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Review Article

## Ethosomes: Transdermal Drug Delivery System

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### ABSTRACT

The skin is one of the most extensive and readily accessible organs of the human Body. One of the greatest disadvantages to transdermal drug delivery is the skin's low permeability that limits the number of drugs that can be delivered in this manner. Ethosomes as novel vesicles in transdermal drug delivery show significant effects on drug penetration through the biological membrane. Now-a-days we better know vesicles have importance in cellular communication. Ethosomes, Although ethosomes are conceptually sophisticated, they are simple in preparation and safe for use. Transdermal route is promising alternative to drug delivery for systemic effect. An attempt was made to formulate the highly efficient ethosomal drug delivery system and enalapril meleteate is used as model drug. Ethosomes have higher penetration rate through the skin as compared to liposomes hence these can be used widely in place of liposomes. Ethosomes enhanced skin permeation, improved drug delivery, increased drug entrapment efficiency etc. Ethosomes have become an area of research interest, because of its enhanced skin permeation, improved drug delivery, increased drug entrapment efficiency etc. The purpose of writing this review on ethosomes drug delivery was to compile the focus on the various aspects of ethosomes including their mechanism of penetration, preparation, advantages, composition, characterization, application and marketed product of ethosomes. Characterizations of ethosomes include Particle size, Zeta potential, Differential Scanning Calorimetry, Entrapment efficiency, Surface tension activity measurement, Vesicle stability and Penetration Studies etc.

**Keywords:** Transdermal Drug Delivery System, Ethosomes, Drug absorption

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### 1. INTRODUCTION

The skin is one of the most extensive and readily accessible organs of the human body and the skin as a route of drug delivery can offer many advantages over traditional drug delivery systems including lower fluctuations in plasma drug levels, avoidance of gastrointestinal disturbances and first-pass metabolism of the drugs, and high patient compliance<sup>1, 2</sup>. 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.

A Transdermal delivery of drugs and vaccines is an effective alternative to oral and parenteral routes of administration<sup>7</sup>. Closely monitored intravenous infusion can provide the advantages of both direct entry of drug into the systemic circulation and control of circulating drug levels Recently, it is becoming evident that the benefits of intravenous drug

infusion can be closely duplicated, without its hazards, by using the skin as the port of drug<sup>3-6</sup>

The use of lipid vesicles in delivery systems for the skin treatment has attracted increasing attention recent years. However, it is generally agreed that classic liposomes are of little or no value as carriers for transdermal drug delivery because they do not deeply penetrate the skin, but rather remain upper layer of the stratum corneum. Only specially designed vesicles were shown to be able to allow transdermal delivery Ethanol is known as an efficient permeation enhancer. However, due to the interdigitation effect of ethanol on lipid bilayers, it was commonly believed that vesicles cannot coexist with high concentrations of ethanol. Currently, ethanol can only be found in relatively low concentrations in liposome formulations.<sup>5-7</sup>

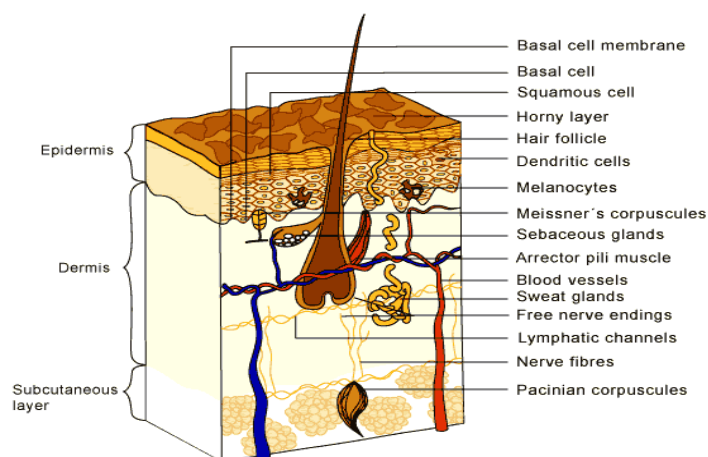


Figure 1: Structure of Skin

- Epidermis is the outermost layer of skin and composed off our strata: the stratum germinativum (or basal layer), the stratum granulosum (the malpighian layer), the stratum lucidum (the granular layer), and stratum corneum (the

horny layer).

• TTDS avoids 1 st pass metabolism lower fluctuation in place drug concentration and good patien compliance.

