Therapeutic and cosmeceutical potential of ethosomes: An overview

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Introduction

Human skin is an effective, selective barrier to chemical permeation, although the skin as a route for delivery can offer many advantages, including avoidance of first-pass metabolism, lower fluctuations in plasma drug levels, targeting of the active ingredient for a local effect, and good patient compliance. Water soluble molecules and drugs are normally not able to cross the skin as the skin is a natural barrier to water. The stratum corneum is composed of insoluble bundled keratins surrounded by a cell envelope, stabilized by cross-linked proteins and covalently bound lipids as shown in Figure 1.

In general, the epidermis (specifically the stratum corneum) provides the major control element; most small, water-soluble, and non-electrolytes diffuse into the systemic circulation a thousand times more rapidly when the horny layer is present. Thus, to maximise the flux of the drug, the barrier hindrance is reduced by various approaches. Several technological advances have been made in the recent decades to overcome skin barrier properties. Examples include physical means such as iontophoresis, sonophoresis, microneedles, and chemical means, using penetration enhancers and biochemical means, such as, liposomal vesicles and enzyme inhibition. The physical means like iontophoresis, microneedles, and sonophoresis are relatively complicated to use, and will affect patient compliance. The use of chemical enhancers such as surfactants and organic solvents induce irritation, cause damage, and reduce skin barrier function, therefore, it is desirable to deliver the therapeutic agents that maintain the normal skin barrier function without the aid of a chemical enhancer. One such approach is the use of vesicular systems. In the past decade, topical delivery of drugs by liposomal formulation has evoked considerable interest. Deformable liposomes and transferosomes were the first generation of elastic vesicles introduced by Ceve and Blume, in 1992, and were reported to penetrate intact skin while carrying a therapeutic concentration of drugs, when applied under nonoccluded conditions. The drug, encapsulated in lipid vesicles, prepared from phospholipids and nonionic surfactants is known to be transported into and across the skin. The lipids...
present in the skin contribute to the barrier properties of the skin and prevent the systemic absorption of drugs. Due to the amphiphilic nature, lipid vesicles may serve as non-toxic penetration enhancers for drugs. In addition, the 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 a significant quantity of drugs across the skin, thus enhancing the systemic absorption of drugs. The use of lipid vesicles in the delivery system for skin treatment has attracted increasing attention in recent years, however, it is generally agreed that classic liposomes are of little or no value as carriers for drug delivery, because they do not penetrate the skin deeply, but rather remain confined to the upper layer of the stratum corneum; only specifically designed vesicles are shown to enhance permeation into the stratum corneum barrier. It has been investigated and reported that lipid vesicular systems embodying ethanol in relatively high concentrations, called ethosomes, are very efficient at enhancing the skin permeation of a number of drugs.

**ETHOSOMES**

Ethosomes were developed by Touitou et al., 1997, as additional novel lipid carriers composed of ethanol, phospholipids, and water. They are reported to improve the skin delivery of various drugs. Ethanol is an efficient permeation enhancer that is believed to act by affecting the intercellular region of the stratum corneum. Ethosomes are soft malleable vesicles composed mainly of phospholipids, ethanol (relatively high concentration), and water. These soft vesicles represent novel vesicles carriers for enhanced delivery through the skin. The size of the ethosomes vesicles can be modulated from tens of nanometers to microns as shown in Figure 2.

Ethosomes are non-invasive delivery carriers that enable drugs to reach the deep skin layers and/or the systemic circulation. The high concentration of ethanol makes the ethosomes unique, as ethanol is known for its disturbance of skin lipid bilayer organization. Therefore, when integrated into a vesicles membrane; it gives the vesicle the ability to penetrate the stratum corneum. Also, because of their high ethanol concentration, the lipid membrane is packed less tightly than the conventional vesicles, although it has equivalent stability, allowing a more malleable structure and improves the drug distribution ability in the stratum corneum lipids.

**Ethosomes as Carriers for Dermal and Transdermal Drug Delivery**

Ethosomes were reported to be effective at delivering molecules to and through the skin to the systemic circulation. The ethosomal carrier was previously tested for dermal delivery of the antiviral drug acyclovir. The authors in the study reported a two-armed, double-blinded, randomized clinical trial, and demonstrated the efficiency of the ethosomal 5% acyclovir system, compared to a 5% acyclovir cream (Zovirax, ZC) for the topical treatment of herpetic infection.

