ETHOSOMES: A NOVEL VESICULAR CARRIER FOR TRANSDERMAL DRUG DELIVERY

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ABSTRACT

Transdermal drug delivery system is a type of convenient drug delivery system where drug goes to the systemic circulation through the protective barrier i.e., skin which is the main target of topical and transdermal preparations. Major aim of transdermal drug delivery system is to cross the stratum corneum. Vesicular system is one of the most controversial methods for transdermal drug delivery system. Ethosomes are non-invasive delivery carriers that enable drugs to reach the deep skin layers and/or the systemic circulation. Ethosomal system comprises of phospholipids, high concentration of ethanol and water. Characterization of ethosomes include Particle size, Zeta potential, Differential Scanning Colorimetry, Entrapment Efficiency etc. The purpose of writing this review on ethosomes drug delivery is to compile the focus on the various aspects of ethosomes including their mechanism of penetration, advantages, composition, preparation, characterization, and applications.

KEYWORDS: Ethosomes, vesicular system, phospholipids, zeta potential, entrapment efficiency.

INTRODUCTION

Drug delivery is the process of administering a pharmaceutical compound to achieve a therapeutic effect in human or animals. In comparison to oral drug delivery systems, transdermal drug delivery system (TDDS) shows promising result, eliminating gastrointestinal interferences and first pass metabolisms. However, the main advantage of TDDS is that it only works with lipophilic drugs due to the stratum corneum’s barrier properties. Molecular weights of less than 500 Da can pass through it. TDDS have been created to augment the permeability of the skin or the driving power of drug diffusion.

To combat this characteristic of skin, a variety of methods have been tried, including the use of chemical boosters such surfactants, organic solvents, and physical enhancers. Many techniques including iontophoresis, sonophoresis, micro needling, electroporation etc., have been evaluated to promote penetration; nevertheless, lipid vesicles are the best because they can change the barrier property of stratum corneum. Vesicles serve as a carrier system that can carry medications with high molecular weight into the skin or even into the bloodstream.

Drug permeability across the stratum corneum has also been found to be improved by liposomes, niosomes, transferosomes and ethosomes. Enhancers of permeation makes the skin more permeable, allowing medications to pass through the skin more readily. Ethosomes can improve permeation through the stratum corneum barrier in contrast to traditional liposomes, which are known for delivering medications mostly to the skin’s outer layers.

Ethosomes are ethanolic liposomes. Ethosomes can be defined as non-invasive delivery carriers that enable drugs to reach deep into the skin layers and/or the systemic circulation. These are soft malleable vesicles tailored for enhanced delivery of active agents. Ethosomes are lipid vesicles containing phospholipids, alcohol (ethanol and isopropyl alcohol) in relatively high concentration and water.

Figure 1: Structure of ethosomes.

TYPES OF ETHOSOMAL SYSTEMS

Classical ethosomes

Classical ethosomes are a variation of classical liposomes, consisting of phospholipids, high ethanol concentrations of up to 45% w/w and water. Classical ethosomes for transdermal drug delivery are stated to be superior to classical liposomes because of smaller size.
and have negative zeta potential for greater efficiency without clogging. Moreover, in contrast with classical liposomes, classical ethosomes displayed improved skin permeation and stability profiles. The molecular weights of drugs entrapped in traditional ethosomes ranged from 130.077 Da to 24 kDa.\(^5\)

**Binary ethosomes**

Binary ethosomes are introduced by Zhou et al. In essence, they were created by mixing a different form of alcohol with the traditional ethosomes. Propylene glycol (PG) and isopropyl alcohol (IPA) are the two alcohols that are most frequently utilised in binary ethosomes.\(^6\)

**Transethosomes**

The new generation of ethosomal systems known as transethosomes was initially described by Song et al. This ethosomal system includes a substance such as a penetration enhancer or an edge activator (surfactant), in addition to the fundamental elements of traditional ethosomes in their formula. These unique vesicles were created in an effort to create transethosomes by fusing the benefits of traditional ethosomes with deformable liposomes (transferosomes) into a single formulation. Many studies have found that transethosomes have better qualities than traditional ethosomes. To create ethosomal systems with better properties, many edge activator and penetration enhancers types have been researched. According to reports, transethosomes can entrap drugs with molecular weights ranging from 130.077 Da to 200-325 kDa.\(^7\)

**MECHANISM OF PENETRATION**

![Figure 2: Schematic representation of the different types of ethosomal systems.](image)

![Figure 3: Mechanism of penetration of ethosomal drug delivery system.](image)
The drug penetration mechanisms
Stratum corneum has two probable routes which encompasses intercellular and transcellular pathways. Drug delivery into skin via locally imposed vesicles is influenced by oodles of divisors. Vesicles that are more modest in size penetrate substantially into the deeper layers of skin. The size of ethosomes is affected by the concentration of phospholipid and ethanol. As the concentration of ethanol increases the size of the ethosomes decreases. Ethosomes permeate via transcutaneous pathway of skin which comprises of Stratum corneum and open hair follicles. The vesicles are fragmented in the upper layer of skin during transcutaneous permeation which allows penetration of therapeutic agents progressively although the epidermis retains the phospholipid. This phenomenon is based on the interdependent effects of the lipid and ethanol to escalate the ethosome permeation.[9]

