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ETHOSOMAL TRANSDERMAL PATCHES: A NEW FRONTIER IN PARKINSONISM THERAPY

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ABSTRACT

Ethosomes are carriers for painless medicine delivery system that permit drugs to reach the deeper dermal parts or sometimes helps to reach bloodstream. Despite the advanced concept behind ethosomal systems, they are easy to prepare and offer both safety, effectiveness and suitable for a wide range of advancements. These smooth bendable vesicular forms are engineered to improve the site specific targeting of medicaments. Ethosomes carriying unique structure, so can encapsulate and deliver highly lipophilic drugs indicates that ethosomal carriers may also enhance the delivery of these molecules. The improved transport of medicinal substances through skin and cell membranes using ethosomes loaded transdermal patch opens new possibilities and improvements for future research and the expansion of advanced applications.

KEYWORDS: Parkinsonism, Ethosomes, Transdermal patch, Targeting.

1. INTRODUCTION

Parkinson's disease is a progressive neurodegenerative disorder characterized by tremors and slowed movement making it a common neurological condition. Male gender and increasing age are independent risk factors and as the population grows older the disease places a greater burden on productivity and healthcare systems. Diagnosing Parkinson's can be difficult due to the presence of other extrapyramidal disorders with similar symptoms.[1-4]

Skin the largest organ of the body, offers a promising way for drug delivery to achieve both local and systemic effects. Stratum corneum (SC), the skin's outermost layer acts as a strong barrier that restricts the penetration of hydrophilic and high molecular weight of drugs.[5-8] Transdermal drug delivery systems have been in use for many years with topical creams and ointments traditionally applied for skin conditions. The development of systemic side effects in some cases suggests that drugs can penetrate and be absorbed through the skin. Many medications have been administered via the skin for systemic therapy. In general, transdermal delivery systems include all topical drug formulations designed to transport active ingredients into the bloodstream. These systems are developed to provide slow and persistent release of drugs through the skin into blood stream. Moreover, transdermal delivery bypasses issues like non invasive drug administration and oral hepatic first-pass metabolism compared to other routes. As a result, transdermal drug delivery has become an area developing interest. Its primary advantages are sustained release of the drug and painless application. The drugs are typically delivered through patches that adhere to the skin.[9-13]

Ethosomes are newly developed vesicular system named for the ethanol present in their structure. This approach has become most extensively researched methods for transdermal drug delivery. These are non-invasive carriers that allow drugs to penetrate deep into the skin or reach blood stream. Created specifically for transdermal delivery, ethosomes can easily enter into the intact skin because to their remarkable rubberiness. These soft deformable lipid vesicles consist mainly of

phospholipids, ethanol (in concentrations ranging from 20-45%) and water. Their size can range from 10 nm to several microns. Not only do ethosomes transport drugs to deeper skin layers, but they also meet the key requirements for efficiently and safely administering both lipophilic and hydrophilic drugs. Ethosomes can encapsulate a variety of molecules, including hydrophilic, lipophilic, and high-molecular-weight compounds. They are also capable of delivering drugs through the skin, whether under obstructed or non-obstructed conditions.

Ethonolic vesicles an innovative class of advanced nanovesicular carriers, have brought a breakthrough in transdermal drug delivery, playing a key role in the advancement of transdermal patch development. By integrating the flexible structure of ethosomes with the penetration-enhancing properties of surfactants, ethosomes effectively overcome the skin's barrier to deliver a wide range of therapeutic agents. These vesicles significantly enhance drug permeation, increase bioavailability, and provide controlled and sustained release, offering a superior alternative to conventional delivery methods. This review examines the unique composition, functional mechanisms, and transdermal penetration pathways of transethosomes, emphasizing their clinical potential in fields such as pain management, dermatology, and hormone replacement therapy. Furthermore, the ability of ethosomes to selectively focus specific skin layers or cells enables localized drug delivery and decreases systemic side effects. Critical challenges, including formulation stability, inter-individual skin variability, and regulatory constraints, are also discussed, along with emerging areas of interest such as the delivery of macromolecules and multi-drug formulations. The article also highlights future trends, including personalized therapeutics, combination drug regimens, and stimuli-responsive systems, pointing to the growing importance of ethosomes in next-generation transdermal drug delivery technologies. Through this comprehensive analysis, the review underscores the transformative potential of ethosomes in modern pharmaceutical applications.[14-17]

ETHOSOMES

As vesicular carriers for transdermal drug release, ethosomes facilitate drugs penetrating deeply into the skin or entering the bloodstream.

