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Ethosomes: A Novel Approach in Transdermal Drug Delivery System

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Abstract

Transdermal drug delivery system was first introduced more than 20 years ago. Transdermal drug delivery system is a type of convenient drug delivery system where drug goes to the systemic circulation through the protective barrier i.e. skinis the main target of topical and transdermal preparations. Major aim of transdermal drug delivery system is to cross the stratum corneum. Vesicular system is one of the most controversial methods for transdermal drug delivery system. Ethosomes are non-invasive delivery carriers that enable drugs to reach the deep skin layers and/or the systemic circulation. Ethosomes are innovative novel vesicular system. Ethosomes are composed of phospholipid, alcohol, polyglycol and water. Ethanol increases the penetration rate of the skin and delivers the drug into the deeper layers of skin.

These systems are more efficient in delivering substances to the skin because of the presence of ethanol, Ethosomes are simple to prepare and safe to use. The purpose of this review is to focus on various aspects of ethosomes including their mechanism of penetration, preparation, composition, characterization, and application of ethosomes.

Keywords: Ethosomes, Transdermal, Ethanol, Phospholipid

Introduction

Transdermal drug delivery systems have recently been developed, aiming to achieve the objective of systemic medication through topical application to the intact skin surface[1]. Transdermal therapeutic system is defined as self-contained discrete dosage forms which, when applied to the intact skin, delivery the drug, through the skin at controlled rate to the systemic circulation[2]. Transdermal delivery can provide a number of advantage including enhanced efficacy increased safety, improved patient compliance. This route of drug administration avoids the hazards and discomfort associated with parenteral therapy and improves patient compliance[3]. Transdermal route is an interesting option in this respect because transdermal route is convenient and safe[4].

Transdermal drug delivery system is it encounters the barrier properties of the horny layer (Stratum Corneum) and hence only the lipophilic drugs that have molecular weight <500 Da can pass through it[5]. TDD has some other therapeutic benefits such as sustained drug delivery to provide a steady state plasma profile and hence reduced systemic side effect, thus generating the potential for improved patient compliance, the bypass of first pass metabolism effect for drug with poor oral bioavailability[6]. Now-a-days liposomes, niosomes, transferosomes and ethosomes (vesicular and non- invasive drug delivery) are used to increase the permeation of drug through the stratum corneum[7].

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Ethosomes

"Ethosomes are ethanolic vesicles". Touitou invented a new vesicular system which was named ethosomes, due to the presence of ethanol in the vesicular structure[8].Vesicular system is most widely investigated approach for transdermal drug delivery nowadays[9]. Ethosomes are non-invasive delivery carriers that enable drugs to reach deep into the skin layers or the systemic circulation[10]. Ethosomes has been developed for transdermal delivery of a drug. This system can permeate intact through the human skin due to its high elasticity. Ethosome are soft malleable lipidvesicles composed mainly of phospholipid, alcoholin relatively high concentration (20-45%) and water. Ethosomes were first developed by tauitou & her colleagues in 1997[11]. It is a soft vesicle. The size range of ethosome may vary from tens nanometers to microns. Ethosomes permeate through the skin layers more rapidly and possess significantly higher transdermal flux[1.] Ethosomes not only delivers the drug to the deep skin layer but also meet the essential criteria for efficient and safe administration of lipophilic or hydrophilic drugs[12, 13].

Ethosomes are able to entrap a wide range of molecules, including hydrophilic, lipophilic and high molecular weight entities. Ethosomes are able to deliver the drug across the skin both under occlusive and non-occlusive conditions[14].

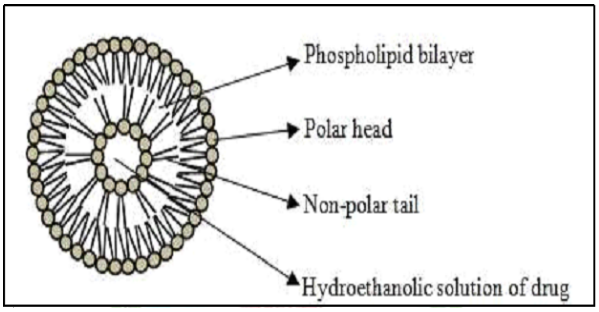

Fig. 1: Structure of Ethosomes[15]

Types of ethosomal systems

There are three types of ethosomal systems based on their composition.

