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**Review Article**

# Ethosomal Drug Delivery System: A Novel Approach to Transdermal Drug Delivery- A Review

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**Abstract:** Ethosomes are novel lipid vesicular carriers containing a relatively high percentage of ethanol andthe novel approach for the current drug delivery as a transdermal drug delivery system which is employed for the assessment of the targeted drug to the site of action. There are many application in the development of the formulation for the better release to the systemic circulation. The therapeutic effect of these category of formulation totally depends upon the medium of the drug release, in which we can observe the amount of drug in the formulation and drug released to the site of action.Ethosomes are vesicular carrier comprise of hydroalcoholic orhydro/alcoholic/glycolic phospholipid in which theconcentration of alcohols or their combination is relativelyhigh.Ethosomes can entrap drug molecule with variousphysicochemical characteristics i.e. of hydrophilic, lipophilic,or amphiphilic. These formulations are better alternative of oral drug delivery in that patients, those cannot take orally.

**Keywords:** Ethosomes, Current drug delivery,Vesicular carrier,Transdermal drug delivery system



## INTRODUCTION

Transdermal drug delivery system (TDDS) showed promising result in comparison to oral drug delivery system as iteliminates gastrointestinal interferences and first passmetabolism of the drug but the main drawback of TDDS is itencounters the barrier properties of the Stratum Corneum i.e.only the lipophilic drugs having molecular weight < 500 Dacan pass through it (Satyam, G. *et al.*, 2010; & Kumar, K. P. *et al.*, 2010). To improve the permeation ofdrugs through the skin various mechanisms have beeninvestigated, including use of chemical or physical enhancers,such as iontophoresis, sonophoresis, etc. Liposomes, niosomes,transferosomes and ethosomes also have been reported toenhance permeability of drug through the stratum corneumbarrier. Permeation enhancers increase the permeability ofthe skin, so that the drugs can cross through the skin easily.Unlike classic liposomes (Heeremans, J. L. M. *et al.*, 1995), that are known mainly to deliverdrugs to the outer layers of skin, ethosomes can enhance permeation through the stratum corneum barrier (Asbill, C. S. *et al.*, 2000; & Touitou, E. *et al.*, 1998). Ethosomes permeate through the skin layers more rapidlyand possess significantly higher transdermal flux incomparison to conventional liposomes (Verma, P., & Pathak, K. 2010; Jain, S. *et al.*, 2004; & Touitou, E. *et al.*, 2001).Ethosomes are lipid vesicles containing phospholipids, alcohol (ethanol and isopropyl alcohol) in relatively highconcentration and water. Ethosomes are soft vesicles made ofphospholipids and ethanol (in higher quantity) and water (Satyam, G. *et al.*, 2010; & Verma, P., & Pathak, K. 2010). The size range of ethosomes may vary from tens of nanometers to microns (μ) (Bhalaria, M. K. *et al.*, 2009; & Verma, D. D., & Fahr, A. 2004). One of the major advances in vesicle research was the finding that some modified vesicles possessed properties that allowed them to successfully deliver drugs in deeper layers of skin. Transdermal delivery is important because it is a noninvasive procedure for drug delivery. Further, problem of drug degradation by digestive enzymes after oral administration and discomfort associated with parenteral drug administration can be avoided. It is the most preferred route for systemic delivery of drugs to pediatric, geriatric and patients having dysphasia. To overcome the stratum corneum barrier, various mechanisms have been investigated, including useof chemical or physical enhancers such as iontophoresis, sonophoresis, etc. liposomes, niosomes,transferosomes and ethosomes also have the potential of overcoming the skin barrier and have beenreported to enhance permeability of drug through the stratum corneum barrier.

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**ADVANTAGES OF ETHOSOMAL DRUG DELIVERY**

1. Delivery of large molecules (peptides, protein molecules) is possible.
2. It contains non-toxic raw material in formulation.
3. Enhanced
4. Ethosomal drug permeation of drug through skin for transdermal drug delivery delivery system can be applied widely in pharmaceutical, veterinary, cosmetic fields.
5. High patient compliance: the ethosomal drug is administrated in semisolid form (gel or cream) hence producing high patient compliance.
6. Simple method for drug delivery in comparison to iontophoresis and phonophoresis and othercomplicated methods
7. The ethosomal system is passive, non-invasive and is available for immediate commercialization (Dhamecha, D. L. *et al.,* 2009; & Touitou, E. 1996).

