Int J Pharma Res Health Sci. 2018; 6 (3): 2586-90
DOI:10.21276/ijprhs.2018. 2018. 03.03
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CODEN (USA)-IJPRUR, e-ISSN: 2348-6465

PHS Scientific House
PHARMAHEALTHSCIENCES

International Journal of Pharma Research and Health Sciences

Available online at www.pharmahealthsciences.net


Review Article

# Ethosomes - Newer Trend in Transdermal Drug Delivery: A Review

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ARTICLE INFO

Received:27 Apr 2018
Accepted:14 May 2018

ABSTRACT

Ethosomes are noninvasive delivery carriers that enable drugs to reach the deep skin layers and/or the systemic circulation. Even though ethosomal systems are theoretically sophisticated, they are simple in their preparation, safe for use a combination that can highly expand their application. Ethosomes are soft, malleable vesicles designed for enhanced delivery of active agents. Due to their unique structure, ethosomes are able to encapsulate and deliver through the skin highly lipophilic molecules like cannabinoids, testosterone and minoxidil, as well as cationic drugs such as propranolol, trihexaphenidyl, Cyclosporine, insulin, salbutamol etc.Ethosomes are 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, encapsulate, lipophilic molecules, bioactive molecules.

## 1. INTRODUCTION

Transdermal delivery embodies an attractive alternative to oral delivery of drugs and is composed to provide an alternative to hypodermic injection too [1-4]. For thousands of years, people have placed substances on the skin for therapeutic effects and, in the modern era, a variety of topical formulations have been developed to treat local symptoms. The first transdermal system for systemic delivery—a three-day patch that delivers scopolamine to treat motion sickness—was approved for use in the United States in 1979. A decade later, nicotine patches became the first transdermal blockbuster, raising the profile of

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transdermal delivery in medicine and for the public in general. Today, there are 19 transdermal delivery systems for such drugs as estradiol, fentanyl, lidocaine and testosterone; combination patches containing more than one drug for contraception and hormone replacement; and iontophoretic and ultrasonic delivery systems for analgesia.

Transdermal delivery has a variety of benefits compared with the oral route. In specific, it is used when there is a significant first-pass effect of the liver that can prematurely metabolize drugs. Transdermal delivery also has leads over hypodermic injections, which are painful, generate dangerous medical waste and stance the risk of disease transmission by needle re-use, especially in developing countries [5]. Furthermore, transdermal systems are non-invasive and can be self-administered. Also they provide release for long periods of time (up to one week) and improve patient compliance. These systems are generally inexpensive.

Perhaps the utmost challenge for transdermal delivery is that only a constrained number of drugs are pliable to administration by this route. With recent delivery techniques, prosperous transdermal drugs have molecular masses that are only up to a few hundred Daltons, exhibit octanol-water partition coefficients that greatly favor lipids and need doses of milligrams per day or less [1-4]

**Ethosomes:** The "Somes" are the cell like formulations of novel drug delivery system. There are different types of somes, viz. Liposomes, Phytosomes, Niosomes, Colloidosomes, Ethosomes, Cubosomesetc [6]. Ethosomes are non-invasive delivery transferors that enable drugs to reach the deep skin layers and/or the systemic circulation. Ethosomes contain phospholipids, alcohol (ethanol and isopropyl alcohol) in comparatively high concentration and water. Ethosomes are soft, malleable vesicles poised mainly of phospholipids, ethanol (relatively high concentration) and water. These "soft vesicles" signifies novel vesicular carrier for boosted delivery through the skin. The size of ethosomes vesicles can be controlled from tens of nanometers to microns.

Ethosomes contain phospholipids like conventional liposomes; however, they also contain high levels of alcohol. It has also been demonstrated that its components can reach deeper layers of the skin or enter into systemic circulation. Action mechanisms of these transporters in improving permeation is explained by their alcohol content as penetration enhancers as well as disruption of intercellular lipid structure of SC by the phospholipids in their content.

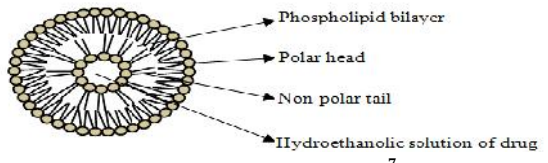


**Fig 1: Diagram showing structure of Ethosome** [7]

The Ethosomes can be prepared by using a range of additives that is best suited with the drug and its properties. The table below shows the ingredients that could be used while formulating Ethosomes.