Classical ethosomes:

Classical ethosomes are modified ethosomes, composed of phospholipids, water, and high concentration of ethanol up to 45 %w/v. Due to small size, negative zeta potential and higher entrapment efficiency, classical ethosomes found to be superior over classical liposomes. Drugs whose molecular weight ranges from 130.077 Da to 24 k Da are ideal for the entrapped in classical ethosomes. Classical ethosomes also shows better skin permeation and stability profiles than classical liposomes[16].

Binary ethosomes:

Binary ethosomes were introduced by Zhou et al. basically, they were developed by adding another type of alcohol to the classical ethosomes. The most commonly used alcohols in binary ethosomes are propylene glycol (PG) and isopropyl alcohol (IPA)[17].

Transethosomes:

Transethosomes are the new form of ethosomal systems and were developed to combine the advantages of classical ethosomes and transfersomes in one formula. In their composition it contains basic components as that of classical ethosomes and a penetration enhancer or an edge activator (surfactant)[18].

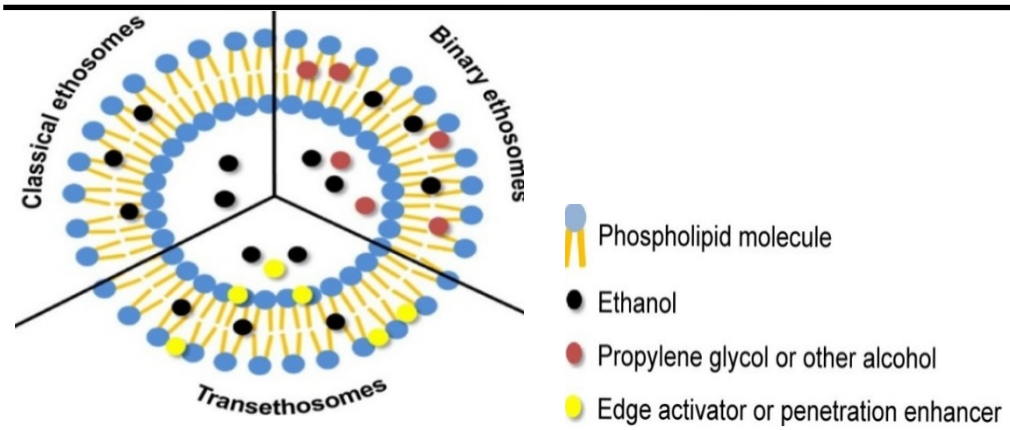

Fig. 2: Schematic representation showing different types of ethosomes[19].

Advantages of ethosomal drug delivery

- Delivery of large molecules (peptides, protein molecules) is possible.
- It contains non-toxic raw material in formulation.
- Enhanced permeation of drug through skin for transdermal drug delivery.
- Ethosomal drug delivery system can be applied widely in Pharmaceutical, Veterinary, Cosmetic fields.
- High patient compliance: The ethosomal drug is administrated in semisolid form (gel or cream) hence producing high patient compliance.
- Simple method for drug delivery in comparison to Iontophoresis and Phonophoresis and other complicated methods.
- The Ethosomal system is passive, non-invasive and is available for immediate commercialization[20, 21].

Disadvantages of ethosomal drug delivery

- Ethosomes with poor shells may clump together and leads to precipitation.
- Adequate solubility of the drug in both lipophilic and aqueous environments to reach dermal microcirculation and gain access to the systemic circulation.
- Skin irritation or dermatitis due to excipients and enhancers of drug delivery systems.
- Ethosomal administration is not a means to achieve rapid bolus type drug input, rather it usually designed to offer slow, sustained drug delivery.
- Drugs that require high blood levels cannot be administered –limited to only potent drugs (daily dose -10mg or less)
- Poor practical yield.
- Transfer of ethosomes from organic to aqueous layer leads to loss of product
- The molecular size of the drug should be reasonable that it should be absorbed percutaneously.
- Adhesive may not adhere well to all types of skin.
- May not be economical[22].

