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Ethosomes: A Novel Vesicular Drug Delivery System

Sachin B. Somwanshi*[1], Monali Adke[1], Ramdas T. Dolas[1], Vivekanand A. Kashid[1], Vinayak M. Gaware[2]

[1]Department of Pharmaceutics, P.R.E.S.'s, College of Pharmacy (For Women), Chincholi, Nashik, Maharashtra, India-422 102.
[2]Department of Pharmaceutical Chemistry, P.R.E.S.'s, College of Pharmacy (For Women), Chincholi, Nashik, Maharashtra, India-422 102.

A B S T R A C T

Vesicular drug delivery systems, such as, liposomes and ethosomes are used for increasing the skin penetration of drugs and many cosmetic chemicals. Several methods have been tried to increase the permeation rate of drugs temporarily. One simple and convenient approach is application of drugs in formulation with elastic vesicles or skin enhancers. Ethosomes are noninvasive delivery carriers that enable drugs to reach the deep skin layers and/or the systemic circulation through phospholipid-based elastic nanovesicles, composed of hydroalcoholic or hydro/glycolic phospholipids in which the concentration of alcohols is relatively high. The high concentration of ethanol brings increase in fluidity of lipids hence increase in permeability of the skin and improves the drug penetration. It can interact with the polar head group region of the lipid molecules, resulting in the reduction of the melting point of the stratum corneum lipid, thereby increasing lipid fluidity and cell membrane permeability. The high flexibility of vesicular membranes from the added ethanol permits the elastic vesicles to squeeze themselves through the pores, which are much smaller than their diameters. 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. The scope of this small review is to introduce the novel concept of ethosomes and to describe some approaches, mechanisms and applications of stimulating ethosomal drug delivery system.

Keywords: Ethosomes, liposomes, novel drug delivery, vesicles, phospholipids

A R T I C L E I N F O

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***Corresponding Author**
Sachin B. Somwanshi
Department of Pharmaceutics,
P.R.E.S.'s, College of Pharmacy
(For Women), Chincholi, Nashik-422102.
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1. Introduction

Ethosomes are noninvasive delivery carriers that enable drugs to reach the deep skin layers and/or the systemic circulation. [1]. Ethosomes are soft, malleable vesicles tailored for enhanced delivery of active agents. It has been shown that the physicochemical characteristics of ethosomes allow this vesicular carrier to transport active substances more efficaciously through the stratum corneum into the deeper layers of the skin than conventional liposome [2, 3]. Ethosomes are lipid vesicles containing phospholipids, alcohol (ethanol and isopropyl alcohol) in relatively high concentration and water [4]. The size of Ethosomes can be modulated to range anywhere from 30nm to a few microns. The synergistic effects of combination of phospholipids and high concentration of ethanol in vesicular formulations have been suggested to be responsible for deeper distribution and penetration in the skin lipid bilyers. Ethosomes are mainly used for the delivery of drugs through transdermal route. Lipophilic drugs can pass through the skin but the drugs which are hydrophilic in nature can't pass through. Water soluble drugs either show very less or no permeation. To improve the permeation of drugs through the skin various mechanisms have been investigated, including use of chemical or physical enhancers, such as iontophoresis, sonophoresis, etc. Liposomes, niosomes, transferosomes and ethosomes also have been reported to enhance delivery of drug. [5]

