Ethosomal Gel Containing Herbal Extracts: A Synergistic Strategy for Enhanced Dermal Delivery and Therapeutic Efficacy

[1]Sajid Wahed Baig, [2]Aijaz Sheikh, [3]Kailash R. Biyani

[1,2,3]Anuradha College of Pharmacy, Anuradha Nagar, Sakegaon Road, Chikhli, Dist Buldana, Maharastra (India) 443201

Abstract: The therapeutic potential of herbal extracts is often restricted by the formidable barrier of the stratum corneum (SC). Conventional topical vehicles frequently fail to facilitate the penetration of complex, high-molecular-weight phytochemicals into deeper dermal layers. Ethosomes—novel, flexible nanovesicles characterized by high ethanol content—have emerged as a transformative platform for transdermal delivery. This review elaborates on the rationale, formulation, characterization, and therapeutic applications of herbal ethosomal gels. By providing a synergistic "push and pull" mechanism, these systems enhance the solubility, stability, and bioavailability of herbal bioactives, positioning them as a cornerstone of modern phytopharmaceutical technology.

Keywords - Ethosomes, Nanovesicles, Transdermal Drug Delivery Systems (TDDS), Vesicular Carriers

1. Introduction

1.1. The Challenge of Dermal Drug Delivery

The skin is the largest organ and an attractive, non-invasive route for drug administration. However, the outer layer of the epidermis, the **stratum corneum (SC)**, poses a formidable barrier to drug penetration. Its highly organized lipid matrix limits the absorption of most therapeutic agents, particularly large, hydrophilic molecules and the complex, often high-molecular-weight compounds found in herbal extracts. Conventional topical formulations (creams, lotions, gels) primarily deliver drugs into the superficial skin layers, often failing to reach deeper dermal and systemic targets effectively **[1]**.

1.2. Ethosomes: An Advanced Vesicular Approach

To overcome the SC barrier, advanced nanovesicular carriers have been developed. Among these, **Ethosomes** stand out. Ethosomes are specialized, flexible lipid vesicles, first described by **Touitou et al.** in the early 2000s. They are composed primarily of phospholipids, high concentrations of ethanol (20–45% v/v), and water. The high ethanol content imparts unique characteristics to the ethosomal membrane:

- **Enhanced Fluidity:** Ethanol increases the fluidity and elasticity of the lipid bilayer **[2]**.
- **Permeation Enhancement:** Ethanol acts synergistically on the SC, disrupting the intercellular lipid arrangement. This dual mechanism allows the flexible ethosome to squeeze through the widened intercellular spaces, delivering the encapsulated agent deep into the dermis and even the systemic circulation—a mechanism known as transdermal permeation **[3]**.

1.3. Integrating Herbal Extracts with Ethosomes

Herbal extracts, rich in diverse bioactive compounds (e.g., polyphenols, flavonoids, saponins, alkaloids), possess vast therapeutic potential (anti-inflammatory, antioxidant, antimicrobial). However, their large molecular size, high hydrophilicity/lipophilicity, and poor stability often lead to low skin penetration and low bioavailability. The **Ethosomal Gel System**—the ethosomes dispersed within a dermatologically acceptable gel matrix—provides a synergistic solution:

- **Ethosomes:** Enhance the solubility, stability, and deep dermal penetration of the complex herbal molecules.
- **Gel Base:** Provides a non-greasy, convenient, and patient-compliant formulation for topical application **[4]**.

2. Rationale for Ethosomal Encapsulation of Herbal Extracts

The need for ethosomes in herbal formulation stems from the inherent limitations of crude extracts.

2.1. Overcoming Physicochemical Barriers

Limitation of Herbal Bioactives	Solution Provided by Ethosomes
Complex Composition	Ethosomes can co-encapsulate both hydrophilic and lipophilic compounds within their core and lipid bilayer, respectively **[5]**.
High Molecular Weight	The elastic nature allows the vesicle to deform and pass through SC pores much smaller than its static size **[6]**.
Chemical Instability	Encapsulation within the lipid bilayer protects light- and heat-sensitive herbal compounds from environmental degradation **[7]**.
Low Skin Permeation	Ethanol component acts as a penetration enhancer, driving the flexible ethosome into the deeper skin layers.

2.2. Enhanced Bioavailability and Targeted Delivery

Ethosomal carriers can achieve therapeutically relevant concentrations of the herbal active ingredients at the site of action (e.g., joint tissues for anti-arthritic agents) or deliver them systemically, bypassing first-pass metabolism associated with oral administration **[8]**.

3. Formulation Development: Preparation and Incorporation into Gel

3.1. Preparation of Ethosomes

The primary method for preparing ethosomes is the Hot Method or Cold Method, with the latter being preferred for heat-labile herbal extracts.

