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Review Article

Transethosomal Gel in Advanced Transdermal Drug Delivery: Formulation Strategies, Functional Characterization, Therapeutic Applications, and Future Perspectives

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ABSTRACT

Transethosomal gel is considered an innovative approach in advanced transdermal drug delivery, offering improved drug permeation and sustained therapeutic action. Conventional transdermal systems are often restricted by the stratum corneum, which serves as a major barrier to the passage of many drugs through the skin. Transethosomes are highly flexible vesicular carriers containing phospholipids, ethanol, and edge activators, which allow them to deform and penetrate through the skin more efficiently. When incorporated into a gel base, these vesicles provide better skin contact, prolonged residence time, controlled drug release, and convenient application. This review focuses on the formulation approaches used in the preparation of transethosomal gels, with emphasis on the role of vesicle components and gelling agents in optimizing drug delivery. Important evaluation parameters, including vesicle size, surface charge, entrapment efficiency, deformability, drug release, and transdermal permeation, are also discussed. The application of transethosomal gels in the treatment of various disorders, including pain, inflammation, migraine, and other therapeutic conditions, is highlighted. In addition, current challenges related to formulation stability, manufacturing, optimization, and clinical application are considered. Future research may focus on improving formulation performance, establishing large-scale manufacturing methods, and evaluating clinical effectiveness. Overall, transethosomal gel offers a promising and versatile platform for enhancing transdermal drug delivery and may improve drug efficacy, bioavailability, and patient convenience.

INTRODUCTION

The advancement of nanotechnology has revolutionized pharmaceutical research by enabling the development of innovative drug delivery systems that improve therapeutic efficacy while minimizing adverse effects. Conventional drug delivery methods, including oral and

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parenteral administration, remain the most widely employed approaches for the treatment of acute and chronic diseases. However, these routes are frequently associated with several limitations, such as poor aqueous solubility of drugs, extensive first-pass hepatic metabolism, gastrointestinal degradation, low bioavailability, fluctuating plasma drug concentrations, and poor patient compliance. These challenges have encouraged researchers to explore alternative delivery strategies capable of overcoming the drawbacks of traditional dosage forms.

Among the various alternatives, transdermal drug delivery systems (tdds) have emerged as a promising and patient-friendly approach for systemic and localized drug delivery. The transdermal route allows therapeutic agents to penetrate the skin and enter systemic circulation while bypassing gastrointestinal degradation and hepatic first-pass metabolism. This route offers several advantages, including sustained drug release, improved patient compliance, reduced dosing frequency, stable plasma drug concentrations, and the possibility of immediate termination of therapy by removing the formulation from the skin. Despite these benefits, the highly organized structure of the skin, particularly the stratum corneum, presents a significant barrier that restricts the penetration of many therapeutic molecules.

To overcome this challenge, nanotechnology-based vesicular carriers have gained considerable attention. Vesicular systems such as liposomes, niosomes, ethosomes, and transfersomes have been extensively investigated for enhancing transdermal drug delivery. These nanocarriers improve drug solubility, protect encapsulated drugs from degradation, increase skin permeation, and provide controlled drug release. Among these systems, transethosomes represent an advanced generation of lipid vesicles that combine the advantages of ethosomes and transfersomes. They are composed primarily of phospholipids, a relatively high concentration of ethanol, water, and an edge activator such as tween 80, span 80, or sodium cholate. This unique composition imparts exceptional deformability and flexibility, allowing transethosomes to penetrate deeply through the skin and deliver drugs efficiently to target tissues.

The presence of ethanol fluidizes the lipid structure of the stratum corneum, thereby increasing skin permeability, while edge activators enhance vesicle elasticity, enabling the vesicles to pass through microscopic pores significantly smaller than their own diameter. Consequently, transethosomes exhibit superior drug penetration, higher encapsulation efficiency, enhanced stability, and improved therapeutic performance compared with conventional vesicular carriers.