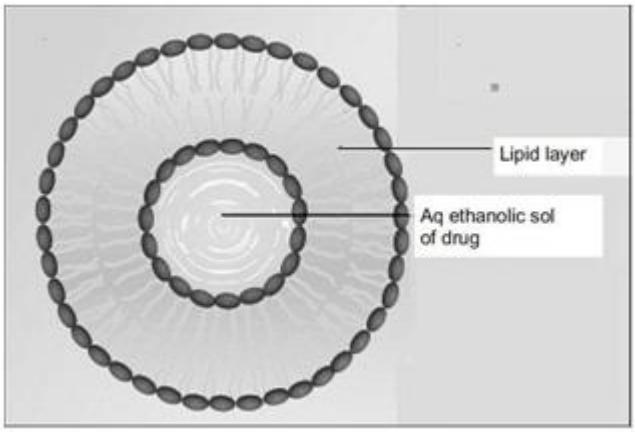

Figure 1: Structure of Ethosomes

2. Composition

Ethosomes are vesicular carrier comprise of hydroalcoholic or hydro/alcoholic/glycolic phospholipids in which the concentration of alcohols or their combination is relatively high. Typically, ethosomes may contain phospholipids with various chemical structures like phosphatidylcholine (PC), hydrogenated PC, phosphatidic acid, phosphatidylserine (PS), phosphatidylethanolamine (PE), phosphatidylglycerol (PPG), phosphatidylinositol(PI), hydrogenated PC, alcohol (ethanolorisopropylalcohol), water and propylene glycol (or other glycols). Such a composition enables delivery of high concentration of active ingredients through skin [6]. Drug delivery can be modulated by altering 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 ranging between 0.1-1% can also be added to the preparation. Examples of alcohols, which can be used, include ethanol and isopropyl alcohol. Among glycols, propylene glycol and Transcutol are generally used. In addition, non-ionic surfactants (PEG-alkyl ethers) can be combined with the phospholipids in these preparations. Cationic lipids like cocoamide, POE alkyl amines, dodecylamine, cetrimide etc. can be added too. The concentration of alcohol in the final product may range from 20 to 50%. The concentration of the non-aqueous phase (alcohol and glycol combination) may range between 22 to 70%.Different additives used in formulation are given in (table 1). [7, 8]

Table 1: Different Additives used in the Ethosomal Formulation

Class	Examples	Uses
Phospholipids	Soya phosphatidyl choline; Egg phosphatidyl choline; Diestearyl phopshatidyl choline	Vesicle forming components
Polyglcerol	Propylene glycol; Transcutol RTM	As a skin penetration enhancer
Alcohol	Ethanol; Isopropyl alcohol	For providing the softness for vesicle membrane; As a skin penetration enhancer
Cholesterol	Cholesterol	For providing the stability for vesicle membrane
Dyes	Rhodamine 123; Rhodamine red	For characterization studies
Vehicles	Carbopol D934	As s gel former

Influence 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 interdigitation effect of ethanol on lipid bilayers, it was commonly believed that vesicles could not coexist with high concentration of ethanol. [9]

Advantages of Ethosomal Drug Delivery System

a. Ethosome composition is safe and the components are approved for pharmaceutical, veterinary and cosmetic use.
b. Enhanced permeation of drug molecules to and through the skin to the systemic circulation. [10]
c. The Ethosomal system is passive, non-invasive and is available for immediate commercialization.
d. The delivery of large molecules (peptides, protein molecule) is possible.
e. It contains non-toxic raw material in formulation.[11]
f. The Ethosomal system is passive, non-invasive and is available for immediate commercialization.
g. Simple method for drug delivery in comparison to Iontophoresis and Phonophoresis and other complicated method. [12]
h. Better stability and solubility of many drugs as compared to conventional vesicles.
i. Relatively smaller size as compared to conventional vesicles.[10]
j. Better patient compliance: can be used in the form of gel, patch.
k. Low risk profile.
l. Ethosomes are platform for the delivery of large and diverse group of drugs. [13]

Disadvantages of Ethosomal Drug Delivery System

a. Loss of product during transfer from organic to water media.
b. Drugs that require high blood levels cannot be administered – limited only to potent molecules, those requiring a daily dose of 10mg or less.
c. If shell locking is ineffective then the coalescence of ethosomes may occur and fall apart on transfer into water and Poor yield. [14, 15, 16]

3. Mechanism of Penetration

The main advantage of ethosomes over liposome 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:

3.1. 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. The intercalation of ethanol into the polar head group environment can result in an increase in the membrane permeability. In addition to the effect of ethanol on stratum corneum structure, the ethosome itself may interact with the stratum corneum barrier.

