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TRANS DERMAL DRUG DELIVERY USING POTENTIAL ETHOSOMES

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ABSTRACT
Ethosomes are vesicular carriers comprise of hydro alcoholic component and Phospholipids for enhanced drug delivery through skin. Drugs irritating gastrointestinal mucosa, drugs which are degradable in stomach, discomfortness with the parenteral method and first pass effect can be avoided using transdermal drug delivery with the help of Ethosomes vesicles. Ethosomes are soft, malleable, keeps the drug in shielded form and controlled release rate of drug over an extended period time. Cationic drugs such as propranolol, trihexaphenidyl, Cyclosporine, insulin, salbutamol, highly lipophilic drugs like cannabis, testosterone and minoxidil delivers bioactive molecules through the skin and cellular membranes in the form of vesicles.

KEYWORDS: Ethosomes; vesicle; transdermal drug delivery; skin permeation.

INTRODUCTION
Transdermal drug delivery system (TDDS) includes all topically administered drug formulations intended to deliver the active ingredient into the systemic circulation. Transdermal patch is a medicated adhesive patch that is placed on the skin to deliver a specific dose of medication through the skin into the bloodstream.[1] Drug released from transdermal patch is absorbed through the layers of the skin namely; stratum corneum (SC), epidermis and dermis into the blood stream and transported to target tissue to achieve desired therapeutic effect. Ideally, entire drug should penetrate through the skin to the underlying blood supply without any drug accumulation in the layers of the skin for successful Transdermal deliver.[2,3]

Ethosomes are vesicular carriers comprise of hydro alcoholic component and Phospholipids.[4] Ethosomes are soft, malleable, keeps the drug in shielded form and controlled release rate of drug over an extended period time.[5] Cationic drugs such as propranolol, trihexaphenidyl, Cyclosporine, Insulin, Salbutamol, highly lipophilic drugs like cannabis, testosterone and minoxidil drugs delivers bioactive molecules through the skin and cellular membranes in the form of vesicles. Ethosomes permeate through the skin layers more rapidly and possess significantly higher transdermal flux in comparison to conventional liposomes.[6,7] Ethosomes are composed mainly of phospholipids, (phosphatitidic acid, phosphatidylcholine, phosph-atidylserine), high concentration of ethanol and water. The non aqueous phase range is from 22% to 70%. The high concentration of ethanol (20-50%) in ethosomal formulation could disturb the skin lipid bilayer organization. Therefore, when integrated into a vesicle membrane, it could give an ability to the vesicles to penetrate the through skin.[8]

Lipid vesicular systems containing ethanol in relatively high concentration are named as Ethosomes. The basic difference between liposomes and Ethosomes lies in their composition. The synergistic effect of a combination of the relatively high concentration of ethanol (20-50%) in vesicular form in Ethosomes was suggested to be the main reason for their better skin permeation ability. The high concentration of ethanol (20-50%) in ethosomal formulation could disturb the skin lipid bilayer organization. Therefore, when integrated into a vesicle membrane, it could give an ability to the vesicles to penetrate through skin. Furthermore, due to high ethanol concentration, the ethosomal lipid membrane was packed less tightly than conventional vesicles but possessed equivalent stability.[9]

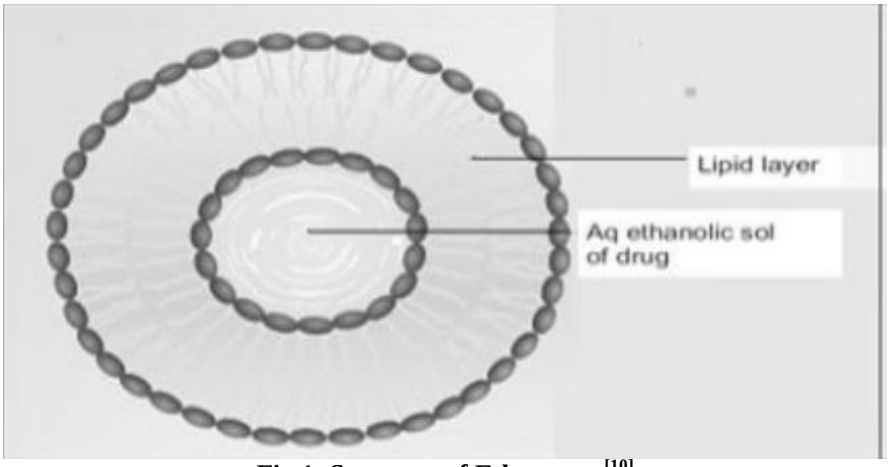

Fig 1: Structure of Ethosomes.[10]

