Review Article

A REVIEW ON ETHOSOMES AS RECENT PROMISING APPROACHES FOR ENHANCED TRANSDERMAL DRUG DELIVERY SYSTEM

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ABSTRACT

The skin serves as a key barrier to the delivery of mucous/topical /transdermal medicines. Different techniques have been made to improve drug skin penetration, and the use of vesicle carrier systems, such as liposomes and niosomes, is utilized for many cosmetic chemicals. One of the latest promising methods with different applications in pharmaceuticals, is the ethosomal drug delivery method.thease are elastic Nano vesicles based on phospholipids that contain a high ethanol content (20-45 percent). Ethosomal carriers are soft vesicles made up of hydro-alcoholic or hydro-glycolic phospholipids with a relatively high alcohol concentration. Theoretically, ethosomal systems are sophisticated, characterized by their ease in planning, effectiveness and protection. Ethosomes are capable of encapsulating and distributing extremely lipophilic molecules such as testosterone, cannabinoids, and minoxidil through the skin due to their exceptional structure, as well as cationic drugs such as trihexyphenidil and propranolol. Crossing the stratum corneum is the main goal of the transdermal drug delivery system. The goal of this review is to concentrate on various aspects of ethosomes, including their mechanism of penetration, preparation, structure, characterization, and implementation.

Keywords: Ethosomes, Nano vesicles, Phospholipids, Hydro-alcoholic, Hydro glycolic, Stratum corneum.

INTRODUCTION

The skin is one of the human body's main organs and the skin may provide several benefits over conventional drug delivery systems as a route of drug delivery, including lower volatility in plasma drug levels, avoidance of gastrointestinal disorders and drug first-pass metabolism, and high patient enforcement. The transdermal therapeutic system is characterized as self-contained discrete dosage forms that deliver the drug through the skin at a controlled rate to systemic circulation when applied to the intact skin[1]. The stratum corneum is the main layer of the skin that governs the skin penetration of most drugs. Many of the medications would be absorbed by the skin, but a very broad application area will be required to achieve levels of concentration in the blood high enough to show therapeutic effects in such limited amount per skin area. Other drug moieties, particularly big, charged molecules such as peptides and proteins, barely pass through the skin[2]. Liposomes, noisomes, transferosomes, and micro emulsions have also been suggested today as low-risk drug carriers, but since they do not deeply penetrate the skin, they do not provide much benefit in the delivery of transdermal drugs. However, as opposed to these commercial transdermal and dermal delivery systems, ethosomal systems are substantially superior in delivering drugs through the skin in terms of both quantity and depth[3].

In this present review, an attempt has been made to summarize the mechanism, advantages and scope of ethosomes and recent approaches for enhanced transdermal drug delivery system.

ETHOSOMES

Due to the presence of ethanol in the vesicular structure they are called ethosomes, Touitou invented a new vesicular method for the ethosomes. The vesicular method is probably the most widely researched approach to the delivery of transdermal drugs. Ethosomes are non-invasive ethanolic delivery carriers that allow drugs to reach deep into the layers of the skin or into the systemic circulation. Ethosomes penetrate more quickly through the skin layers and have much greater transdermal flux. In addition to delivering the drug to the deep skin layer, they also meets the requirements for the successful and healthy administration of lipophilic or hydrophilic drugs[4].