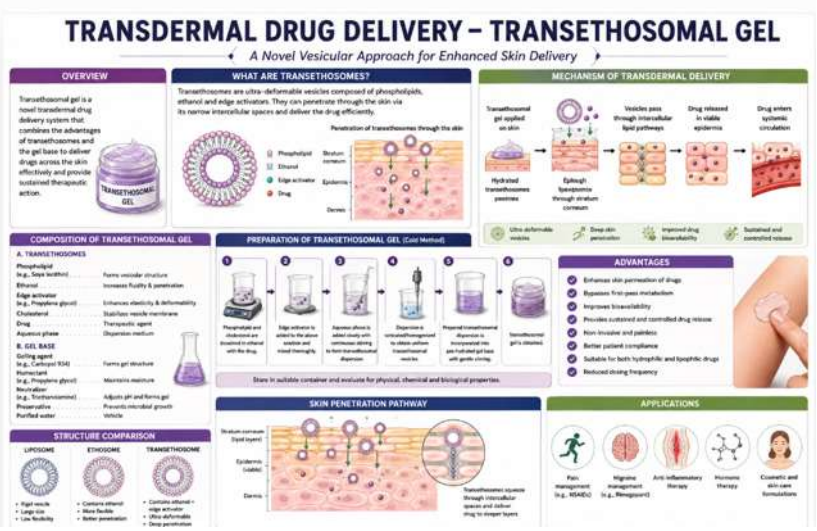
In recent years, transethosomal gel formulations have attracted increasing interest because they combine the advantages of nanovesicular carriers with the convenience of topical gel dosage forms. The incorporation of transethosomes into polymeric gels such as carbopol or hpmc improves formulation viscosity, spreadability, residence time on the skin, and patient acceptability while maintaining the enhanced permeation characteristics of transethosomes. Such formulations have demonstrated promising outcomes in the treatment of inflammatory disorders, fungal infections, pain management, diabetes, cancer, neurological disorders, and migraine therapy.

One of the most promising applications is the incorporation of rimegepant, a calcitonin gene-related peptide (cgrp) receptor antagonist approved for the acute treatment and prevention of migraine. Rimegepant belongs to the biopharmaceutics classification system (bcs) class

ii, characterized by low aqueous solubility and high permeability. Oral administration of rimegepant is associated with limited solubility and variable bioavailability, making it an ideal candidate for transdermal delivery using transethosomal gel technology. Encapsulation within transethosomes has the potential to enhance drug solubility, improve skin permeation, prolong drug release, and reduce dosing frequency, ultimately improving therapeutic efficacy and patient adherence.

The growing interest in nanotechnology, personalized medicine, and targeted drug delivery has further accelerated research on transethosomal formulations. Numerous preclinical studies have demonstrated improved pharmacokinetic behavior, enhanced skin permeation, greater drug retention within skin layers, and superior therapeutic outcomes compared with conventional formulations. However, challenges related to large-scale manufacturing, long-term stability, regulatory approval, and commercialization still require further investigation.

Therefore, this review aims to comprehensively discuss the formulation design, preparation methods, characterization techniques, therapeutic applications, recent advancements, clinical prospects, and future perspectives of transethosomal gel as an advanced transdermal drug delivery platform, with particular emphasis on its potential application in the delivery of rimegepant and other poorly water-soluble therapeutic agents.



Applications of Transdermal Drug Delivery

- Transdermal drug delivery systems are used to provide controlled and sustained release of drugs over an extended period.
- They are useful for administering drugs intended for the treatment of chronic conditions, such as hypertension, diabetes, pain, and hormonal disorders.
- These systems can avoid first-pass metabolism in the liver, which may improve the bioavailability of certain drugs.
- Transdermal delivery may help maintain consistent drug concentrations in the bloodstream, reducing fluctuations associated with conventional oral dosage forms.
- It can improve patient compliance by reducing the frequency of drug administration.

- Transdermal systems are particularly beneficial for drugs with short biological half-lives or those requiring prolonged therapeutic action.
- They provide a non-invasive and convenient alternative to injections and oral medications.
- Advanced systems such as transethosomes, transfersomes, and liposomes can enhance drug permeation through the skin and improve therapeutic effectiveness.