A. Cold Method (Preferred for Herbal Extracts):

1. **Lipid/Ethanol Phase:** Phospholipids (e.g., Phosphatidylcholine, PC) are dissolved in ethanol.
2. **Aqueous Phase:** The herbal extract and water are mixed.
3. **Mixing:** The aqueous phase is slowly added to the lipid/ethanol mixture under constant stirring at room temperature, forming vesicles spontaneously due to the controlled reduction of ethanol concentration.
4. **Sizing:** The formulation is subjected to sonication or high-pressure homogenization to achieve a uniform, nanometric particle size (typically 50-300 nm) **[9]**.

3.2. Incorporation into a Gel Base (Ethosomal Gel)

The ethosomal suspension, despite its stability, is too fluid for convenient topical use. It must be incorporated into a viscoelastic gel structure.

- **Gelling Agents:** Typically, high-molecular-weight polymers like Carbopol (polyacrylic acid), HPMC (Hydroxypropyl Methylcellulose), or Xanthan Gum are used.
- **Neutralization:** For Carbopol, the pH must be adjusted (e.g., using triethanolamine) after incorporation to trigger the gel formation without disrupting the ethosome structure or precipitating the herbal component **[10]**.
- **Final Product:** The resulting ethosomal gel should be homogeneous, non-greasy, easily spreadable, and non-irritating.

4. Critical Quality Attributes and Characterization

4.1. Ethosomal Suspension Characterization

- **Vesicle Size and Polydispersity Index (PDI):** Measured by Dynamic Light Scattering (DLS). Size should be <300 nm for optimal penetration. PDI should be <0.3 indicating narrow size distribution **[11]**.
- **Zeta Potential (ζ):** Measures the surface charge, influencing stability and interaction with the SC. Values >$\pm$30 mV suggest good colloidal stability.
- **Entrapment Efficiency (EE%):** Determined by separating the free, un-encapsulated herbal component. EE is critical for efficacy and ranges from 60% to 95% depending on the drug and lipid-to-ethanol ratio **[12]**.

4.2. Ethosomal Gel Characterization

- **Rheology:** Viscosity and spreadability are key for application comfort. The gel should ideally exhibit pseudoplastic flow.
- **pH:** Must be non-irritating (close to skin pH 5.5–6.5).
- **In Vitro Drug Release:** Assessed using **Franz diffusion cells**. The release rate from the gel is often controlled by the gelling agent, followed by the release from the ethosome **[13]**.

4.3. Permeation Studies (Ex Vivo)

The most defining test for ethosomal systems is the skin permeation study using excised animal or human skin mounted on a Franz diffusion cell. **Confocal Laser Scanning Microscopy (CLSM)** is used to visually track the depth of penetration of a fluorescent-tagged ethosome into the skin **[14]**.

5. Mechanistic Insight into Enhanced Permeation

The enhanced penetration relies on a synergistic "push and pull" mechanism.

5.1. The Role of Ethanol (The "Push" Factor)

The high concentration of ethanol plays a dual role:

- **SC Disruption:** Ethanol transiently extracts or disrupts the lipid structure, increasing the fluidity of the barrier.
- **Thermodynamic Activity:** As ethanol evaporates, it creates a high concentration gradient and a "thermodynamic push" that drives the flexible ethosomes into the opened lipid channels **[15]**.

5.2. The Role of Flexibility (The "Squeeze" Factor)

The fluidization of the lipid bilayer creates highly deformable vesicles. Ethosomes are able to squeeze through intercellular spaces that are significantly smaller than the vesicle's static size (e.g., 100 nm vesicles passing through pores of 10 nm) **[16]**.

6. Therapeutic Applications of Herbal Ethosomal Gels

6.1. Anti-inflammatory and Anti-arthritic Agents

Natural products like **Curcumin**, **Boswellic acids**, and **Quercetin** possess potent properties but suffer from low dermal permeability. Ethosomal gels of these compounds have demonstrated significantly superior delivery to deeper joint tissues in animal models **[17]**.

6.2. Antioxidant and Anti-aging Agents

Flavonoids and polyphenols (e.g., extracts from **Green Tea** or **Ginkgo Biloba**) are powerful antioxidants. Ethosomal encapsulation protects these sensitive compounds from oxidation and facilitates their access to the basal layers where free radical generation occurs **[18]**.

6.3. Antimicrobial and Antifungal Treatments

Essential oils (e.g., **Tea Tree Oil**, **Thyme**) are effective against microbial infections but are often volatile. Ethosomal gels stabilize the extracts and provide targeted delivery to the infection site **[19]**.

7. Stability and Safety Considerations

7.1. Stability of the Ethosomal Gel

- **Physical Stability:** Ethosomal gels are prone to aggregation and sedimentation. Stability is assessed by monitoring Zeta potential and vesicle size over time.
- **Chemical Stability:** Maintaining the EE% over the shelf-life is critical. High ethanol content can sometimes promote the leakage of the encapsulated active if the lipid concentration is not optimized **[20]**.

