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Ethosome: A Novel Drug Carrier

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Subject: Pharmaceutics

Abstract

Skin acts as a major target as well as a principal barrier for topical or transdermal drug delivery. Despite many advantages of this system, the major obstacle is the low diffusion rate of drugs across the stratum corneum. Ethosomes as novel vesicles in transdermal drug delivery show significant effects on drug penetration through the biological membrane. Ethosomes are phospholipid-based elastic nanovesicles containing a high content of ethanol (20-45%). Ethosomal systems are much more efficient in delivering substances to the skin in the terms of quantity and depth, than either conventional liposomes or hydroalcoholic solutions. 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, Transdermal, Vesicular Carriers, Ethanol, Phospholipid.*

Introduction

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 including lower fluctuations in plasma drug levels, avoidance of gastrointestinal disturbances and first-pass metabolism of the drugs, and high patient compliance. 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. The skin offers an excellent barrier to molecular transport, as stratum corneum is the most formidable barrier to the passage of most of the drugs, except for lipophilic and low molecular weight drugs. For transdermal and topical drug delivery system to be effective, the drug must obviously be able to penetrate the skin barrier and reach the target site [1]. During the past several decades, researchers have developed numerous techniques to weaken or disrupt the skin barrier and deliver drugs into the body through the intact skin. Chemical skin permeation enhancers, iontophoresis, sonophoresis, electroporation, microneedles, and many other methods have been investigated to increase the efficacy of transdermal transport. Owing to their limited efficacy, resulting skin irritation, complexity of usage, and or high cost, none of these methods have been broadly applied to date [2, 3, 4]. Lipid-based suspensions such as liposomes, niosomes, and microemulsions, have also been proposed as low- risk drug carriers, but they do not offer much value in transdermal drug delivery because they do not deeply penetrate the skin, but rather remain on the upper layers of skin strata [5].

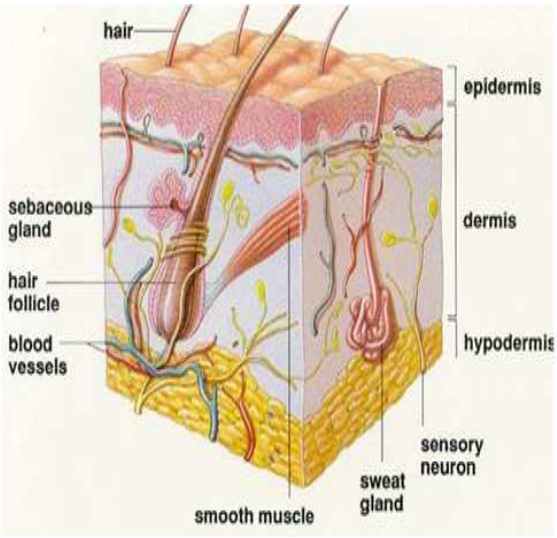
Several researchers have developed novel elastic lipid vesicular systems in order to deeply and easily penetrate through the skin. Phospholipids, ethanol, bile salts and many surfactants have been used to prepare these elastic vesicles. The high flexibility of vesicular membranes allows these elastic vesicles to squeeze themselves through the pores in stratum corneum, which are much smaller than their vesicular sizes [6]. In 1992, Cevc et al introduced the first generation elastic lipid vesicular carrier, Transfersomes, mainly consisting of phospholipids and an edge activator (non-ionic surfactant). They were reported to penetrate intact skin and able to deliver the drug into and across the

skin, when applied under non-occlusive conditions [7, 8].

Structure of Skin:

Stratum corneum is the outermost layer of the epidermis. It consists of 10 to 25 layers of dead, elongated, fully keratinized corneocytes, which are embedded in a matrix of lipid bilayers. It has been shown that the stratum corneum is the main barrier to penetration through the skin. When a topical formulation is placed on the skin, the active drug is required to penetrate through the stratum corneum into the viable tissue. The limiting factor for these processes is the slow diffusion through the dead horny layer of skin. Stratum corneum behaves as a hydrophobic membrane. The rates of permeation of skin by low and high molecular weight organic nonelectrolytes are mostly determined within the stratum corneum [9, 10].