3.2. Ethosomal 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. In the ethosomes encapsulating drugs, the higher positive zeta potential imparted by the drug can improve skin attachment of the vesicles. While encapsulated drug in classic liposomes remained primarily at the surface of the skin the Ethosomal system was showed to be highly efficient carrier for enhanced drug delivery through the skin due to increased fluidity of the lipid. [17, 18]

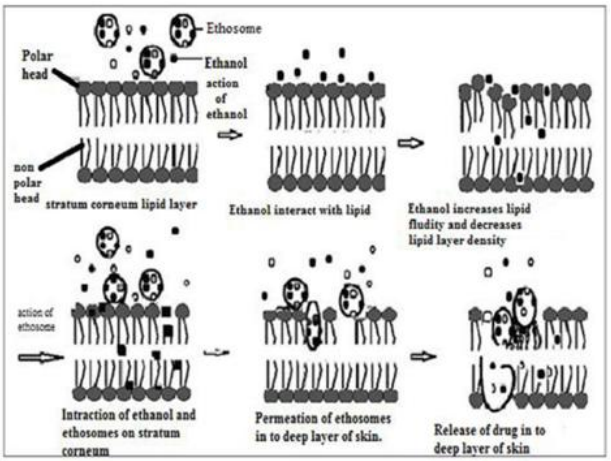

Figure 2: Mechanism for penetration of molecule from Ethosomal Drug Delivery System

4. Preparation of Ethosomes

Ethosomal formulation may be prepared by hot or cold method as described below. Both the methods are convenient, do not require any sophisticated equipment and are easy to scale up at industrial level. [19]

4.1. 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 to desire extend using sonication or extrusion method. Finally, the formulation is stored under refrigeration.

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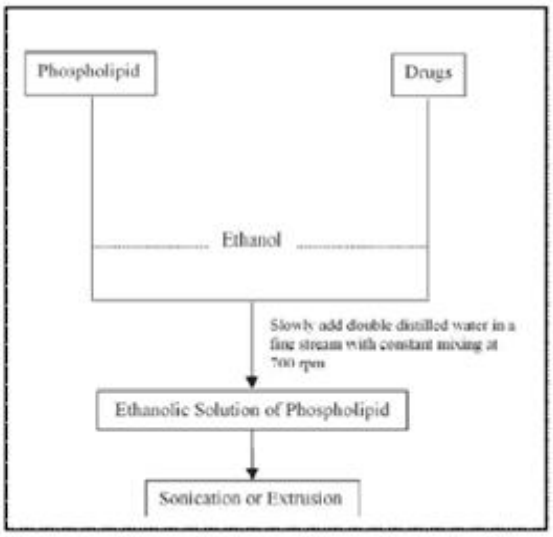

Figure 3: General method for the preparation of ethosomes

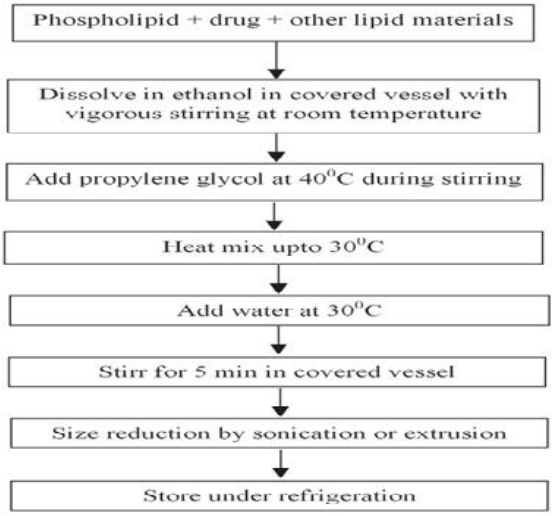

Figure 4: Hot method for the preparation of ethosomes

4.2. Hot Method

In this method phospholipids 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/ hydrophobic properties. The vesicle size of ethosomal formulation can be decreased to the desire extent using probe sonication or extrusion method. [20, 21]

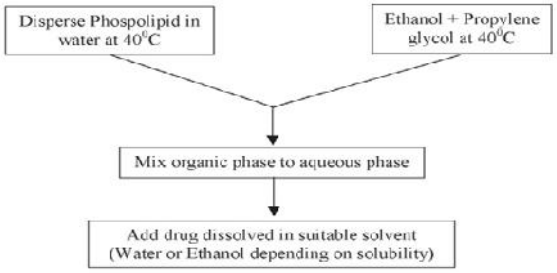

Figure 5: Hot method for the preparation of ethosomes

Physicochemical Characterisation of Ethosomes

Visualization: Visualization of ethosomes can be done using transmission electron microscopy (TEM) and by scanning electron microscopy (SEM). [22]