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

| Sr. No. | Class | Example | Uses |
|---|---|---|---|
| 1 | Phospholipids | Soya phosphatidylcholine, Egg phosphatidylcholine, Diplamityl phosphatidylcholine, Distearyl phosphatidylcholine | Vesicles forming agent |
| 2 | Polyglycol | Propylene glycol, Transcutol RTM | As a skin penetration enhancer |
| 3 | Alcohol | Ethanol, Isopropyl alcohol | For providing the softness for vesicle membrane, as a penetration enhancer |
| 4 | Cholesterol | Cholesterol | For providing stability to vesicle membrane |
| 5 | Dye | Rhodamine-123, Rhodamine red, FluoresceneIsothiocynate (FITC), 6-Carboxy fluorescence | For characterization only |
| 6 | Vehicle | Carbopol 934 | As a gel former |

Barupal et al. (2010) prepared ethosomes to explore dermal administration of aceclofenac. They confirmed that ethosomes have a high drug loading capacity and a good stability.

The main role in the loading of the drug and increased entrapment efficiency is played by the concentration of the Ethanol and also Phospholipid. The higher the concentration of the phospholipid (1%-5% w/v), the more shall be the drug entrapment. Also the more the concentration of the Ethanol (20%-50% v/v), the increased is the percent drug entrapped. In all, both the constituents acts as two important factors for the entrapment efficiency of the Ethosomes.

**Drug Penetration through Ethosomes:** However, the process of drug delivery by ethosomes remains a matter of guesswork; it is likely to be a combination of processes contributing to the penetration enhancement. At physiological temperature, the stratum corneum lipid multilayer remain densely packed and in highly conformational order. The uniqueness of Ethosomes in characterized by high concentration of ethanol, as it is known for its disturbance causing nature for skin lipid bilayer organization and hence, when incorporated into a vesicle membrane, it gives that vesicles an ability to penetrate the stratum corneum. Also because they have high ethanol concentration, the lipid membrane remains less tightly packed than in conventional vesicles but has equivalent stability, allowing a more flexible structure that gives it more freedom and ability to penetrate through small places,openings created by disturbing the stratum corneum lipid. [9]

Ethanol has got a property to interact with lipid molecules in the polar hard group region that results in a reducing the stringency of the stratum corneum lipids and increasing their fluidity. By introducing ethanol into the polar head group environment, it results in an increase in the membrane permeability. With the fact of effect of ethanol on stratum

corneum structure, another way the ethosome itself interact with the stratum corneum barrier which adds to the permeation. [10]

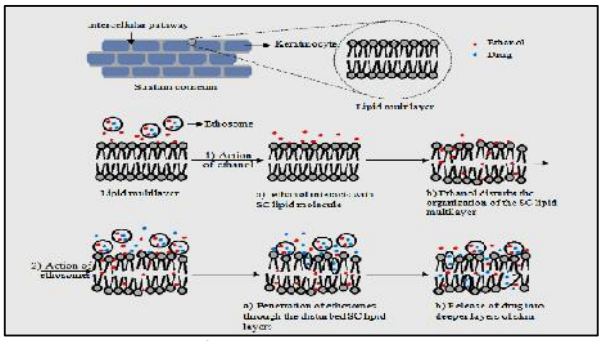


**Fig 2: Mechanism of Skin Permeation and Drug delivery by Ethosomes.**[7]

## 2. METHODS OF PREPARATION

Cold method and hot method are the two conventional methods used for the preparation of ethosomes. Classic mechanical dispersion method and transmembrane pH-gradient active loading method [11] are also reported in various literatures. Among this cold method is the most common method used.

**1. Cold method**

Take phospholipid and dissolve in ethanol in a covered vessel at room temperature with vigorous stirring. Add propylene glycol or other polyol during stirring. Heat this mixture at $30^0$C in a water bath. Heat the water up to $30^0$C in a separate vessel and add to the above mixture slowly in a fine stream. The drug can be dissolved either in water or in ethanol depending on the hydrophilic/hydrophobic properties it bears. Continue stirring for another 5 min and cool the resultant ethosomal suspension at room temperature. The vesicle size of ethosomal formulation is modulated to desire extend using sonication or extrusion method. Finally, the formulation should be stored under refrigeration. [12]

**2. Hot method**

Phospholipid here is taken and dispersed in water by heating in a water bath at $40^0$C until a colloidal solution is attained. In a separate vessel mix ethanol and glycols and heat this mixture up to $40^0$C. Once both mixtures reach $40^0$C, add the organic phase to the aqueous one. Continue stirring for another 5 min and cool the resultant ethosomal suspension at room temperature. The drug can be dissolved either in water or in ethanol depending on the hydrophilic/hydrophobic properties it bears. Modulation of ethosomal vesicle size is done using sonication or extrusion method.[13]