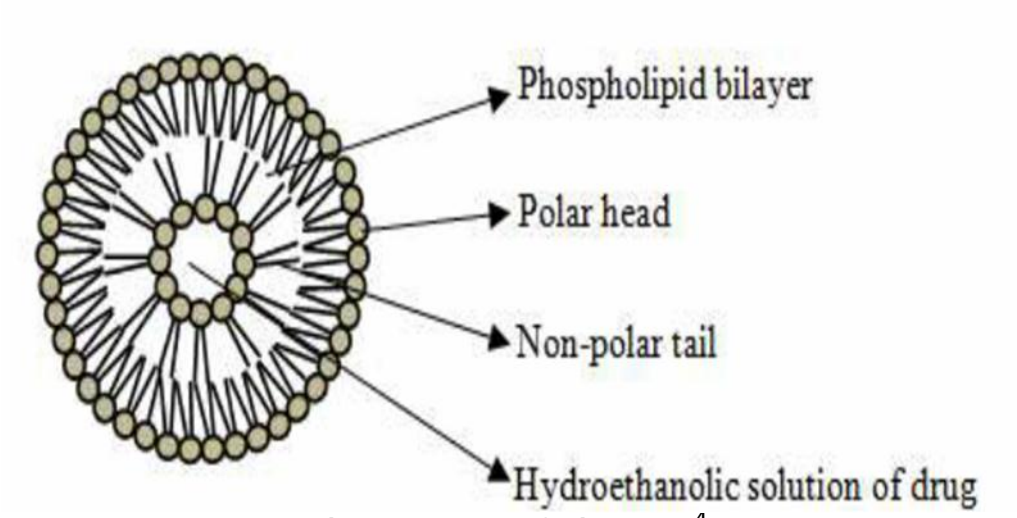


Fig. 1: Structure of ethosomes[4]

Advantages of ethosomal drug delivery[5,6]

1. Delivery of large molecules (peptides, protein molecules) is possible.
2. It contains non-toxic raw material in formulation.
3. Enhanced permeation of drug through skin for transdermal drug delivery.
4. Ethosomal drug delivery system can be applied widely in Pharmaceutical, Veterinary and Cosmetic fields.

Disadvantages of ethosomal drug delivery[7]

1. Skin irritation of contact dermatitis may occur due to the drug and/or excipients.
2. Possibility of allergenic reactions.
3. Can be used only for drugs that require very small plasma concentration for action.
4. Enzyme in the epidermis may denature the drugs.
5. Drugs of larger particle size not easy to absorb through the skin.

Ethosomes composition[8]

Ethosomes primarily consist of phospholipids, ethanol, and water concentrations. Ethosomes are unique because of their high ethanol concentration. this consist of phospholipids with different chemical structures, such as phosphatidylcholine (PC), hydrogenated PC, phosphatidic acid (PA), phosphatidylserine (PS), phosphatidylglycerol (PPG), phosphatidylinositol (PI). Alcohol: water: polyol, here water ratio may modulate the delivery of ethosomal drugs. The different kinds of additives used in the Ethosomal preparations are shown in Table 1.

Table 1: Different additives employed in formulation of Ethosomes[8]

Additives	Uses	Examples
Phospholipid	Vesicles forming Component	Soyaphosphatidyl choline, Egg Phosphatidylcholine, Dipalmityl phosphatidyl Choline, Distearyl phosphatidyl choline
Polyglycol	Skin penetration enhancer	Propylene glycol, Transcutol
Cholesterol	Stabilizer	Cholesterol
Alcohol	For providing the softness for vesicle membrane as a penetration enhancer	Ethanol, Isopropyl alcohol
Vehicle	As a gel former	Carbopol 934
Dye	For characterization study	6-Carboxy Fluorescence, Rhodamine-123, Rhodamine red, Fluorescence

Mechanism of drug penetration

The greater permeation of the substance into the stratum corneum is the key benefit of Ethosomes over the liposome. Two overlapping mechanisms of ethanol effect and ethosome effect on the stratum corneum lipid bilayer include the process of penetration of the ethosomes. The deformability of the vesicles is increased due to the use of ethanol in the preparation of the ethosomes. It is expected that the high alcohol content would partially remove the stratum corneum lipids. These mechanisms are

responsible for improving ethosome inter and intracellular permeability. In the direction of the disordered stratum corneum, the ultra-deformable vesicles will travel and ultimately release drugs into the deeper skin layers. Drug absorption happens in two steps - the effect of ethanol and the effect of ethosomes[9].