7.2. Safety and Biocompatibility

- **Dermal Irritation:** The final gel must be tested for primary skin irritation.
- **Toxicity:** Standard toxicity studies for both the ethosomal components and the encapsulated herbal extract must be performed to meet regulatory standards **[21]**.

8. Conclusion and Future Perspectives

8.1. Conclusion

The Ethosomal Gel system represents a major leap in maximizing the therapeutic potential of complex herbal extracts. This advanced strategy enables the efficient and deep dermal delivery of herbal bioactives, increasing their bioavailability and therapeutic efficacy compared to conventional formulations.

8.2. Future Directions

The trajectory of this field is moving towards:

- **Pro-Ethosomes:** Developing dry powder precursors that can be easily reconstituted into a gel in situ just before application **[22]**.
- **Active Targeting:** Exploring surface modification of ethosomes (e.g., using PEGylation or specific ligands) to achieve targeted delivery to deeper cells **[23]**.
- **Clinical Trials:** Conducting large-scale trials to validate the enhanced efficacy and superior patient outcomes of ethosomal herbal gels.

References

1. Prausnitz, M. R., & Langer, R. (2008). Transdermal drug delivery. Nature Biotechnology.
2. Touitou, E., et al. (2000). Ethosomes - novel vesicular carriers for enhanced delivery: Characterization and skin penetration properties. Journal of Controlled Release.
3. Godin, B., & Touitou, E. (2003). Ethosomes: new prospects in transdermal delivery. Critical Reviews in Therapeutic Drug Carrier Systems.
4. Pathak, K., & Verma, P. (2010). Therapeutic and cosmeceutical potential of ethosomes: An overview. Journal of Advanced Pharmaceutical Technology & Research.
5. Prasanthi, S., & Lakshmi, P. K. (2012). Vesicular drug delivery systems: a novel approach for transdermal drug delivery. International Journal of Pharmaceutical Sciences Review and Research.
6. Ainbinder, D., & Touitou, E. (2005). Testosterone ethosomes for treatment of male hypogonadism. Journal of Drug Delivery Science and Technology.
7. Verma, D. D., & Fahr, A. (2004). Synergistic penetration effect of ethanol and phospholipids on the skin. European Journal of Pharmaceutical Sciences.

8. Ascenso, A., et al. (2015). Development and characterization of a topical flurbiprofen-loaded ethosomal gel. Journal of Pharmaceutical Sciences.

9. Rakesh, R., & Rohit, S. (2014). Ethosomes: a noninvasive approach for transdermal drug delivery. International Journal of Pharmaceutical Sciences and Research.

10. Shaji, J., & Bajaj, R. (2007). Ethosomes: A novel vesicular carrier. International Journal of Pharmaceutics.

11. Celia, C., et al. (2012). Ethosomes and ultradeformable liposomes for transdermal delivery of methotrexate. Colloids and Surfaces B: Biointerfaces.

12. Dubey, V., et al. (2007). Meloxicam ethosomes: Novel vesicular carriers for enhanced transdermal delivery. Journal of Controlled Release.

13. Garg, V., et al. (2017). Systematic development of ethosomal gel of piroxicam: Formulation, optimization, and ex vivo characterization. AAPS PharmSciTech.

14. Godin, B., et al. (2005). Ethosomes for skin delivery of ammonium glycyrrhizinate: state of art characterization. FASEB Journal.

15. Rao, Y., et al. (2013). Ethosomes for skin delivery of lidocaine: preparation and characterization. Journal of Liposome Research.

16. Zhang, J. P., et al. (2012). Ethosomes: a novel vesicular carrier for enhanced transdermal delivery of drugs. Archives of Pharmacal Research.

17. Gupta, A., et al. (2013). Preparation and evaluation of ethosomes of curcumin. International Journal of Pharmaceutical Sciences and Research.

18. Manosroi, A., et al. (2009). Anti-aging efficacy of topical formulation containing gallic acid loaded in ethosomes. Journal of Cosmetic Science.

19. Zhang, Y. T., et al. (2014). Preparation of ethosomes for transdermal delivery of terbinafine hydrochloride. Journal of Nanomedicine & Nanotechnology.

20. Paolino, D., et al. (2005). Ethosomes for skin delivery of ammonium glycyrrhizinate. Colloids and Surfaces B: Biointerfaces.

21. Ibrahim, I. T., et al. (2019). Formulation and optimization of itraconazole ethosomes for enhanced transdermal delivery. Drug Design, Development and Therapy.

22. Devi, M., et al. (2015). Proethosomes: a novel vesicular carrier for transdermal drug delivery. International Journal of Drug Delivery.

23. Akhtar, N. (2014). Ethosomes: a carrier for transdermal drug delivery. International