Ethosomes composition

Ethosomal drug delivery can be modulated by altering alcohol: water or alcohol: polyol: water ratio. 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[23, 24].

Table 1: Different additives employed in formulation of ethosomes[25].

Class	Examples	Uses
Phospholipid	Soya phosphatidyl choline, Egg phosphatidyl choline, Dipalmityl phosphatidyl choline, Distearryl phosphatidyl choline	Vesicles forming component.
Polyglycol	Propylene glycol, Transcutol RTM	As a skin penetration enhancer.
Alcohol	Ethanol, Isopropyl alcohol	For providing the softness for vesicle membrane. As a penetration enhancer.
Cholesterol	Cholesterol	For providing the stability to vesicle membrane.
Dye	Rhodamine-123, Rhodamine Red fluorescene isothiocynate 6- carboxy fluorescence	For characterization study.
Vehicle	Carbopol D 934	As a gel former.

Mechanism of drug penetration

The mechanism of the drug absorption from ethosomes is not clear. The drug absorption probably occurs in following two phases.

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[26].

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[27].

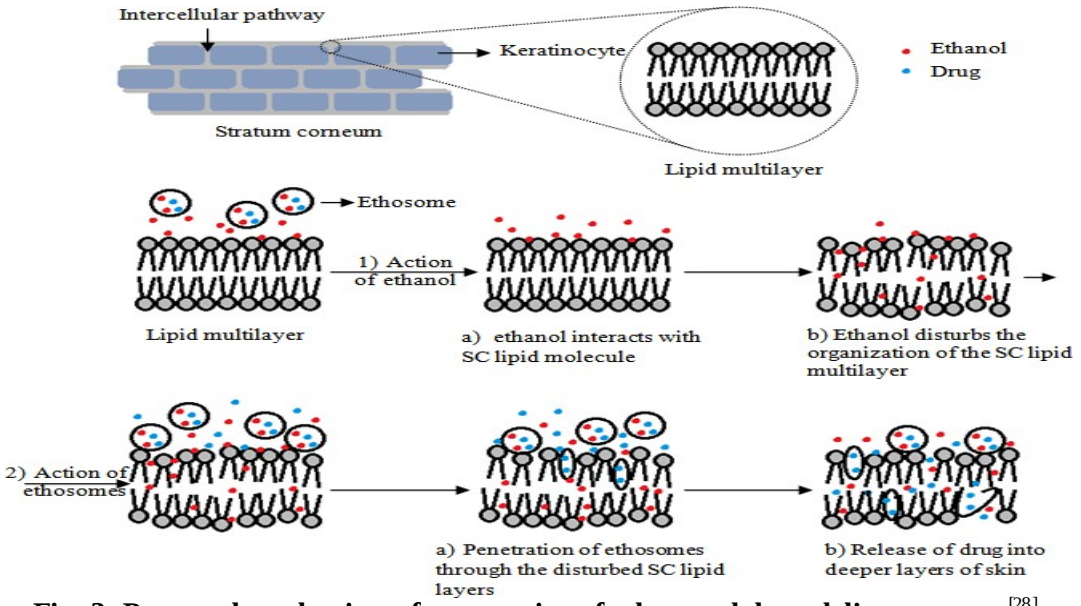

Fig. 3: Proposed mechanism of penetration of ethosomal drug delivery system[28].