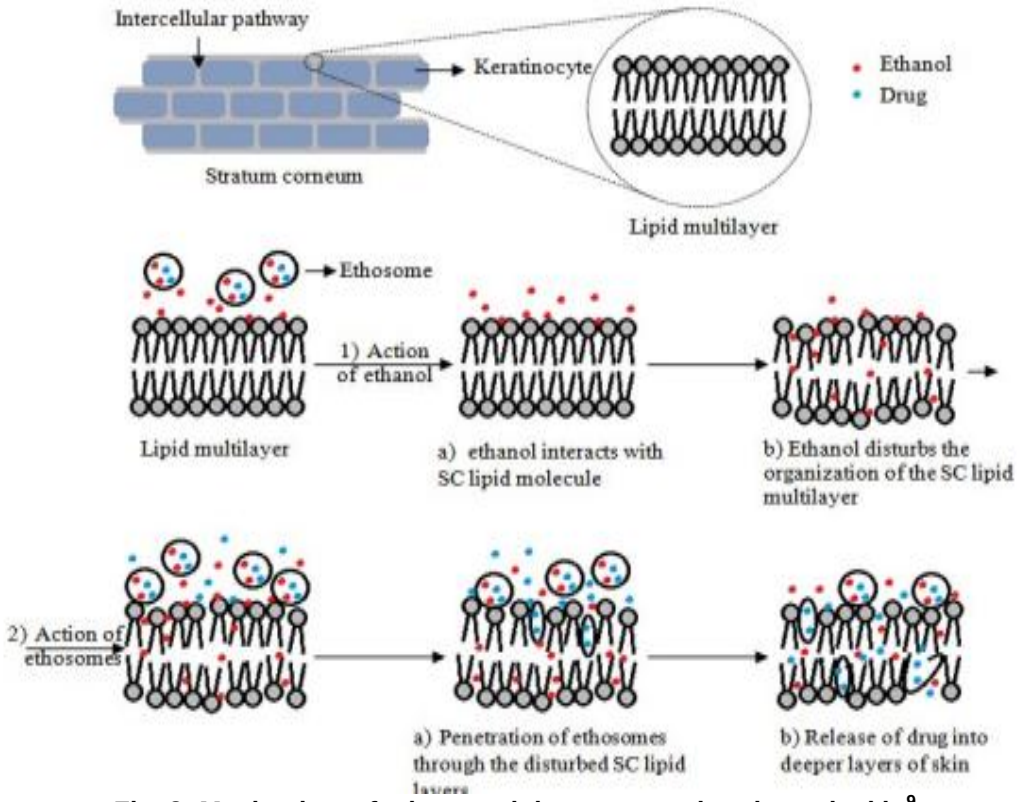


Fig. 2: Mechanism of ethosomal drug penetration through skin[9]

Effect of ethanol

The main ingredient used here is ethanol, which serves as a skin penetration enhancer. Ethanol penetrates into intercellular lipids and increases cell membrane lipid fluidity and decreases the lipid multilayer density of the cell membrane, resulting in increased permeability of the membrane[10].

Effect of ethosomes

Inflated lipid fluidity of the cytomembrane accompanied by the gift effect of ethyl alcohol inside the ethosome contributes to inflated skin porosity of the associated degree. As a consequence, ethosomes merely penetrate deep skin layers, wherever they have amalgamated with skin lipids and release the drug deeply into the skin layers[11].

METHOD OF PREPARATION OF ETHOSOMES[13-15]

Ethosomes can be prepared by two methods that is

1. Cold method
2. Hot method

Cold method

This is the most popular approach used for ethosomal formulation preparation. In a water bath, Take phospholipid and dissolve in ethanol in a covered vessel at room temperature with vigorous stirring. Add propylene glycol or other polyol during stirring, this mixture is heated to 30C. In a separate bowl, water heated to 30C is applied to the mixture, which is then stirred in a covered vessel for 5 minutes. Using sonication or extrusion process, the vesicle sizes can be reduced to expand desire. Finally, under refrigeration, the formulation is processed.