ADVANTAGES[11 – 18]

1. Topical application on skin is more comfortable to the patient.
2. All the excipients used are compatible with skin.
3. Permeation enhancers allow to penetrate the drug through skin easily.
4. The simple method for drug delivery in comparison to Iontophoresis and Phonophoresis etc.
5. The main advantage of ethosomes over liposomes is the increased permeation of the drug.

DISADVANTAGES[19]

1. In case the dose is 10 mg or less than 10 mg it is difficult to achieve high blood levels as required for therapeutic effect.
2. Due to slow absorption in to the systemic circulation effect will be delayed and sustained.
3. The adequate solubility of the drug in both lipophilic and aqueous environments to reach Dermal microcirculation and gain access to the systemic circulation.
4. The molecular size of the drug should be reasonable that it should be absorbed percutaneously.
5. Poor yield and may get patch adherence problem to all the types of skin.
6. May not be economical.

FORMULATION[20]

Table 1: Formulation.

S.NO	EXCIPIENT	PURPOSE	EXAMPLE
1	Phospholipid	Vesicles forming component	Egg phosphatidyl Choline, Soya phosphatidyl Choline, Distearylphosphatidyl Choline
2	Polyglycol	As a skin Penetration ENHANCER	Propylene glycol, Transcutol RTM
3	Alcohol	As a penetration enhancer, For providing the softness for vesicle membrane	Isopropyl alcohol, Ethanol,
4	Dye	For characterization study	FluoresceneIsothiocynate (FITC, Rhodamine-123
5	Cholesterol	For providing the stability to vesicle membrane	Cholesterol
6	Vehicle	As a gel former	Carbopol D 934

METHODS OF PREPARATIONS

Ethosomes prepared by different methods as per the convenience, depending on the requirement of sophisticated equipment and to scale up at industrial level. These include

1. Cold method
2. Hot method
3. Classic method
4. Mechanical dispersion method

1. Cold Method[21]

In this method Phospholipids, drug and other lipid materials are dissolved in ethanol in a covered vessel at room temperature (RT) 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 30C 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 to the desire extent using probe sonication or extrusion method. Finally, the formulation is stored under refrigeration.