**DISADVANTAGES OF ETHOSOMES**

1. Drugsthat require high blood levels cannot be administered – limited only to potent molecules, those requiring a daily dose of 10mg or less.
2. Ethosomal administration is not a means to achieve rapid bolus type drug input, rather it is usually designed to offer slow, sustained drug delivery.
3. Adequatesolubility of the drug in both lipophilic and aqueous environments to reach dermalmicrocirculation and gain access to the systemic circulation.
4. The molecular size of the drug should be reasonable that it should be absorbed percutaneous.
5. Adhesive may not adhere well to all types of skin. Uncomfortable to wear.
6. May not be economical. Poor yield.
7. Skin irritation or dermatitis due to excipients and enhancers of drug delivery systems.
8. In case if shell locking is ineffective then the ethosomes may coalescence and fall apart on transfer into water. 9. Loss of product during transfer from organic to water media.
9. The main advantage of ethosomes over liposomes is the increased permeation of the drug.

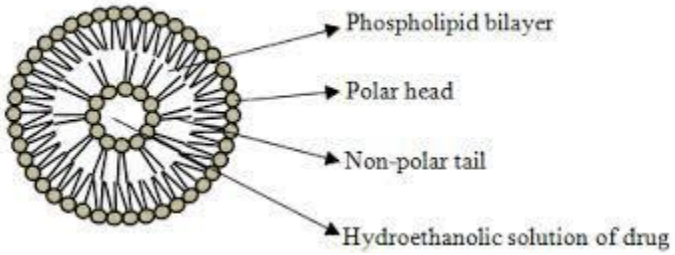


**Figure 2:** Structure of Ethosomes

**COMPOSITION OF ETHOSOMES** (Kumar, K. P. *et al.,* 2010)

Typically, Ethosomes may contain phospholipids withvarious chemical structures like phosphatidylcholine (PC), hydrogenated PC, phosphatidic acid (PA), phosphatidylserine (PS), phosphatidylethanolamine (PE), phosphatidylglycerol (PPG), phosphatidylinositol (PI), hydrogenated PC, alcohol (ethanol or isopropyl alcohol), water and propylene glycol (or other glycols). Such acomposition enables delivery of high concentration of activeingredients through skin. Drug delivery can be modulated byaltering alcohol: water or alcohol-polyol: water ratio. Some preferred phospholipids are soya phospholipids such as Phospholipon 90 (PL-90). It is usually employed in a range of 0.5-10% w/w. Cholesterol at concentrations rangingbetween 0.1 1% can also be added to the preparation.Examples of alcohols, which can be used, include ethanol andisopropyl alcohol. Among glycols, propylene glycol and Transcutol are generally used. In addition, non-ionicsurfactants (PEG-alkyl ethers) can be combined with thephospholipids in these preparations. Cationic lipids likecocoamide, POE alkyl amines, dodecylamine, cetrimide etc.can be added too. The concentration of alcohol in the finalproduct may range from 20 to 50%. The concentration of thenon-aqueous phase (alcohol and glycol combination) mayrange between 22 to 70% (**Table 1**).

**MECHANISM OF DRUG PENETRATION**

The main advantage of ethosomes over liposomes is theincreased permeation of the drug. The mechanism of thedrug absorption from ethosomes is not clear. The drugabsorption probably occurs in following two phases:

1. Ethanol effect
2. Ethosomes effect

**1. Ethanol effect:**

Ethanol acts as a penetration enhancer through theskin. The mechanism of its penetration enhancingeffect is well known. Ethanol penetrates intointercellular lipids and increases the fluidity of cellmembrane lipids and decrease the density of lipidmultilayer of cell membrane.

**2. Ethosome effect:**

Increased cell membrane lipid fluidity caused bythe ethanol of ethosomes results increased skinpermeability. So the ethosomes permeates veryeasily inside the deep skin layers, where it gotfused with skin lipids and releases the drugs intodeep layer of skin (Satyam, G. *et al.,* 2010).