Figure1. Structure of skin:



Rational for Transdermal Drug Delivery:

Given that the skin offers such an excellent barrier to molecular transport, the rationale for this delivery strategy needs to be carefully identified. There are several instances where the most convenient drug intake methods (oral route) were not feasible and alternative routes had to be sought. Although, intravenous introduction of the medicament avoids many of these shortfalls (such as gastrointestinal and hepatic metabolism), its invasive and apprehensive nature (particularly for chronic administration) has encouraged the search for alternative strategies. Transdermal drug delivery (TDD) offers several distinct advantages including relatively large and readily accessible surface area for absorption, ease of application and termination of therapy. Further, evolution of better technologies for delivering drug molecules, safe penetration enhancers and the use of vesicular carriers have rejuvenated the interest for designing TDD system for drugs that were thought to be unfit for transdermal delivery [11,12].

Vesicular approaches for topical drug delivery:

Drug encapsulated in lipid vesicles prepared from phospholipids and nonionic surfactants is known to be transported into and across the skin. Lipids present in the skin contribute to the barrier properties of skin and prevent systemic absorption of drugs. Due to the amphiphilic nature, lipid vesicles may serve as non-toxic penetration enhancer for drugs. In addition, vesicles can be used for encapsulating hydrophilic and lipophilic as well as low and high molecular weight drugs. Therefore, these lipid rich vesicles are hypothesized to carry significant quantity of drugs across the skin thus, enhancing the systemic absorption of drugs.

Drug delivery from liposomes in transdermal formulation has been studied for many purposes but unstable nature and poor skin permeation limits their use for topical delivery. In order to increase the stability of liposomes, the concept of proliposomes was proposed. This approach was extended to niosomes, which exhibited superior stability as compared to liposomes. However, due to poor skin permeability, liposomes and niosomes could not be successfully used for systemic drug delivery and their use was limited for topical use. To overcome problems of poor skin permeability Cevc et al., and Touitou et al., recently introduced new vesicular carrier system ethosomes, for non-invasive delivery of drugs into or across the skin. Ethosomes incorporated penetration enhancers (alcohols and polyols), to influence the properties of vesicles and 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, which would to tag the vesicle for cell specificity. One of the major advances in vesicle research was the development of vesicle derivatives, known as an ethosomes [13].

Ethosomes:

Ethosomes are soft, malleable lipid vesicles composed mainly of phospholipids, alcohol (ethanol or isopropyl alcohol) in relatively high concentration (20-45%) and water. Ethosomes were first developed by Touitou and her colleagues in 1997 [14, 15, 16]. This carrier presents interesting features correlated with its ability to permeate intact through the human skin due to its high deformability. The physicochemical characteristics of ethosomes allow these vesicular phospholipids as the vesicle forming component of ethosomal system. Phospholipids with various chemical structures like phosphatidyl choline (PC), hydrogenated PC, phosphatidyl ethanolamine (PE) are used at concentrations ranging from 0.5-10%.

The source of the phospholipids can be egg, soybean, semi-synthetics, and synthetics. Some preferred phospholipids are soya phospholipids such as Lipoid S100, Phospholipon 90 (PL-90). High concentration of alcohol (20-45%) in the formulation provides soft, flexible characteristics and stability to the vesicles and it also disrupts lipid bilayers structure of the skin results in an increase in the membrane permeability [17].

Examples of alcohols, which can be used, include ethanol (commonly used) and isopropyl alcohol. Glycols can also be used in preparations as a penetration enhancer. Among glycols propylene glycol and transcutol are generally use [18]. For providing further stability to ethosome vesicles cholesterol at concentrations ranging between about 0.1-1% can also be incorporated.