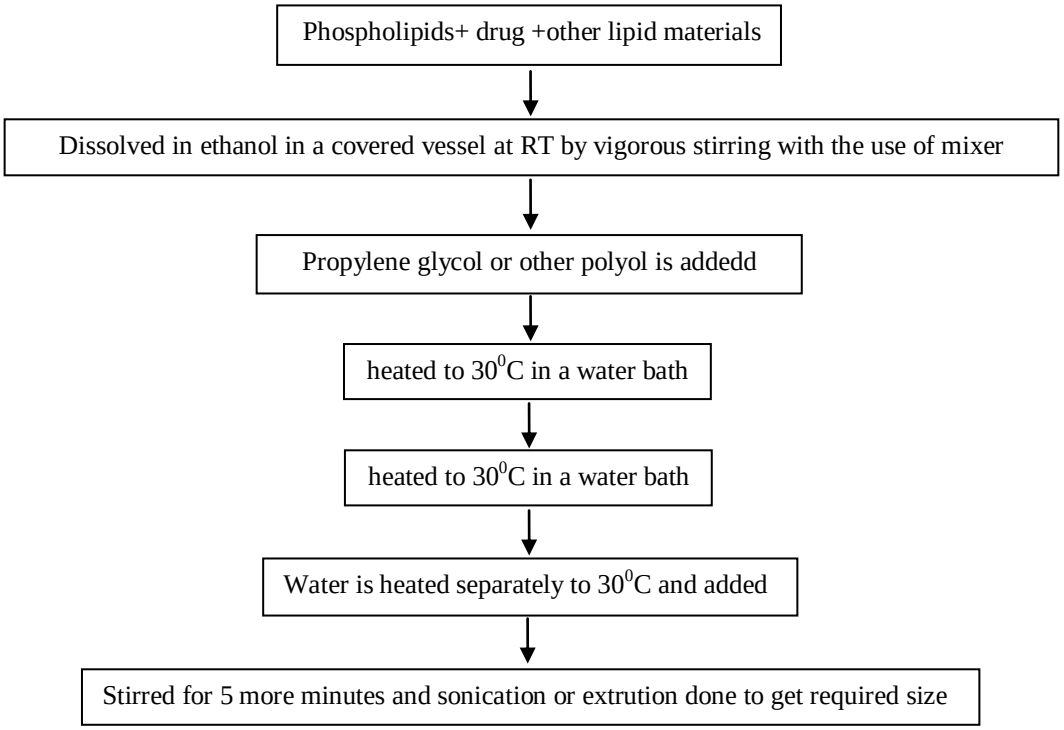

Fig 2: cold method for the preparation of ethosomes.

2. Hot Method[21]

In this method Phospholipid is dispersed in water by heating in a water bath at 40^0C until a colloidal solution is obtained. In a separate vessel ethanol and propylene glycol are mixed and heated to 40^0C. Once both mixtures reach 40^0C, the organic phase is added to the aqueous one. The drug is dissolved in water or ethanol depending on its hydrophilic or hydrophobic properties. The vesicle size of ethosomal formulation can be decreased to the desire extent using probe sonication or extrusion method.

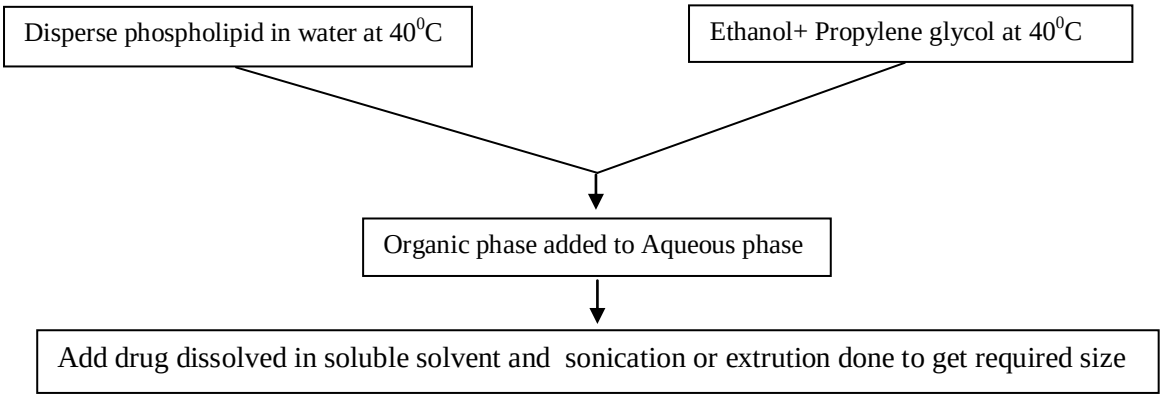

Fig 3: Hot Method For The Preparation of Ethosomes.

3. Classic method[22-25]

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.

4. Mechanical dispersion method[26, 27]

Soya phosphatidylcholine is dissolved in a mixture of chloroform: methanol in the round bottom flask (RBF). The organic solvents are removed using rotary vacuum evaporator above lipid transition temperature to form a thin lipid film on the wall of the RBF. Finally, traces of solvent mixture are removed from the deposited lipid film by leaving the contents under vacuum overnight.

Hydration is done with different concentration of hydroethanolic mixture containing drug by rotating the RBF at the suitable temperature.

MECHANISM OF ACTION

Ethosomal formulations contain high ethanol content that interacts with lipid molecules in the polar head group regions, resulting in an increased fluidity of the subcutaneous lipids. The high alcohol content is also expected to partial extract the sub cutaneous lipids. These processes are responsible for increasing inter and intracellular permeability of Ethosomes. In addition, ethanol imparts flexibility to the ethosomal membrane that shall facilitate their skin permeation.[28] 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.[29]

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 lipids and increases the fluidity of cell membrane lipids and decrease 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.

