REVIEW ARTICLE

Ethosomes as Promising Novel Transdermal Drug Delivery System and their Therapeutic Applications – A Review

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Abstract

Inadequate penetration of therapeutically active chemicals is the main factor affecting transdermal drug delivery system networks. The stratum corneum (SC) serves as the skin's initial line of defense against drug molecule penetration. To date, this field has employed a number of tactics to overcome the SC barrier limits. The main purpose of a few innovative methods, including as liposomes, niosomes, ethosomes, and transfersomes, is to make pharmaceutical and cosmetic substances more permeable through the SC barrier. The melting point of SC lipids is lowered by ethosomes, which are stable, elastic, nanoscale vesicles with high phospholipid and ethanol content that interact with the polar head domain of lipid molecules. Finally, it increases lipid fluidity and cell membrane permeability. This section provides an overview of the most recent ethosome updates, depending on several pharmacological dose forms, involving gels, patches, and creams. There is also a brief discussion on updated ethosome patents. To sum up, ethosomes are an ideal vehicle for the delivery of drugs, cosmetics, and other substances and can be used in place of traditional pharmaceutical applications.

Key words: Anti-psoriatic, ethosomes, liposomes, stratum corneum, transferosomes

INTRODUCTION

The most versatile and broad route for topical and systemic drug administration is the skin. An approach to pharmaceutical administration that is less invasive is transdermal drug delivery (TDD), which provides less frequent dosage, controlled drug distribution, patient compliance, as well as prevention of first-pass metabolism.[1-4] Following transferosomes, groundbreaking research led to the identification of ethosomes, a distinct lipid vesicular system.[5] Ethosomes are novel modified lipid carriers composed of phospholipids, water, and ethanol. In addition to phospholipids and water, ethosomes contain comparatively high amounts of ethanol, which may have enhanced vesicular properties and epidermal penetration.[6-10]

WORKING MECHANISM OF ETHOSOMES

In the activity of ethosomes, ethanol, vesicles, and skin lipids work in concert.[11] The dispersion of active substances is improved over liposomes by ethosomes and skin lipids because they interact more effectively. In addition, ethanol renders vesicles flexible and smooth, allowing for deeper penetration into the epidermal layer.[12]

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Table 1

Ethosomal system types

Table 1.Difference between various ethosomes for transdermal drug delivery [11]

S.no	Parameter	Classical Ethosomes	Binary Ethosomes	Transethosomes
1	Composition	Phospholipids, ethanol and stabilizer	Phospholipids, ethanol stabilizer and propylene glycol	Phospholipids, ethanol, edge activator and charge inducer
2	Morphology	Spherical	Spherical	Spherical
3	Size	Smaller than classical ethosomes	Equal or Smaller than classical ethosomes	Size varies based on change of the inducer concentration
4	Entrapment efficiency	Greater than traditional ethosomes	Often Greater than traditional ethosomes	Higher than majority of ethosomes
5	Skin permeation	High	High	High
6	Stability	Highly robust	Stable	No evidence

ETHOSOMAL SYSTEM TYPES

Ethosomal systems, used for transdermal drug delivery, are generally categorized into three types based on their composition: classical ethosomes, binary ethosomes, and transethosomes. These systems are characterized by the presence of ethanol, phospholipids, and water (Table 1 and Figure 1).

MECHANISM OF PENETRATION

Ethanol decreases "transition temperature of lipids in the stratum corneum (SC), increases their fluidity, and decreases the density of lipid multilayers through interacting with lipid molecules in the polar head group region. "Ethosome" effect" follows, whereby the medicine is released into deep layers of skin by lipid penetration as well as permeation through the creation of new routes as a result of the ethosomes' fusing and malleability with skin lipids.[13,14]

RATIONALE FOR TDD

In other instances, the most practicable method of drug ingestion – the oral route – was impractical; therefore, other methods had to be looked for. TDD has numerous obvious advantages, including convenience of administration, ease of stopping therapy, and a relatively large as well as easily accessible surface area for absorption.[15,16]

COMPOSITION OF ETHOSOMES

Although ethersomes and liposomes both have a lipid bilayer, their composition (high ethanol concentration) sets them apart. Hydroalcoholic or glycolic/hydrophospholipids that make up ethosomes have comparatively high alcohol content. Between 22% and 70% of the alcohol and glycol mixture may be present in the non-aqueous phase.[17]

PREPARATION OF ETHOSOMES

Ethosomes can be prepared in a variety of ways, which might change based on the particular circumstances and needs of the process. They are a good substitute for conventional medication delivery methods because of their rather easy and affordable manufacture.[18]

Table 2 highlights "the most important methods that can be used to prepare ethosomes.