Disadvantages of Transdermal Drug Delivery

- The skin acts as a strong protective barrier, which limits the absorption of many drugs.
- Only drugs with suitable molecular size, lipophilicity, and potency can be effectively delivered through the skin.
- The absorption rate may vary depending on skin condition, age, hydration, and anatomical site.
- Some formulations may cause skin irritation, redness, itching, or allergic reactions.
- The delivery system may be affected by sweating, washing, or excessive friction, which can reduce drug absorption.
- Transdermal systems are generally not suitable for high-dose drugs because the amount that can cross the skin is limited.
- The formulation and manufacturing of advanced transdermal systems can be complex and costly.
- Improper application or poor adhesion of patches may lead to inconsistent drug delivery

Pharmaceutical Uses and Route of Administration of Transethosomal Gel

Pharmaceutical Uses:

- Used for controlled and sustained delivery of therapeutic drugs.
- Helps improve skin penetration and drug permeation through the stratum corneum.
- Can be used for the treatment of migraine, pain, inflammation, arthritis, and hormonal disorders.
- May enhance the bioavailability and therapeutic effectiveness of drugs with poor oral absorption.
- Provides prolonged drug release and may help reduce dosing frequency.
- Useful for delivering drugs that undergo significant first-pass metabolism when administered orally.

Routes of Administration of Gel Formulations

- **Topical administration:** The gel is applied directly to the skin to provide a localized therapeutic effect.
- **Transdermal administration:** The drug permeates through the skin and reaches the systemic circulation, allowing prolonged drug action.
- **Dermal administration:** The formulation is applied to the skin to manage various localized dermatological conditions.
- **Ophthalmic administration:** Gel formulations are placed in the eye for the treatment of different ocular disorders.

- **Nasal administration:** The gel is delivered through the nasal cavity to achieve either local or systemic therapeutic effects.
- **Buccal administration:** The gel is applied to the inner lining of the cheek, where the drug can be absorbed into the systemic circulation.
- **Vaginal administration:** The formulation is administered through the vaginal route for localized treatment or systemic drug delivery.
- **Rectal administration:** The gel is introduced into the rectum to produce local effects or facilitate systemic drug absorption.

In the case of transethosomal gel, the transdermal route is the most important route of administration, as it facilitates enhanced drug penetration through the skin and supports controlled and sustained drug delivery.

General Considerations Before Preparation

Before initiating the formulation process, the following factors should be considered:

- Selection of suitable phospholipids
- Drug compatibility with formulation components
- Ethanol concentration
- Type and concentration of edge activator
- Selection of hydration medium
- Temperature during preparation
- Sonication time
- Storage conditions

Cold Method

Principle

The cold method is based on the formation of lipid vesicles by dissolving phospholipids and edge activators in ethanol, followed by gradual hydration with an aqueous phase under continuous stirring. The spontaneous self-assembly of phospholipid molecules results in the formation of nanosized transethosomes.

Materials Required

- Drug (e.g., Rimegepant)
- Soya phosphatidylcholine (SPC)
- Ethanol
- Tween 80 or Span 80
- Distilled water or phosphate buffer
- Magnetic stirrer
- Probe sonicator

Procedure

1. Accurately weigh the drug, phospholipid, and edge activator.
2. Dissolve phospholipid and edge activator in ethanol.
3. Dissolve the drug in the same ethanolic phase or aqueous phase depending on its solubility.
4. Heat the aqueous phase to approximately 30–40°C.
5. Add the aqueous phase slowly to the ethanolic phase under continuous stirring (700–1000 rpm).
6. Continue stirring for 30–60 minutes to obtain a homogeneous dispersion.

7. Sonicate the dispersion using a probe sonicator for 5–10 minutes to reduce vesicle size.
8. Store the prepared transethosomal suspension at 4°C until further use.

Advantages

- Simple and economical
- Suitable for heat-sensitive drugs
- High entrapment efficiency
- Uniform vesicle size
- Good reproducibility

Limitations

- Possible ethanol evaporation
- Vesicle aggregation during storage
- Requires optimization of stirring and sonication parameters

Hot Method

Principle

In the hot method, phospholipids are dissolved in hot water, while ethanol containing the drug and edge activator is heated separately. Both phases are mixed at the same temperature to produce vesicles.