ETHOSOMES TYPES

Based on their composition, Ethosomal systems are classified into three types,

1. **Classical Ethosomes**: These are an advanced form of ethosomes, composed of phospholipids, water, and ethanol in concentrations up to 45% w/v. Classical ethosomes have been shown to outperform conventional liposomes due to their smaller particle size, more negative zeta potential, and higher drug entrapment efficiency.
2. **Binary Ethosomes**: This type of ethosomal system was developed by incorporating an additional alcohol into the classical ethosome formulation, aiming to enhance its delivery properties.
3. **Transethosomes**: Representing a novel generation of ethosomal systems, transethosomes were designed to integrate the benefits of both classical ethosomes and transfersomes into a single formulation, offering improved skin penetration and stability.(Figure 1)

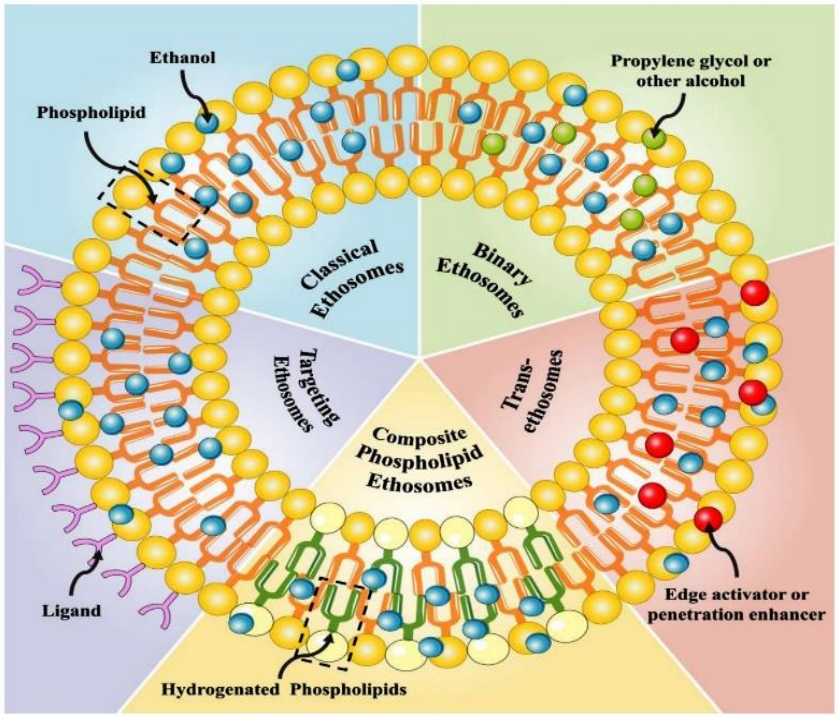

Figure 1: Types of ethosomes.

ADVANTAGES

- Use for delivering large molecules such as peptides and proteins.
- Formulated with non-toxic raw materials.
- Improves drug penetration.
- Applicable across various fields, including pharmaceuticals, veterinary care, and cosmetics.
- Provides high patient compliance.
- Offers a simpler drug delivery method compared to techniques such as iontophoresis and phonophoresis.
- These are painless drug delivery system.

DISADVANTAGES

- Weak ethosome shells may cause clumping and precipitation.
- Drug must be soluble in both lipids and water to reach systemic circulation.
- Some excipients may cause skin irritation.
- Ethosomes provide slow, sustained release—not rapid delivery.
- Not suitable for drugs needing high blood levels.
- Limited to potent drugs (≤10 mg/day).
- Low practical yield.
- Product loss can occur during phase transfer.
- Drug size must allow skin absorption.
- Adhesive may not suit all skin types.
- Can be cost-inefficient.[18-19]

MECHANISM OF ACTION OF ETHOSOMES

The transepidermal penetration and permeation mechanisms, particularly the influence of ethanol and ethosomes, are depicted in (Figures 2 and 3).