## METHODS OF PREPARATION ETHOSOMES

Ethosomes can be prepared by two very simple andconvenient methods that are hot method and cold method.

### 1. Cold Method:

This is the most common method utilized for the preparationof ethosomal formulation. In this method phospholipid, drugand other lipid materials are dissolved in ethanol in acovered vessel at room temperature by vigorous stirring withthe use of mixer. Propylene glycol or other polyol is addedduring stirring. This mixture is heated to 300˚C in a waterbath. The water heated to 300˚C in a separate vessel isadded to the mixture, which is then stirred for 5 min in acovered vessel. The vesicle size of ethosomal formulation canbe decreased to desire extend using sonication or extrusionmethod. Finally, the formulation is stored under refrigeration (Pratima, N. A., & Shailee, T. 2012; & Dhamecha, D. L. *et al.,* 2009).

### 2. Hot method:

In this method phospholipid is dispersed in water by heatingin a water bath at 400C until a colloidal solution is obtained.In a separate vessel ethanol and propylene glycol are mixedand heated to 400˚C. Once both mixtures reach 400˚C, theorganic phase is added to the aqueous one. The drug isdissolved in water or ethanol depending on its hydrophilic/hydrophobic properties. The vesicle size of ethosomalformulation can be decreased to the desire extent usingprobe sonication or extrusion method (Pratima, N. A., & Shailee, T. 2012; & Dhamecha, D. L. *et al.,* 2009).

## CHARACTERIZATIONS OF ETHOSOMES

### 1. Visualization

Visualization of ethosomes can be done using transmissionelectron microscopy (TEM) and by scanning electronmicroscopy (SEM) (Pratima, N. A., & Shailee, T. 2012).

### 2. Vesicle size and Zeta potential

Particle size and zeta potential can be determined bydynamic light scattering (DLS) using a computerizedinspection system and photon correlation spectroscopy (PCS) (El Maghraby, G. M. *et al.,* 2000).

### 3. Differential Scanning Calorimetry (DSC)

Transition temperature (Tm) of the vesicular lipid systems was determined by using the Mettler DSC 60computerized with Mettler Toledo star software system (Mettler, Switzerland).The transition temperature wasmeasured by using the aluminium crucibles at a heatingrate 10 degree/minute, within a temperature range from20˚C–300˚C (Cevc, G. *et al.,* 1995; & Fry, D. W. *et al.,* 1978).

### 4. Surface Tension Activity Measurement

The surface tension activity of drug in aqueous solutioncan be measured by the ring method in a Du Nouy ringtensiometer (Cevc, G. *et al.,* 1995; & Fry, D. W. *et al.,* 1978).

### 5. Entrapment Efficiency

The entrapment efficiency of drug by ethosomes can bemeasured by the ultracentrifugation technique (Fry, D. W. *et al.,* 1978).

### 6. Penetration and Permeation Studies

Depth of penetration from ethosomes can be visualizedby confocal laser scanning (Pratima, N. A., & Shailee, T. 2012).

### 7. Vesicle Stability

The stability of vesicles can be determined by assessingthe size and structure of the vesicles over time. Mean sizeis measured by DLS and structure changes are observedby TEM (Pratima, N. A., & Shailee, T. 2012; Cevc, G. *et al.,* 1995; & Fry, D. W. *et al.,* 1978)**.**

## EVALUATION TESTS

### 1. Filter Membrane-Vesicle Interaction Study by ScanningElectron Microscopy

Vesicle suspension (0.2 mL) was applied to filtermembrane having a pore size of 50 nm and placed indiffusion cells. The upper side of the filter was exposedto the air, whereas the lower side was in contact with PBS(phosphate buffer saline solution), (pH 6.5). The filterswere removed after 1 hour and prepared for SEMstudies by fixation at 4°C in Karnovsky's fixativeovernight followed by dehydration with graded ethanolsolutions (30%, 50%, 70%, 90%, 95%, and 100%vol/vol in water). Finally, filters were coated with goldand examined in SEM (Leica, Bensheim, Germany) (Kumar, K. P. *et al.,* 2010; Pratima, N. A., & Shailee, T. 2012; & Lopez-Pinto, J. M. *et al.,* 2005)**.**

