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ETHOSOMES: A NOVEL DRUG CARRIER FOR TRANSDERMAL DRUG DELIVERY

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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 be 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 invasive 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, safe 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 aspects of ethosomes including their preparation, characterization, potential advantages and their applications in drug delivery.

KEY WORDS: Ethosomes, Phospholipids, Stratum corneum, Transdermal.

INTRODUCTION

Transdermal drug delivery uses the skin as an alternative route for the delivery of systemically acting drugs. This has the advantage that high concentrations of drugs can be localized at the site of action, reducing the systemic drug levels and therefore also reducing the systemic side effects. Transdermal delivery route includes several advantages compared with oral route [1,2]. This route has advantages of avoidance of first pass metabolism, predictable and extended duration of action, minimizing under able side effects, utility of short half- life drugs, improving physiological and pharmacological response, avoiding the fluctuation in drug levels, inter and intra patient valuations, and most importantly it provides patient compliance [3,4].

Ethosomes

Ethosomes have been the vesicles well known for their important in cellular communications and particles transportation for many years .Researchers have understood the properties of vesicles structures for use in better drug delivery was being soft vesicles and are composed mainly of phospholipids (phosphotidyl choline), ethanol at relatively high concentration and water .It was found that ethosomes penetrate the skin and allow enhanced delivery of various compounds to the deep strata of the skin or to the systemic circulation ,within their cavities that would allow to tag the vesicle for all specificity [5,6]. Ethosomes are non-invasive delivery carriers that enable drugs to reach the deep skin layers or to the systemic circulation. These are soft, malleable vesicles tailored for enhanced delivery of active agents. Ethosomes are soft lipid vesicles containing phospholipids, alcohol in relatively high concentration and

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water. The size range of ethosomes may vary from tens of nanometres to microns (μ). Hot and cold methods are used for formulation of ethosomes. Ethosomes are soft, malleable vesicles tailored for enhanced delivery of active agents. It has been shown that the physicochemical characteristics of ethosomes allow this vesicular carrier to transport active substances more efficaciously through the stratum corneum into the deeper layers of the skin than conventional liposomes [7,8,9].

Vesicles would also allow to control .The release rate of drug over an extended time, keeping the drug shielded from immune response or other removal systems and would be able to release just the right amount of drug and keep that concentration constant for longer period of time.

Composition

Ethosomes are vesicular carriers composed of hydro alcoholic or hydro/alcoholic /glycolic phospholipids in which the concentration of alcohols or their combination is relatively high [10].

METHOD OF PREPARTION OF ETHOSOMES

Cold Method

In this method phospholipids, drug and other lipid materials are dissolved in ethanol in a covered vessel at room temperature by vigorous stirring with the use of mixer. Propylene glycol or other polyol is added during stirring. This mixture is heated to 300°C in a water bath. The water heated to 300°C in a separate vessel is added to the mixture, which is then stirred for 5 min in a covered vessel. The vesicle size of ethosomal formulation can be de-creased to desire extend using sonication or extrusion method. Finally, the formulation is stored under refrigeration [11,12].

Hot Method

In this method phospholipid is dispersed in water by heating in a water bath at 400C until a colloidal solution is obtained. In a separate vessel ethanol and propylene glycol are mixed and heated to 400°C. Once both mixtures reach 400°C, the organic phase is added to the aqueous one. The drug is dissolved in water or ethanol depending on its hydrophilic/ hydrophobic properties. The vesicle size of ethosomal formulation can be decreased to the desire extent using probe sonication or extrusion method [12,13].

Injection Method

Ethosomes were prepared using different concentrations of lecithin, ethanol, isopropyl alcohol, propylene glycol. Phospholipids and drug was dissolved in ethanol and propylene glycol. The mixture was heated to 30º C in water bath. In this solution distilled water was added slowly in a fine stream with a constant mixing at700 rpm in a closed vessel. The temperature was maintained at 30º C during the experiment. The mixing was continued for 5 minutes. The preparation was stored at 4º C. Ethosome prepared by the above procedure were subjected to sonication at 4ºc using probe sonicator in 3 cycles of 5 minutes with 5 minutes rest between the cycles [14,15].

