



## ETHOSOMES:- A NOVEL DRUG CARRIER FOR TRANSDERMAL DRUG DELIVERY

Priyanka\*, Bhandarineeraj and Kumari Neha

Sri Sai College of Pharmacy, Badhani, Pathankot.

Article Received on  
30 October 2018,  
Revised on 20 Nov. 2018,  
Accepted on 10 Dec. 2018  
DOI: 10.20959/wjpps20191-12930

### \*Corresponding Author

Priyanka

Sri Sai College of Pharmacy,  
Badhani, Pathankot.

### ABSTRACT

Skin acts as a major target as well as a principal barrier for topical/transdermal drug delivery. Despite the many advantages of this system, the major obstacle is the low diffusion rate of drugs across the stratum corneum. Several methods have been tried to increase the permeation rate of drugs temporarily. One simple and convenient approach is application of drugs in formulation with elastic vesicles or skin enhancers. Vesicular system is one of the most controversial methods for transdermal delivery of active substances in that ethosome

are the ethanolic phospholipids vesicles which are used mainly for transdermal delivery of drugs. Ethosomes have higher penetration rate through skin due to its ethanolic content. In this article reviews various aspect of ethosomes including their mechanism of penetration, preparation, advantages, characterization, composition, preparation, application and marketed product. These carriers open new challenges and opportunities for the development of novel improved therapies. Ethosomes are noninvasive delivery carriers that enable drugs to reach the deep skin layers and/or the systemic circulation. Although ethosomal systems are conceptually sophisticated, they are characterized by simplicity in their preparation, safety, and efficacy a combination that can highly expand their application. Ethosomes are soft, malleable vesicles tailored for enhanced delivery of active agents. This article reviews various aspect of ethosomes including their preparation, characterization, potential advantages and their applications in drug delivery. Because of their unique structure, ethosomes are able to encapsulate and deliver through the skin highly lipophilic molecules such as cannabinoids, testosterone, and minoxidil, as well as cationic drugs such as propranolol, trihexyphenidil, Cyclosporine A, insulin, salbutamol etc. Ethosomes provides a number of important benefits including improving the drug's efficacy, enhancing patient compliance and comfort and reducing the total cost of treatment. Enhanced delivery of

bioactive molecules through the skin and cellular membranes by means of an ethosomal carrier opens numerous challenges and opportunities for the research and future development of novel improved therapies.

**KEYWORDS:** Ethosomes, Noninvasive, Transdermal, Skin permeation, Vesicles.

## INTRODUCTION

Ethosome are novel carrier system used for delivery of drugs having low penetration through the biological membrane mainly skin. Ethosomes are the slight modification of well established drug carrier liposome. Ethosomes are lipid vesicles containing phospholipids, alcohol (ethanol and isopropyl alcohol) in relatively high concentration and water.<sup>[1]</sup> Ethosomes are soft vesicles made of phospholipids and ethanol (in higher quantity) and water. The size range of ethosomes may vary from tens of nanometers to microns ( $\mu$ ).<sup>[2]</sup> ethosomes permeate through the skin layers more rapidly and possess significantly higher transdermal flux in comparison to conventional liposomes.<sup>[1,3]</sup> Although, the exact mechanism for better permeation into deeper skin layers from ethosomes is still not clear. The synergistic effects of combination of phospholipids and high concentration of ethanol in vesicular formulations have been suggested to be responsible for deeper distribution and penetration in the skin lipid bilayers. Ethosomes are mainly used for the delivery of drugs through transdermal route. The transdermal delivery is one of the most important routes of drug administration. The main factor which limits the application of transdermal route for drug delivery is the permeation of drugs through the skin. Human skin has selective permeability for drugs. Lipophilic drugs can pass through the skin but the drugs which are hydrophilic in nature can't pass through. Water soluble drugs either show very less or no permeation. To improve the permeation of drugs through the skin various mechanisms have been investigated, including use of chemical or physical enhancers, such as iontophoresis, sonophoresis, etc. Liposomes, niosomes, transferosomes and ethosomes also have been reported to enhance permeability of drug through the stratum corneum barrier. Permeation enhancers increase the permeability of the skin, so that the drugs can cross through the skin easily. Unlike classic liposomes, that are known mainly to deliver drugs to the outer layers of skin, ethosomes can enhance permeation through the stratum corneum barrier.<sup>[3,4]</sup> Ethosomes can entrap drug molecule with various physicochemical characteristics i.e. of hydrophilic, lipophilic, or amphiphilic. Ethosomal drug delivery is noninvasive and delivers the drug to the deep skin layers or the systemic circulation. These are soft, malleable vesicles tailored for