### 2. Vesicle-Skin Interaction Study by FluorescenceMicroscopy

Fluorescence microscopy was carried according to theprotocol used for TEM and SEM study. Paraffin blocksare used, were made, 5-µm thick sections were cut usingmicrotome (Erma optical works, Tokyo, Japan) andexamined under a fluorescence micro Cytotoxicity AssayMT-2 cells (T-lymphoid cell lines) were propagated inDulbecco's modified Eagle medium (HIMEDIA, Mumbai,India) containing 10% fetal calf serum, 100 U/M penicillin, 100 mg/mL streptomycin, and 2 mmol/Lglutamine at 37°C under a 5% CO2 atmosphere.Cytotoxicity was expressed as the cytotoxic dose 50(CD50) that induced a 50% reduction of absorbance at540 nm (Satyam, G. *et al.,* 2010; Kumar,

K. P. *et al.,* 2010; & Pratima, N. A., & Shailee, T. 2012).

**3. Vesicle-Skin Interaction Study by TEM and SEM**

From animals ultrathin sections were cut (Ultracut, Vienna,Austria), collected on formvar-coated grids andexamined under transmission electron microscope. ForSEM analysis, the sections of skin after dehydration weremounted on stubs using an adhesive tape and werecoated with gold palladium alloy using a fine coat ionsputter coater. The sections were examined underscanning electron microscope (Pratima, N. A., & Shailee, T. 2012; & Lopez-Pinto, J. M. *et al.,* 2005**).**

**4. HPLC Assay**

The amount of drug permeated in the receptorcompartment during in vitro skin permeation experimentsand in MT-2 cell was determined by HPLC assay usingmethanol: distilled-water :acetonitrile (70:20:10 vol/vol)mixture as mobile phase delivered at 1 mL/min by LC10-AT vp pump (Shimadzu, Kyoto, Japan). A twentymicroliterinjection was eluted in C-18 column (4.6×150mm, Luna, 54, Shimadzu) at room temperature. Thecolumn eluent was monitored at 271 nm using SPDM10Avp diode array UV detector. The coefficient of variance(CV) for standard curve ranged from 1.0% to 2.3%, andthe squared correlation coefficient was 0.9968 (Kumar, K. P. *et al.,* 2010; Pratima, N. A., & Shailee, T. 2012; & Lopez-Pinto, J. M. *et al.,* 2005)**.**

**5. Drug Uptake Studies**

The uptake of drug into MT-2 cells (1×106 cells/mL) wasperformed in 24-well plates (Corning Inc) in which 100 μLRPMI medium was added. Cells were incubated with 100μL of the drug solution in PBS (pH 7.4), ethosomalformulation, or marketed formulation, and then druguptake was determined by analyzing the drug content byHPLC assay (Satyam, G. *et al.,* 2010; Kumar, K. P. *et al.,* 2010; Pratima, N. A., & Shailee, T. 2012)(Pratima, N. A., & Shailee, T. 2012; & Lopez-Pinto, J. M. *et al.,* 2005)**.**

**6. Skin Permeation Studies**

The hair of test animals (rats) were carefully trimmedshort (<2 mm) with a pair of scissors, and the abdominalskin was separated from the underlying connective tissue with a scalpel. The excised skin was placed on aluminiumfoil, and the dermal side of the skin was gently teasedoff for any adhering fat and/or subcutaneous tissue. Theeffective permeation area of the diffusion cell andreceptor 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 ofpH 6.5). Excised skin was mounted between the donorand the receptor compartment. Ethosomal formulation(1.0 mL) was applied to the epidermal surface of skin.Samples (0.5 mL) were withdrawn through the samplingport of the diffusion cell at 1-, 2-, 4-, 8-, 12-, 16-, 20-,and 24-hour time intervals and analyzed by highperformance liquid chromatography (HPLC) assay (Kumar, K. P. *et al.,* 2010; & Pratima, N. A., & Shailee, T. 2012).

**7. Stability Study**

Stability of the vesicles was determined by storing thevesicles at 4°C ± 0.5°C. Vesicle size, zeta potential, andentrapment efficiency of the vesicles was measured after180 days using the method described earlier (Kumar, K. P. *et al.,* 2010).