Phospholipids + ethanol+ propylene glycol +drug + stirred

⇩

Heated to 30 °C

⇩

Then previously heated water was added to above

⇩

Desired vesicle size is obtained

⇩

Refrigerated

2. Hot method

Phospholipid is taken in water and spread by heating at 40C in a water bath until a colloidal solution is reached. Mix ethanol and glycol in a separate vessel and heat this mixture up to 40C. Add the organic phase to the aqueous one until both mixtures exceed 40C. Continue stirring to cool the resulting ethosomal suspension at room temperature for another 5 minutes. Depending on the hydrophilic/hydrophobic properties it holds, the substance may be dissolved either in water or in ethanol. Ethosomal vesicle size modulation is achieved using the technique of sonication or extrusion.

Phospholipids +water +drug at 40° Cantinueus dispersed

⇩

Formulation of colloid solution

⇩

Ethanol and glycol mixed separately 40°C

⇩

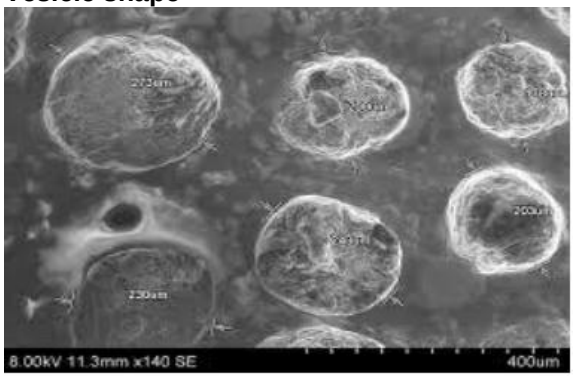
Organic phase added to aqueous phase

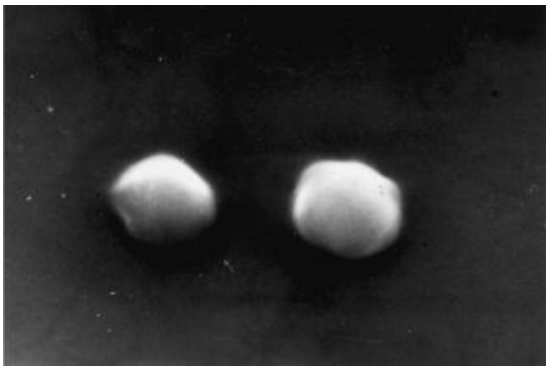
Methods for the Characterization of Ethosomal Formulation[16-18]

Table 2: Methods for the Characterization of Ethosomal Formulation

Parameters	Methods
Vesicle shape (morphology)	Transmission electron microscopy Scanning electron microscopy
Entrapment efficiency	Mini column centrifugation method Fluorescence spectrophotometry
Vesicle size and size distribution	Dynamic light scattering method
Vesicle Skin interaction study	Confocal laser scanning microscopy Fluorescence microscopy Transmission electron microscopy Eosin-Haematoxylin staining
Phospholipid ethanol interaction	31P NMR Differential scanning calorimeter
Degree of deformability	Extrusion method
Zeta potential	Zeta meter
Turbidity	Nephalometer
In vitro drug release study	Franz diffusion cell with artificial or biological membrane, Dialysis bag diffusion
Drug deposition study	Franz diffusion cell
Stability study	Dynamic light scattering method Transmission electron microscopy

Vesicle shape[19]





(b)

Fig. 3: Visualization of ethosomal vesicles, (a) Sem Image of Ethosome, (b) Tem image of ethosomes.[19]

For characterising the surface morphology of the ethosomal vesicles, transmission electron microscopy (TEM) and scanning electronic microscopy (SEM) are used. Mount the ethosomes on double-sided tape previously secured on copper tubes and coated with platinum prior to examination, then analysed at various magnifications.