Figure 6: Visualization of ethosomes by TEM

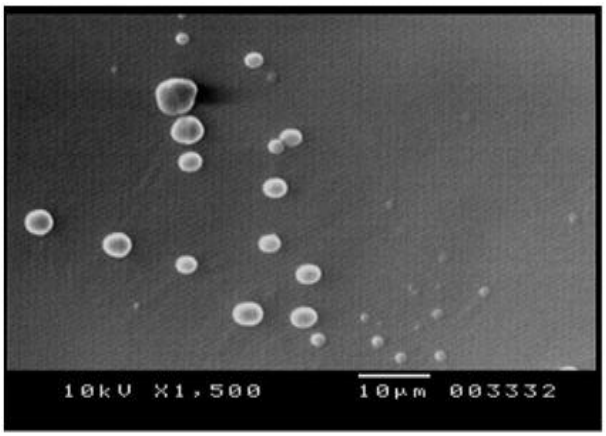

Figure 7: Scanning electron microscope photo-micrograph

Vesicle size and Zeta potential:

Particle size and zeta potential can be determined by dynamic light scattering (DLS) using a computerized inspection system and photon correlation spectroscopy (PCS).

Differential scanning calorimertry (DSC):

Transition temperature (Tm) of the vesicular lipid systems was determined by using the Mettler DSC 60 computerized with Mettler Toledo star software system (Mettler, Switzerland).The transition temperature was measured by using the aluminum crucibles at a heating rate 10 degree/minute, within a temperature range from 20˚C–300˚C.

Surface Tension Activity Measurement:

The surface tension activity of drug in aqueous solution can be measured by the ring method in a Du Nouy ring tensiometer.

Entrapment Efficiency:

Differential scanning calorimetry thermograms and anisotropy measurement of AVPC (a fluorescent analog of phosphatidylcholine), revealed that ethosomes possessed lower Tm compared to classical liposomes and that the bilayers had a high degree of fluidity. This imparted a soft and malleable character to the vesicles. Godin and Touitou [23] used confocal laser scanning microscopy (CLSM) to show that ethosomes can efficiently entrap both hydrophobic and hydrophilic fluorescent probes. Also entrapment efficiency of drug can be measured by the ultra centrifugation technique.[24]

Penetration and Permeation Studies: Depth of penetration from ethosomes can be visualized by confocal laser scanning.

Vesicle Stability:

The stability of vesicles can be determined by assessing the size and structure of the vesicles over time. Mean size is measured by DLS and structure changes are observed by TEM. [19, 25, 26]

Degree of deformability

The elasticity of ethosomal vesicle membrane can be determined by extrusion method. The ethosomal formulation is extruded through the filter membrane (pore diameter 50nm) using stainless steel filter holder of diameter 25nm, by applying a pressure of 2.5bar.

Turbidity: It can be measured by nephloturbidometer [27].

5. Evaluation Tests

Filter Membrane-Vesicle Interaction Study by Scanning Electron 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). [28]

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 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-, and 24-hour time intervals and analyzed by high performance liquid chromatography (HPLC) assay.

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.

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. [19]

Vesicle Skin Interaction Study

For evaluating the mechanism of better skin permeation of ethosomal formulation different visualization techniques e.g. transmission electron microscopy, eosin-hematoxylin staining, fluorescence microscopy and confocal scanning laser microscopy (CSLM) have been used. Often, when used in combination these visualization techniques gave better idea about structure modulation and penetration pathways of vesicles [29, 30].

Statistical Analysis

Statistical significance of all the data generated was tested by employing ANOVA followed by studentized range test. A confidence limit of $P < .05$ was fixed for interpretation of the results using the software PRISM (GraphPad) [31]

Table 2: Evaluation Parameters and Instruments / Methods Used In Ethosomes.