**PATENTED AND MARKETED FORMULATION OFETHOSOME**

Ethosome was invented and patented by Prof. Elka Touitoualong with her students of department of Pharmaceutics atthe Hebrew University School of Pharmacy. NovelTherapeutic Technologies Inc (NTT) of Hebrew University hasbeen succeeded in bringing a number of products to themarket based on ethosome delivery system. Noicellex TM ananti – cellulite formulation of ethosome is currently marketedin Japan. Lipoduction TM another formulation is currentlyused in treatment of cellulite containing pure grape seedextracts (antioxidant) is marketed in USA. Similarly Physonicsis marketing anti – cellulite gel Skin Genuity in London.Nanominox© containing monoxidil is used as hair tonic topromote hair growth is marketed by Sinere (Touitou, E. 1996; & Touitou, E. 1998). Table 2shows examples of ethosomes as a drug carrier.

**APPLICATIONS OF ETHOSOMES**

**1. Delivery of Anti-Viral Drugs**

Zidovudine is a potent antiviral agent acting on acquiredimmunodeficiency virus. Oral administration of zidovudineis associated with strong side effects. Therefore, anadequate zero order delivery of zidovudine is desired tomaintain expected anti-AIDS effect (Kim, S., & Chien, Y.W. 1996). Jain *et al.,* (2004) concluded that ethosomes could increase the transdermalflux, prolong the release and present an attractive routefor sustained delivery of zidovudine.Acyclovir is another anti-viral drug that widely usedtopically for treatment of Herpes labialis (Spruance, S. L. 1992, September).Theconventional marketed acyclovir external formulation isassociated with poor skin penetration of hydrophilicacyclovir to dermal layer resulting in weak therapeuticefficiency. It is reported that the replication of virus takesplace at the basal dermis. To overcome the problemassociated with conventional topical preparation of Acyclovir (Fiddan, A. P. *et al.,* 1983). Horwitz *et al.,* formulated the acyclovirethosomal formulation for dermal delivery. The resultsshowed that shorter healing time and higher percentageof abortive lesions were observed when acyclovir wasloaded into ethosomes.

**2. Topical Delivery of DNA**

Many environmental pathogens attempt to enter thebody through the skin. Skin therefore, has evolved into anexcellent protective barrier, which is

also immunologicallyactive and able to express the gene (Fang, J. Y. *et al.,* 2001). On the basis ofabove facts another important application of ethosomesis to use them for topical delivery of DNA molecules toexpress genes in skin cells. Touitou *et al.,* in their studyencapsulated the GFP-CMV-driven transfecting constructinto ethosomal formulation. They applied this formulationto the dorsal skin of 5-week male CD-1 nude mice for 48hr. After 48 hr., treated skin was removed andpenetration of green fluorescent protein (GFP)formulation was observed by CLSM. It was observed thattopically applied ethosomes-GFP-CMV-driventransfecting construct enabled efficient delivery andexpression of genes in skin cells. It was suggested thatethosomes could be used as carriers for gene therapyapplications that require transient expression of genes.These results also showed the possibility of usingethosomes for effective transdermal immunization. Gupta *et al.,* recently reported immunization potential usingtransfersomal formulation. Hence, better skin permeationability of ethosomes opens the possibility of using thesedosage forms for delivery of immunizing agents (Kumar, K. P. *et al.,* 2010).

**3. Transdermal Delivery of Hormones**

Oral administration of hormones is associated withproblems like high first pass metabolism, low oralbioavailability and several dose dependent side effects.The risk of failure of treatment is known to increase witheach pill missed (Johnsen, S. *et al.,* 1974). Touitou *et al.,* compared the skinpermeation potential of testosterone ethosomes(Testosome) across rabbit pinna skin with marketedtransdermal patch of testosterone (Testoderm patch,Alza). They observed nearly 30-times higher skinpermeation of testosterone from ethosomal formulation ascompared to that marketed formulation.

**4. Delivery of anti-parkinsonism agent**

Dayan and Touitou prepared ethosomal formulation ofpsychoactive drug trihexyphenidyl hydrochloride (THP)and compared its delivery with that from classicalliposomal formulation. THP is a M1 muscarinic receptorsantagonist and used in the treatment of Parkinsondisease. The results indicated better skin permeationpotential of ethosomal-THP formulation and its use forbetter management of Parkinson disease (Kumar, K. P. *et al.,* 2010).