Enhanced delivery of chemicals from the ethosomal carrier was observed in permeation experiments with fluorescent probes. The amphiphilic fluorescent probe D-289 was used to study skin penetration from trihexphenyl HCl ethosomes into nude mouse skin, after the non-occlusive application (Dayan and Touitou 2000) results showed that classic liposomes did not facilitate probe penetration into this skin, rather, resulted in only a small reservoir in the upper layers of skin. Using hydroethanolic solutions, a relatively deep penetration, but of relatively very low fluorescent activity was observed. The use of the ethosomal system resulted in increase in both depth and fluorescent activity. Ethosomes have also been reported to improve in vivo and in vitro skin delivery of many drugs both under occlusive and non-occlusive conditions.

**Mechanism of Action of the Ethosomal Drug Delivery System**

A synergistic mechanism was suggested between ethanol, vesicles, and skin lipids. The enhanced delivery of actives

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**Figure 1:** Simplified diagram of skin

**Figure 2:** Proposed diagram of Ethosomes
using ethosomes over liposomes can be ascribed to an interaction between ethosomes and skin lipids. A possible mechanism for this interaction has been proposed.

From Figure 3, it is thought that the first part of the mechanism is due to the ethanol effect, where ethanol interacts with the lipid molecules in the polar head group region resulting in a reduction in the transition temperature of the lipids in the stratum corneum, increasing their fluidity and decreasing the density of the lipid multilayer. This is followed by the ‘ethosome effect,’ which includes lipid penetration and permeation by the opening of new pathways, due to the malleability and fusion of ethosomes with skin lipids, resulting in the release of the drug into the deep layers of the skin. Ethanol may also provide vesicles with soft flexible characteristics, which allow them to penetrate more easily into the deeper layers of the skin. The release of the drug in the deep layers of the skin and its transdermal absorption could then be the result of a fusion of ethosomes, with skin lipids and drug release at various points along the penetration pathway.\(^\text{[13]}\)

**Commercial Products Powered by Ethosomes bringing Novelty in the World Market**
The commercialization of ethosome technology began in 2000, and it is a rapidly evolving field. There are now two companies exclusively devoted to product development, using ethosomes. Many large pharmaceutical houses and cosmetic firms are also engaged in active research and development. The list of some commercial products based on ethosomal technology are listed in Table 1.

**Advantages of Ethosomal Drug Delivery**
In comparison to other transdermal and dermal delivery systems,
- Ethosomes enhance permeation of the drug through skin transdermal and dermal delivery.
- Ethosomes are platforms for the delivery of large and diverse groups of drugs (peptides, protein molecules).
- Ethosomal systems are much more efficient at delivering a fluorescent probe (quantum dots) to the skin in terms of quantity and depth.
- Low risk profile — The technology has no large-scale drug development risk, as the toxicological profiles of the ethosome components are well-documented in the scientific literature.
- High patient compliance — The ethosome drugs are administrated in a semisolid form (gel or cream), producing high patient compliance. In contrast, iontophoresis and phonophoresis are relatively complicated to use, which will affect patient compliance.
- High market attractiveness for products with proprietary technology. Relatively simple to manufacture with no complicated technical investments required for the production of ethosomes.
- The ethosomes system is passive, non-passive, and available for immediate commercialization.
- Various applications in the pharmaceutical, veterinary, and cosmetic fields.

**Methods of Preparation of Ethosomes**
The literature reports various methods for the preparation of ethosomes and some commonly used methods have been compiled in the proceeding text.

**Hot method**
The drug is dissolved in a mixture of ethanol and propylene glycol and the mixture is added to the phospholipid

![Figure 3: Proposed mechanism of penetration of ethosomal drug delivery system](image)
Verma and Pathak: Ethosomal drug delivery system

**Table 1: Commercial products based on ethosomal technique**

| Name of the product | Uses                                                                 | Manufacturer                     |
|---------------------|----------------------------------------------------------------------|----------------------------------|
| 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                   |
| 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. Skin permeation experiments showed that the cream retained its initial penetration enhancing properties even after three years | Trima, Israel                     |
| 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, U.S. |
| Noicellex           | Topical anti-cellulite cream                                        | Novel Therapeutic Technologies, Israel |
| Skin genuity        | Powerful cellulite buster, reduces orange peel                       | Physonics, Nottingham, UK         |

dispersion in water at 40°C. After mixing for five minutes the preparation is sonicated at 4°C for three cycles of five minutes, with a rest of five minutes between each cycle, using the Probe Sonicator. The formulation is then homogenized at 15,000 psi pressure, in three cycles, using a high pressure homogenizer to get nano-sized ethosomes. \[14\]