Parameters	Instruments/Methods used	Importance
Vesicle Shape	Transmission Electron Microscopy (TEM) Scanning Electron Microscopy (SEM)	Determines skin penetration
Vesicle Size and Zeta Potential	Dynamic Light Scattering (DLS), Photon Correlation Spectroscopy (PCS) and Zeta Meter	Determines skin penetration and stability of vesicles

Transition Temperature	Differential Scanning Calorimetry (DSC)	Determines transition temperature of lipid vesicles
Drug Entrapment	Ultracentrifugation Technique	Suitability of method
Drug Content	UV Spectrophotometer, High Performance Liquid Chromatographic Method (HPLC)	Important in deciding the amount of vesicle preparation to be used
Surface Tension Measurement	Ring Method in a Du Nouy ring tensiometer	Determines surface tension activity of drug in aqueous solution
Stability Studies	Dynamic Light Scattering (DLS), Transmission Electron Microscopy (TEM)	To determine the shelf-life of vesicle formulation
Skin Permeation Studies	Confocal Laser Scanning Microscopy (CLSM)	Determines rate of drug transport through skin
In-vitro dissolution	Franz diffusion cell	Determines the drug release rate from vesicle

Application of Ethosomes as A Drug Carrier

Various studies employing ethosomal formulation have shown better skin permeability of drugs. Ethosomes are mainly used as replacement of liposomes. Ethosomes can be used for transdermal delivery of hydrophilic and impermeable drugs through the skin. Following drugs have been used with ethosomal carrier. [2]

Table 3: Ethosome as a Drug Carrier

Name of drug	Drug incorporated in ethosomal carrier	Uses
Acyclovir	Improved skin permeation. Improved in pharmacodynamics profile. Improved in biological activity two to three times.	Treatment of Herpes labialis
Anti-HIV agents (Zidovudine, Lamivudine)	Reduced drug toxicity. Prolonging drug action. Improved transdermal flux. Affected the normal histology of skin. Improved in biological activity two to three times.	Anti-HIV
Azelaic acid Ammonium glycyrrhizinate	Prolong drug release. Improved in biological anti-inflammatory activity. Improved dermal deposition exhibiting sustained release.	Treatment of various inflammatory based skin diseases
Bacitracin	Increased bioavailability. Improved dermal deposition. Improved intracellular delivery.	Anti-bacterial
Cannabidol	Improve bioavailability. Increased skin permeation. Improved GIT degradation.	Treatment of Rhematoid arthritis
Cyclosporin A	Prolong drug action. Improved bioavailability. Improved skin deposition.	Treatment of inflammatory skin
DNA	Better expression of genes. Selective targeting to dermal cells.	Treatment of genetic disorders
Erythromycin	Better cellular uptake	Anti-microbial
Fluconazole	Better skin permeation	Treatment of Candidiasis
Insulin8	Provide control release. Significant decrease in blood glucose level.	Treatment of diabetes
Minoxidol	Pilocebaceous targeting. Accumulation in skin increased significantly.	Treatment of baldness
Methotrexate	Better skin permeation	Treatment of Proriasis
NSAIDs (Diclofenac)	Selective delivery of drug to described side for prolong period of time	Analgesic and anti-inflammatory
Testosterone	Improved oral bioavailability. Reduced side effects.	Steroidal hormone

1. Pilosebaceous targeting

Hair follicles and sebaceous glands are increasingly being recognized as potentially significant elements in the percutaneous drug delivery. Furthermore, considerable attention has also been focused on exploiting the follicles as transport shunts for systemic drug delivery. Minoxidil is a lipid-soluble drug used topically on the scalp for the treatment of baldness by pilosebacious delivery. Interest in pilosebaceous units has been directed towards their use as depots for localized therapy, particularly for the treatment of follicle-related disorders such as acne or alopecia. [32]

2. Delivery of Anti-Viral Drugs

Zidovudine is a potent antiviral agent acting on acquired immunodeficiency virus. Oral administration of zidovudine is associated with strong side effects. Therefore, an adequate zero order delivery of zidovudine is desired to maintain expected anti-AIDS effect. Jain *et al.* concluded

that ethosomes could increase the transdermal flux, prolong the release and present an attractive route for sustained delivery of zidovudine. Acyclovir is another anti-viral drug that widely used topically for treatment of Herpes labialis .The conventional marketed acyclovir external formulation is associated with poor skin penetration of hydrophilic acyclovir to dermal layer resulting in weak therapeutic efficiency. It is reported that the replication of virus takes place at the basal dermis. To overcome the problem associated with conventional topical preparation of acyclovir. Horwitz *et al.* formulated the acyclovir ethosomal formulation for dermal delivery. The results showed that shorter healing time and higher percentage of abortive lesions were observed when acyclovir was loaded into ethosomes.