**5. Transcellular Delivery**

Touitou *et al.,* in their study demonstrated betterintracellular uptake of bacitracin, DNA and erythromycin using CLSM and FACS techniques in different cell lines.Better cellular uptake of anti-HIV drug zidovudine andlamivudine in MT-2 cell line from ethosomes as comparedto the marketed formulation suggested ethosomes to bean attractive clinical alternative for anti-HIV therapy (Verma, P., & Pathak, K. 2010; & Touitou, E. *et al.,* 2001).

**6. Delivery of Anti-Arthritis Drug**

Topical delivery of anti-arthritis drug is a better optionfor its site-specific delivery and overcomes the problemassociated with conventional oral therapy. Cannabidol(CBD) is a recently developed drug candidate fortreating rheumatoid arthritis. Lodzki *et al.,* prepared CBDethosomalformulation for transdermal delivery. Resultsshows significantly increased in biological anti-inflammatoryactivity of CBD-ethosomal formulation wasobserved when tested by carrageenan induced rat pawedema model. It was concluded encapsulation of CBD inethosomes significantly increased its skin permeation,accumulation and hence it's biological activity (Kumar, K. P. *et al.,* 2010).

**7. Delivery of Problematic drug molecules**

The oraldelivery of large biogenic molecules such as peptides orproteins is difficult because they are completelydegraded in the GI tract. Non-invasive delivery ofproteins is a better option for overcoming the problemsassociated with oral delivery (Chetty, D. J., & Chien, Y. W. 1998). Dkeidek and Touitouinvestigated the effect of ethosomal insulin delivery inlowering blood glucose levels (BGL) *in vivo* in normal and diabetic SDI rats. In this study a Hill Top patch containinginsulin ethosomes was applied on the abdominal area ofan overnight fated rat. The result showed that insulindelivered from this patch produced a significantdecrease (up to 60%) in BGL in both normal and diabeticrats. On the other hand, insulin application from a controlformulation was not able to reduce the BGL (Verma, D. D., & Fahr, A. 2004) reported the cyclosporine A, ethosomal formulation for the treatment of inflammatoryskin disease like psoriasis, atopic dermatitis and diseaseof hair follicle like *alopecia areata* etc. Paolino *et al.,* (2005) investigated the potential application of ethosomesfor dermal delivery of ammonium glycyrrhizinate.Ammonium glycyrrhizinate is naturally occurringtriterpenes obtained from Glycyrrhizinate Glabra anduseful for the treatment of various inflammatory basedskin diseases (Fu, Y. *et al.,* 2004).

**8. Delivery of Antibiotics**

Topical delivery of antibiotics is a better choice forincreasing the therapeutic efficacy of these agents.Conventional oral therapy causes several allergicreactions along with several side effects. Conventionalexternal preparations possess low permeability to deepskin layers and subdermal tissues (Fang, J. Y. *et al.,* 2001). Ethosomes cancircumvent this problem by delivering sufficient quantityof antibiotic into deeper layers of skin. Ethosomespenetrate rapidly through the epidermis and bringappreciable amount of drugs into the deeper layer ofskin and suppress infection at their root. With this purposein mind Godin and Touitou prepared bacitracin anderythromycin loaded ethosomal formulation for dermaland intracellular delivery. The results of this study

showedthat the ethosomal formulation of antibiotic could behighly efficient and would overcome the problemsassociated with conventional therapy.

