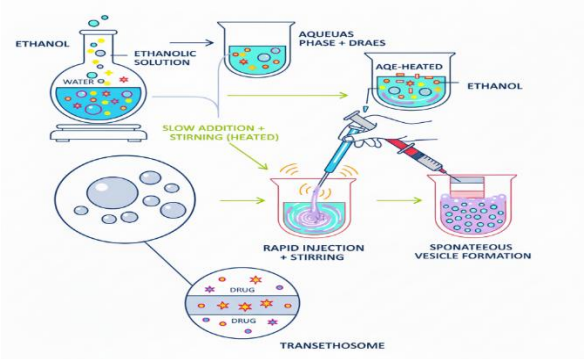


Figure 7. Ethanol injection method

4. Thin Film Hydration Method

The thin film hydration method involves forming a lipid film by solvent evaporation, followed by hydration with a hydroethanolic drug solution. The resulting vesicles are reduced in size using sonication or extrusion. Despite high drug loading, this method is time-consuming and less suitable for large-scale production [60].

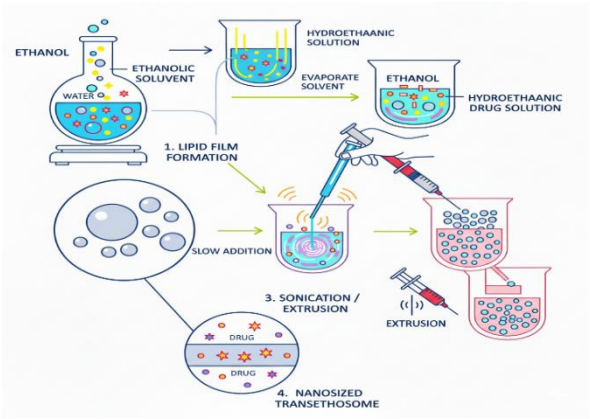


Figure 8. Thin film hydration method

Among the available techniques, the cold method is most widely adopted for transethosome preparation due to its operational simplicity, reproducibility, and compatibility with dermatological drugs. Optimization of formulation and processing parameters is essential to achieve enhanced skin penetration and therapeutic efficacy [55][57].

ADVANTAGES OF TRANSETHOSOMES

Enhanced Skin Penetration: Ethanol and edge activators improve vesicle flexibility and enable deeper drug penetration into the skin [78].

High Drug Entrapment Efficiency: Transethosomes effectively encapsulate both hydrophilic and lipophilic drugs with improved stability [79].

Controlled Drug Release: They provide sustained drug release, reducing dosing frequency and improving patient compliance [77].

Reduced Systemic Side Effects: Localized drug delivery minimizes systemic absorption and adverse effects [78].

Versatile and Stable Carrier: Suitable for various dermatological drugs and stable even for thermolabile compounds [79].

LIMITATIONS AND CHALLENGES OF TRANSETHOSOMES

Stability Issues: Transethosomes may show vesicle aggregation, fusion, and drug leakage during storage [80].

Scale-Up Challenges: Large-scale production with consistent quality remains difficult [81].

Skin Irritation: High ethanol content may cause irritation or dermatitis on sensitive skin [82].

Limited Clinical Data: More in vivo studies and clinical trials are needed to confirm safety and efficacy [83].

Drug Loading Limitations: Achieving consistent drug entrapment for different drugs is challenging [80].

CHARACTERIZATION OF TRANSETHOSOMES

Characterization of transethosomes is essential to evaluate their physicochemical properties, stability, and effectiveness as dermal and transdermal drug delivery systems [61][62]. Proper characterization ensures reproducible quality, enhanced skin permeation, and predictable therapeutic performance. Important parameters include vesicle size, zeta potential, entrapment efficiency, morphology, deformability, drug release, and stability.

1.Vesicle Size and Size Distribution:

Particle size plays an important role in skin penetration, drug release, and formulation stability. Smaller vesicles enhance permeation through the stratum corneum. Dynamic light scattering (DLS) is commonly used to determine vesicle size and polydispersity index (PDI). Optimized transethosomes usually exhibit nanosized vesicles with low PDI values, indicating uniform distribution [63][64].

2.Zeta Potential:

Zeta potential indicates the surface charge and colloidal stability of vesicles. High absolute zeta potential values help prevent vesicle aggregation through electrostatic repulsion, thereby improving formulation stability during storage [65].

3.Entrapment Efficiency (EE%):

Entrapment efficiency represents the percentage of drug successfully encapsulated within the vesicles. High EE% improves drug loading, therapeutic efficacy, and prolonged drug action. It is commonly determined using ultracentrifugation or dialysis methods [62][66].

4.Morphology and Structural Integrity:

Morphological studies provide information about vesicle shape and surface characteristics. Techniques such as transmission electron microscopy (TEM), scanning electron microscopy (SEM), and atomic force microscopy (AFM) are used to confirm spherical shape, uniformity, and absence of aggregation [67].

5.Deformability Index:

Deformability is a unique feature of transethosomes that enables them to pass through narrow skin pores. The deformability index measures vesicle elasticity and is directly related to enhanced skin penetration ability [61][63].