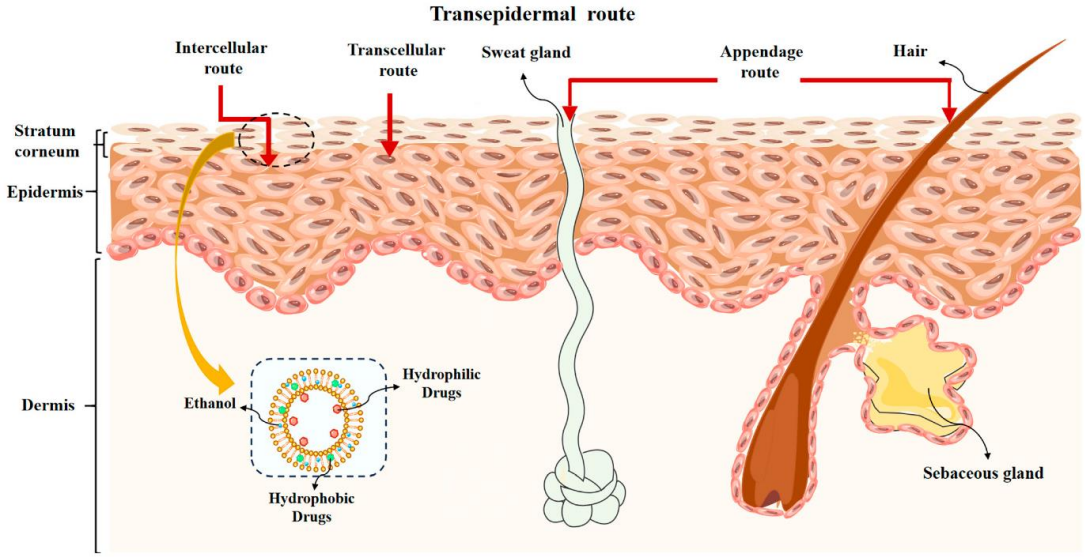

Figure 2: Transepidermal skin penetration.

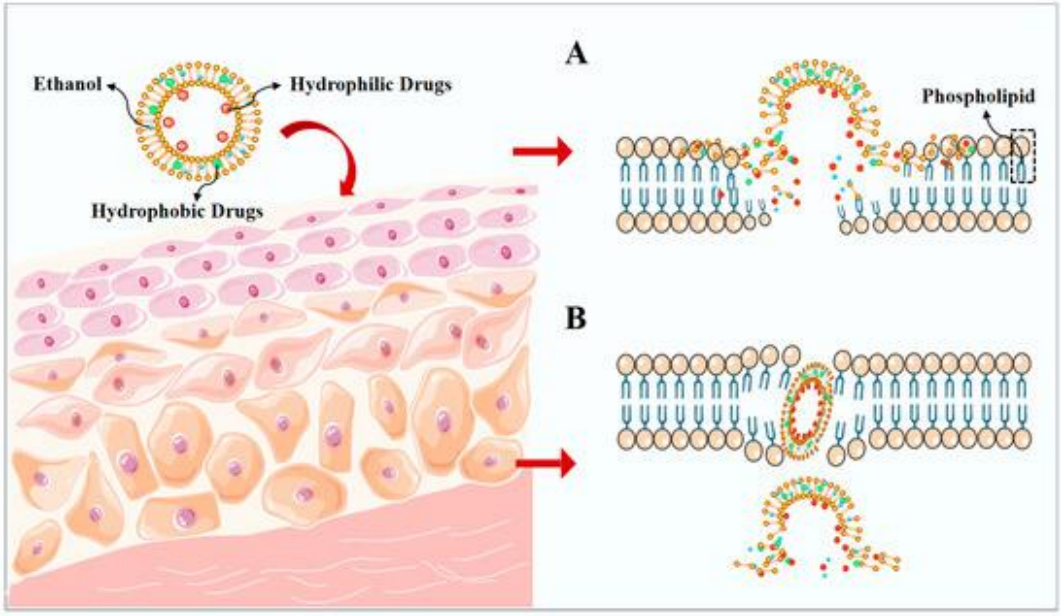

Figure 3: Permeation mechanisms (1) Ethanol effect (2) ethosomes effect.