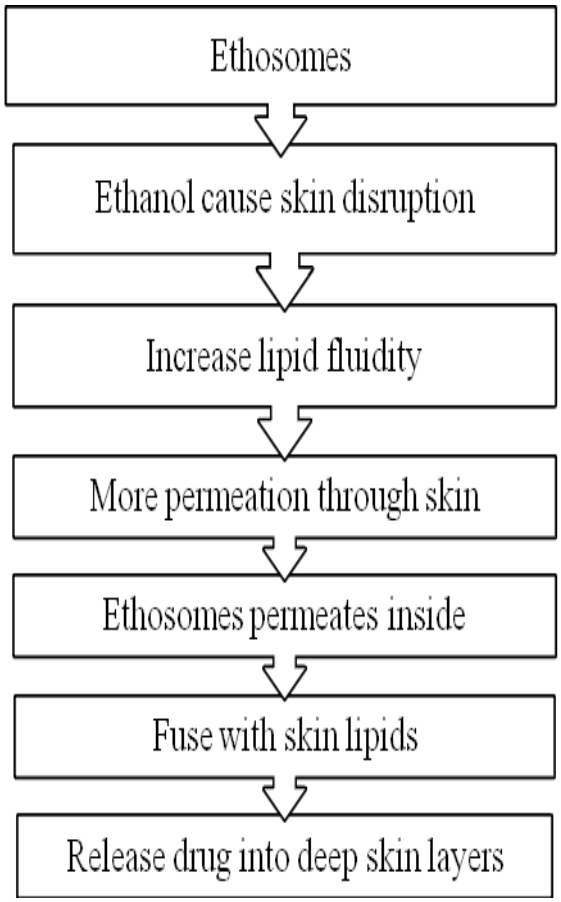

Fig 4: Mechanism of action of ethosomes[29, 30].

Method for preparation of ethosomes

Cold Method:

This is the most common method utilized for the preparation of ethosomal formulation. 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 30^0c in a water bath. The water heated to 30^0c 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 decreased o desire extend using sonication or extrusion method. Finally, the formulation is stored under refrigeration[31, 32, 33].

Hot Method:

In this method, phospholipid is dispersed in water by heating in a water bath at 40ºC until a colloidal solution is obtained. In a separate vessel, ethanol and propylene glycol are mixed and heated to 40ºC. Once both mixtures reach 40ºC, 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 an ethosomal formulation can be decreased to the desired extent using probe sonication or extrusion method[33, 34].

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[35].

Thin-film hydration technique:

The lipids will be dissolved using organic solvent in a round bottom flask, and the organic solvent is evaporated above the lipid transition temperature using a rotary evaporator. The thin film formed

around the inner walls of the round bottom flask will be hydrated using ethanolic mixture and dispersed with a probe sonicator to obtain a suspension of ethosomes[36].

Characterization of ethosomes[37,38].

Table 2: Characterization of ethosomes[37,38].

Test	Technique/Instrument
Particle shape	Scanning Electron Microscopy, Transmission Electron Microscopy
Particle size analysis	Optical Microscopy
Drug Content	High Performance Liquid Chromatography/UV.
Drug Entrapment Efficiency	Ultra centrifugation technique.
In Vitro drug release study	Franz Diffusion cell
In Vitro skin permeation study	Franz Diffusion cell
Transition Temperature	Differential scanning calorimetry

Visualization:

Visualization of Ethosomes can be done using transmission electron microscopy (TEM) and by scanning electron microscopy (SEM)[39].

Vesicle size and Zeta potential:

Particle size of the ethosomes can be detected by dynamic light scattering (DLS) and photon correlation spectroscopy (PCS). Zeta potential of the ethosome suspension can be measured by Zeta meter[40, 41].

PH Measurement:

The pH measurement of the formulation was carried out using a pH meter by dipping the glass electrode completely into the semisolid formulation as to cover the electrode[42].

Transition Temperature:

The transition temperature of the vesicular lipid systems can be determined by using differential scanning calorimetry (DSC)[43].

Drug Entrapment:

The entrapment efficiency of ethosomes can be measured by the ultracentrifugation technique[44].

Drug Content:

Drug can be quantified by a modified highperformance liquid chromatographic method and UV spectrophotometer[16, 45].

Surface tension measurement:

Du Novy ring tensiometer is a ring method which used for measuring the surface tension of a drug[46].

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)[47].

