REVIEW ARTICLE

Ethosomes: Carrier for Enhanced Transdermal Drug Delivery System

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J. Adv. Pharm. Edu. & Res.

ABSTRACT

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. In transdermal drug delivery system the drug goes to the systemic circulation through the protective barrier i.e. Skin. Skin acts as a major target as well as a principal barrier for topical/transdermal drug delivery. 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. This review article will focus on the various aspects of Ethosomes including their mechanism of penetration, preparation, advantages, characterization, composition, application and marketed product of Ethosomes.

Key words: Transdermal drug delivery, Ethosomes, Stratum corneum, Permeation enhancement.

INTRODUCTION

Skin is the largest human organ and consists of three functional layers: epidermis, dermis, and sub cutis. It has a wide variety of functions. One major task of the skin is to protect the organism from water loss and mechanical, chemical, microbial and physical influences. The protective properties are provided by the outermost layer (epidermis) of the skin. Dermal drug delivery is used for the treatment of various skin diseases. This has the advantage that high concentrations of drugs can be localized at the site of action, reducing the systemic side effects. Transdermal drug delivery system can be used as an alternative delivery of drug into the systemic circulation.[1-2,]

Transdermal drug delivery offers many advantages as compared to traditional drug delivery systems, including oral and parenteral drug delivery system. Transdermal route is a better alternative to achieve constant plasma levels for prolonged periods of time, which additionally could be advantageous because of less frequent dosing regimens (Cal *et al* 2008). Advantages claimed are increased patient acceptability, avoidance of first pass metabolism, predictable and extended duration of activity, minimizing side effects and utility of short half life drugs, improving physiological and pharmacological response, avoiding the fluctuation in drug levels. The barrier function govern by stratum coneum is main problem for delivery of drugs across the skin.[5-12] The stratum corneum consists of corneocytes surrounded by lipid layers, which play an essential role in the barrier properties of the stratum corneum. In order to increase the number of drugs administered via transdermal route, novel drug delivery systems have to be designed. These systems include use of physical means, such as iontophoresis, sonophoresis, micro needles, etc. and chemical means like penetration enhancers (surfactants and organic solvents) and biochemical means using liposome, noisome, transferosomes and Ethosomes also have been reported to enhance permeability of drug through the stratum corneum .The vesicles have been well known for their importance in cellular communication and particle transportation for many years. Researchers have understood the properties of vesicles structure for use in better drug delivery within their cavities,

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which would to tag the vesicle for cell specificity. One of the major advances in vesicle research was the finding a vesicle derivatives, known as an Ethosomes.[3]

Ethosomes:

They are mainly used for the delivery of drugs through transdermal route. Drug can be entrapped in Ethosomes which have various physicochemical characteristics *i.e.* hydrophilic, lipophilic, or amphiphilic. Ethosomes are soft, malleable vesicles used for delivery of drugs to reach the deep skin layers and/or the systemic circulation. The size range of Ethosomes may vary from tens of nano meters to microns (μ) (Patel, 2007). Ethosomes are the modified forms of liposome's that are high in ethanol content (**Figure 1**).[5-6] The Ethosomes system is composed of phospholipids (Phosphatidylcholine, phosphatidylserine and phosphatitidic acid), high concentration of alcohol (ethanol and isopropyl alcohol) and water. The high concentration of ethanol makes Ethosomes unique because ethanol causes disturbance of skin lipid bilayer organization, hence when incorporated into a vesicle membrane, it enhances the vesicles' ability to penetrate the stratum corneum.[7, 20-26]

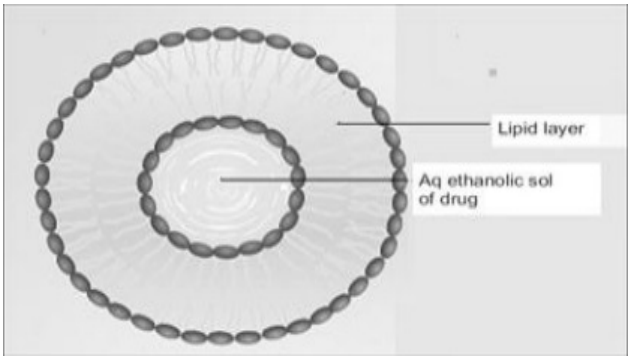

Fig.1: Representation of Ethosomes contents
Ethosomal drug delivery can be modulated by altering alcohol: water or alcohol: polyols: water ratio.