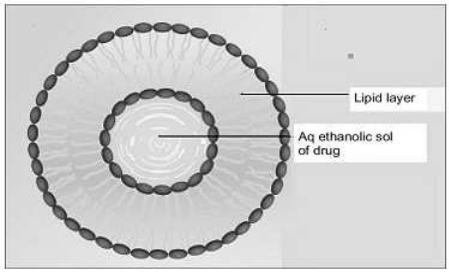


Fig.: 2 Structure of Ethosomes:

Ethosomes Composition:

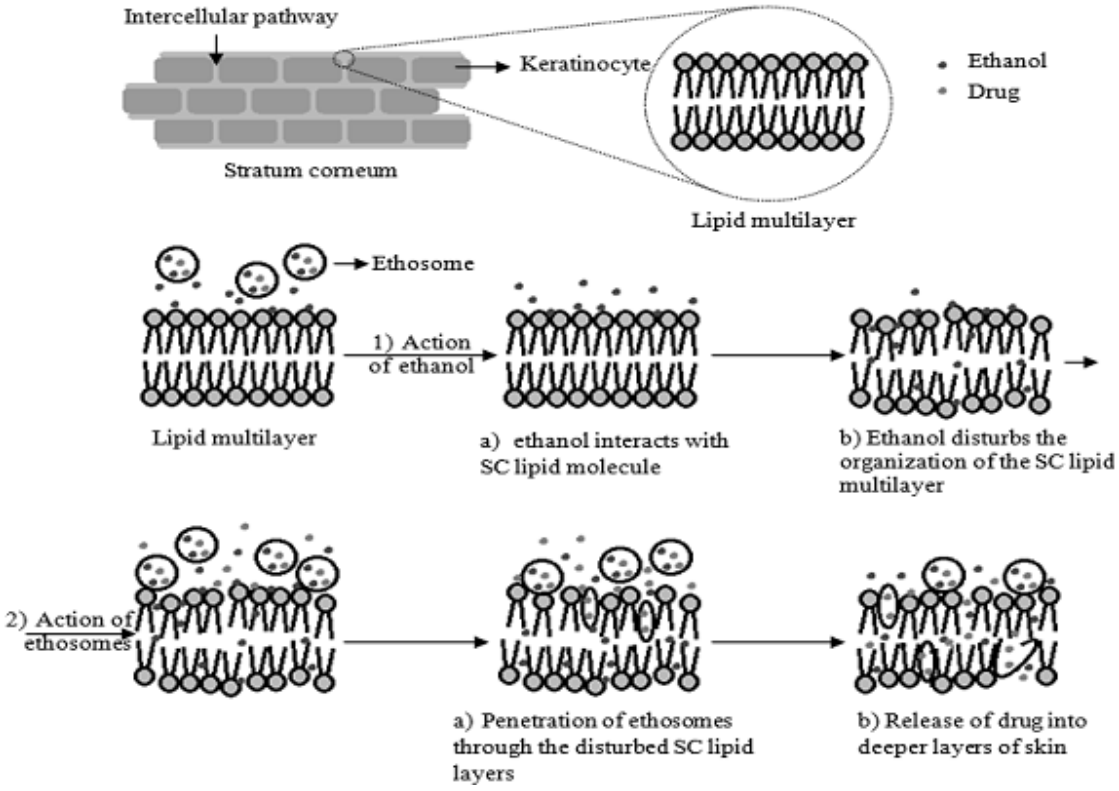
The ethosomal system consists of phospholipids, ethanol and water .The phospholipids with various chemical structure includes phosphatidyl choline (PC), hydrogenated PC, phosphatidyl ethanolamine(PE), phosphatidyl glycerol (PPG), phosphatidyl inositol (PI), hydrogenated PC etc.The non aqueous phase range between 22 % to 70 %. The alcohol may be ethanol or isopropyl alcohol. Dyes or amphiphilic fluorescent probe such as D–289, Rhodamine – 123 , fluorescence isothiocynate (FITC), 6 – carboxy fluorescence are often added to ethosomes for characterization study [19,20].