**ADVANTAGE OF HIGH ALCOHOL CONTENT**

Ethanol is an established efficient permeation enhancer and is present in quite high concentration (20-50%) in ethosomes. However, due to the inter-digitation effect of ethanol on lipid bilayers, it was commonly believed that vesicles could not coexist with high concentration of ethanol. Touitou discovered and investigated lipid vesicular systems embodying ethanol in relatively high concentration and named them ethosomes. The basic difference between liposomes and ethosomes lies in their composition. The synergistic effect of combination of 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 theskin lipid bilayer organization. therefore, when integrated into a vesicle membrane, it could give an ability to the vesicles to penetrate the sc. furthermore, due to high ethanol concentration the ethosomal lipid membrane was packed less tightly than conventional vesicles but possessed equivalent stability. This allowed a softer and malleable structure giving more freedom and stability to its membrane, which could squeeze through small openings created in the disturbed sc lipids. in addition, the vesicular nature of ethosomal formulations could be modified by varying the ratio of components and chemical structure of the phospholipids. The versatility of ethosomes for systemic delivery is evident from the reports of enhanced delivery of quite a few drugs like acyclovir, minoxidil, triphexyphenidyl,testosterone, cannabidol and zidovudine (Johnsen, S. *et al.,* 1974; & Fu, Y. *et al.,* 2004).

**Table 4.** Marketed Products of Ethosomes

| Name Of Product | Uses | Manufacturer |
|---|---|---|
| Cellutight 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 Hyperpigmentation | Genome Cosmetics, Pennsylvania, Us |
| Nanominox | First Minoxidil Containing Product, Which Uses Ethosomes. Contains 4% Minoxidil, 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, Uk |
| Supravir Cream | For The Treatment Of Herpes Virus, Formulation Of Acyclovir Drug Has A Long Shelf Life With No Stability Problems, Stable For At Least Three Years, At 25°C. Skinpermeation Experiments Showed That The Cream Retained Its Initial Penetration Enhancing Propertieseven After Three Years | Trima, Israel |

## CONCLUSION

The main limiting factor of transdermal drug delivery systemi.e. epidermal barrier can be overcome by ethosomes tosignificant extent. The ethosomes more advantages whencompared to transdermal and dermal delivery. Ethosomesare the noninvasive drug delivery carriers that enable drugsto reach the deep skin layers finally delivering to thesystemic circulation. It delivers large molecules such aspeptides, protein molecules. Simple method for drug deliveryin comparison to Iontophoresis and Phonophoresis and othercomplicated methods. High patient compliance as it isadministrated in semisolid form (gel or cream) and variousapplication in Pharmaceutical, Veterinary, Cosmetic field.

## REFERENCES


1. Anitha, P., Ramkanth, S., Alagusundaram, M., & Gnanapraksah, K. (2017). Ethosomes-A noninvasive vesicular carrier for transdermal drug delivery. *International Journal of Research in Phytochemistry and Pharmacology*, *7*(3), 71-78.
2. Asbill, C. S., El-Kattan, A. F., & Michniak, B. (2000). Enhancement of transdermal drug delivery: chemical and physical approaches. *Critical Reviews™ in Therapeutic Drug Carrier Systems*, *17*(6).
3. Bhalaria, M. K., Naik, S., & Misra, A. N. (2009). "Ethosomes: A noveldelivery system for antifungal drugs in thetreatment of topical fungal diseases",

*Indian Journalof Experimental Biology* 47, 368-375.