Mechanism of Penetration Mechanism of Drug Penetration

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 [16,17].

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 lipid sand increases the fluidity of cell membrane lipids and decreases 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.

Ethanol- As Penetration Enhancer

Substances that reversibly reduce the barrier resistance of the stratum corneum are known as chemical penetration enhancers.[20] Ethanol is one of the most commonly used permeation enhancers. A number of mechanisms have been proposed for permeation en-hancing action of ethanol. As a solvent, ethanol can be included in the formulation to enhance the solubility of the drug. This is particularly important for poorly so-luble permeants, as they are prone to depletion in the donor vehicle. Ethanol is a relatively volatile solvent and will rapidly evaporate at skin tem-perature. Ethanol loss from a formulation may lead to the drug becoming supersaturated, which will influ-ence drug flux across the membrane [18].

VARIOUS METHODS OFCHARACTERIZATION OF ETHOSOMES

1. Vesicle shape

Ethosomes can be easily visualized by using transmission electron microscopy (TEM)and by scanning electron microscopy (SEM) and optical microscopy [19].

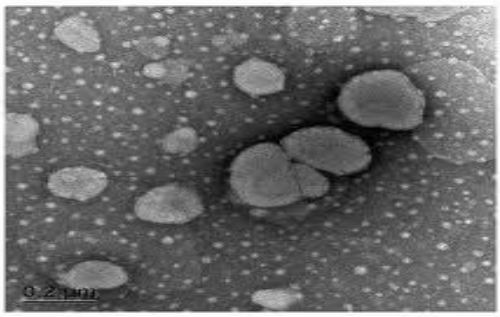
2. Optical Microscope Observation

The ethosomal dispersion was spread on the glass slide using a glass rod. Formation of multilamellavesicles wasconfirmed by examining the ethosomal suspension under an optical microscope with the magnification power of 100 X. Photographs of vesicles

were taken using Olympus camera [20].

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 [21].



3. Transition temperature

The transition temperature of the vesicular rlipid systems can be determined by using differential scanning calorimetry (DSC) [22].

4. Drug entrapment

The entrapment efficiency of ethosomescan 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[23].

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).

ADVANTAGES OF ETHOSOMAL DRUG DELIVERY

In comparison to other transdermal and dermal drug delivery systems [24-27]

1. The Ethosomal system is passive, non-invasive and is available for immediate commercialization.
2. Ethosomes are platform for the delivery of lare and diverse group of drugs (peptides, protein molecules).
3. Ethosome composition is safe and the components are approved for pharmaceutical and cosmetic use .
4. 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.
5. The ethosomal drug is administrated in semisolid form (gel or semisolid form (gel or cream), producing high patient compliance by is high. In contrast, Iontophoresis and phonophoresis are relatively complicated to use which will affect patient compliance.
6. Ethosomes are enhanced permeation of drug through skin for transdermal and dermal delivery.
7. High market attractiveness for products with proprietary technology. Relatively simple to manufacture with no on its hydrophilic/ hydrophobic properties. The vesicle size of ethosomal formulation can be decreased to the desire extent using probe sonication or extrusion method.

Therapeutic Applications

Ethosomes, the high ethanol containing vesicles are able to penetrate the deeper layers of the skin and hence appear to be vesicles of choice for transdermal drug delivery of hydrophilic and impermeable drugs through the skin. Various drugs have been used with ethosomal carrier [25]. Because of their unique structure, ethosomes are able to encapsulate and deliver through the skin highly lyphophilic 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 [26].