**Cold method**

This is the most common and widely used method for ethosomal preparation. The phospholipids, drug, and other lipid materials are dissolved in ethanol, in a covered vessel, at room temperature, with vigorous stirring. The mixture is heated up to 30°C in a water bath. The water is heated to 30°C in separate vessel, and added to the above mixture and then stirred for five minutes in a covered vessel. The vesicle size of the ethosomal formulation can be decreased if desired, to extend using the sonication or extrusion. Finally the formulation must be properly stored under refrigeration.

**Classic Mechanical Dispersion Method**

Soya phosphotidylcholine 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 vaccum overnight. Hydration is done with different concentration of hydroethanolic mixture containing drug by rotating the flask at suitable temperature. \[15,16\]

**Classic method**

The phospholipid and drug are dissolved in ethanol and heated to 30°C±1°C in a water bath. Double distilled water is added in a fine stream to the lipid mixture, with constant stirring at 700 rpm, in a closed vessel. The resulting vesicle suspension is homogenized by passing through a polycarbonate membrane using a hand extruder for three cycles. \[17\]

**Various Methods for Characterization of Ethosomes**

The vesicle shape can be easily visualized by using a photomicrograph, or transmission electron microscopy (TEM) and scanning electron microscopy (SEM) micrographs. \[18,19\] The vesicle size and zeta potential of the formulation can be measured with the Zeta meter. \[20\] The size of the ethosomes range between tens of nanometers to microns and it is influenced by the composition of the formulation. Various factors affect the size and zeta potential of the ethosomes. Reduction in mean vesicle diameter is due to the presence of ethanol, as it causes a modification of the net charge of the system and confers it some degree of stearic stabilization that may finally lead to a decrease in the mean vesicle size, \[21\] while the size of the vesicles increase with increasing the phospholipid concentration. This can be explained in terms of the tendency of lipid coalesces at high lipid concentration. \[22,23\]

The transition temperature of the vesicular lipid systems can be determined by using differential scanning calorimetry, which also detects ethanol-skin phospholipid interaction, a characteristic attributed to the fluidizing effect of ethanol on the phospholipid bilayers. \[24\]

The entrapment efficiency of ethosomes can be measured by the ultracentrifugation technique. The ability of ethosomes to efficiently entrap lipophilic and hydrophilic drugs can be explained by the high degree of lamellarity and the presence of ethanol in the vesicles. In addition, ethosomal formulations possess greater entrapment capability than liposomes. \[25\]

The ability of the ethosomal preparation to penetrate into the skin layers can be determined by using confocal laser
scanning microscopy. In vitro and in vivo skin permeation studies have demonstrated the ability of the ethosomal formulation to enhance permeation of both hydrophobic and hydrophilic molecules as compared to conventional liposomes. Different workers have reported a 5 – 10 fold better skin permeation of drugs formulated in ethosomes, as compared to the conventional liposomal formulation.[26,27]

Therapeutic Applications of Ethosomes

Mishra et al., 2007, reported ethosomes for transcutaneous immunization, and antigen-loaded ethosomes for transcutaneous immunization against Hepatitis B were prepared and characterized, which showed greater entrapment efficiency, optimal size range, and a unilamellar, spherical shape in comparison to conventional liposomes. Spectral bio imaging and flow cytometric studies showed an efficient uptake of HBsAg-loaded ethosomes by murine dendritic cells in vitro, reaching a peak by 180 minutes. The transcutaneous delivery potential of the antigen-loaded antigen system, using human cadaver skin, demonstrated a much higher skin permeation of the antigen in comparison to the conventional liposomes and soluble antigen preparation. The topically applied HBsAg-loaded ethosomes in mice showed a robust systemic and mucosal humoral immune response compared to the intramuscularly administered alum-adsorbed HBsAg suspension, the topically applied plain HBsAg solution, and the hydroethanolic (25%) HBsAg solution. HBsAg-loaded ethosomes are able to generate a protective immune response and their ability to transverse and target the immunological milieu of the skin finds a potential application in the development of a transcutaneous vaccine against Hepatitis B virus.[28]

