Nanomed. J. 9(4):273-280, Autumn 2022

REVIEW PAPER

Potential of ethosomes for enhanced transdermal drug delivery in skin diseases

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ABSTRACT

Ethosomes are novel ethanolic phospholipid vesicles which are significantly used for the transdermal drug delivery. Ethanol is an efficient permeation enhancer which is used in ethosomes about 20-45%. These are non-invasive in nature and have emerged as an area of active research interest because they significantly lead to enhanced skin penetration, improvement in drug delivery, increased drug entrapment efficiency it can deliver both hydrophilic and lipophilic drugs efficiently. Increased patient compliance etc. The drug penetrates the skin surface and gets absorbed by two phases i.e., the ethanol effect and ethosomes effect. Ethosomes are predominantly being used over liposomes because of their greater penetration rate which is attributed to the high concentration of ethanol. Hence it is an active area of research. The primary aim of the review is to provide a comprehensive account on the methods of preparation, properties, characterization, advantages and applications of ethosomes in the management of several skin diseases.

Keywords: *Ethanol, Ethosomes, Transdermal drug delivery system, Permeation enhancers*

How to cite this article

Kumar B, Sahoo PK. Potential of ethosomes for enhanced transdermal drug delivery in skin diseases. Nanomed J. 2022; 9(4):273-280. DOI: 10.22038/NMJ.2022.66753.1703

INTRODUCTION

Human skin is a multi-layered diverse structure which is composed of three different layers i.e., the stratified, avascular, cellular epidermis, the underlying dermis of connective tissue and the fatty subcutaneous layer or the hypodermis. The uppermost layer of the epidermis is the stratum corneum, also called the horny layer which is a protective barrier. Transdermal drug delivery system because of its non-invasive procedure of administration is gaining importance. It overcomes various limitations of the oral route like first pass metabolism, irritation of the gastrointestinal tract and degradation of the drug by the digestive enzymes. It also provides relief from the painful parenteral drug delivery. It is a Patient compliance mode of drug delivery [1]. Despite all these advantages, low permeability of the skin offers the biggest disadvantage which limits the drug delivery. The skin is an active barrier towards the molecular transport. The stratum corneum restricts the access of drugs across it. For an effective transdermal drug delivery, the drug moiety must permeate across the stratum corneum barrier to reach the targeted site [2,3].

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Note. This manuscript was submitted on May 15, 2022; approved on August 31, 2022

Ethosomes

Ethosomes are soft ethanolic phospholipid vesicular system which were formulated by *Touitou* and colleagues in 1995 [2,4]. They are the novel vesicular systems which are extensively used in the topical and transdermal drug delivery. They are composed of phospholipids, alcohol and water. Alcohol concentration in ethosomes is relatively high. Such a composition enables a higher concentration of the drug to be transported through the skin. A change in the water: alcohol, alcohol: phospholipid ratio can alter the drug delivery. Soya phospholipids are commonly used in a concentration range of about 0.5-10% in ethosomal formulation. These phospholipids can be derived from soybean, egg, synthetic and semi synthetic sources. Cholesterol in a concentration range of 0.1-1% is often used for enhancing the

stability of the ethosomes. Research has revealed that reduced concentration of ethanol leads to an increased size of the ethosomal vesicle [5-8].

Benefits of ethosomal drug delivery [4,5]

• Drugs having various physicochemical qualities, such as big molecules (proteins and peptides), hydrophilic and lipophilic properties, can be successfully administered.
• Increased drug permeation across the skin for transdermal, dermal, and intracellular delivery of the drug.
• The ethosomal formulation's composition is safe, and the excipients are recognized for use in pharmaceutical and cosmetic formulations.
• Increased patient compliance as the ethosomal formulation can be given in form of gel or creams.
• It is a simple method of drug delivery as compared to other tedious techniques like iontophoresis and phonophoresis.
• It can be widely utilised and applied in the fields of pharmaceuticals, veterinary sciences, nutraceutical and cosmetics.
• It is non-invasive method which can be commercialized on a large scale as it does not require any sophisticated equipment.