METHOD OF PREPARATION OF ETHOSOMES

1. Thin Film Dispersion Method

Phospholipids and cholesterol are dissolved in organic solvents, evaporated to form a thin lipid film and hydrated with drug-containing water–ethanol mixture. Sonication reduces particle size and enhances stability. This method generally yields larger ethosomes, which can be refined by ultrasonic treatment.[20–22]

2. Ethanol Injection Method

Lipids are dissolved in ethanol and aqueous phase is added gradually while stirring. The solution is then filtered through a microporous membrane. Lipophilic drugs are typically dissolved in ethanol, while hydrophilic drugs go into water. This method has been used for drugs like ursolic acid, paeonol, and vancomycin.[23–29]

3. Injection–Ultrasound Combination Method

Phospholipids along with drugs are mixed with ethanol, then added slowly to buffer under stirring. The mixture undergoes ultrasonication in an ice bath, followed by filtration. This results in ethosomes with smaller, more uniform particles and improved stability.[30]

4. pH Gradient Method

Ethanol solution of lipids is stirred with buffer to form blank ethosomes. The drug is added, followed by NaOH to create a pH difference across the vesicle membrane. Suitable for pH-stable lipophilic drugs due to low encapsulation of hydrophilic ones.[20,24,31–32]

5. Microfluidic Techniques

Lipids and drugs are dissolved in ethanol and mixed with water at a specific ratio using a Nano Assembler. This method produces uniform, reproducible liposomes with a monolayer structure. It has been used for dexamethasone-loaded liposomes.[33–35]

EVALUATION OF ETHOSOMES

1. Scanning Electron Microscopy SEM

A 0.2 mL vesicle suspension was applied to 50 nm pore-size membranes in diffusion cells. After 1 hour, filters were fixed in Karnovsky's fixative at 4°C and dehydrated using graded ethanol, gold-coated, and examined through SEM.[36–38]

1. Vesicle–Skin Interaction by Fluorescence Microscopy

5-µm skin sections from paraffin blocks were prepared using a microtome and examined under a fluorescence microscope, following protocols similar to TEM/SEM studies.[36–38]

2. Vesicle–Skin Interaction

Ultrathin skin sections from animals were placed on grids for TEM analysis. For SEM, dehydrated skin samples were mounted, gold-palladium coated, and examined under SEM.[36–38]

3. HPLC Assay

HPLC using a methanol:water:acetonitrile (70:20:10 v/v) mobile phase at 1 mL/min, detected at 271 nm can be used for Drug content in skin permeation and MT-2 cell studies was quantified. The standard curve showed R^2 = 0.9968, CV = 1.0–2.3%.[36–38]

4. Drug Uptake Studies

Drug uptake in MT-2 cells was assessed using HPLC after treatment with PBS (pH 7.4), ethosomal, or marketed formulations.[36–38]

5. Skin Permeation Studies

Excised rat skin should properly attached on diffusion cells. Ethosomal formulation (1.0 mL) was applied, and samples were collected at intervals over 24 hours. Permeated drug was quantified by HPLC.[36–38]

6. Stability Study

Vesicles stored at 4°C ± 0.5°C were evaluated after 180 days for size, zeta potential, and entrapment efficiency using standard methods.[36–38]

TRANSDERMAL PATCHES

A transdermal patch is designed to deliver a specific dose of medication through the skin, reaching either the deeper skin layers or entering systemic circulation. (Figure 4)

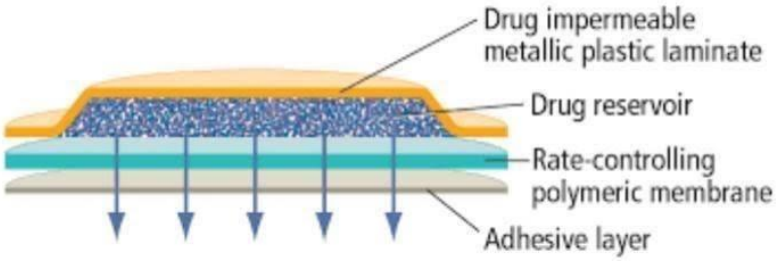

Figure 4: Transdermal patch.

PARTS OF TDDS SYSTEM (TDDS)

1. Polymer Matrix

Controls the drug release rate.

- Natural Polymers: Cellulose derivatives, zein, gelatin, shellac, waxes, gums, starch, natural rubber etc.

- Synthetic Elastomers: Polybutadiene, silicone rubber, hydrin rubber, nitrile, neoprene etc.
- Synthetic Polymers: PVA, PVC, Polyethylene, Polypropylene, Polyacrylate, Polyamide, Polyurea, PVP, PMMA, epoxy etc.