4. Cevc, G., Schätzlein, A., & Blume, G. (1995). Transdermal drug carriers: basic properties, optimization and transfer efficiency in the case of epicutaneously applied peptides. *Journal of Controlled Release*, *36*(1-2), 3-16.
5. Chetty, D. J., & Chien, Y. W. (1998). Transdermal Delivery of CaCO3-Nanoparticles Containing Insulin. *Crit Rev Ther Drug Carrier Syst*, *15*, 629-670.
6. Dhamecha, D. L., Rathi, A. A., Saifee, M., Lahoti, S. R., & Dehghan, M. H. G. (2009). Drug vehicle based approaches of penetration enhancement. *Int J Pharm Pharm Sci*, *1*(1), 24-46.
7. El Maghraby, G. M., Williams, A. C., & Barry, B. W. (2000). Oestradiol skin delivery from ultradeformable liposomes: refinement of surfactant concentration. *International journal of pharmaceutics*, *196*(1), 63-74.
8. Fang, J. Y., Hong, C. T., Chiu, W. T., & Wang, Y. Y. (2001). Effect of liposomes and niosomes on skin permeation of enoxacin. *International journal of pharmaceutics*, *219*(1-2), 61-72.
9. Fiddan, A. P., Yeo, J. M., Strubbings, R., & Dean, D. (1983). Vesicular Approach for Drug Delivery into or Across the Skin. *Br. Med. J*, *286*, 1699.
10. Fry, D. W., White, J. C., & Goldman, I. D. (1978). Rapid separation of low molecular weight solutes from liposomes without dilution. *Analytical biochemistry*, *90*(2), 809-815.
11. Fu, Y., Hsieh, J., Guo, J., Kunicki, J., Lee, M. Y., Darzynkiewicz, Z., & Wu, J. M. (2004). Antiinflammatory efficacy of Licochalcone A: correlation of clinical potency and in vitro effects. *Biochem. Biophys. Res. Commun*, *322*, 263-270.
12. Heeremans, J. L. M., Gerrttsen, H. R., Meusen, S. P., Mijnheer, F. W., Gangaram Panday, R. S., Prevost, R., ... & Crommelin, D. J. A. (1995). The preparation of tissue-type plasminogen activator (t-PA) containing liposomes: entrapment efficiency and ultracentrifugation damage. *Journal of Drug targeting*, *3*(4), 301-310.
13. Jain, S., Umamaheshwari, R. B., Bhadra, D., & Jain, N. K. (2004). Ethosomes: a novel vesicular carrier for enhanced transdermal delivery of an antiHIV agent. *Indian journal of pharmaceutical sciences*, *66*(1), 72-81.
14. Johnsen, S., Bennett, E., & Jensen, V. G. (1974). Therapeutic effectiveness of oral testosterone. *The Lancet*, *304*(7895), 1473-1475.
15. Kim, S., & Chien, Y.W. (1996). "Toxicity of cationic lipids andcationic polymers in gene delivery", *J. Control.Release 40*, 67-76.
16. Kumar, K. P., Radhika, P. R., & Sivakumar, T. (2010). Ethosomes-a priority in transdermal drug delivery. *International Journal of Advances in Pharmaceutical Sciences*, *1*(2).
17. Lopez-Pinto, J. M., Gonzalez-Rodriguez, M. L., & Rabasco, A. M. (2005). Effect of cholesterol and ethanol on dermal delivery from DPPC liposomes. *International journal of pharmaceutics*, *298*(1), 1-12.
18. Paolino, D., Lucania, G., Mardente, D., Alhaique, F., & Fresta, M. (2005). "Innovative Drug Delivery Systems for theAdministration of Natural Compounds", J. Control.Release, 106, 99-110.
19. Pratima, N. A., & Shailee, T. (2012). Ethosomes: A Novel Tool for Transdermal Drug Delivery. *International Journal of Research in Pharmacy & Science*, *2*(1).
20. Satyam, G., Shivani, S., & Garima, G. (2010). Ethosomes: A novel tool for drug delivery through the skin. *J Pharm Res*, *3*(4), 688-691.
21. Spruance, S. L. (1992, September). The natural history of recurrent oral-facial herpes simplex virus infection. In *Seminars in dermatology* (Vol. 11, No. 3, pp. 200-206).
22. Touitou, E. (1996). "Composition of applying activesubstance to or through the skin", US Patent, 5716638.
23. Touitou, E. (1998). "Composition of applying activesubstance to or through the skin", US Patent, 5540934.
24. Touitou, E., Dayan, N., Levi-Schaffer, F., & Piliponsky, A. (1998). Novel lipid vesicular system for enhanced delivery. *Journal of Lipid Research*, *8*, 113.
25. Touitou, E., Godin, B., Dayan, N., Weiss, C., Piliponsky, A., & Levi-Schaffer, F. (2001). Intracellular delivery mediated by an ethosomal carrier. *Biomaterials*, *22*(22), 3053-3059.
26. Verma, D. D., & Fahr, A. (2004). Synergistic penetration enhancement effect of ethanol and phospholipids on the topical delivery of cyclosporin A. *Journal of controlled release*, *97*(1), 55-66.
27. Verma, D. D., & Fahr, A. (2004). Synergistic penetration enhancement effect of ethanol and phospholipids on the topical delivery of cyclosporin A. *Journal of controlled release*, *97*(1), 55-66.
28. Verma, P., & Pathak, K. (2010). Therapeutic and cosmeceutical potential of ethosomes: An overview. *Journal of advanced pharmaceutical technology & research*, *1*(3), 274-282.