3. Topical Delivery of DNA

Many environmental pathogens attempt to enter the body through the skin. Skin therefore, has evolved into an excellent protective barrier, which is also immunologically active and able to express the gene. On the basis of above facts another important application of ethosomes is to use them for topical delivery of DNA molecules to express genes in skin cells. Touitou et al. in their study encapsulated the GFP-CMV-driven transfecting construct into ethosomal formulation. They applied this formulation to the dorsal skin of 5-week male CD-1 nude mice for 48 hr. After 48 hr, treated skin was removed and penetration of green fluorescent protein (GFP) formulation was observed by CLSM. It was observed that topically applied ethosomes-GFP-CMV-driven transfecting construct enabled efficient delivery and expression of genes in skin cells. It was suggested that ethosomes could be used as carriers for gene therapy applications that require transient expression of genes. These results also showed the possibility of using ethosomes for effective transdermal immunization. Gupta et al. recently reported immunization potential using transfersomal formulation. Hence, better skin permeation ability of ethosomes opens the possibility of using these dosage forms for delivery of immunizing agents.

4. 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. The risk of failure of treatment is known to increase with each pill missed. Touitou *et al.* compared the skin permeation potential of testosterone ethosomes (Testosome) across rabbit pinna skin with marketed transdermal patch of testosterone (Testoderm patch, Alza). They observed nearly 30-times higher skin permeation of testosterone from ethosomal formulation as compared to that marketed formulation.

5. 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.

6. Transcellular Delivery

Touitou *et al.* in their study demonstrated better intracellular uptake of bacitracin, DNA and eryth using CLSM and FACS techniques in different cell lines. Better cellular uptake of anti-HIV drug zidovudine and lamivudine in MT-2 cell line from ethosomes as compared to the marketed formulation suggested ethosomes to be an attractive clinical alternative for anti-HIV therapy.

7. Delivery of Anti-Arthritis Drug

Topical delivery of anti-arthritis drug is a better option for its site-specific delivery and overcomes the problem associated with conventional oral therapy. Cannabidol (CBD) is a recently developed drug candidate for treating rheumatoid arthritis. Lodzki *et al.* prepared CBD ethosomal formulation for transdermal delivery. Results shows significantly increased in biological anti-inflammatory activity of CBD-ethosomal formulation was observed when tested by carrageenan induced rat paw edema model. It was concluded encapsulation of CBD in ethosomes significantly increased its skin permeation, accumulation and hence it's biological activity.

8. Delivery of Problematic drug molecules

The oral delivery of large biogenic molecules such as peptides or proteins is difficult because they are completely degraded in the GI tract. Non-invasive delivery of proteins is a better option for overcoming the problems associated with oral delivery. Dkeidek and Touitou investigated the effect of ethosomal insulin delivery in lowering blood glucose levels (BGL) *in vivo* in normal and diabetic SDI rats. In this study a Hill Top patch containing Insulin ethosomes was applied on the abdominal area of an overnight fated rat. The result showed that insulin delivered from this patch produced a significant decrease (up to 60%) in BGL in both normal and diabetic rats. On the other hand, insulin application from a control formulation was not able to reduce the BGL. Verma and Fah reported the cyclosporine. An ethosomal formulation for the treatment of inflammatory skin disease like psoriasis, atopic dermatitis and disease of hair follicle like alopecia areata etc. Paolino *et al.* investigated the potential application of ethosomes for dermal delivery of ammonium glycyrrhizinate. Ammonium glycyrrhizinate is naturally occurring triterpenes obtained from Glycyrrhizinate Glabra and useful for the treatment of various inflammatory based skin diseases.