ETHOSOME COMPOSITION:

Ethosomes are vesicular carrier comprising of hydro alcoholic or hydro/alcoholic/glycolic phospholipid in which the concentration of alcohols or their combination is relatively high.[4-9]The various type of additives used in the Ethosomes. Preparation are represented in table1.

Table 1: Different additives employed in formulation of Ethosomes

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

Advantages of Ethosomes drug delivery:

Ethosomal drug delivery system has much advantage as compared to other transdermal and dermal delivery systems. These advantages include enhanced permeation of drug through skin for transdermal drug delivery; Ethosomes provide platform for the delivery of large and diverse group of drugs across the skin (peptides, protein molecules); Ethosomes contain non-toxic materials in formulation, Ethosomal drug is administered in semisolid form (gel or cream) hence producing high patient compliance; Ethosomal drug delivery system can be used widely in pharmaceutical, veterinary, cosmetic fields; Ethosomal system is passive, non-invasive and is available for immediate commercialization; Ethosomal drug delivery is very simple in comparison to iontophoresis and phonophoresis and other complicated methods.[18,22,24]

Mechanism of drug penetration:

The main advantage of Ethosomes over the liposome is the increased permeation of the drug into the stratum corneum. The mechanism of the drug absorption from Ethosomes is not clear. The drug absorption probably occurs in following two phases - ethanol effect and Ethosomes effect.[33]

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 shown in **Figure 2**.[33-36]

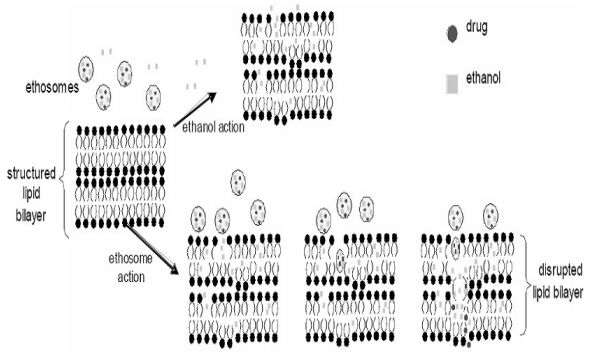

Fig.2: Drug penetration through Ethosomes

Method of preparation:

Cold method:

This is the most common method utilized for the preparation of Ethosomal formulation. In this method, phospholipid, drug and other lipid materials is mixed. 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 vesicles sizes can be decreased to desire extend using sonication or extrusion method. Finally, formulation is stored under refrigeration. [**Figure 3**][21-23]

Hot method:

In this method, phospholipid is dispersed in water by heating in a water bath at 400°C 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 desired extent using probe sonication or extrusion method. [**Figure 3**][23]

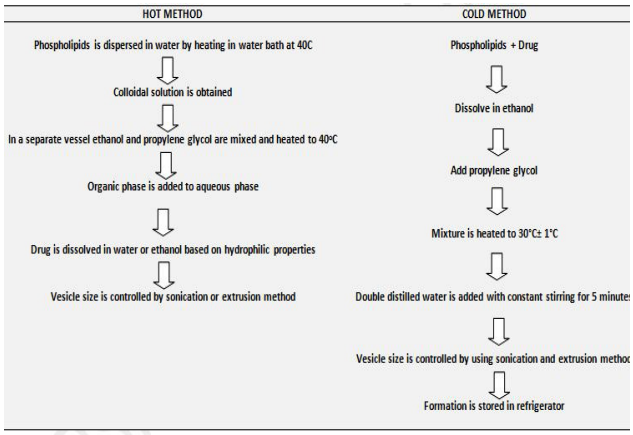

Figure 3: Flow chart representation of hot method and cold method

Classic method:

The phospholipid and drug are dissolved in ethanol and heated to 30°C±1°C in a water bath. Double distilled water is added in a fine stream to the lipid mixture, with constant stirring at 700 rpm, in a closed vessel. The resulting vesicle suspension is homogenized by passing through a polycarbonate membrane using a hand extruder for three cycles.[21]

Characterization of Ethosomes:

Visualization of vesicles:

Transmission electron microscopy (TEM) and scanning electron microscopy (SEM)

Vesicle size and zeta potential:

Dynamic light scattering (DLS) and photon correlation spectroscopy (PCS). Zeta potential is an important parameter that affects the aggregation of vesicles and depicts the physical stability of vesicular systems and it can be measured by Zeta meter.[10]

Entrapment efficiency:

Ultracentrifugation technique

Surface tension activity measurement:

Ring method in a Du Nouy ring tensiometer

Transition temperature:

Differential scanning calorimetry

Penetration and permeation studies:

Depth of penetration from Ethosomes can be visualized by co focal laser scanning microscopy (CLSM)

Stability of Ethosomes:

The ability of Ethosomal formulations to retain the drug was checked by keeping the preparations at different temperatures, *i.e.* 25±2°C (room temperature), 37±2°C and 45±2°C for different periods of time. The stability of Ethosomes can also be determined quantitatively by monitoring size and morphology of the vesicles using DLS and TEM.[16]

Degree of deformability and turbidity:

The degree of deformability of the Ethosomal preparation can be performed by extrusion method and the turbidity of the preparation can be performed by using nephelometer.

ADVANTAGES OF ETHOSOMES:

Ethosomes enhance the permeation of drug through skin for transdermal drug delivery. & delivery of large molecules (peptides, protein molecules) is possible. Ethosomal formulation generally contains nontoxic raw materials. Better stability and solubility of many drugs can be achieved in comparison to conventional vesicles. Ethosomes are relatively smaller in size as compared to conventional vesicles. High patient compliance can be achieved. The Ethosomal drug is administrated in semisolid form (gel or cream) hence producing high patient compliance. Ethosomal drug delivery system can be applied widely in Pharmaceutical, Veterinary, Cosmetic fields.[30-32]

OTHER ADVENTAGES:

- *Transdermal delivery of hormones*
- *Delivery of anti-parkinsonism agent*
- *Pilosebaceous targeting*
- *Transcellular delivery*
- *Delivery of anti-arthritis drug*
- *Delivery of problematic drug molecules*
- *Delivery of antibiotics*
- *Delivery of anti-viral drugs*
- *Ethosomes used for cosmetics*

LIMITATIONS OF ETHOSOMES:

There are certain limitations to the use of Ethosomes like poor yield, in case if shell locking is ineffective then the Ethosomes may coalescence and fall apart on transfer into water & loss of product during transfer form organic to water media.[34]

EVALUATION OF ETHOSOMES:

1. Filter Membrane-Vesicle 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). The filters were removed after 1 hour and were prepared for SEM studies by fixation at 4°C in Karnovsky's fixative overnight followed by dehydration with graded ethanol solutions (30%, 50%, 70%, 90%, 95%, and 100% v/v in water). Finally, filters were coated with gold and examined in SEM.[36-38]

2. Skin Permeation Studies:

The hair of test animals (rats) were carefully trimmed short (<2 mm) with a pair of scissors, and the abdominal skin was separated from the underlying connective tissue with a scalpel. The excised skin was placed on aluminium foil, and the dermal side of the skin was gently teased off for any adhering fat and/or subcutaneous tissue. The effective permeation area of the diffusion cell and receptor cell volume was 1.0 cm2 and 10 mL, respectively. The temperature was maintained at 32°C ± 1°C. The receptor compartment contained phosphate buffer saline solution (10 mL of pH 6.5). Excised skin was mounted between the donor and the receptor compartment. Ethosomal formulation (1.0 mL) was applied to the epidermal surface of skin. Samples (0.5 mL) were withdrawn through the sampling port of the diffusion cell at 1, 2, 4, 8, 12, 16, 20 & 24 hour time intervals and analyzed by high performance liquid chromatography assay.[36]

3. Stability Study:

Stability of the vesicles was determined by storing the vesicles at 4°C ± 0.5°C. Vesicle size, zeta potential, and entrapment efficiency of the vesicles was measured after 180 days using the method described earlier.