Ethanol Effect: Via the skin, ethanol enhances permeation. Its penetration-enhancing effect has a well-known mechanism. Ethanol permeates into intracellular lipids and increases the fluidity of cell membrane lipids and decreases the density of lipid multilayer of cell membrane.[9]

Ethosomes Effect: The ethosomal ethanol increases the lipid fluidity in the cell membrane, which increases the skin’s permeability. Hence, the ethosomes penetrate fast into the skin lipids and releases the medications into the bloods deep layer.[9]

Advantages of ethosomal drug delivery[10,11,12]
- Large molecules (peptides protein molecules) can be delivered.
- Its formulation uses non-toxic raw materials.
- Improved transdermal drug administration by the skin penetration of the drug.
- Good patient compliance as a result of the ethosomal medication being administered in semisolid form (gel or cream).
- The ethosomal system is quiet, non-invasive, and readily available.
- The ethosomal drug delivery technology is widely used in the medical, veterinary and cosmetics industries.
- In contrast to iontophoresis, phosphoremias and other complex procedure, this is simple method of drug administration.

Disadvantages of ethosomal drug delivery[13,14]
- Extremely low yield, possibly not economically viable.
- Some people may develop skin rashes or dermatitis as a result of the excipients or penetration enhancers employed.
- Product loss during the transition from organic to water media.
- Ethosomal administration is often intended to provide steady, sustained medication delivery, not quick bolus type drug input.
- The drug molecules size should be appropriate for percutaneous absorption.
- Not all skin types may respond well to the adhesive.
- Only potent drugs (daily dose of 10 mg or less) that require low blood levels can be administered.

Composition of ethosomes
Phospholipids
Phospholipids from different sources are used in formulation of the ethosomal scheme. The selection of phospholipid type and concentration for formulation are important factors during the production of ethosomal system since they will affect the effectiveness of the trapping, zeta Potential, vesicular properties, stability, and penetration. In general, in an ethosomal formulation, the concentration range of phospholipids is 0.5%–5%. Rising phospholipid concentration can increase vesicular size marginally or moderately, but will greatly improve the efficiency of trapping. Typically, ethosomes may contain phospholipids with various chemical structures like phosphatidylcholine (PC), hydrogenated PC, phosphatidic acid (PA), phosphatidylserine (PS), phosphatidylethanolamine (PE), phosphatidylylglycerol (PPG), phosphatidylinositol (PI), hydrogenated PC,[12,13]

Ethanol
Ethanol is an efficient penetration enhancer. It plays an important role in ethosomal systems by giving the vesicles special dimensional characteristics size, zeta potential, stability, prevention of clogging and increased permeability of the skin. Concentrations of ethanol in ethosomal systems have been reported to be 10%–50%. Many researchers concluded that when the concentration of ethanol is increased, the size of the ethosomes would decrease.

Cholesterol
Cholesterol is a stable steroid molecule, and its integration into ethosomal structures increases medication stability and clogging effectiveness. This avoids leakage and decreases permeability of the vesicles and vesicular fusion. Generally, it is used at a concentration of 3% but in some formulations, it was used up to 7% of the total phospholipid concentration in the formulation. Several studies have recorded that the vesicular size of ethosomal systems increased with cholesterol.

Propylene glycol (PG)
PG is a widely used penetration enhancer. This is used at a concentration range of 5%–20% in the preparation of binary ethosomes and has been found to influence the ethosomal properties of size, trapping capacity, permeation, and stability. PG integration into ethosomal systems will result in more reduction of particle size relative to systems without PG.[15,16]
Methods of preparations of ethosomes

Cold method
This technique for ethosomal preparation is the most popular and commonly utilised method. The phospholipids, drug, and other lipid materials are dissolved in ethanol, in a covered vessel, at room temperature, with vigorous stirring. The mixture is heated up to 30°C in a water bath. Water is heated to 30°C in a separate vessel before being added to the above mixture and mixture is stirred for five minutes. If desired, the ethosomal formulation’s vesicle size can be reduced by sonication or extrusion in order to increase its extensibility. Finally, the formulation needs to be carefully stored under refrigeration.\[^{[13]}\]

Hot method
This process involves heating phospholipid in a water bath at 40°C till a colloidal solution is formed. Propylene glycol and ethanol must be correctly combined in a separate vessel. The organic phase is added to the aqueous phase once both mixtures reach 40°C. The drug solution is then added and the phospholipid dispersion is continuously stirred for 10 minutes using a magnetic stirrer set at 1500 rpm. Finally, a refrigerator is used to keep the created formulations.\[^{[14]}\]