Entrapment Efficiency[19]

Ethosomal vesicles entrapment efficiency can be calculated by the process of centrifugation. The vesicles were separated at 20,000 rpm for 90 minutes at a temperature held at 4 ° C in a high-speed cooling centrifuge. The sediment and supernatant liquids in the sediment is divided by the amount of drug that can be measured using methanol by lysing the vesicles. From this, the efficacy of entrapment can be calculated by the following equation,

Entrapment Efficiency = DE / DT x 100

Where

DE - Amount of drug in the ethosomal sediment

DT - Theoretical amount of drug used to prepare the formulation (equal to amount of drug in supernatant liquid and in the sediment)

Transition Temperature[19]

The Transition temperature (T) of vesicular lipids can be measured in duplicate by DSC in an aluminium pan at a heating rate of 10° C per min, under a constant nitrogen stream.

Drug content[19]

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

Surface tension measurement[19]

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

Vesicle Stability studies[19]

The drug retention potential of ethosomal preparations can be tested by holding the preparations at different temperatures, i.e. 25 ± 2 °C (room temperature, RT), 37 ± 2 °C and 45 ± 2 °C for different periods of time (1, 20, 40, 60, 80 and 120 days). The ethosomal preparations were stored after flushing with nitro-gen in sealed vials (10 ml capacity). Ethosome stability was also quantitatively calculated by monitoring vesicle size and morphology using DLS and TEM.

Skin permeation studies[19]

Confocal laser scanning microscopy may assess the capacity of the ethosomal preparation to penetrate into the skin layers (CLSM). Studies of Skin Permeation. Confocal laser scanning microscopy may assess the capacity of the ethosomal preparation to penetrate into the skin layers (CLSM).

Application[20-23]

Ethosomes have wide range of applications in different categories of drugs like Antifungal, Antibiotics, anti-parkinsonism, anti-acne, Skin infections and Cosmetic field as shown in table 3.

Table 3: Application of ethosomes

Formulation	Rationale of ethosomal delivery	Application	Route of administration
Colchicine ethosome	Enhance skin accumulation, prolong release and improve the specificity	Anti-gout	Topical
Matrine Ethosome	Improve percutaneous Permeation	Cardio protective, Anti inflammatory	Topical
Salbutamol ethosome	Enhanced drug delivery through skin with ethosomes	Anti-asthmatic Antiarrhythmic	Topical
Finasteride ethosome	Enhanced percutaneous absorption of finasteride 5-α reductase inhibitor	Anti-Fungal	Topical
Acyclovir ethosome	Binary combination of the Lipophilic drug ACV-C16 and the ethosomes enhanced ACV absorption into synergistically the skin	Anti-viral	Topical
Ligustrazine ethosome	Ethosome patch enhances the permeation the skin	Pulmonary vasodilator	Topical
Methotrexate ethosome	Ethosomes showed favourable skin permeation	Anti- pyretic	Topical
Azelaic acid ethosome	Release rate was higher from ethosomes than from liposomes	Ant keratinizing	Topical
Ibuprofen ethosomes	Transdermal Nano system, designed by using an ethosomal carrier	Antipyretic	Topical
Isoeugenol ethosome	Chemicals (allergen) in vesicular carrier system can enhance the sensitizing capacity.	Allergen	Topical
Trihexyphenidyl HCL ethosome	Increased drug entrapment efficiency, reduced side effect and constant systemic levels	Antiparkinsonian	Topical

CONCLUSION

Ethosome is the latest promising new vesicular carrier for the transdermal drug delivery system. Ethosomes are smooth, elastic malleable vesicles and potential drug delivery carriers that offer enhanced therapies. Ethosomes have greater penetration of the skin than liposomes. It can therefore be inferred that in the future, ethosomes can become a promising drug carrier not just for topical treatment but also for the local and systemic diseases, cosmetic and cosmeceutical fields in order to create new improved therapies. Ethosomal encapsulation can be easily administered by various hydrophilic drugs, cationic drugs, proteins and peptides through the transdermal route. Protection and ease of usage is the ethosomal methodology.

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