4. Vesicle-Skin Interaction Study by TEM and SEM:

From animals ultra thin sections were cut (Ultra cut, Vienna, Austria), collected on form coated grids and examined under transmission electron microscope. For SEM analysis, the sections of skin after dehydration were mounted on stubs using an adhesive tape and were coated with gold palladium alloy using a fine coat ion sputter coater. The sections were examined under scanning electron microscope.[39]

5. Vesicle-Skin Interaction Study by Fluorescence Microscopy:

Fluorescence microscopy was carried according to the protocol used for TEM and SEM study. Paraffin blocks are used, were made, 5-µm thick sections were cut using microtome (Erma optical works, Tokyo, Japan) and examined under a fluorescence micro Cytotoxicity Assay MT-2 cells (T-lymphoid cell lines) were propagated in Dulbecco's modified Eagle medium (HIMEDIA, Mumbai, India) containing 10% fetal calf serum, 100 U/mL penicillin, 100 mg/mL streptomycin, and 2 mmol/L L glutamine at 37°C under a 5% CO2 atmosphere. Cytotoxicity was expressed as the cytotoxic dose 50 (CD50) that induced a 50% reduction of absorbance at 540 nm.[40]

6. Drug Uptake Studies:

The uptake of drug into MT-2 cells (1×106 cells/mL) was performed in 24-well plates (Corning Inc) in which 100 µL RPMI medium was added. Cells were incubated with 100 µL of the drug solution in phosphate buffer saline solution (pH 7.4), Ethosomal formulation, or marketed formulation, and then drug uptake was determined by analyzing the drug content by HPLC assay.[42, 51]

7. 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 delivered at 1 mL/min by LC 10-AT vp pump (Shimadzu, Kyoto, Japan). A twenty-micro liter injection was eluted in C-18 column (4.6×150 mm, Luna, 54, Shimadzu) at room temperature. The column Eluent was monitored at 271 nm using SPDM10A VP diode array UV detector. The coefficient of variance (CV) for standard curve ranged from 1.0% to 2.3%, and the squared correlation coefficient was 0.9968.[46-48]

8. 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.[50]

PATENTED AND MARKETED FORMULATION OF ETHOSOME:

Ethosomes was invented and patented by Prof. Elka Touitou along with her students of department of Pharmaceutics at the Hebrew University School of Pharmacy. Novel Therapeutic Technologies Inc (NTT) of Hebrew University have been succeeded in bringing a number of products to the market based on Ethosomal delivery system. Noicellex TM an anti – cellulite formulation of Ethosome is currently marketed in Japan. Lipoduction TM another formulation is currently used in treatment of cellulite containing pure grape seed extracts (antioxidant) is marketed in USA. Similarly Physonics is marketing anti – cellulite gel Skin Genuity in London. Nanominox© containing monoxidil is used as hair tonic to promote hair growth is marketed by Sinere.[56-57]

Table 2: Marketed products based on Ethosomal drug delivery system

Name of product	Uses	Uses Manufacturer
Celltight EF	Topical cellulite cream, contains a powerful combination of ingredients to increase metabolism and break down fat	Hampden Health,USA
Decorin cream	Anti-aging cream, treating, repairing, and delaying the visible aging signs of the skin including wrinkle lines, sagging, age spots, loss of elasticity, and hyper pigmentation	Genome Cosmetics, Pennsylvania, US
Nanominox	First monoxidil containing product, which uses Ethosomes. Contains 4% Monoxidil, well-known hair growth promoter that must be metabolized by sulfation to the active compound	Sinere, Germany
Noicellex	Topical anti-cellulite cream	Novel Therapeutic Technologies, Israel
Skin genuity	Powerful cellulite buster, reduces orange peel	Physonics, Nottingham,

CONCLUSION

The main disadvantage of transdermal drug delivery is the poor penetration of most compounds into the human skin. The main barrier of the skin is located within its uppermost layer, the stratum corneum. Ethosomes has initiated a new area in vesicular research for transdermal drug delivery which can provide better skin permeation than liposomes or hydro alcoholic solution. Ethosomes are soft, malleable vesicles and potential carrier for transportation of drugs. 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.

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How to cite this article: Ghule Arpan Ramakrishna*, Shinkar Dattatraya Manohar, Saudagar Ravindra Bhanudas; Carrier for Enhanced Transdermal Drug Delivery System; J. Adv. Pharm. Edu. & Res. 2014: 4(4): 380-387.

Source of Support: Nil, **Conflict of Interest:** Nil