Procedure

1. Heat phospholipids in purified water (approximately 40–45°C).
2. Prepare the ethanolic drug solution separately.
3. Mix both phases while maintaining constant temperature.
4. Stir continuously.
5. Sonicate the dispersion.
6. Cool to room temperature.

Advantages

- Suitable for drugs stable at elevated temperatures
- Uniform mixing

Limitations

- Not suitable for thermolabile drugs
- Risk of drug degradation

Thin-Film Hydration Method

Principle

A thin lipid film is first formed by evaporating organic solvents under reduced pressure. Hydration of the dry lipid film with an aqueous phase results in vesicle formation.

Procedure

1. Dissolve phospholipids, edge activator, and drug in chloroform–methanol (2:1).
2. Remove solvents using a rotary evaporator.
3. Form a thin lipid film on the flask wall.
4. Hydrate the film using ethanol-water mixture.
5. Stir continuously.
6. Sonicate to reduce vesicle size.

Advantages

- High entrapment efficiency
- Uniform vesicle formation
- Suitable for lipophilic drugs

Limitations

- Time-consuming
- Requires rotary evaporator
- Uses organic solvents

Ethanol Injection Method

Principle

An ethanolic solution of phospholipids is injected into an aqueous phase under continuous stirring, leading to spontaneous formation of vesicles.

Procedure

1. Prepare ethanolic lipid solution.
2. Prepare aqueous phase separately.
3. Inject ethanolic phase slowly into aqueous phase.
4. Stir continuously.
5. Sonicate to reduce particle size.

Advantages

- Simple procedure
- No complex equipment
- Good reproducibility

Limitations

- Lower drug loading for some drugs
- Ethanol removal may be necessary

Reverse-Phase Evaporation Method

Principle

Water-in-oil emulsions are prepared first, followed by solvent evaporation to produce large unilamellar vesicles.

Advantages

- High encapsulation efficiency
- Suitable for hydrophilic drugs

Limitations

- Uses organic solvents
- Complex procedure
- Longer preparation time

Probe Sonication

Purpose

Probe sonication is employed to reduce vesicle size and achieve a narrow particle size distribution.

Procedure

- Place dispersion in an ice bath.
- Sonicate for 5–10 minutes using pulse mode.
- Prevent overheating.

Advantages

- Produces nanosized vesicles
- Improves uniformity
- Reduces PDI

Preparation of Transethosomal Gel

After preparing the transethosomal suspension, it is incorporated into a gel base.

Materials

- Carbopol 934 or Carbopol 940
- Triethanolamine (TEA)
- Purified water
- Transethosomal suspension

Procedure

1. Disperse Carbopol in purified water.
2. Allow hydration for 12–24 hours.
3. Adjust pH using triethanolamine.
4. Slowly incorporate the transethosomal suspension.
5. Stir gently to obtain a homogeneous gel.
6. Store in airtight containers at 4–8°C.

Factors Affecting Preparation

Several process parameters influence vesicle quality.

Parameter	Effect
Stirring speed	Controls vesicle formation
Sonication time	Reduces particle size
Ethanol concentration	Affects skin permeation
Hydration temperature	Influences vesicle stability
Lipid concentration	Affects entrapment efficiency
Edge activator concentration	Controls deformability

Storage of Transethosomal Gel

Prepared formulations should be stored under refrigerated conditions.