Oral administration of hormones is associated with complications like high first pass metabolism, low oral bioavailability, and several dose-dependent side effects such as virilization, acne, and gynecomastia. In addition along with these side effects, oral hormonal preparations rely highly on patient compliance. The risk of failure of treatment is known to increase with each pill missed. Touitou et al., 2000,[29] compared the skin permeation potential of testosterone ethosomes (Testosome) across rabbit pinna skin, with the marketed transdermal patch of testosterone (Testoderm® patch, Alza corporation, California). The authors observed nearly 30 times higher skin permeation of testosterone from the ethosomal formulation as compared to the marketed formulation. The AUC and Cmax of testosterone significantly improved after the application of Testosome as compared to Testoderm®. Hence, both in vitro and in vivo studies demonstrated improved skin permeation and bioavailability of testosterone from the ethosomal formulation. This group, in their further study, designed a testosterone non-patch formulation to reduce the area of application. They found that with ethosomal testosterone formulation, the area of application required to produce the effective plasma concentration was 10 times less than that required by the commercial gel (AndroG, US) formulation.

Lodzki et al., 2003,[30] prepared the CBD-ethosomal formulation for transdermal delivery of cannabinol for the treatment of rheumatoid arthritis. Results of the skin deposition study showed significant accumulation of Cannabidiol (CBD) in the skin, and underlying muscles after application of CBD-ethosomal formulation to the abdomen of mice. A plasma concentration study showed that a steady state level was reached in 24 hours, which was maintained through 72 hours. A significant increase in biological anti-inflammatory activity of CBD-ethosomal formulation was observed when tested by using the carrageenan-induced rat paw edema model. Finally, it was concluded that encapsulation of CBD in ethosomes significantly increased its skin permeation, accumulation, and hence, its biological activity.

In another study, Dayan and Touitou, 2001, prepared ethosomal formulation of the psychoactive drug trihexyphenidyl hydrochloride (THP) and compared its delivery with that with the classical liposomal formulation for the treatment of parkinsons disease. THP is an M1 muscarinic receptors antagonist and used in the treatment of Parkinson disease. THP has a short biological half-life (3 hours) and its oral administration is difficult due to motor disorders and neurological manifestations associated with parkinsonian syndrome. THP ethosomal formulation, when visualized under transmission and scanning electron microscopes, were viewed as small phospholipid vesicles. The value of the transdermal flux of THP through nude mouse skin from ethosomes was 87-, 51-, and 4.5-times higher than that from liposome, phosphate buffer, and hydroethanolic solution, respectively. The quantity of THP remaining in the skin at the end of 18 hours was significantly higher after the application of ethosomes than after the application of liposome or hydroethanolic solution (control). These results indicated the better skin permeation potential of ethosomal-THP formulation and its use for the better management of Parkinson disease.

Yet another report on methotrexate an anti-psoriatic, anti-neoplastic, highly hydrosoluble agent with limited transdermal permeation was researched by Dubey et al. 2007. The authors developed optimized ethosomes- loaded methotrexate and the skin permeation profile of the developed formulation revealed an enhanced permeation of rhodamine red loaded formulation to the deeper layers of the skin. The formulation retained its penetration power after storage and the vesicle skin interaction study also highlighted the penetration enhancing effect of ethosomes, with some visual penetration pathways and cornocyte swelling.

In addition to improved transdermal delivery by ethosomes,
investigations on dermal delivery have also been cited in literature. Paolino et al., 2005,[31] investigated the potential application of ethosomes for dermal delivery of ammonium glycyrrhizinate. Ammonium is useful for the treatment of various inflammatory based skin diseases. In vitro skin permeation experiments have shown that a significantly higher cumulative amount of drug has permeated from ethosomes (63.2%) than from the hydroalcoholic solution (22.3%) and aqueous solution (8.9%) of ammonium glycyrrhizinate. Ethosomal formulation showed a very good skin tolerability in human volunteers for 48-hour application. Biological anti-edema activity was also significantly enhanced in case of ethosomal formulation as compared to ethanolic or aqueous solution of the drug.

Maiden et al., 2004, prepared and evaluated the minoxidil ethosomal formulation. Minoxidil is a lipid-soluble drug used topically on the scalp for the treatment of baldness. The conventional topical formulation has very poor skin permeation and retention properties. It was found that the quantity of minoxidil accumulated into nude mice skin after application of its ethosomal formulation was 2.0-, 7.0-, and 5.0-fold higher when compared to ethanolic phospholipid dispersion, hydroethanolic solution, and ethanolic solution of the drug, each containing 0.5% of the drug. These results showed the possibility of using ethosomes for pilosebaceous targeting of minoxidil to achieve better clinical efficacy.