Table-1: Different Additives Employed In Formulation of Ethosomes:

Class	Example	Uses
Phospholipid	Soya phosphatidyl choline Egg phosphatidyl choline Dipalmityl phosphatidyl choline Distearyl phosphatidyl choline	Vesicles forming component
Polyglycol	Propylene glycol Transcutol RTM	As a skin penetration enhancer
Alcohol	Ethanol Isopropyl alcohol	For providing softness to the vesicle membrane, as a penetration enhancer
Cholesterol	Cholesterol	For providing stability to the vesicle membrane
Dyes	Rhodamine -123 Rhodamine red Fluorescence isothiocyanate 6-carboxy fluorescence	For characterization study
Vehicle	Carbopol 934	As a gel provider

Mechanism:

The depth of skin penetration from ethosomal systems can be assessed by confocal laser scanning microscopy (CLSM). For skin penetration studies various fluorescent probes with different physicochemical properties, like rhodamine red, rhodamine B, β-carotene (βC), rhodamine 6G, can be entrapped within the ethosomal vesicles [21,22]. The transition temperature of the lipid in the vesicular systems can be determined as a measure of vesicle softness. Both the drug and concentration of ethanol influence the transition temperature of vesicular lipids. Storage stability of ethosomal systems can be determined by comparing the shape, average size and entrapment capacity of the vesicles over time at different storage conditions. Based on various stability studies performed, researchers suggest refrigerated condition (4-8°C) as the suitable storage condition for ethosomal formulations. Higher temperatures may cause degradation of vesicular lipids, lose of structural integrity of vesicles and an accelerated leakage of the entrapped contents.



Advantages of ethosomal drug delivery [23]**:**

Although, the exact mechanism for comparison to other transdermal & dermal delivery systems:

1) Enhanced permeation of drug through skin for transdermal drug delivery.
2) Delivery of large molecules (peptides, protein molecules) is possible.
3) It contains nontoxic raw material in formulation.
4) High patient compliance the ethosomal drug is administered in semisolid form (gel or cream) hence producing high patient compliance.
5) Ethosomal system is passive, non invasive and is available for immediate commercialization.
6) Ethosomal drug delivery system can be applied widely in Pharmaceutical, Veterinary, Cosmetic fields.

7) Simple method for drug delivery in comparison to Iontophoresis and Phonophoresis and other complicated methods.
8) Ethosomes are enhanced permeation of drug through skin for transdermal and dermal delivery.
9) Ethosomes are platform for the delivery of large and diverse group of drugs (peptides, protein molecules)
10) Ethosome components are approved for pharmaceutical and cosmetic use.
11) Low risk profile-Technology has no large-scale drug development risk since toxicological profiles of the ethosomal components are well documented in the scientific literature.
12) High patient compliance- The ethosomal drug is administrated in 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.
13) High market attractiveness for products with proprietary technology. Relatively simple to Manufacture with no complicated technical investments required for production of Ethosomes.

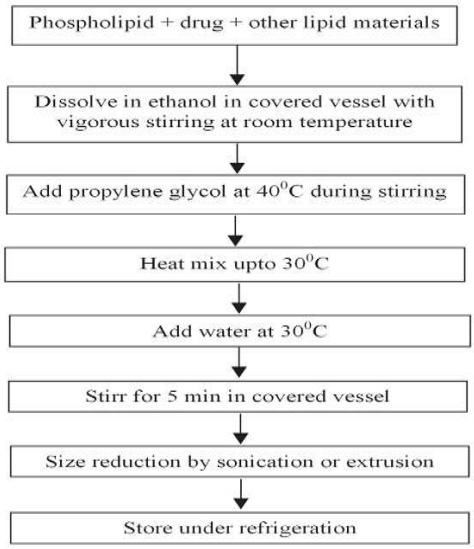
Limitations of ethosomes:

1. Poor yield [24].
2. In case if shell locking is ineffective then the ethosomes may coalescence and fall apart on transfer into water.
3. Loss of product during transfer form organic to water media [25].

Method Of Preparation Of Ethosome: [19, 20, 26, 27].