Recommended storage conditions:

- Temperature: 4 ± 2°C
- Protected from light
- Airtight containers
- Avoid repeated freeze–thaw cycles

Advantages of the Cold Method

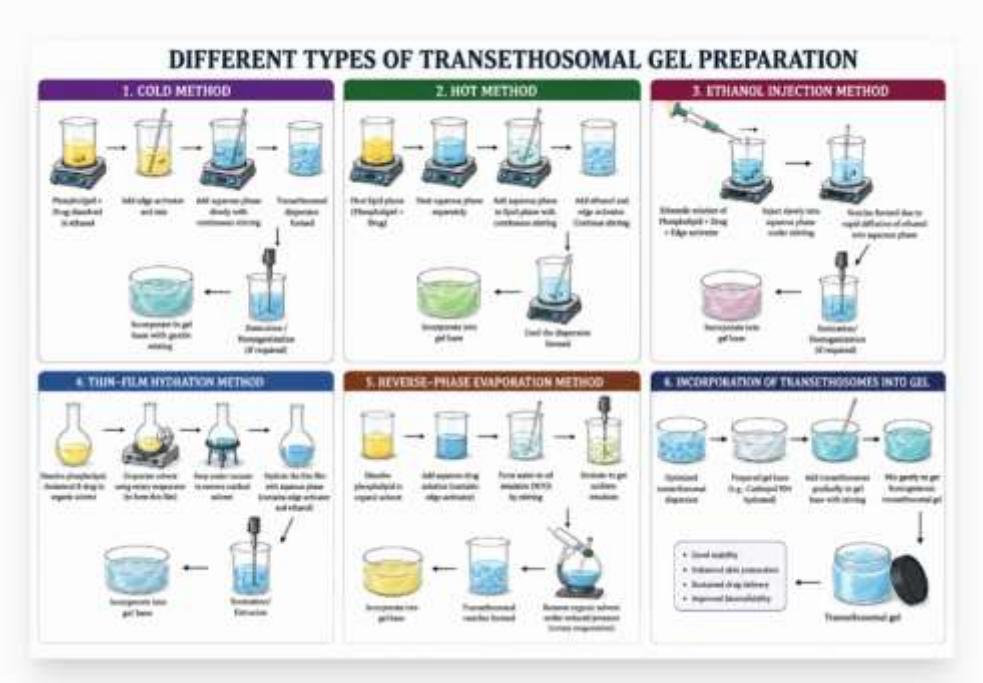
- Simple
- Economical
- Suitable for heat-sensitive drugs
- High drug encapsulation
- Reproducible
- Easy scale-up
- Most commonly used in pharmaceutical research

Challenges During Preparation

- Ethanol evaporation
- Vesicle aggregation
- Drug leakage
- Batch-to-batch variation
- Difficulty in scale-up
- Maintaining sterility
- Optimization of sonication

The preparation method plays a pivotal role in determining the physicochemical properties and therapeutic performance of transethosomal formulations. Among the available techniques, the cold method is the most widely preferred due to its simplicity, high reproducibility, and suitability for thermolabile drugs. Other methods, including the hot method, thin-film hydration, ethanol injection, and reverse-phase evaporation, may be selected based on drug characteristics and formulation requirements. Following vesicle preparation, incorporation into a suitable polymeric gel base yields a stable transethosomal gel with improved skin retention, enhanced permeation, and sustained drug release. Careful optimization of formulation and process variables is essential for obtaining a robust, reproducible, and clinically effective transethosomal gel.

Method	Principle	Advantages	Limitations
Cold method	Ethanol-based hydration	Simple, suitable for heat-sensitive drugs	Ethanol evaporation
Hot method	Mixing heated phases	Uniform mixing	Not suitable for thermolabile drugs
Thin-film hydration	Hydration of lipid film	High entrapment efficiency	Requires rotary evaporator
Ethanol injection	Injection of ethanolic phase	Easy and reproducible	Lower encapsulation for some drugs
Reverse-phase evaporation	Water-in-oil emulsion	High drug loading	Complex and solvent-intensive



CHARACTERIZATION OF TRANSETHOSOMAL GEL

Vesicle Size, Polydispersity Index (PDI), and Zeta Potential

Vesicle size is a critical factor influencing the stability and transdermal performance of transethosomal formulations. The size distribution and uniformity of the vesicles are commonly assessed by dynamic light scattering. PDI provides information regarding the homogeneity of the

vesicle population, while zeta potential indicates the surface charge and helps predict the physical stability of the formulation.