ADVANTAGE OF ETHOSOMAL DRUG DELIVERY SYSTEM

Comparing ethosomal drug delivery systems to other transdermal and dermal administration techniques reveals several advantages. The ability to distribute large molecules (like protein or peptide molecules), use of non-toxic raw ingredients in formulation, and enhanced drug penetration through the skin for transdermal drug administration are some advantages.

DISADVANTAGES OF ETHOSOMAL DRUG DELIVERY

Precipitation might result from ethosomes with poor shelling grouping together. Sufficient medication solubility conditions are required to enter the cutaneous microcirculation and systemic circulation. When transferred into water, the ethosomes may aggregate and break down if shell locking is insufficient.[19-25]

EVALUATION OF ETHOSOMES[26]

Vesicle-skin interaction study by transmission electron microscopy (TEM) and scanning electron microscopy (SEM)

By "interacting with lipid molecules in the polar head group region, ethanol lowers the transition temperature of lipids in the SC, enhances their fluidity, and reduces the density of lipid multilayers.

Filter membrane-vesicle interaction study by SEM

Before being placed in diffusion cells, filter membrane with 50 nm pore size was coated with vesicle suspension (0.2 mL). Phosphate buffer saline solution (PBS), which has a pH of

Table 2: Preparation of ethosomes with key characteristics

Method	Advantages	Cost	Manufacturing scale
Hot method	• Quick and easy method • Smaller particle size • Stable at RT • Suitable for hydrophilic and hydrophobic drugs • High encapsulation efficiency	Low to moderate	Small to large
Cold method	• Simple and mild preparation method • Loading capacity is good • Stable at RT • Suitable for hydrophilic and hydrophobic drugs • Scalability is good	Low to moderate	Small to large
Vortex method	• Encapsulation capacity is high • Particle size is small • Loading capacity is good • Stable at RT • Suitable for hydrophilic and hydrophobic drugs	Moderate to high	Small to moderate
Rotary film evaporation	• Loading capacity is high • Stable • Suitable only for hydrophobic drugs	Moderate to high	Small to moderate
Classic dispersion method	• Simple and mild preparation method • Suitable for hydrophilic and hydrophobic drugs	Low to moderate	Small to large
Transmembrane pH-gradient method	• Stable • Suitable for only hydrophobic drugs	High	Small to moderate

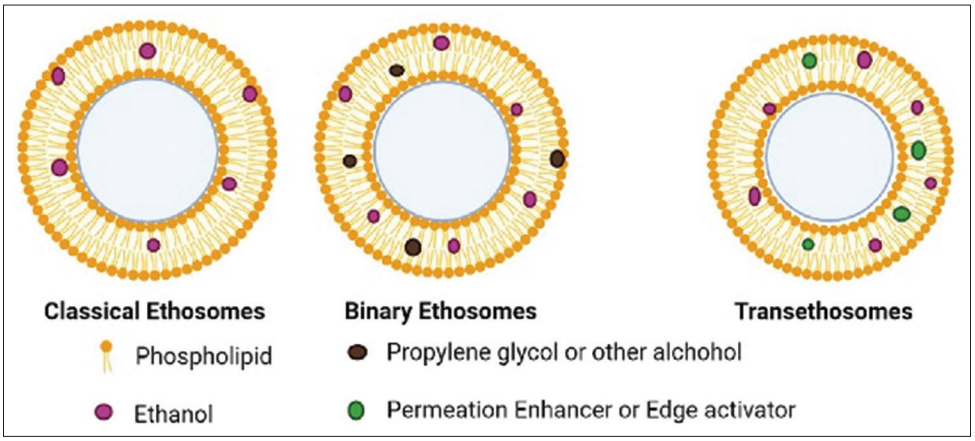

Figure 1: Pictorial representation of ethosomes

6.5, came into contact with the lower side of the filter while the upper side has been left open to air.

Vesicle-skin interaction study by fluorescence microscopy

The fluorescence microscopy has been examined using TEM and SEM techniques. Five µm-thick pieces of paraffin blocks that had been cut with "microtome (Erma Optical Works, Tokyo, Japan) have been examined underfluorescence microscope. MT-2 Cell" Cytotoxicity Test.

STABILITY OF ETHOSOMES

Entrapment capacity and particle size have been used to assess the compositions' long-term stability. The entrapment efficiency is improved by raising the ethanol level from 15% to 45% because the membranes are more flexible. The vesicle membrane may become more porous at ethanol concentrations above 45%, which would reduce the efficiency of entrapment. As a result, the ethosomes become unstable. Lipid hydrolysis produces lyso-PC. Because lyso-PC enhances ethosome permeability, it is crucial to keep a minimum in a given preparation.[27-29]

ETHOSOMES INCORPORATED IN SUITABLE DOSAGE FORM

Before being placed in diffusion cells, filter membrane with 50 nm pore size was coated with vesicle suspension (0.2 mL). Upper portion of filter has been exposed to air, while lower portion has been in contact with PBS, which has a pH of 6.5.