Mechanism of drug permeation [9]

The main benefit of ethosomes over liposomes is increased drug penetration over the skin. The drug absorption mechanism from the ethosomal system still remains unclear. The drug absorption process from the ethosomal system apparently occurs by two different effects firstly the ethanol effect and secondly ethosomes effect.

Ethanol is a widely used permeability enhancer which increases the rate of permeation across the skin. It permeates into the intercellular lipids which leads to an increased fluidity of lipids and a reduced lipid density in the cell membrane. Increased fluidity of membrane lipids attributed to ethanol present in the ethosomes leads to an increase in skin permeability.

Increased fluidity of membrane lipids allows the ethosomes ethosomes to permeate skin barrier with an ease, where the ethosomes can fuse with the lipids of the skin and they release the drug into the deeper layer of the skin [10].

Methods for preparing ethosomes

There are two methods namely hot and cold method which are commonly used for the production of ethosomes.

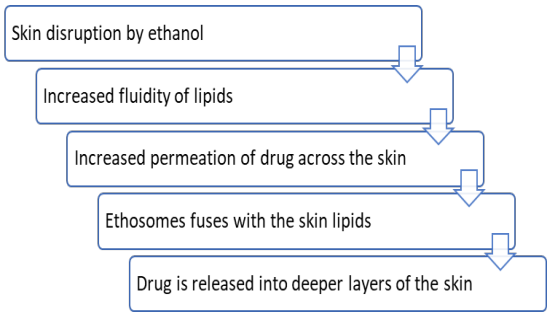

Fig. 1. Mechanism of Drug Release by Ethosomes

Cold Method: This is a frequently used method which is utilized for the preparation of ethosomal formulations. The first step is to dissolve the medication and phospholipids in ethanol in a closed container at room temperature while stirring. Propylene glycol or other polyols are then added to the mixture while it is constantly stirred. A water bath is used to heat the prepared mixture to 30 degrees Celsius. Water is boiled to 30 ° C. in a separate vessel before being introduced to the mixture and stirred for 5 minutes in a closed container. To attain the necessary vesicle size, sonication or extrusion procedures were applied [11, 12].

Hot method: This method involves dispersing phospholipid in water with simultaneously heating in a water bath at 40°C such that a colloidal solution is obtained. Ethanol and propylene glycol are mixed in a separate vessel and heated to 40˚C. When the temperatures of both the mixtures reaches 40˚C, the organic phase is added to the aqueous one. The drug is dissolved in water or ethanol depending on its hydrophilic/ hydrophobic properties. Probe sonication or extrusion methods are used for achieving desired vesicle size [11, 12].

Techniques for characterization of ethosomes

Scanning electron microscopy (SEM) and

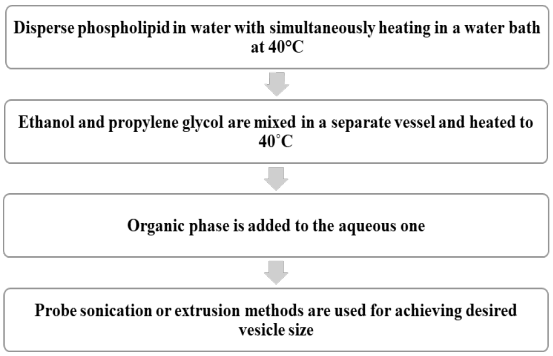

Fig. 2. Cold Method

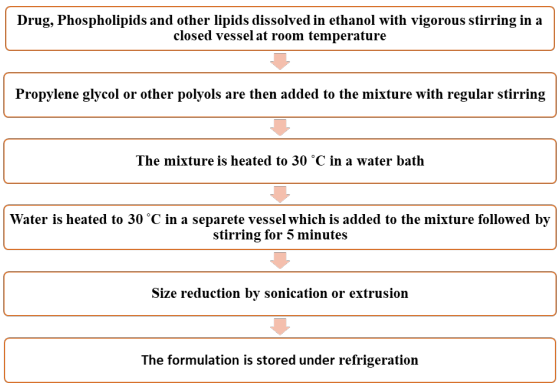

Fig. 3. Hot Method

Transmission electron microscopy (TEM) are utilized for studying the shape and surface morphology of the ethosomal vesicle [13]. Size of the ethosomal vesicle is determined using dynamic light scattering (DLS) and photon correlation spectroscopy (PCS). Zeta potential is helpful in predicting and controlling the stability of the ethosomal vesicle as it is significant indicator of surface charge of the particle [14]. The composition of the ethosomal formulation influences the size of ethosomes. Several other factors also affect the zeta potential and vesicle size. The ethanol present in ethosomes reduces the mean vesicle diameter which is responsible for change in net charges which provides steric stabilization thereby reducing the mean vesicle size. Studies suggest that increased concentration of phospholipids leads to increased vesicle size.