enhanced delivery of active agents. They are composed mainly of phospholipids, (phosphatidylcholine, phosphatidylserine, phosphatidic acid), high concentration of ethanol and water. The high concentration of ethanol makes the ethosomes unique. The ethanol in ethosomes causes disturbance of skin lipid bilayer organization, hence when incorporated into a vesicle membrane, it enhances the vesicle's ability to penetrate the stratum corneum. Also, because of their high ethanol concentration, the lipid membrane is packed less tightly than conventional vesicles but has equivalent stability, allowing a more malleable structure and improves drug distribution ability in stratum corneum lipids.<sup>[5,6]</sup>

### **Advantages of Ethosomal Drug Delivery<sup>[7]</sup>**

In comparison to other transdermal & dermal delivery systems:-

- Enhanced permeation of drug through skin for transdermal drug delivery.
- Delivery of large molecules (peptides, protein molecules) is possible.
- It contains non-toxic raw material in formulation.
- High patient compliance- The ethosomal drug is administered in semisolid form (gel or cream) hence producing high patient compliance.
- The Ethosomal system is passive, non-invasive and is available for immediate commercialization.
- Ethosomal drug delivery system can be applied widely in Pharmaceutical, Veterinary, Cosmetic fields.
- Simple method for drug delivery in comparison to Iontophoresis and Phonophoresis and other complicated methods.

### **Mechanism of Drug Penetration<sup>[8]</sup>**

The main advantage of ethosomes over liposomes is the increased permeation of the drug. The mechanism of the drug absorption from ethosomes is not clear. The drug absorption probably occurs in following two phases:

1. Ethanol effect
2. Ethosomes effect

#### **1. Ethanol effect**

Ethanol acts as a penetration enhancer through the skin. The mechanism of its penetration enhancing effect is well known. Ethanol penetrates into intercellular lipids and increases the

fluidity of cell membrane lipids and decrease the density of lipid multilayer of cell membrane.

## 2. Ethosomes effect

Increased cell membrane lipid fluidity caused by the ethanol of ethosomes results increased skin permeability. So the ethosomes permeates very easily inside the deep skin layers, where it got fused with skin lipids and releases the drugs into deep layer of skin.

### Method of Preparation<sup>[9,10]</sup>

There are two methods which can be used for the formulation and preparation of ethosomes. Both of the methods are very simple and convenient and do not involve any sophisticated instrument or complicated process.

Ethosomes can be formulated by following two methods.

#### Hot method

In this method disperse phospholipid in water by heating in a water bath at 400<sup>0</sup>C until a colloidal solution is obtained. In a separate vessel properly mix ethanol and propylene glycol and heat upto 400c. Add the organic phase into the aqueous phase. Dissolve the drug in water or ethanol depending on its solubility.<sup>[11]</sup> The vesicle size of ethosomal formulation can be decreased to the desire extent using probe sonication or extrusion method.

#### Cold method<sup>[11,12]</sup>

This is the most common and widely used method for the ethosomal preparation. Dissolve phospholipid, drug and other lipid materials in ethanol in a covered vessel at room temperature with vigorous stirring. Add propylene glycol or other polyol during stirring. Heat the mixture upto 300<sup>0</sup>C in a water bath. Heat the water upto 300c in a separate vessel and add to the mixture and then stir it for 5 min in a covered vessel. The vesicle size of ethosomal formulation can be decreased to desire extend using sonication or extrusion<sup>[13]</sup> method. Finally, the formulation should be properly stored under refrigeration.

### Various Methods of Characterization of Ethosomes<sup>[14,15]</sup>

#### 1. Vesicle shape

Ethosomes can be easily visualized by using transmission electron microscopy (TEM) and by scanning electron microscopy (SEM).

## 2. Vesicle size and zeta potential

Particle size of the ethosomes can be determined by dynamic light scattering (DLS) and photon correlation spectroscopy (PCS). Zeta potential of the formulation can be measured by Zeta meter.

## 3. Transition temperature

The transition temperature of the vesicular lipid systems can be determined by using differential scanning calorimetry (DSC).

## 4. Drug entrapment

The entrapment efficiency of ethosomes can be measured by the ultracentrifugation technique.

## 5. Drug content

Drug content of the ethosomes can be determined using UV spectrophotometer. This can also be quantified by a modified high performance liquid chromatographic method.