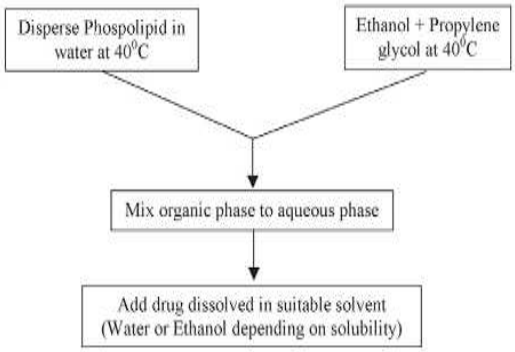
Ethosomes can be formulated by following two methods.

1) **Hot Method**:
In this method disperse phospholipid in water by heating in a water bath at 40°C until a colloidal solution is obtained. In a separate vessel properly mix ethanol and propylene glycol and heat up to 40°C. Add the organic phase into the aqueous phase. Dissolve the drug in water or ethanol depending on its solubility. The vesicle size of ethosomal formulation can be decreased to the desire extent using probe sonication or extrusion method.



2) Cold Method:

This is the most common and widely used method for the ethosomal preparation. Dissolve phospholipids, drug and other lipid materials in ethanol in a covered vessel at room temperature with vigorous stirring. Add propylene glycol or other polyglycol during stirring. Heat the mixture up to 30°C in a water bath. Heat the water up to 30°C in a separate vessel and add to the mixture and then stir it for 5 min in a covered vessel. The vesicle size of ethosomal formulation can be decreased to desire extend using sonication or extrusion method.



2) **Classic Mechanical Dispersion Method**:

Soya phosphatidylcholine is dissolved in a mixture of chloroform: methanol (3:1) in round bottom flask. The organic solvents are removed using rotary vacuum evaporator above lipid transition temperature to form of a thin lipid film on wall of the flask. 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 flask at suitable temperature. [28, 29]

3) Classic Method:

The phospholipid and drug are dissolved in ethanol and heated to 30ºC±1ºC 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 [29].

Various Methods of Characterization of Ethosomes: [30- 37].

1) **Vesicle shape:**
Ethosomes can be easily visualized by using transm ission electron microscopy (TEM) and by Scanning electron microscopy.(SEM)
2) **Vesicle size and zeta potential:**
Particle size of the ethosomes can be determined by dynamic light scattering (DLS) and photo correlati on spectroscopy (PCS). Zeta potential of the formul ation can be measured by Zeta meter.
3) **Transition temperature:**
The transition temperature of the vesicular lipid sys tems canbe determined by using differential Scanning calorimetry (DSC).
4) **Drug entrapment:**
The entrapment efficiency of ethosomes can be me asured by the ultracentrifugation technique.
5) **Drug content:**
Drug content of the ethosomes can be determined u sing UV spectrophotometer. This can also be quanti fied by modified high performance liquid chromato graphic 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 asses sing the size and structure of the vesicles over time. Mean size is measured by DLS and structure chang es are observed by TEM.
8) **Skin permeation studies:**
The ability of the ethosomal preparation to penetrat e into the skin layers can be determined by using confocal laser scanning microscopy (CLSM)

EVALUATION TESTS: [38].

1) Filter Membrane-Vesicle Interaction Study by Scanning Electron Microscopy: [39].
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).

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 PBS (10 mL of pH 6.5).Excised skin was mounted between the donor and receptor compartment. Ethosomal formulation (1.0ml) was applied to the epidermal surface of the skin. Samples(0.5ml) were withdrawn to through the sampling port of the diffusion cell at 1-, 2-, 4-, 8-, 12-, 16-, 20,- & 24 hr time intervals & 24 hr time intervals & analysed by high performance liquid chromatography (HPLC) assay

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 (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.

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.

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

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 - microliter 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.

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 prism (GraphPad, Version 2.01, and San Diego, CA).

Different Studies Related to the Application of Ethosomes as a Carrier System:
Various studies employing ethosomal formulation have shown better skin permeability of drugs. The uses of ethosomes as carrier system for transdermal/topical drug delivery are summarized below.