Both hydrophilic and lipophilic drug candidates can be efficiently entrapped by ethosomes which is attributed to ethanol presence and the greater lamellarity degree of ethosomal vesicle. Ultracentrifugation method is used for determining the entrapment efficiency of the ethosomal formulation [12].

UV spectrophotometry is commonly used for determining the drug content in the ethosomes. For quantification High performance liquid chromatography is utilized [16]. Differential scanning calorimetry is used for determining the transition temperature of the vesicles.

For determining the stability of the ethosomal vesicle, mean size of the vesicle is measured using DLS and structural changes are examined using TEM [15]. The amount of ethosomal formulation penetrating the skin layer can be analysed using confocal laser scanning microscopy (CLSM) [16].

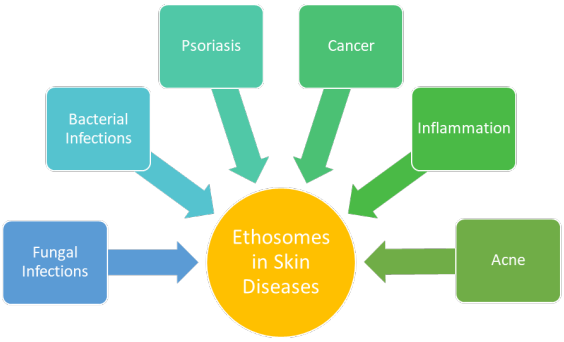

Fig. 4. Application of Ethosomes in Skin diseases

Ethosomes for enhanced drug delivery across the skin for amelioration of skin diseases

Ethosomes offer a significant advantage of increased permeability of an active pharmaceutical ingredient across the skin which helps in providing an enhanced transdermal delivery. Literature suggests that the use of ethosomal formulation in skin diseases can help overcome the stratum corneum barrier which restricts the passage of drugs across the skin. Transdermal drug delivery using ethosomal formulations can help reduce the side effects associated with oral therapies. In several diseases like psoriasis, fungal infection of the skin, cellulitis etc use of topical therapy is more beneficial as compared to oral treatments. Table 1 summarizes the applications of ethosomes as potential drug delivery system in skin diseases.

Ethosomes in fungal infections

Fungal infections are commonly called as mycosis which are caused by a wide range of fungi, living on plants, dirt, surfaces and on the human skin. They lead to several skin infections causing a lot of discomfort to the patient. Ringworm, Cutaneous candidiasis, athlete's foot, jock itch, and yeast infections are some of the common types of fungal skin infection.

Maheshwari *et al*. did a comparative study in which ethosomal and ultra-deformable (UL) liposomal formulations of clotrimazole were formulated, evaluated and compared for transdermal potency. Clotrimazole is an active antifungal agent which is used in the treatment of candidiasis. The entrapment efficiency of the ethosomal formulation was better than the UL liposomal formulation which was due to better solubility and retentivity of clotrimazole in ethanol. Further, the ethosomal formulation provided an enhanced transdermal flux and permeation, decreased the lag time and demonstrated a higher zone of inhibition than the UL liposomal

formulation as well as the marketed formulation. Moreover, the findings showed accumulations on the skin without significant ultrastructural changes on treatment with ethosomal formulation which justifies partial lipid extraction and skin lipid fluidization capability of ethanol thus proving the integrity of ethosomes over UL liposomes [17].

Verma *et al*. created an econazole nitrate ethosomal gel for the management of candidiasis, which was compared to liposomal and hydroethanolic gels. In terms of size, zeta potential, and *in vitro* permeability, ethosomal gel outperformed the other gels. Prepared ethosomal gel formulation of Econazole nitrate significantly showed a higher zone of inhibition which suggest that it has a higher potential of treating candidiasis [18].