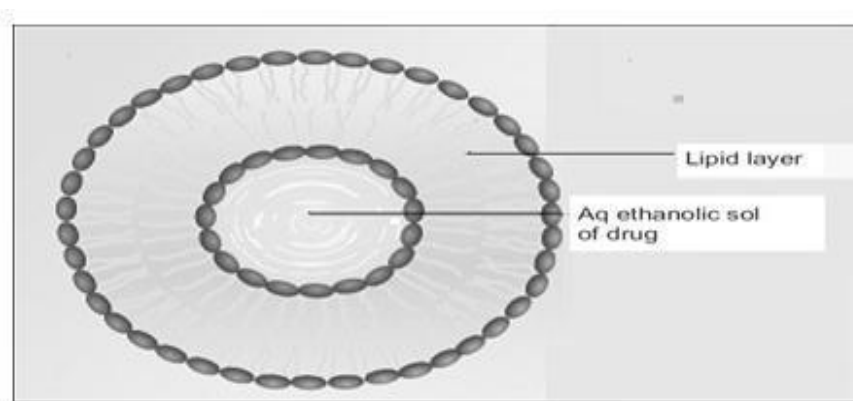


Figure 2: Structure of ethosome.(2)

-The size of ethosomes can be modulated from tens of nanometers to microns. Permeation Enhancers Increase The Permeability Of The Skin, So That The Drugs Can Cross Through The Skin Easily.<sup>7</sup>

-Dermis is 10–40-fold thicker than the epidermis, depending on the area of the body. It is a matrix of loose connective tissue composed of polysaccharides and protein (collagen and elastin) and metabolically less active than the epidermis. This matrix contains nerves, blood vessels, hair follicles, sebaceous and sweat glands <sup>7, 8</sup>. Mast cells, macrophages, leukocytes, and endothelial cells of the blood vessels are also located in the dermis. The function of the dermis is to nourish the epidermis and anchor it to the subcutaneous tissue. Subcutaneous tissue serves as a receptacle for the formation and storage of fat. It acts as both heat regulator and shock absorber <sup>2</sup>.

## 2. BASIC COMPONENTS OF TRANSDERMAL DRUG DELIVERY SYSTEMS <sup>5</sup>

The components of transdermal devices include:

1. Polymer matrix or matrices
2. Drug
3. The drug permeation enhancers
4. Other excipients

## 3. ADVANTAGES OF ETHOSOMES <sup>8</sup>

- 1) GIT degradation, Poor oral absorption and bioavailability.
- 2) Improved drug penetration and Systemic effect
- 3) It contains nontoxic raw material in formulation.
- 4) High patient compliance the ethosomal drug is administered in semisolid form (gel or cream) hence producing high patient compliance.
- 5) Ethosomal system is passive, non-invasive and is available for immediate commercialization.
- 6) Ethosomes are Increased drug entrapment Efficiency, reduced side effect & constant systemic levels.
- 7) Significant accumulation of the drug in the skin.
- 8) Ethosomes are enhanced permeation of drug through skin for transdermal and dermal delivery.

## 4. DISADVANTAGE OF ETHOSOMES <sup>4</sup>

- 1) Drugs that require high blood levels cannot be administered – limited only to potent molecule, those requiring a daily dose of 10mg or less.
- 2) Adequate solubility of the drug in both lipophilic and aqueous environments to reach dermal microcirculation and gain access to the systemic circulation.

- 3) The molecular size of the drug should be reasonable that should be absorbed percutaneously.
- 4) May not be economical poor yield.
- 5) Skin irritation or dermatitis due to excipients and enhancers of drug delivery systems.
- 6) the main advantage of ethosomes over liposomes is the increased permeation of the drug.
- 7) Loss of product during transfer from organic to water media.

## 5. METHOD OF PREPARATION<sup>9,10</sup>

Ethosomes can be prepared by two very simple and

convenient methods that is

1. Cold Method
2. Hot Method

### 1. Cold method

This is the most common method utilized for the preparation of ethosomal formulation. This mixture is heated to 30°C in a water bath. The water heated to 30°C in a separate vessel is added to the mixture, which is then stirred for 5 min in a covered vessel. The vesicles sizes can be decreased to desire extend using sonication or extrusion method. Finally, formulation is stored under refrigeration.