## 6. Surface tension measurement

The surface tension activity of drug in aqueous solution can be measured by the ring method in a Du Nouy ring tensiometer.

## 7. Stability studies

The stability of vesicles can be determined by assessing the size and structure of the vesicles over time. Mean size is measured by DLS and structure changes are observed by TEM.

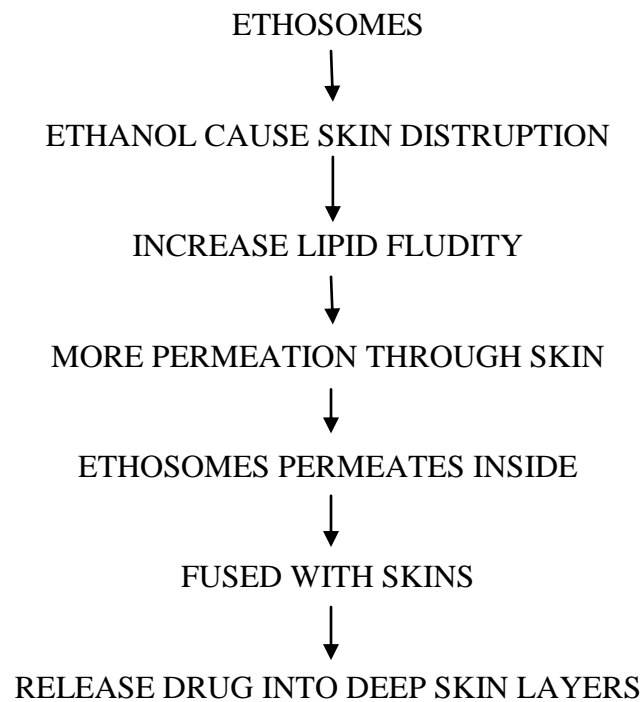
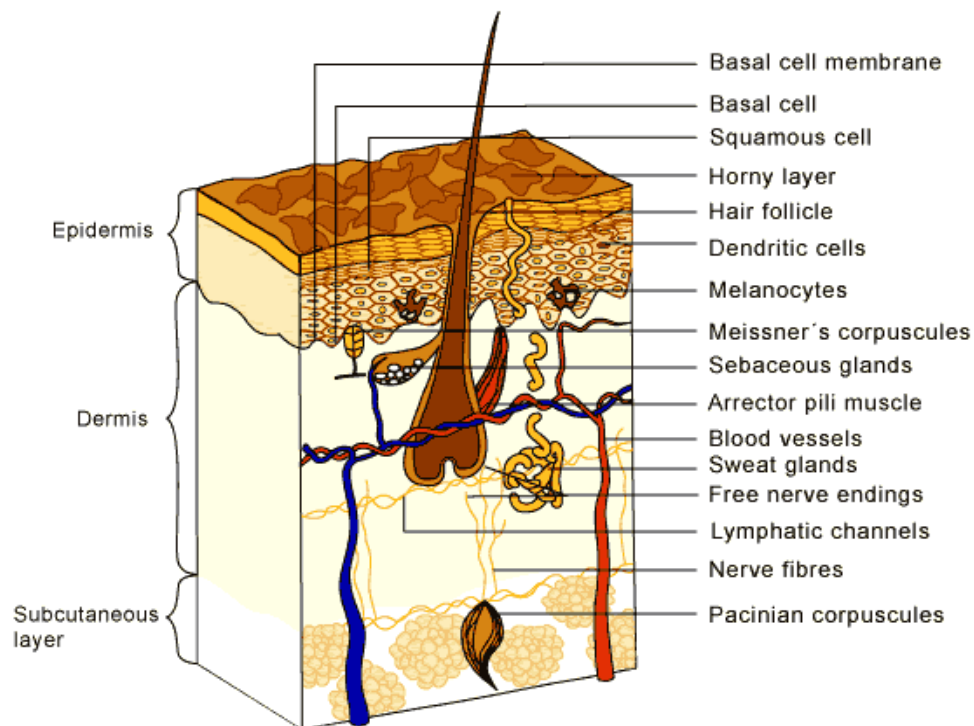
## 8. Skin permeation studies

The ability of the ethosomal preparation to penetrate into the skin layers can be determined by using confocal laser scanning microscopy (CLSM).

## Therapeutics Application of Ethosomes<sup>[16,17]</sup>

Ethosomes can be used for many purposes in drug delivery. Ethosomes are mainly used as replacement of liposomes. Mainly the transdermal route of drug delivery is preferred. Ethosomes can be used for the transdermal delivery of hydrophilic and impermeable drugs through the skin. Various drugs have been used with ethosomal carrier.