ETHOSOMES IN GEL FORM

Ethosomal gels are distinguished by their pH, viscosity, extrudability, and spreadability. In all of their related categories, carbopol and hydroxypropyl methylcellulose are the two most widely utilized gel-forming agents for integrating ethosomal systems.[30-35]

APPLICATION OF ETHOSOMES IN DRUG DELIVERY

In recent two decades, ethosomes were widely utilized for transdermal/topical drug delivery applications. The plentiful literature survey suggested that the novel ethosomes have to gain immense importance in advanced drug delivery systems, especially delivery through skin membranes.

ANTIFUNGAL AGENT DELIVERY

In the lipid carrier system, ethosomes show an incredible ability to enhance transdermal permeation. Ethosomes-based formulations have been designed to achieve a rapid onset of action, maximum drug release, and fewer side effects. There is no harmful effect to the skin during drug transport to systemic circulation across undamaged skin. Furthermore, it reduces the duration of treatment.[36,37] The *in vivo* research confirmed that drug-loaded ethosomes were more active and effective against *Candida parapsilosis* than *Aspergillus niger* due to the synergistic effect from need and drug. Therefore, it can be used as a potential antifungal agent in biomedical applications.[38,39] Finally, ethosomes have the potential to be a vehicle for topical administration of fluconazole.[40-42]

ANTI-INFLAMMATORY DRUG

From its inception, an anti-inflammatory agent involving non-steroidal anti-inflammatory drugs (NSAIDs) is generally utilized for the treatment of chronic pain and inflammation. When taking NSAIDs orally, one may experience stomach ulcers, abdominal pain, irregularities, and various vascular problems. In addition, NSAIDs can fail a quick onset of action owing to their low bioavailability and half-life.[43-50] Furthermore, the paeonol-ethosomes *in vitro* skin penetration and skin retention study confirmed the high permeation rate (138.58 μg/cm^2) and skin retention (52.60 μg/cm^2). In nutshell, ethosomes could be an exceptional nanocarrier for potential drug delivery applications, especially transdermal administration of paeonol.[51,52] The ethanol offers softness and flexibility to the ethosomal vesicles, which results in high penetration. As well, the high concentration of ethanol increased the skin permeation rate.[53,54]

ANTI-VIRAL DRUGS

Acyclovir-loaded ethosomal gel has been reported for the management of Herpes zoster. It has been prepared using ethanol, phospholipid, and PEG through the cold method. The optimized batch showed about –20.5 mV zeta potential and about 331.69 nm vesicle size. Finally, 1% w/w carbopol 980 showed better *in vitro* acyclovir drug release (82.23%) after 8 h, and release kinetics was found in the zero-order model ($R^{2:}$ 0.989). Therefore, it can be used as a budding vehicle for the delivery of the antiviral agent for an extended time in the case of the affected skin part.[55,56]

ETHOSOMES IN COSMECEUTICALS

Various cosmetic preparations contain numerous active ingredients that only help to offer appropriate penetration to the SC layer of the skin. However, a few of the formulations used topically have relatively lower potency because the SC is resistant to being transported into the skin. For this reason, the formulation needs to be modified. Accordingly, the appropriate modification in the formulation will lead to the high permeability of the formulation containing a drug. Interestingly, ethosomes can be used as an excellent carrier to supply a wide range of ingredients through topical routes.[57,58]

ANTICANCER DRUG DELIVERY

In the world of medical sciences, cancer therapy is still a challenging task. It may be due to the inefficiency of the existing clinical approaches used for the treatment, which results in a large number of deaths occurring each year. Hence, there is an urge to expand a suitable carrier for the delivery of the drug to the targeted area and systemic application.[59-61]

DELIVERY OF ANALGESIC AGENT

Nowadays, effective pain management is a challenging task for researchers. It may be because of severe side effects of the different analgesic agents.[62]

DELIVERY OF ANTI-PSORIATIC AGENT

Psoriasis is a chronically non-infectious skin condition, joint, and/or both with relapsing inflammatory and hyperkeratotic plaque episodes. In such conditions, efficient delivery of the drug is an important factor during formulation design.[63]

DELIVERY OF ANTI-HYPERTENSIVE AGENT

Over the past decades, hypertension incidence has increased dramatically. Moreover, it is also the leading cause of death also. For the last couple of decades, the scientific fraternity has been working on various effective carriers for the delivery of anti-hypertensive agents through different routes.

CONCLUSION

Ethosomes have demonstrated encouraging outcomes in the pharmaceutical industry as drug delivery systems, and research into their potential for skin care applications is growing. Targeted drug delivery, improved drug-loading capacity, and higher stability are made possible by the inclusion of ethanol in their composition.

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