Stability measurements:

Ethosome stability was determined by TEM visualization and DLS size determination at various times following vesicle preparation[48].

Evaluation Tests

Filter Membrane-Vesicle Interaction Study by ScanningElectron Microscopy:

Vesicle suspension (0.2 mL) was applied to filter membrane having a pore size of 50 nm and placed in diffusion cells. The upper side of the filter was exposed to the air, whereas the lower side was in contact with PBS (phosphate buffer saline solution), (pH 6.5). The filters were removed after 1 hour and 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% vol/vol in water). Finally, filters were coated with gold and examined in SEM (Leica, Bensheim, Germany)[49].

Vesicle-Skin Interaction Study by TEM and SEM:

From animals ultra-thin sections were cut (Ultracut, Vienna, Austria), collected on formvar 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[50].

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).Which 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[51].

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[20, 52].

Drug uptake study:

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 PBS (pH 7.4), ethosomal formulation, or marketed formulation, and then drug uptake was determined by analyzing the drug content by HPLC assay[53, 54].

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 10AT vp pump (Shimadzu, Kyoto, Japan)[55].

Application of ethosomes as a drug carrier

Delivery of Anti-Viral Drugs:

Antiviral agent acting on acquired immunodeficiency virus. Ethosomes could increase the transdermal flux, prolong the release e.g. Zidovudine[56].

Transdermal Delivery of Hormones:

Oral administration of hormones is associated with problems like high first pass metabolism, low oral bioavailability and several dose dependent side effects. Ethosomes reduce these problem and improved drug permeation through skin. Eg.Testosterone (Testoderm patch, Alza)[56, 57].

Delivery of Anti-Arthritis Drug:

Cannabidol (CBD) is a recently developed drug candidate for treating rheumatoid arthritis. CBD-ethosomal formulation for transdermal delivery has been prepared by Lodzki et al. Results shows considerably increased its skin penetration, and hence it's activity[58].

Cosmaceutical Applications of Ethosomes:

The advantage of applying ethosomes in cosmaceuticals isn't solely to extend the steadiness of the cosmetic chemicals and reduce skin irritation from the irritating cosmetic chemicals, however conjointly for percutaneous sweetening, particularly within the elastic forms. However, the compositions and sizes of the vesicles are the most factors to be thought of to get these blessings of the elastic vesicles for cosmaceuticals applications[59].

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 roots. Bacitracin and erythromycin loaded ethosomal formulation for dermal and intracellular delivery were developed and the studies indicated the penetration of ethosomes into the cellular membrane and released the entrapped drug molecules within the cells[60].

Delivery of Anti-Parkinsonism Agent:

Dayan and Touitou prepared ethosomal formulation of psychoactive drug trihexyphenidyl hydrochloride (THP) and compared its delivery with that from classical liposomal formulation. THP is a M1 muscarinic receptors antagonist and used in the treatment of Parkinson disease. The results indicated better skin permeation potential of ethosomal-THP formulation and its use for better management of Parkinson disease.[61].

Delivery of problematic drug molecules:

Oral delivery of large biogenic molecules such as peptides or proteins and insulin is difficult because they are completely degraded in the GIT tract hence transdermal delivery is a better alternative. But conventional transdermal formulation of biogenic molecules such as peptides or protein and insulin has poor permeation. Formulating these above molecules into ethosomes significantly increase permeation and therapeutic efficacy[62].

Conclusion

The main limiting factor of transdermal drug delivery system i.e. epidermal barrier can be overcome by ethosomes to significant extent. Transdermal route is promising alternative to drug delivery for systemic effect. The ethosomes more advantages when compared to transdermal and dermal delivery. Ethosomes are the non-invasive drug delivery carriers that enable drugs to reach the deep skin layers finally delivering to the systemic circulation. It delivers large molecules such as peptides, protein molecules. Application of ethosomes provides the advantages such as improved permeation through skin and targeting to deeper skin layers for various skin diseases. . High patient compliance as it is administrated in semisolid form (gel or cream) and various application in Pharmaceutical, Veterinary, Cosmetic field.

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