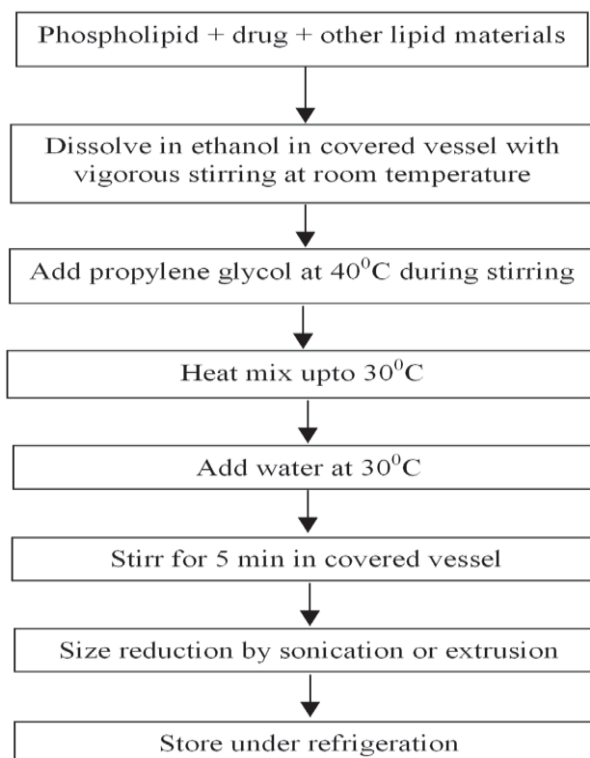


Figure 3: Cold Method For The Preparation Of Ethosomes<sup>4</sup>

**2. Hot method.** This method, the phospholipid is dispersed in water in a water bath at 40°C until a colloidal solution is obtained. In a separate vessel, ethanol and glycols are mixed

and heated up to 40°C. As temperature of both mixtures reaches 40°C, the organic phase is added to the aqueous phase. The final procedure is quite similar to cold method<sup>7</sup>.

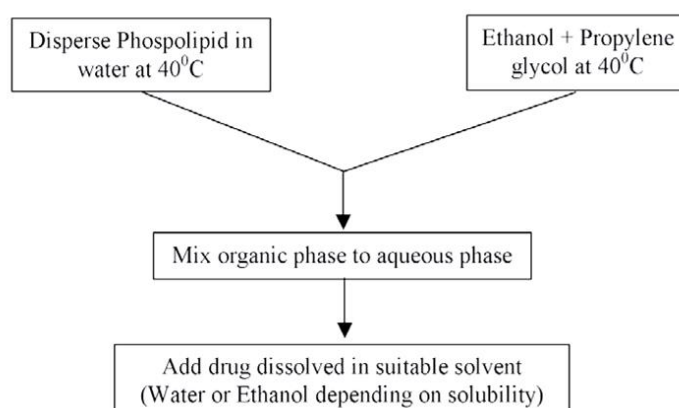


Figure 4: Hot Method for Preparation of Ethosomes<sup>1</sup>

## 6. MECHANISM OF DRUG PENTRATION <sup>2, 11</sup>

The mechanism of drug absorption from ethosomes followed by two phases.

1. Ethanol effect
2. Ethosomes effect

### 1. Ethanol effect:

•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. Ethosome 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