Many environmental pathogens attempt to enter the body through the skin. Skin has, therefore, evolved into an excellent protective barrier, which is also immunologically active and able to express the gene. On the basis of the above-mentioned facts another important application of ethosomes, is to use them for topical delivery of DNA molecules, to express genes in the skin cells. Toutou et al., 2003, in their study, encapsulated the GFP-CMV-driven transfecting construct into the ethosomal formulation. They applied this formulation to the dorsal skin of five-week-old, male CD-1 nude mice for 48 hours. After 48 hours, the treated skin was removed and penetration and expression of genes in the skin cells. It was suggested that ethosomes could be used as carriers for gene therapy applications that required transient expression of genes. These results also showed the possibility of using ethosomes for effective transdermal immunization. Gupta et al., 2004,[32] recently reported the immunization potential of using transfersomal formulation. Hence, better skin permeation ability of ethosomes opens the possibility of using these dosage forms for the delivery of immunizing agents. Table 2 is a short compilation of research reports on ethosomes as a carrier for a variety of drugs researched of late.

### Cosmeceutical Applications of Ethosomes

The advantage of applying ethosomes in cosmeceuticals 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.[33] However, the compositions and sizes of the vesicles are the main factors to be considered to obtain these advantages of the elastic vesicles for cosmeceutical applications. Topical administration of many antioxidants is one of the several approaches to diminish oxidative injury in the skin for

### Table 2: A compilation of research reports on ethosomes as a carrier for topical and transdermal delivery of drugs

| Drug | Aim of work | Formulation | Results |
|------|-------------|-------------|---------|
| Lamivudine (Jain et al. 2007)[33] | To improve skin permeation and intracellular uptake of antiviral drug | Suspension | Better intracellular skin delivery, as the ethosomal formulation affected the normal histology of the skin by producing lipid perturbation and increased the intercellular lipid lamellar space in the stratum corneum |
| Erythromycin (Godin et al. 2005)[34] | To treat deep skin and soft tissue bacterial infections by dermal application | Gel | Ethosomal erythromycin applied to the skin of S. aureus infected mice was as effective as systemically administered erythromycin |
| Gold nanoparticles (Presa et al. 2009)[35] | Gold nanoparticles generated in ethosomes bilayers, as revealed by cryo electron tomography | Suspension | Gold nanoparticles encapsulated ethosomes offer a versatile platform for the enhancement of pharmacological efficacy in transdermal and dermal delivery systems |
| Colchicine (Singh et al. 2009)[36] | Elastic liposomal formulation for sustained delivery of colchicine: In vitro characterization and In vivo evaluation of anti gout activity | Suspension | This reveals that elastic liposomal formulation of colchicine possesses a greater potential to enhance skin accumulation, prolong release, and improve the site specificity of colchicine |
| Vitamin A palmitate, vitamin e, vitamin c (Koli et al. 2008)[37] | Development of anti-oxidant ethosomes of vitamin a palmitate, vitamin e, vitamin c for topical delivery | Gel | The anti oxidation of PC was found to increase due to the synergistic interaction of all three together, as compared to individual use |
cosmetic and cosmeceutical 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. 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.\[36\]

In a study by Esposito et al., 2004,\[38\] ethosomes and liposomes 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.

A USA company, Osmotics 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.

**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 ethosomal 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 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 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.\[36,40\]

**Future perspectives**

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 the physician to make the therapy more effective. Ethosomes offer a good opportunity for the non-invasive delivery of small-, medium-, and large-sized drug molecules. The results of the first clinical study of the acyclovir-ethosomal formulation support this conclusion. 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. NTT, Novel Therapeutic Technology Inc., is a biopharmaceutical company with a portfolio of pharmaceutical formulations based on ethosome technology including formulations for the treatment of alopecia, deep skin infection, herpes, hormone deficiencies, inflammation, postoperative nausea, atopic dermatitis, and erectile dysfunction.

**CONCLUSION**

The last decade has shown a huge growth in the application of ethosomal technology to monitor skin permeability. The previously proposed mechanism of penetration enhancement with the ethosomal system suggested that the intercalation of ethanol into the polar head group environment results in increased membrane permeability. The understanding of the mechanisms of absorption and enhancement has improved and different determinants at a molecular level are beginning to be understood. With this it should be possible to achieve bioavailabilities comparable
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