6.In Vitro Drug Release and Skin Permeation Studies:

Franz diffusion cell studies are commonly used to evaluate drug release behavior and skin permeation. Parameters such as cumulative drug permeation and flux help determine the effectiveness of transethosomes in providing sustained and enhanced drug delivery [64][68].

7.Stability Studies:

Stability studies assess changes in vesicle size, zeta potential, entrapment efficiency, and drug content under different storage conditions. Stable formulations show minimal physicochemical changes over time, indicating suitability for long-term use [65][69].

APPLICATIONS OF TRANSETHOSOMES IN DERMATOLOGICAL DRUG DELIVERY

Transethosomes are smart vesicular nanocarriers with improved deformability and superior penetration ability in skin which are highly effective in precision dermatological drug delivery.[70]

1.Anti-Inflammatory and Anti-Psoriatic Therapy: Enhance penetration and retention of corticosteroids and/or anti-psoriatic drugs, which will lead to better efficacy and less systemic side effects.[71][72]

2.Enhanced Delivery of Antifungal Drugs: Improve the delivery of antifungal drugs such as ketoconazole and terbinafine, leading to deeper penetration and improved therapeutic outcomes. [73]

3.Anti-Cancer Therapy: Enhance the delivery of anti-cancer drugs like 5-fluorouracil and curcumin directly to the tumor site, thereby increasing the targeting of the tumor and minimizing systemic side effects. [74]

4.Anti-Acne Therapy: Better targeting of the anti-acne drugs at the follicles, resulting in an improved antimicrobial effect and decreased inflammation of the skin [75].

5.Cosmeceutical Applications: Improved penetration and sustained release to deliver antioxidants, vitamins and anti-aging agents. [70][76]

6.Targeted Dermatological Therapy: Allow targeted delivery of drugs to targeted areas of the skin to achieve optimal therapeutic response with minimal side effects. [71]

Current developments in transethosomes

The recent developments in the vesicular nanocarrier systems have emphasized the great therapeutic potential of ethosomes and transethosomes for transdermal and topical drug delivery. The company Galatage et al. (2025) has formulated ethosomes with Acacia senegal extract and assessed their ability to penetrate the skin and have high anticancer potential against MCF-7 cells as compared with the plain extract. Likewise, Patil et al. (2024) optimized anti-acne activity, entrapment efficiency and skin permeation of transethosomal gel formulation of nadifloxacin using Box–Behnken design. Kushkiwala et al. (2024) have developed flurbiprofen-loaded ethosomal gel that exhibited improved anti-inflammatory properties and permeation characteristics. Xiao et al. (2024) used the paeoniflorin–glycyrrhizic acid transethosomal gel for the treatment of melasma, with the results demonstrating a significant decrease in pigmentation and markers of oxidative stress. In addition to that, Asghar et al. (2023) showed that miconazole nitrate transethosomal gel was effective against fungi and had better permeation into skin. Furthermore, using agomelatine loaded nano-transethosomes with sustained release behavior for drug delivery, Ansari et al. (2019) reported the enhancement of transdermal delivery of antidepressant drugs with improved therapeutic efficacy. Güzel et al. (2022) demonstrated higher drug deposition in the deeper layers of the skin with naftifine loaded transethosomes and Wongsirojkul et al. (2025) successfully improved the stability, skin permeation, and wound healing potential of retinyl acetate by transethosomal delivery. In sum, these studies suggest that ethosomal and transethosomal formulations represent potential strategies for enhancing the penetration, stability, therapeutic efficacy and patient adherence of topical and transdermal formulations.[87-94]

FUTURE PERSPECTIVES AND CLINICAL POTENTIAL OF TRANSETHOSOMES

Transethosomes are advanced vesicular nanocarriers that combine the advantages of ethosomes and transferosomes, providing enhanced skin penetration and targeted drug delivery. Their flexible structure makes them promising carriers for modern dermatological therapy.

Recent studies focus on smart and multifunctional transethosomes, including stimulus-responsive systems that release drugs in response to pH, temperature, or enzymes. Surface-modified transethosomes with polymers or ligands are also being explored for better skin targeting and prolonged drug retention. Incorporation into gels, creams, and nanofibrous mats further improves patient compliance and therapeutic outcomes [83].

Transethosomes show great potential in precision dermatology for treating psoriasis, acne, fungal infections, skin cancer, and inflammatory skin disorders. They enhance localized drug delivery while reducing systemic side effects, making them suitable for personalized therapy [80].

Despite promising preclinical results, challenges such as large-scale production, stability, reproducibility, and regulatory approval still limit clinical translation. Further toxicological studies and clinical trials are essential to establish their safety and efficacy for commercialization [81].

Conclusion

Transethosomes are advanced vesicular nanocarriers which include phospholipids, ethanol and edge activators to improve the penetration and targeted delivery of drugs to the skin. They have the ability to deform, which enhances the permeation of drugs, the depth of penetration into the skin and their therapeutic effects compared to traditional topical systems and other vesicular systems.

Experimental investigation revealed that transethosomes have high drug entrapment efficiency, controlled release of drug, better bioavailability and less systemic toxicity. They have been successfully applied to the delivery of anti-inflammatory, antifungal, anti-acne, anticancer and cosmeceutical agents.

Finally, transethosomes are an emerging new drug delivery system that has a tremendous potential for the effective, targeted and patient-friendly treatment of a wide range of skin diseases.

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