In another study, ethosomal gel of Fluconazole was prepared for treating candidiasis. It was compared with the liposomal gel, marketed product and hydroethanolic solution of the drug. The formulated ethosomes showed a good entrapment efficiency, drug diffusion and higher fluidity. Clinical studies revealed that the ethosomal gel reduced the skin lesions from 50-75% which was highest among the other formulated gels [19].

Dave *et al.* developed and optimised herbal ethosomal gels of luliconazole which was capped with neem. The herbal ethosomal gel provided sustained and targeted delivery of the drug and it was having a significant drug release and antifungal activity. Development of ethosomal gel of luliconazole enhanced its bioavailability [20]. Zhang *et al.* developed a multi-ethosome (ME) system loaded with Terbinafine Hydrochloride and used cinnamaldehyde for enhancing penetration. The ME system possessed great targeting efficiency, entrapment efficiency, colloidal stability and was non-irritant to the skin in contrast to the marketed formulation. Further the developed system showed a reduced Minimum Inhibitory Concentration and an improved antifungal effect [21].

Marto *et al.* prepared Griseofulvin ethosomal system to combat the poor solubility of the drug and its low bioavailability from a typical formulation. The prepared formulation had the adequate drug retention, optimal skin diffusion and developed no cytotoxicity. In addition, it provided the desired antifungal activity at a reduced concentration [22].

Ethosomes in bacterial infections

Many different types of bacteria can infect the human skin but the infections caused by Streptococcus pyogenes or Staphylococcus aureus are very common. Depending on the type, location and the age of the infected person, a bacterial infection can take various forms.

In some severe cases, the bacterial infection can invade the blood stream where it can cause sepsis which can be life threatening for a person. Impetigo, cellulitis, folliculitis, erysipelas, carbuncles and furuncles are some common types of bacterial infections which are affecting the human population.

Conventional antibiotic therapy which is administered orally have several side effects and allergic reactions associated with it. Delivering antibiotics through topical route is a better choice for enhancing the therapeutic efficiencies of these drugs. The traditional formulations which are used externally on the skin possess a major drawback of low permeability across the skin layer and sub dermal tissues. Ethosomes are the novel vesicular systems which can easily circumvent the problem of poor permeability by delivering the antibiotics into the deeper layers of skin. They can penetrate rapidly through the epidermis and delivers satisfactory amount of drugs into the deeper layer of skin and crushes the infection at their roots.

Godin *et al.* developed a new system of erythromycin administration through ethosomal carrier to combat the shortcomings of traditionally administered systemic antibiotics and to treat dermal and subdermal infections. Efficacy of ethosomal formulation of erythromycin was found to be better when compared to erythromycin administered intraperitoneally as well as hydroethanolic solution applied locally. The study concluded that the ethosomal formulation of erythromycin was as effective as systemically administered antibiotics [23].

In a study, Khan *et al.* developed an ethosomal gel of ciprofloxacin for topically treating bacterial infections of the skin. [24]. Linezolid (LZD) loaded ethosomes for treating deep skin infection in diabetic patients were developed by Sahu *et al*. These ethosomes were compared with liposomes loaded with LZD and hydroethanolic drug solution. Ethosomes loaded with LZD proved to be better than liposomes and hydroethanolic drug solution. The formulation showed better entrapment efficiency, smaller size and spherical shape, optimal PDI, highest in-vitro drug release and permeation, highest drug deposition, lower irritability, and better antimicrobial effects against S. aureus skin infection in diabetic rats [25].

Ethosomes for psoriasis

Psoriasis is a chronic, persistent anti-

inflammatory disease which is affecting 1-3% population around the globe. It hampers the physical, social, and psychologically balance of an individual. It is as an autoimmune disease which is characterized by the skin cell hyperplasia which is defined rapid skin cell growth, which leads to abnormal itchy scales and skin patches.

Conventional drug delivery systems offer a limited treatment strategy for managing psoriasis as it faces large number of setbacks like poor bioavailability, poor patient compliance and side effects associated with the drugs.

Ethosomes have fluidity and an adaptable lipid bilayer which makes it a promising candidate for penetration into the deeper layers of the skin. They also help in overcoming the various drawbacks of the conventional treatment approaches.