Fig 1. Structures of Ethosomes

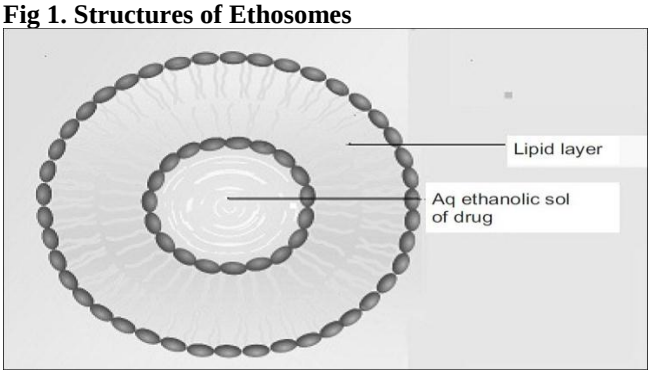


Fig 2. Preparation Method of Ethosomes

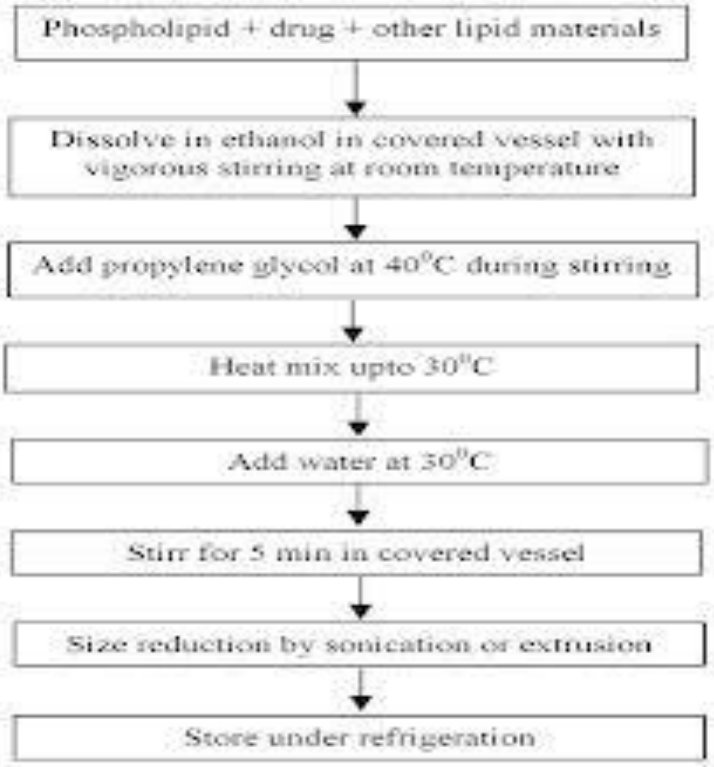


Fig 3. Mechanism of Penetration

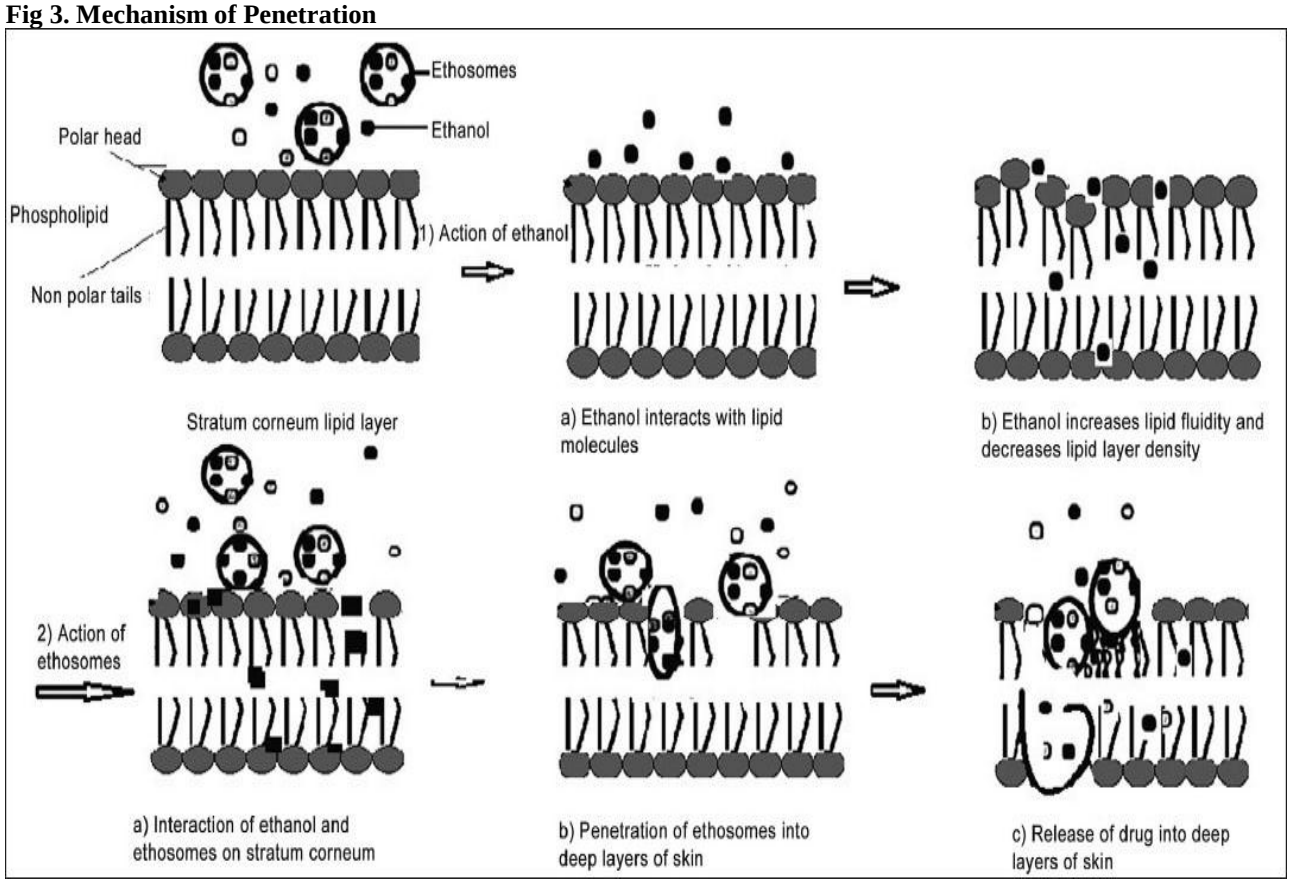
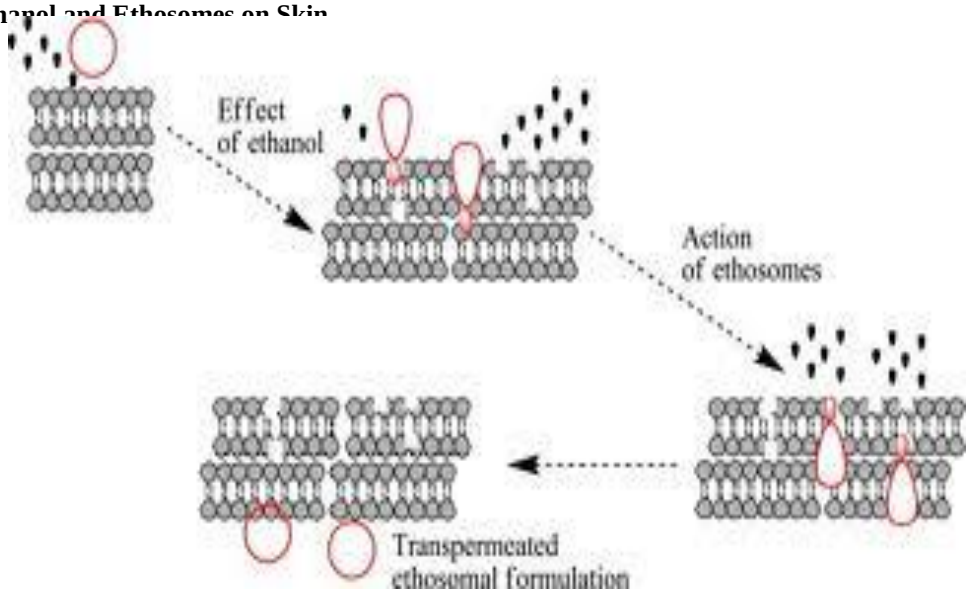


Fig 4. Effect of Ethanol and Ethosomes on Skin



CONCLUSION

Transdermal route is promising alternative to drug de-livery for systemic effect. Ethosomes has initiated a new area in vesicular research for transdermal drug delivery which 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. Further, research in this area will allow better control over drug release in vivo and long-term safety data, allowing the therapy more effective. Thus, ethosomal formulations possess promising future in effective dermal/transdermal deli-very of bioactive agents. 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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