9. Delivery of Antibiotics

Topical delivery of antibiotics is a better choice for increasing the therapeutic efficacy of these agents. Conventional oral therapy causes several allergic reactions along with several side effects. Conventional external preparations possess low permeability to deep skin layers and subdermal tissues. Ethosomes can circumvent this problem by delivering sufficient quantity of antibiotic into deeper layers of skin. Ethosomes penetrate rapidly through the epidermis and bring appreciable amount of drugs into the deeper layer of skin and suppress infection at their root. With this purpose in mind Godin and Touitou prepared bacitracin and erythromycin loaded ethosomal formulation for dermal and intracellular delivery. The results of this study showed that the ethosomal formulation of antibiotic

could be highly efficient and would overcome the problems associated with conventional therapy. [2, 19, 33, 34]

9.1. Cosmeceutical Applications of Ethosomes

The advantage of applying ethosomes in cosmaceuticals is not only to increase the stability of the cosmetic chemicals and decrease skin irritation from the irritating cosmetic chemicals, but also for transdermal permeation enhancement, especially in the elastic forms. However, the compositions and sizes of the vesicles are the main factors to be considered to obtain these advantages of the elastic vesicles for cosmaceuticals applications.[35] Topical administration of many antioxidants is one of the several approaches to diminish oxidative injury in the skin for cosmetic and cosmaceuticals applications. However, antioxidants are usually not stable and can be degraded by exposing to light. These antioxidants include vitamin E, vitamin C, and flavonoids. Vitamin E is one of the major exogenous lipophilic antioxidants, which is usually found in tissues. Its topical application can enhance the skin protection from exogenous oxidants. When vitamin E is added to cosmetics and many dermatological products, it is found to decrease the production of lipid peroxides in the epidermis as well as to protect against UV exposure and some destructive chemicals and physical agents. In order to deliver vitamin E into the deeper layer of SC, Koli *et al*., 2008, have formulated 'Anti-oxidant Ethosomes for Topical Delivery Utilizing the Synergistic Properties of Vitamin A Palmitate, Vitamin E, and Vitamin C,' and the findings have revealed that the synergistic interaction of Vitamin C in the aqueous core and Vitamin A and E in the lipid bilayer, provide complete protection from the oxidation of the ethosome formulations. [36] This has suggested that although elastic and non-elastic liposomes are not beneficial for the delivery of α-tocopherol through the skin, the entrapment of the vitamin either in elastic or non-elastic liposomes can increase its photo-stability under UVB irradiation.In a study by Esposito *et al*., 2004, ethosomes and liposome of azelaic acid (Anti-keratinizing agent used in the treatment of acne) were prepared as a topical vehicle (gel) and the result demonstrated that ETHOS 40 could be responsible for a higher azelaic acid, with respect to ETHOS 20 and liposomes [37]. A USA company, Osmotic Inc., reported new cellulite cream called lipoduction, which used ethosome technology that penetrated the skin lipid barrier and delivered ingredients directly into the fat cells. Ingredients in lipoduction improved the appearance of cellulite by up to 80% in less than 60 days.

6. Stability of Ethosomes

Stability of the formulations was evaluated in terms of the 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 stearic 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 more leaky, 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 phospholipids 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. [38]

Future Perspectives

Introduction of ethosomes has initiated new vicinity in vesicular probe for the delivery of large and diverse group of drugs. A promising future of ethosomes in making transdermal delivery of various agents becomes 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. Studies will continue to further improve the skin delivery of drugs using lipid vesicles. Special emphasis seems to be given to the skin delivery of proteins and other macromolecules and for transcutaneous immunization. The near future also holds the emergence of new commercial ethosome-based topical products. Thus, it can be a logical conclusion that ethosomal formulations possess promising future in effective dermal/transdermal delivery of bioactive agents.

7. Conclusion

It can be easily concluded that ethosomes are characterized by simplicity in their preparation, safety and efficacy and provide better skin permeation for active drugs. Ethosomes have been found to be much more efficient at delivering drug to the skin. Ethosomes have been tested to encapsulate hydrophilic drugs, cationic drugs, proteins and peptides. Most of the device-induced transdermal drug delivery techniques are still in the early stages of commercialization. Ethosomal drug deliver have high patient compliance as it is administrated in semisolid form (gel or cream) and also

its composition is safe and the components are approved for pharmaceutical, veterinary and cosmetic use.

8. References

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