Fathalla *et al*. analysed and compared Anthralin liposomal and ethosomal formulations for the management of psoriasis. After ethosomal therapy, the mean change in Psoriasis Area and Severity Index (PASI) was substantially greater. Ethosomal gel also demonstrated greater penetration through rat abdomen skin. [26].

Chandra *et al.* prepared methotrexate-salicylic acid (MTX-SA) ethosomal gel and evaluated its potential in the Imiquimod-induced psoriasis animal model. It was inferred from the study that the formulated MTX-SA ethosomal gel decreased the PASI score in mice [27].

Zhang *et al.* prepared and compared ethosomes and liposomes loaded with psoralen for an effective treatment of psoriasis. In-vitro skin permeation study demonstrated the superiority of ethosomes over liposomes as the former provided better transdermal permeation of the drug. The transdermal flux and skin deposition of the drug was also found to be higher through ethosomes. [28].

Zhang *et al.* prepared modified ethosomes of curcumin by linking them to Hyaluronic acid (HA). The HA gel network lessened the leakage of curcumin which is poorly water soluble. Also, there was an enhanced transdermal delivery of curcumin through modified ethosomes, and the amount retained in the skin in-vitro as well as in-vivo was also higher. It was suggested that HA-ES adheres to the highly expressed CD44 protein which is responsible for the enhanced drug accumulation in the skin. Inflammatory symptoms and interleukin levels were also reduced after the topical administration of the modified ethosomes [29].

Ethosomes for inflammation

Our immune system is extremely important in preserving overall health. It actively detects and fights against any foreign body such as microbes that invades our body. Human skin actively participates in immune responses. Inflammation is a response that our skin shows towards the immune system in conditions like infections, allergic conditions etc. The symptoms of inflammation include redness of the skin, heat, swelling, pain and loss of function.

In a study ethosomal suspension of ammonium glycyrrhizinate was evaluated for its dermal application. The study revealed that ethosomes had a good skin tolerability in human that is for 48 h. It remarkably increased the anti-inflammatory activity of ammonium glycyrrhizinate in contrast to ethanolic or aqueous solution of the drug. The results show that ethosomes boosted the percutaneous penetration of ammonium glycyrrhizinate, enhancing the drug's anti-inflammatory efficacy [30]

Choi *et al*. developed ethosomes and transferosome for the topical delivery of ginsenosides Rh1 isolated from red ginseng which is used to treat inflammation along with other conditions of tumor and diabetes. The skin permeation of ginsenoside was higher with Transferosomes when compared to ethosomes as well as from conventional liposome [31].

Caddeo *et al*. prepared conventional ethosomes loaded with diclofenac phospholipid vesicles to examine the skin inflammation in mice. The study suggested that Vesicular formulation results in better drug accumulation and reduced permeation. Delivering diclofenac through ethosomes (vesicular) on TPA-inflamed skin reduced oedema and leucocyte infiltration. Proposed technique may contribute in promising therapeutic value to different inflammatory skin disorders [32].

Shen *et al.* prepared ethosomes that were loaded with apigenin, a flavonoid with anti-inflammatory and antioxidant effects. *In vitro* and *in vivo* investigations indicated that formed ethosomes had high skin targeting capacity and effectively lowered cyclooxygenase-2 levels in mouse skin inflammation. [33].

Ethosomes for skin cancer

Moolakkadath *et al.* prepared fisetin loaded ethosomes for treating skin cancer. *In vivo* studies showed that the mice treated with fisetin ethosomes had a reduced level of TNF-α and IL-1α. The study suggested that fisetin loaded ethosomes formulation could be the possible dermal delivery system for managing skin cancer [34].

Curcumin loaded ethosomes were prepared by Rao Peram *et al*. for treating melanoma. It was revealed in the *in vitro* studies that the curcumin loaded ethosomes were better than traditional liposomes in terms of drug penetration and deposition in the skin [35].