Morphology of Transethosomes

The morphology of transethosomal vesicles is examined using techniques such as transmission electron microscopy (TEM), scanning electron microscopy (SEM), or atomic force microscopy (AFM). These methods provide information about the shape, surface characteristics, and structural integrity of the vesicles.

Entrapment Efficiency

Entrapment efficiency determines the proportion of drug incorporated within the transethosomal vesicles. The free drug is separated from the vesicular dispersion using an appropriate separation technique, and the amount of entrapped drug is quantified by a suitable analytical method. Higher entrapment efficiency indicates effective incorporation of the drug into the vesicular system.

Deformability

Deformability is a significant characteristic of transethosomes that facilitates their passage through the narrow intercellular spaces of the stratum corneum. The flexibility of the vesicles allows them to undergo deformation without losing their structural integrity, thereby supporting enhanced transdermal drug permeation.

Drug Content

Drug content analysis is carried out to determine the quantity and uniformity of drug present in the transethosomal gel. A known amount of formulation is appropriately diluted or extracted, and the drug concentration is estimated using a validated analytical technique.

In-vitro Drug Release

In-vitro release studies are performed to evaluate the release pattern and rate of drug liberation from the transethosomal gel. The released drug is collected at predetermined time intervals and analyzed using a suitable method. The obtained data can be further fitted to different kinetic models to understand the mechanism of drug release.

Ex-vivo Skin Permeation

Ex-vivo skin permeation studies are conducted using suitable excised skin to investigate the ability of the transethosomal gel to transport the drug across the skin barrier. The cumulative amount of drug permeated and other permeation parameters are determined to evaluate the efficiency of transdermal delivery.

Stability Studies

Stability studies are performed under predetermined storage conditions to evaluate the physical and chemical stability of the transethosomal gel. Changes in appearance, pH, drug content, viscosity, vesicle size, PDI, and zeta potential are monitored at specific intervals to confirm the stability and integrity of the formulation.

Therapeutic Applications

Transethosomal gels have attracted considerable interest as advanced transdermal and topical delivery systems because their highly deformable vesicles can enhance drug permeation through the skin while the gel matrix improves skin retention and sustained release. Their therapeutic applications include the following:

- **Pain and Inflammation:** Used to deliver anti-inflammatory and analgesic drugs for

localized pain, inflammation, arthritis, rheumatoid arthritis, and osteoarthritis.

- **Antifungal Therapy:** Transethosomal gels can enhance the topical delivery of antifungal agents such as econazole and other antifungal drugs for the management of cutaneous fungal infections.
- **Antibacterial and Antimicrobial Therapy:** They can facilitate the delivery of antimicrobial agents and natural bioactives for treating bacterial and microbial skin infections.
- **Dermatological Disorders:** Transethosomal gels have potential applications in conditions such as psoriasis, vitiligo, melasma, and dermatitis, where improved penetration into the skin may enhance therapeutic outcomes.
- **Wound Healing:** Their ability to improve skin delivery makes them promising carriers for therapeutic agents involved in wound healing and tissue repair.
- **Cancer Therapy:** Transethosomal gels have been explored for topical delivery of anticancer agents, particularly for potential treatment of superficial skin cancers and localized tumors.
- **Antioxidant and Natural Therapeutics:** They are suitable for delivering plant-derived compounds and bioactive molecules with antioxidant and other pharmacological properties, improving their skin permeation and stability.
- **Autoimmune and Chronic Diseases:** Research has investigated their potential for delivering therapeutics in conditions such as rheumatoid arthritis and chronic disorders including hyperlipidemia.

Transethosomal gel provides a versatile platform for localized and systemic transdermal drug delivery, with promising applications in pain management, inflammation, fungal and bacterial infections, dermatological disorders, wound healing, cancer therapy, and delivery of natural bioactive compounds. Its ability to enhance skin permeation while providing sustained drug release makes it a promising approach for advanced drug delivery

Future Perspectives

The field of transethosomal drug delivery continues to evolve rapidly with advances in pharmaceutical nanotechnology, biomaterials, and personalized medicine. Future research should focus on the following areas:

1. Clinical Translation

- Conduct well-designed clinical trials to establish the safety, efficacy, and long-term therapeutic benefits of transethosomal formulations.
- Compare transethosomal formulations with conventional dosage forms in large patient populations.