**3. Classic mechanical dispersion method**

Phospholipid is dissolved in an organic solvent or a mixture of organic solvents in a round-bottom flask (RBF). Remove the organic solvent using a rotory vacuum evaporator above lipid transition temperature so as to form a thin lipid film on the wall of the RBF. Traces of the solvent should be removed from the deposited lipid film by keeping the contents under vacuum overnight. The lipid film is then hydrated with hydroethanolic solution of drug by rotating the flask at suitable temperature with or without intermittent sonication and finally, cool the resultant ethosomal suspension at room temperature. The formulation should be stored under refrigeration. [14]

**Characterization of Ethosomes:** There are various methods for the characterization of ethosomes. They are as follows-

- Physical Characterization: Ethosomes can be physically characterized using Motic Image Plus software. It is an economic way to find out whether the ethosomes have been prepared or not. Also a primary particle size evaluation can be done for the formulation. Further evaluation and appropriate sizing should be done using Malvern Zetasizer.
- Visualization: Ethosomes can be visualized using transmission electron microscopy (TEM) and scanning electron microscopy (SEM). [15]
- Vesicle size and Zeta potential: Particle size and zeta potential for ethosomes can be done by dynamic light scattering (DLS) using a computerized inspection system and photon correlation spectroscopy (PCS). [16]
- Entrapment Efficiency: The entrapment efficiency of drug entrapped inethosomes can be measured by the ultracentrifugation technique. [17]
- Transition Temperature: The transition temperature of the vesicular lipid systems can be determined by using differential scanning calorimetry (DSC).[18]
- Surface Tension Activity Measurement: The surface tension activity of drug in aqueous solution can be measured by the ring method in a Du Nouy ring tensiometer. [19]
- Vesicle Stability: The stability of ethosomal 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.[20]
- Drug Content: Drug can be quantified by a modified high performance liquid chromatographic (HPLC) method.[21]
- Penetration and Permeation Studies: Depth of penetration from ethosomes can be visualized by confocal laser scanning microscopy (CLSM).[22]

**Advantages of Ethosomal Drug Delivery:** When compared to other transdermal & dermal delivery systems,

- Ethosomes have enhanced permeation of drug through skin for transdermal and dermal delivery.
- Ethosomes have platform for the delivery of large and diverse group of drugs (peptides, protein molecules).
- Ethosomal composition is safe and the components are approved for pharmaceutical and cosmetic use.
- Low risk profile- The technology has no large-scale drug development risk since the toxicological profiles of the ethosomal components are well documented in the scientific literature.
- High patient compliance- The ethosomal drug is administrated in semisolid form (gel or cream), that

gives high patient compliance. In contrast, iontophoresis and phonophoresis are complicated to use which affects patient compliance.

- High market attractiveness for products with proprietary technology. Relatively simple to manufacture with no complicated technical investments required for production of Ethosomes.
- The Ethosomal system is passive, non-invasive and is available for immediate commercialization.
- Various applications in pharmaceutical, veterinary, cosmetic field. [23]

**Stability of ethosomes:** Ethosomes extend better stability as compared to conventional pharmaceutical liposomes.[24, 25] iposomes, on storage tend to fuse and grow into larger vesicles and this fusion and breakage of liposome vesicles on storage describes an important problem of drug leakage from the vesicles. [26] The absence of electrostatic repulsion is likely to be the reason for the tendency of neutral liposomes to aggregate, whereas in ethosomes, ethanol grounds a modification of the net charge of the system (imparts negative charge to the system) and confers it some degree of steric stabilization, resulting into increased stability of vesicles against agglomeration and drug leakage from vesicles. Increasing the concentration of ethanol from 20 to 45% increases the entrapment efficiency owing to an upsurge in the fluidity of the membranes. However, anextra increase in the ethanol concentration (>45%) destabilizes the vesicles and possibly makes the vesicle membrane further leaky, thus leading to a decline in entrapment efficiency [27].

**Applications of Ethosomes [28, 29] :** Ethosomes have got various applications and can be used for many purposes in drug delivery. Ethosomes prove to be the best replacement of liposomes. Mainly the transdermal route of drug delivery is preferred for ethosomes as they offer better penetration capability as compared to other transdermal delivery systems. Ethosomes can be used for the transdermal delivery of hydrophilic as well as impermeable drugs through the skin. Various drugs have been proved therapeutically successful when given with ethosomal carrier.

## 3. CONCLUSION

Ethosomesare a newer trend of Transdermal drug delivery and are proving to be one of the successful technique to deliver drug through skin. Many drugs those who have got major side effects like cardiac arrest, gastric irritation or ulceration and drugs which are meant to be given for local action in a particular part can be directly given through Ethosomal drug delivery system where the side effects are minimized as well as better penetration is observed as compared to other transdermal drug delivery systems. Ethosomes is a Novel idea which satiates the requirement of patient compliance and it shall be useful for the delivery of various drugs for local as well as systemic drug delivery.

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**Conflict of Interest: None**

**Source of Funding: Nil**