1. **Pilosebaceous targeting:**
Pilosebaceous units have been use for localized therapy, particularly for the treatment of follicle related disorders such as acne or alopecia. Ethosomal formulation of minoxidil a lipid soluble drug used for baldness accumulate into nude mice skin two to seven fold higher and thus can be use for pilosebaceous targeting for better clinical efficacy. [40, 41].

2. **Transdermal delivery**:
Since ethosomes enhance permeability of drug through stratum corneum barrier, it can be use for administration of drugs having poor skin permeation, low oral bioavability, first pass metabolism and dose skin and suppress infection at their root. [42, 43, 44].

3 **Delivery of HIV drugs:** An effective antiretroviral therapy is required on a long term basis and is associated with strong side effects [45]. Adequate zero order delivery of zidovudine, Lamivudine a potent antiviral agent is required to maintain expected anti – AIDS effect. Subheet Jain et al reported that ethosomal formulation of the above drugs prolong the release with increased transdermal flux [46]. Conventional topical preparation acyclovir an topically used antiviral drug for treatment of herpes labials show low therapeutic efficiency due to poor permeation through skin as replication of virus take places at the basal dermis. Ethosomal formulation of acyclovir show high therapeutic efficiency with shorter healing time and higher percentage of abortive lesions.

4 **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 [47].

Patented and marketed formulation of ethosome:

- Ethosome was invented and patented by Prof. ElkaTouitou along with her students of Department of Pharmaceutics at the Hebrew University School of Pharmacy.19,20.
- Novel Therapeutic Technologies Inc (NTT) of Hebrew University has been succeeded in bringing a number of products to the market based on ethosome delivery system.

1. **Noicellex TM** an anti – cellulite formulation of ethosome is currently marketed in Japan.
2. **Lipoduction TM** another formulation is currently used in treatment of cellulite containing pure grape seed extracts (antioxidant) is marketed in USA. Similarly
3. **Physonics** is marketing anti – cellulite gel Skin Genuity in London.
4. **Nanominox©** containing monoxidil is used as hair tonic to promote hair growth. It is marketed by Sinere.

Stability of Ethosomes:

- Stability of the ethosomal formulations was evaluated by entrapment capacity and the particle size for a specified period.
- Basically, the proper choice of the lipid composition appeared to be an important factor in obtaining stable ethosomes dispersions with optimum pharmaceutical and therapeutic characteristics. In case of liposomes, upon storage, many different changes could occur.
- Liposomes tend to fuse and grow into bigger vesicles and this fusion and breakage of liposomes on storage pose an important problem of drug leakage from the vesicles.
- The absence of electrostatic repulsion is likely to account for the tendency of the neutral liposome to aggregate, but in case of ethosomes, ethanol causes a modification of the net charge of the system and confers it some degree of steric stabilization leading to increased stability of the dispersion against agglomeration that may also lead to a decrease in the mean vesicle size.
- Increasing the concentration of ethanol from 15 to 45% increases the entrapment efficiency owing to an increase in the fluidity of the membranes.
- However, a further increase in the ethanol concentration (> 45%) probably makes the vesicle membrane leakier, thus leading to a decrease in entrapment efficiency. Therefore, it causes destabilization of the ethosomes.
- The lipid portion of the ethosomes is derived from natural and / or synthetic phospholipid sources.
- Phospholipids containing unsaturated fatty acids are known to undergo oxidative reactions. The reaction products can cause permeability changes in the ethosomes bilayers.
- Oxidative degradation of the lipids in general can be minimized by protecting the lipid preparation from light, by adding antioxidants such as α - tocopherol.Furthermore, hydrolysis of lipids leads to the formation of lyso-PC.
- The presence of lyso-PC enhances the permeability of ethosomes, and thus, it is essential to keep its level to a minimum in a given preparation.[48,49]

Future Prospects:

- Introduction of ethosomes has initiated a new area in vesicular research for transdermal drug delivery.
- Different reports show a promising future of ethosomes in making transdermal delivery of various agents more effective.
- Further, research in this area will allow better control over drug release *in vivo*, allowing physician to make the therapy more effective.
- Ethosomes offers a good opportunity for the non-invasive delivery of small, medium and large sized drug molecules.
- The results of the first clinical study of acyclovir-ethosomal formulation support this conclusion. Multiliter quantities of ethosomal formulation can be prepared very easily.
- It, therefore, should be not before long that the corresponding drug formulation would have found their way into clinics to be tested for widespread usage.
- Thus, it can be a logical conclusion that ethosomal formulations possess promising future in effective dermal/transdermal delivery of bioactive agents.