2. Drug
Ideal drugs for TDDS should
- Have a molecular weight <1000 Da
- Possess both lipophilic and hydrophilic balance
- Should possess low melting point, potent and non-irritant and have a short half-life

Natural: Eugenol – low toxicity, non-irritant

b) Surfactants: Enhance hydrophilic drug transport.
Types:
Anionic: dioctyl sulphosuccinate, Sodium lauryl sulfate,
Nonionic: Pluronic F127, F68
Bile Salts: Sodium deoxycholate, taurocholate

c) Miscellaneous
Urea, calcium thioglycolate, N,N-dimethyl-m-toluamide, anticholinergics.
New candidates: Eucalyptol, soybean casein and di-o-methyl-β-cyclodextrin.

4. Other Excipients
a) Adhesives
Ensure patch adherence without irritating skin or interfering with drug/enhancer release. Should be compatible and easily removable.

b) Backing Membrane
Protects the formulation and prevents drug loss.
Examples: Metallic laminates, plastic films with absorbent pads, aluminium foil-based systems

Advantages
- Easy, weekly application improves adherence
- Ideal for patients who can't take oral meds (e.g., unconscious, nauseated)
- Bypasses GI tract, avoids enzyme degradation and first-pass metabolism
- Suitable for drugs needing stable plasma levels
- Incorporates lamellar structured lipid matrices

Disadvantages
- May cause local irritation, itching, erythema, or allergic reactions
- Requires drugs <500 Da with suitable log P (1–3) for skin permeation [39–41]

TYPES
A. Single-layer Drug-in-Adhesive
The adhesive layer holds patch and delivers drug. It includes a backing and protective liner.

B. Multi-layer Drug-in-Adhesive
Similar to single-layer but with two drug-in-adhesive layers separated by a membrane provides immediate and sustained release.

C. Reservoir System
The drug is stored in a liquid/semi-liquid reservoir, separated from the skin by a rate controlling membrane and adhesive. Delivers the drug at a constant (zero-order) rate.

D. Matrix System (Monolithic Device)
The drug is embedded in a semisolid polymer matrix, partly covered by an adhesive layer for skin contact.

E. Vapour Patch
Delivers vapours (e.g., essential oils) through the adhesive layer. Commonly used for decongestion, smoking cessation, and sleep enhancement.

Evaluation of Transdermal Patches
To ensure performance and reproducibility, patches are evaluated using the following methods:

1. Physicochemical Evaluation
Thickness
Measured using tools like micrometers or screw gauges.

Weight Uniformity
Weigh 10 patches individually; values should be close to the average.

Drug Content
100 mg film dissolved in solvent, shaken, sonicated, filtered, and analyzed via spectrophotometry.

Content Uniformity
9 out of 10 patches must contain 85–115% of drug; 1 may be within 75–125%. If not, 20 more are tested.

Moisture Content
Film weight before and after desiccation.
% Moisture = (Initial - Final) / Final × 100

Moisture Uptake
Weight gain after exposure to 84% RH.
% Uptake = (Final - Initial) / Initial × 100

Flatness: Measured via strip length difference.
% Constriction = (I1 - I2) / I2 × 100

Folding Endurance
The number of times the patch can be folded at the same spot before it breaks.

Tensile Strength
Resistance to breakage under tension.
TensileStrength=F/(a×b)×(1+L/l)Tensile Strength = F / (a × b) × (1 + L / l)

Where:
F = force to break, a = width, b = thickness, L = length, l = elongation [42–44]

CONCLUSION

Ethosomal transdermal patches represent a significant development in topical and transdermal drug delivery systems. By incorporating ethanol and phospholipids, ethosomes enhance the permeation of hydrophilic and lipophilic drugs through stratum corneum, overcoming primary barrier of the skin. Their flexibility, deformability, and high entrapment efficiency make them particularly effective for sustained and prolonged drug release.

Assessing to traditional transdermal systems, ethosomal patches offer improved bioavailability, reduced dosing frequency, and better patient compliance. They also show promise for delivering large protein and peptide molecules those are typically challenging to administer transdermally.

Despite these advantages, further research is needed to optimize formulation stability, scale-up production, and evaluate long-term safety and efficacy in clinical settings. With continued development, ethosomal patches could become a versatile and reliable platform for non-invasive drug delivery across a broad range of therapeutic areas.

4. FUTURE PERSPECTİVES

Historical background of ethosomes related to topical delivery**,** due these carriers unique nature and potential advantages over other carriers and oral controlled drug delivery, provided safe biodegradable polymers are used. The extended drug release, excellent surface properties, good stability, and non-irritating nature paves the way to site-specific prolonged drug delivery. Its application can be extended to ocular, pulmonary rectal, and vaginal drug delivery apart from Transdermal sites.

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