Ethosomes for acne

Yu *et al.* performed a study in which they prepared ethosomes loaded with cryptotanshinone for the treatment of acne. For penetration and deposition in skin, optimised ethosomes were compared to ordinary hydroethanolic gel. The gel showed better anti- acne effect with some minute skin irritation. The presented study promises that ethosomes could be the effective tool for the treatment of acne in future [36]. Nakka *et al*. in a study compared Isotretinoin ethosomal gel with marketed preparations of isotretinoin. It was reported that ethosomal vesicle with 30%w/w ethanol and 2%w/w lecithin showed the best entrapment efficiency and the permeation enhancers in the formulation augmented the skin penetration and enhanced the drug depot formation in the skin [37].

Ethosomes in cosmeceuticals

Ethosomes offer a number of advantages in formulation of cosmeceuticals. They significantly enhance the stability of chemicals used in the preparation of cosmeceuticals, reduces the skin irritation caused by the chemicals and above all it enhances transdermal permeation [38]. All the advantages are attributed to the elastic nature of the vesicle, its size and composition which makes ethosomes a potential candidate for cosmeceutical delivery. Administration of several antioxidants topically is one of the important approaches for the management of oxidative injury to the skin for cosmeceutical applications. These antioxidants such as vitamin C, flavonoids and vitamin E are unstable and susceptible to degradation when exposed to light. Topical administration of these antioxidants can protect the skin from several exogenous oxidants. Addition of vitamin E to dermatological and cosmetics products helps in reducing the lipid peroxides production in the epidermis and protects the skin against harmful chemicals, UV exposure and other environmental agents.

Koli *et al.* developed antioxidant ethosomes for topical application that took use of the synergistic effects of vitamin A, vitamin C, vitamin E, and palmitate.. The results of the study affirmed that a synergistic effect was taking place between the Vitamin C which was present in the aqueous core and Vitamin A and E present in the lipid and it is protecting the ethosomal formulation from oxidation. This demonstrates that elastic and non-elastic liposomes for the delivery of vitamin helps in enhancing their photo stability against UVB irradiation [39]. *Esposito et al.* formulated and compared the ethosomal and liposomal gels of azelaic acid which were prepared for topical application. The results revealed that ethosomal formulation had a rapid release rate when compared to liposomal [40].

Table 1. Application of ethosomes as potential drug delivery system in skin diseases

Name of Drug	Skin Disease	Dosage Form	Result of the studies	Reference
Alfuzosin Hydrochloride	Inflammation	Suspension	Ethosomes showed a better potential in transdermal delivery of Alfuzosin Hydrochloride than the hydroethanolic solution of drug	[41]
Ciclopirox Olamine	Fungal Infection	Suspension	Formulated ethosomes are promising carrier for transdermal delivery of Ciclopirox Olamine	[42]
Azelaic acid	Acne	Gel	Ethosomal formulation showed a rapid drug release as compared to liposomal formulation	[40]
Ammonium Glycyrrhizinate	Inflammation	Suspension	Enhanced the therapeutic action and augmented the topical drug delivery of the drug	[43]
Ketoconazole	Fungal Infections	Suspension	Enhanced drug delivery across the skin with increased concentration of ethanol	[44]
Fluconazole	Fungal Infections	Ethosomal cream	Significant anti-fungal activity was observed as compared to the marketed preparation	[45]

CONCLUSION

Advent of ethosomes has introduced a new arena for research in the transdermal drug delivery. Several studies suggest that ethosomes are highly promising drug delivery system for enhancing the effectiveness of transdermal drug delivery. They provide non-invasive delivery of drugs which have different size ranges. It has a great potential in treating several skin conditions as it increases the residence time of the drug, enhances the drug permeation across the skin and increase the patient compliance. Since past few decades there has been a tremendous growth in ethosomal technology for controlling the permeability of the skin. Research based evidence reveals that the use of ethosomal formulation in skin diseases can help in overcoming the stratum corneum barrier which restricts the passage of drugs across the skin. Transdermal drug delivery using ethosomal formulations can help reduce the side effects associated with oral therapies. In several diseases like psoriasis, fungal infection of the skin, cellulitis etc use of topical therapy is more beneficial as compared to oral treatments. Thus, ethosomes are potential drug delivery systems for managing various skin diseases and they play a vital role in the delivery of cosmeceuticals across the skin.

CONFLICTS OF INTERESTS

The authors declare that they have no competing interests.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

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