Conclusion:

Ethosomal carrier gives opportunities and new challenges for the development of novel improved therapies. Ethosomes are soft malleable vesicles composed mainly of phospholipids, water and ethanol and potential carrier for transportation of drugs. Ethosomes are characterized by simplicity in their preparation, safety and efficacy and can be prepared for enhanced skin permeation of active drugs). Ethosomes have been found to be much more efficient at delivering drug to the skin, than either liposomes or

hydroalcoholic solution. It can be easily concluded that ethosomes can provide better skin permeation than liposomes. The main disadvantage 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 [50].

Application of Ethosome:

Table 2: Compilation of reported works on ethosome

Active Ingredients	Formulations	Applications	Comments
Ketoprofen (2011) [51]	Suspension	Treatment of arthritis related inflammatory pain and musculoskeletal pain	Enhanced transdermal delivery
Linoleic acid (2011) [52]	Suspension	Treatment of melasma	Improved skin permeation and accumulation
Ligustrazine (2011) [53]	Patch	Treatment of angina pectoris	Better drug absorption and Increased bioavailability, Patches showed good storage stability
Buspirone (2010) [54]	Gel	Treatment of Menopausal syndrome (anxiety and hot flushes)	Enhanced transdermal flux, Non-fluctuated and sustained delivery of drug, Reduced side effects
Betamethasone-17-Valerate (2010) [55]	Suspension	Treatment of eczema and psoriasis	Significantly improved the skin penetration
Triptolide (2010) [56]	Suspension	Treatment of skin inflammation	Enhanced skin permeation and biological activity, Better skin accumulation
Ibuprofen (2010) [57]	Gel	Treatment of rheumatoid arthritis	Improved transdermal flux
5-aminolevulinic acid (2009) [58]	Suspension	Treatment of psoriasis	Improved drug penetration in hyperproliferative murine skin in vivo.
Distamycins (2009) [59]	Suspension	Treatment of cancer	Enhanced drug activity, Reduced side effects
Gold nanoparticles (2009) [60]	Suspension	Treatment of skin cancer, Used as a diagnostic agent	High encapsulation efficiency of the gold nanoparticles, Improved pharmacological efficacy
Matrine (2009) [61]	Suspension	Treatment of psoriasis and eczema	Improved the percutaneous permeation and anti-inflammatory activity
Benzocaine (2009) [62]	Gel	Topical anaesthesia	Improved skin penetration and therapeutic efficacy
Flucanazole (2009) [63]	Gel	Treatment of candidiasis	Better antifungal activity compared to marketed formulation

Finasteride (2008) [64]	Suspension	Treatment of androgenetic alopecia	Enhanced skin penetration and accumulation
Melatonin (2007) [65]	Suspension	Treatment of delayed sleep phase syndrome	Enhanced transdermal flux, Reduced lag time, Low skin irritancy potential
Bacitracin (2004) [66]	Suspension	Treatment of dermal infections	Improved dermal and intracellular delivery, Reduced drug toxicity
Zidovudine (2004) [67]	Suspension	Treatment of AIDS	Improved transdermal flux, Reduced drug toxicity
Cyclosporine A (2004) [68]	Suspension	Treatment of psoriasis, atopic dermatitis and alopecia areata	Enhanced skin penetration and deposition
Cannabidiol (2003) [69]	Suspension	Treatment of rheumatoid arthritis	Better skin permeation and accumulation, Improved biological activity, Prolonged drug action
Acyclovir (1999) [70]	Suspension	Treatment of herpes labialis	Improved clinical efficacy in comparison with commercial acyclovir formulation (Zovirax cream)

"Cite this article"

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