## List of Figures

**Figure 1:- Mechanism of Action of Ethosomes.****Figure 2:- Structure of Skin.**

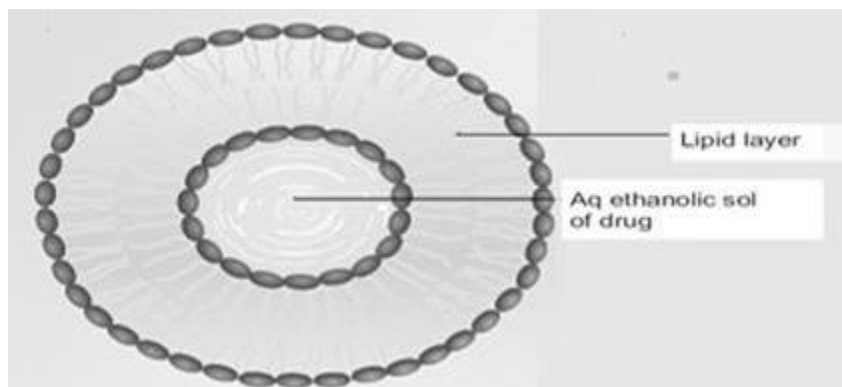


Figure 3:- Structure of Ethosomes.

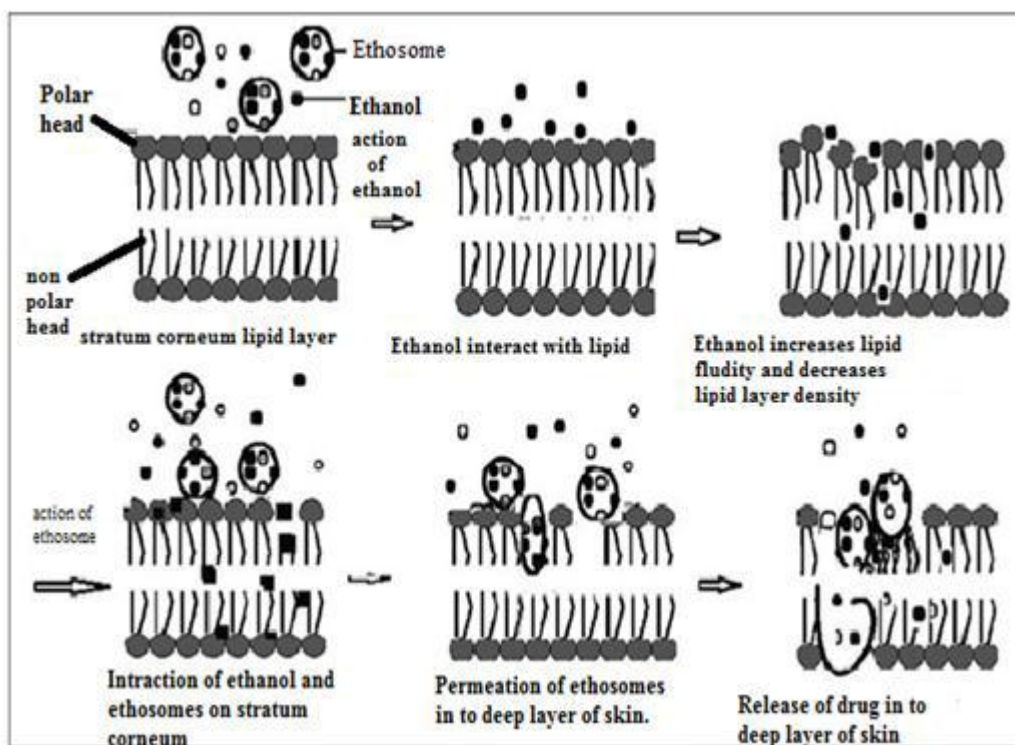


Figure 4:- Mechanism of Penetration.

## CONCLUSION

It can be easily concluded that ethosomes can provide better skin permeation than liposomes. The main limiting factor of transdermal drug delivery system i.e. epidermal barrier can be overcome by ethosomes to significant extent. Application of ethosomes provides the advantages such as improved permeation through skin and targeting to deeper skin layers for various skin diseases. Ethosomes have been tested to encapsulate hydrophilic drugs, cationic drugs, proteins and peptides. Ethosomal carrier opens new challenges and opportunities for the development of novel improved therapies.

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