Classic method
In this procedure, phospholipid and drug are dissolved in ethanol and heated to 30°C±1°C in a water bath. Double distilled water is added in a stream to the lipid mixture, with constant stirring at 700 rpm, in a closed vessel. The resulting vesicle suspension is homogenized by passing through a polycarbonate membrane using a hand extruder for three cycles.\[^{[19]}\]

Evaluation of ethosomes

Vesicle morphology and zeta potential determination
The surface morphology of ethosomal formulation can be studied using scanning electron microscopy (SEM). In the analysis of SEM image, vesicular features with a near spherical shape are plainly seen.\[^{[20]}\] Zeta sizer is used to measure vesicle size, zeta potential and polydispersity index. One drop of ethosomal suspension is diluted in hydroethanolic solution at 25°C in clear disposable zeta cells and analysed by zeta sizer.\[^{[21]}\]

Drug entrapment
The degree of ethosome entrapment can be assessed using the ultracentrifugation technique. The sample is taken and centrifuged at 15000rpm for 2 hours in an ultracentrifuge. Sediment and supernatant are separated and estimated by UV spectrophotometer. The ability of ethosomes to efficiently entrap hydrophilic and lipophilic drugs can be attributed to their high degree of lamellarity and the presence of ethanol in the vesicles.\[^{[22]}\] The entrapment efficiency can be determined by applying the following equation:

$$EE\ (% ) = \frac{\text{Total amount of drug taken-unentrapped drug}}{\text{Total amount of drug taken}} \times 100$$

Stability study
The change in drug entrapment effectiveness is used to assess the stability of ethosomal vesicles. This is determined by storing the vesicles at of 40±2°C and 75±5 RH for 6 months. After appropriate time intervals, samples are withdrawn and analysed for the change in pH, colour, drug content and in vitro drug release.\[^{[23]}\]

In vitro drug permeation study
The modified Franz diffusion cell with egg membrane can be used to conduct the in vitro permeation study. The study is performed with phosphate buffer saline (pH 7.4). The formulation is placed on the upper side of membrane in donor compartment. The temperature is maintained at 37±2°C, where the samples are withdrawn after every hour from the receptor media through the sampling tube and at the same time, same amount of fresh media is added to maintain sink condition. Withdrawn samples are analysed by UV/Vis spectrophotometer.\[^{[24]}\]

Drug content
A UV spectrophotometer can be used to determine the ethosome’s drug content. This can be also measured with the use of modified high performance liquid chromatographic technique. Ethosomal suspension is taken and dissolved in sufficient quantity of methanol where it is stirred on a magnetic stirrer. Then the resulting solution is withdrawn and absorbance is recorded in the UV spectrophotometer.\[^{[25]}\] The drug content can be calculated by the following formula:

$$\text{Amount of drug}= \frac{[\text{concentration} \times \text{DF}]}{100}$$

Applications of ethosomes

Delivery of Anti-viral drugs
An antiviral medication called acyclovir is used to treat Herpes labialis. Due to its traditional marketing composition, acyclovir has poor therapeutic efficiency due to inadequate dermal penetration. The drug can be added to ethosomes to overcome these drawbacks, which delays the drug release and transdermal flux and provides appropriate zero order delivery.

Delivery of problematic drug molecules
Large biogenic compounds like insulin are difficult to give orally since gastrointestinal tract entirely degrades them. Hence, by producing high molecular weight drugs enclosed ethosomes significantly enhances permeability and therapeutic efficacy of high molecular weight medicines.\[^{[26]}\]

Transdermal delivery of Hormones
Hormones taken orally can cause issues such as high first pass metabolism, poor oral bioavailability, and a variety of dose-dependent adverse effects. Touitou et al. compared the ability of testosterone ethosomes (Testosome) to penetrate rabbit pinna skin to that of commercial transdermal testosterone patches (Testoderm patch, Alza). They discovered that the skin absorption of testosterone from the ethosomal formulation was roughly
30 times higher than that of the commercial formulation.\textsuperscript{[27]}

**Delivery of anti-parkinsonism agent**

Dayan and Touitou created an ethosomal formulation of the psychoactive substance trihexyphenidyl hydrochloride (THP) and compared its absorption to that of a more classical liposomal preparation. THP, an antagonist of M1 muscarinic receptors, is used to treat Parkinson’s disease. According to the findings, the ethosomal-THP formulation has a superior skin penetration capacity and can be used to treat Parkinson’s disease more effectively.\textsuperscript{[29]}

**CONCLUSION**

Ethosomes have been proven as an emerging and effective carrier system over two decades. Their ability to provide effective therapeutic effect, topically and systemically through skin have made them an appealing and novel carrier system over time. Drugs that are hydrophilic, cationic, proteins and peptides have all been tested to be enclosed by ethosomes. Moreover, further study in this field will enable more effective therapy by enabling improved control over drug release in vivo and long-term safety data.

**REFERENCES**