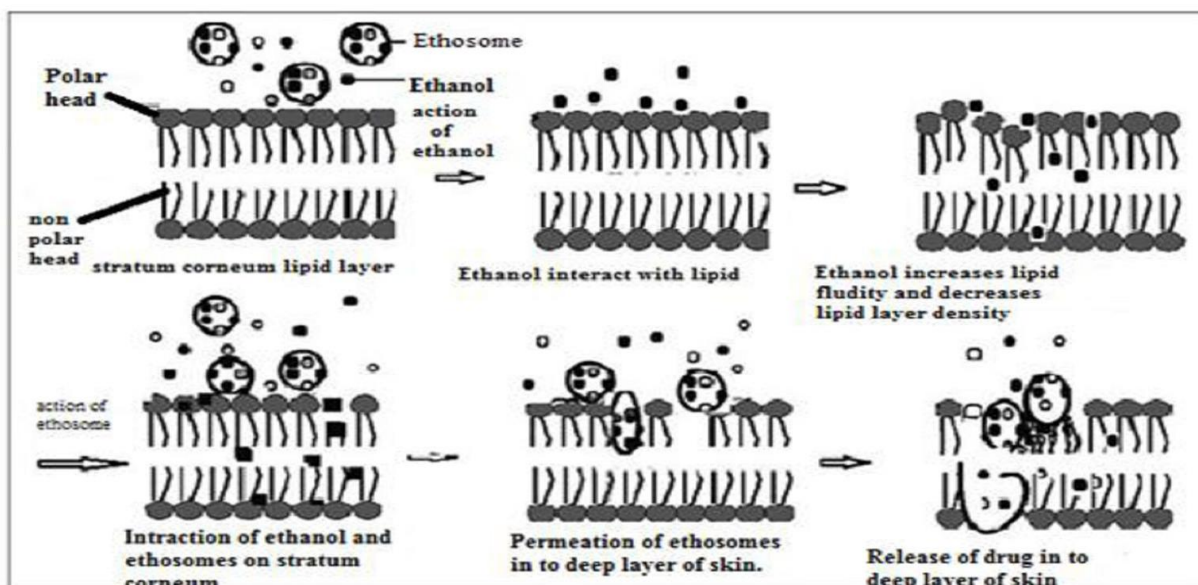


Figure 5: Mechanism of Action of Ethosomes<sup>9</sup>

Table 1: Different Additives Employed In Formulation of Ethosomes<sup>1</sup>

s.no	class	example	uses
1	phospholipid	Soya phosphatidyl choline, Egg phosphatidyl choline	Vesicles forming component
2	alcohol	Ethanol, isopropyl alcohol	For providing the softness for vesicle membrane as a penetration enhancer
3	polyglycol	Propylene glycol, Transcutol RTM	As a skin penetration enhancer
4	cholesterol	cholesterol	As a skin penetration enhancer
5	Dye	Rhodamine-123, Rhodamine red	For characterization study
6	vehicle	Carbapol934	As a gel former

## 7. CHARACTERIZATION OF ETHOSOMAL FORMULATION <sup>8, 12</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 photo correlation spectroscopy (PCS). Zeta potential of the formulation can be measured by Zeta meter.

### 3) Transition temperature:

The transition temperature of the vesicular lipid system can be determined by using differential Scanning calorimetry

(DSC).

### 4) Drug entrapment:

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

### 5) Drug content:

This can also be quantified by modified high performance liquid chromatographic method.

### 6) Surface tension measurement:

The surface tension of drug can be measured by the in a Dunouy tension meter.

### 7) Stability studies:

The stability of vesicles can be determined by asses sing the size and structure of the vesicles over time.

## 8) Skin permeation studies

Preparation of ethosomal to penetrate in the skin layer can be determined by CLSM confocal laser scanning microscopy (CLSM)

## 8. EVALUATION OF ETHOSOMES<sup>10, 12, 13</sup>

### 1. Filter Membrane Vesicles Interaction Study by Scanning Electron Microscopy.

It involves application of vesicle suspension (0.2 mL) to filter membrane having a pore size of 50 nm and placing it in diffusion cells. The upper side of the filter was exposed to the air, whereas the lower side was in contact with phosphate buffer saline solution, (having pH 6.5)

### 2. Transcellular delivery

Ethosomes as compared to the marketed formulation suggested ethosomes to be an attractive clinical alternative for anti-HIV therapy.

### 3. HPLC assay

The amount of drug permeated in the receptor compartment during in vitro skin permeation experiments and in MT-2 cell was determined by HPLC assay using methanol: distilled- water:acetonitrile (70:20:10 vol/vol) mixture as mobile phase 1.

### 4. Transdermal Drug Delivery of Hormones

Oral administration of hormones is associated with problems

Temperature, like high first pass metabolism, low oral bioavailability and several doses dependent side effects. The risk of failure of variance for standard to increase with each pill missed.

### 5 Delivery of Anti-arthritis drug

Its oral administration is associated with a number of problems like low bioavailability, first pass metabolism and GIT degradation.

### 6 Delivery of Antibiotics

Ethosomes penetrate rapidly through the epidermis and bring appreciable amount of drugs into the deeper layer of skin and suppress infection at their root.

### 7. Statistical Analysis

Statistical significance of all the data generated was tested by employing ANOVA followed by studentized range test. A confidence limit of  $P < .05$  was fixed for interpretation of the results using the software PRISM (GraphPad, Version 2.01, San Diego, CA).

## 9. CONCLUSION

Transdermal route is promising alternative to drug delivery

for systemic effect. Ethosomes has initiated a new area in vesicular research for transdermal drug delivery. Ethosomes are soft, malleable vesicles and possible carrier for transportation of drugs. Ethosomes are characterized by simplicity in their preparation, safety and efficacy and can be tailored for enhanced skin permeation of active drugs. Ethosomes have been found to be much more efficient at delivering drug to the skin, than either liposomes or hydro-alcoholic solution. 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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