2. Commercial Scale-Up

- Develop scalable and reproducible manufacturing processes.
- Improve batch-to-batch consistency and industrial feasibility.
- Optimize production costs while maintaining product quality.

3. Quality by Design (QbD)

- Apply QbD principles to optimize formulation variables and manufacturing processes.
- Utilize Design of Experiments (DoE) for systematic product development.

4. Artificial Intelligence and Machine Learning

- Integrate AI-based predictive models for formulation optimization.
- Use computational tools to predict vesicle characteristics, drug release, and stability profiles.

5. Personalized Drug Delivery

- Develop patient-specific transdermal formulations tailored to age, disease severity, and pharmacogenomic profiles.
- Integrate transethosomal systems into personalized medicine strategies.

6. Combination Therapy

- Explore co-delivery of multiple therapeutic agents within a single transethosomal formulation.
- Investigate synergistic treatment approaches for chronic diseases.

7. Biologics and Peptide Delivery

- Expand the application of transethosomes for delivering proteins, peptides, vaccines, and nucleic acid-based therapeutics.
- Improve non-invasive administration of biologics.

8. Smart and Stimuli-Responsive Systems

- Design transethosomes that respond to physiological stimuli such as pH, temperature, enzymes, or light.
- Develop intelligent systems capable of site-specific and controlled drug release.

9. Integration with Advanced Technologies

Future transethosomal systems may be combined with:

- Microneedle arrays
- Wearable transdermal patches
- Iontophoresis
- Sonophoresis
- Electroporation
- 3D-printed drug delivery devices

These technologies can further enhance skin penetration and therapeutic outcomes.

10. Regulatory Standardization

- Establish standardized regulatory guidelines for the characterization, quality control, and commercialization of transethosomal formulations.
- Harmonize international regulatory requirements to facilitate global product approval.

CONCLUSION

Transethosomal gel has emerged as one of the most promising nanovesicular drug delivery systems for topical and transdermal drug administration. The combination of phospholipids, ethanol, and edge activators provides exceptional vesicle deformability, enabling efficient

penetration through the highly organized lipid structure of the stratum corneum. Compared with conventional topical formulations and earlier vesicular systems such as liposomes, niosomes, ethosomes, and transfersomes, transethosomes demonstrate superior skin permeation, higher drug encapsulation efficiency, improved stability, sustained drug release, and enhanced therapeutic efficacy.

This review comprehensively discussed the fundamental concepts of skin anatomy and transdermal drug delivery, the evolution of vesicular drug delivery systems, the composition and mechanism of transethosomes, formulation design, preparation techniques, characterization methods, factors affecting formulation performance, and diverse therapeutic applications. The literature clearly indicates that transethosomal technology has significantly expanded the possibilities for delivering poorly soluble drugs, peptides, proteins, herbal compounds, and other therapeutic agents through the skin.

One of the major advantages of transethosomal gel is its ability to overcome several limitations associated with oral drug delivery, including poor aqueous solubility, hepatic first-pass metabolism, gastrointestinal irritation, and poor patient compliance. The flexible vesicular structure, together with ethanol-induced lipid fluidization, allows enhanced drug permeation and prolonged retention within skin tissues, resulting in improved bioavailability and sustained therapeutic effects.

Although transethosomes have shown excellent performance in preclinical studies, several challenges remain before widespread clinical application can be achieved. These include formulation stability, large-scale manufacturing, quality control, regulatory approval, long-term safety evaluation, and cost-effective commercialization. Addressing these limitations through systematic formulation optimization and robust clinical studies will be essential for translating laboratory research into successful pharmaceutical products.

Overall, transethosomal gel represents a versatile, efficient, and innovative nanocarrier system with significant potential to improve transdermal drug delivery. Its unique physicochemical properties and therapeutic advantages position it as an important platform for the future development of advanced pharmaceutical formulations.

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