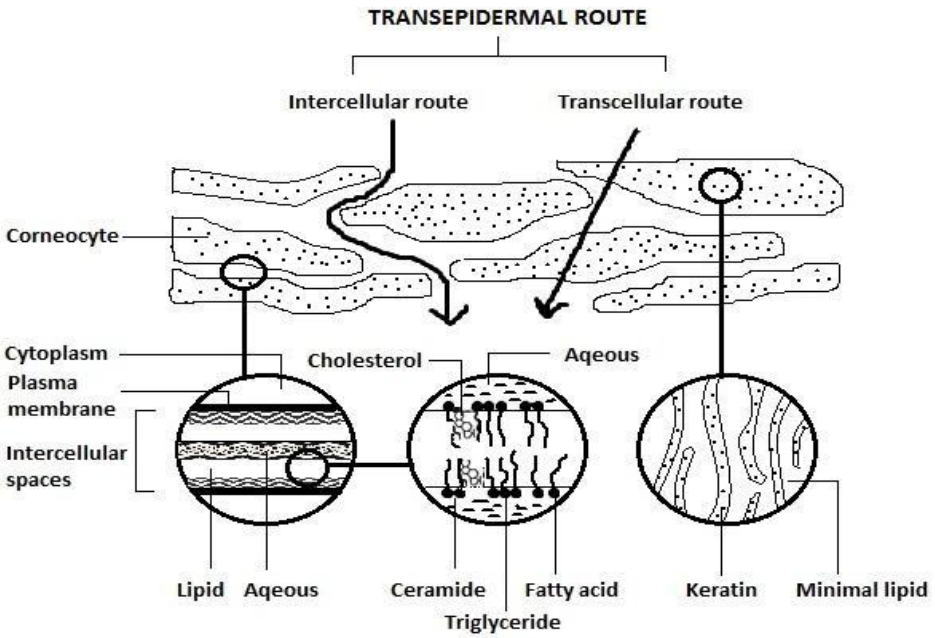

Fig 4: Trans epidermal route.[30]

CHARACTERIZATION OF ETHOSOMAL FORMULATIONS[31-50]

- **Vesicle shape (morphology):** Transmission electron microscopy, Scanning electron microscopy.
- **Entrapment efficiency:** Minicolumn centrifugation method, Fluorescence spectrophotometry, Ultracentrifugation technique.
- **Vesicle size and size distribution:** Dynamic light scattering method, Photon correlation spectroscopy (PCS).
- **Vesicle Skin interaction study:** Confocal laser scanning microscopy-Depth of penetration from ethosomes can be visualized by confocal laser scanning microscopy (CLSM), Fluorescence microscopy, Transmission electron microscopy, Eosin-Hematoxylin staining.
- **Phospholipids-ethanol interaction:** 31P NMR, Differential scanning calorimeter.
- **Degree of deformability:** Degree of deformability of the ethosomal preparation can be performed by extrusion method.
- **Zeta potential:** 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.
- **Turbidity:** Nephelometer.
- ***In-vitro* drug release study:** Franz diffusion cell with artificial or biological membrane, Dialysis bag diffusion. Drug deposition study Franz diffusion cell.
- **Stability study:** 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°Cfor 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.

- **Surface tension activity measurement:** Ring method in a Du Nouy ring tensiometer.

APPLICATIONS[51, 47, 52-57]

Table 2: Applications [Drug name and research conclusion]

DRUG	RESULTS
Trihexyphenidyl hydrochloride	Improved transdermal flux, Provide controlled release and Improved patient compliance
Insulin	Significant decrease in blood glucose level and Provide control release
Acyclovir	Increase skin permeation, Improved in biological activity two to three times, Improved in Pharmacodynamic profile
NSAIDS (Diclofenac)	Selective delivery of drug to desired side for prolong period of time
Bacitracin	Improved dermal deposition, Improved intracellular delivery and Increased bioavailability
Anti-HIV agents Zidovudine Lamivudine	Improved transdermal flux, Improved in biological activity two to three times, Prolonging drug action, Reduced drug toxicity and Affected the normal histology of skin
Ammonium glycyrrhizinate	Improved dermal deposition exhibiting sustained release and Improved biological anti-inflammatory activity

CONCLUSION

Efficient method for the non-invasive delivery of small, medium and large sized drug molecules through the transdermal systems. Ethosomes can provide better skin penetration than other vesicle carriers like liposomes. Ethosomes can overcome the disadvantages of trans dermal drug delivery as it suffers from poor penetration of compounds in to the skin. Though Ethosomes, Liposomes, hydrosomes, peptides have ability to transport easily and increasing their safety for effective therapy.

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