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REVIEW ARTICLE

ETHOSOMES: NOVEL VESICULAR CARRIER FOR ENHANCED TRANSDERMAL DRUG DELIVERY SYSTEM

Lalit Kumar Tyagi[1], Saurabh Kumar[1], Shambhu Sharan Maurya[1] and Mohan Lal Kori[2]*

[1]*Department of Pharmacy, Institute of Bio-Medical Education and Research, Mangalayatan University, Aligarh-202 145, Uttar Pradesh, India*
[2]*Department of Pharmacognosy, Faculty of Pharmacy, RKDF University, Bhopal-462 033, Madhya Pradesh, India*

**E-mail*: mohanlalkori@gmail.com, lktyagi13@yahoo.co.in
Tel.: +91 9893968611, +91 9997306488.

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The dermal route has been recognized as one of the highly potential routes of systemic drug delivery and provides the advantage of avoidance of the first pass effect, ease of use and withdrawal (in case of side effects), and better patient compliance. The skin, in particular the stratum corneum, poses a formidable barrier to drug penetration thereby limiting topical and transdermal bioavailability. Ethosomes are non-invasive delivery carrier system which is mainly used for delivery of drug to the systemic circulation. Ethosomes have higher quantity of ethanol. Ethanol penetration of drug into the stratum corneum by increases the fluidity of cell membrane lipids. The present review includes the composition, mechanism of penetration, advantages, method of preparation and characterization of ethosomes. The applications of ethosomes for various type of drug delivery, cosmetics use and marketed preparations are also described.

Key words: Transdermal drug delivery, Ethosome, Stratum corneum, Permeation enhancement.

INTRODUCTION

Skin is the largest human organ and consists of three functional layers: epidermis, dermis, and subcutis. It has a wide variety of functions. One major task of the skin is to protect the organism from water loss and mechanical, chemical, microbial and physical influences. The protective properties are provided by the outermost layer (epidermis) of the skin (Engstrom *et al* 2000). Dermal drug delivery is used for the treatment of various skin diseases. This has the advantage that high concentrations of drugs can be localized at the site of action, reducing the systemic side effects. Transdermal drug delivery system can be used as an alternative delivery of drug into the systemic circulation (Nandy *et al* 2009; Mohabe *et al* 2011; Talegaonkar *et al* 2011).

Transdermal drug delivery offers many advantages as compared to traditional drug delivery systems, including oral and parenteral drug delivery system. Transdermal route is a better alternative to achieve constant plasma levels for prolonged periods of time, which additionally could be advantageous because of less frequent dosing regimens (Cal *et al* 2008). Advantages claimed are increased patient acceptability, avoidance of first pass metabolism, predictable and extended duration of activity, minimizing side effects and utility of short half-life drugs, improving physiological and pharmacological response, avoiding the fluctuation in drug levels. The barrier function govern by stratum coneum is main problem for delivery of drugs across the skin. The stratum corneum consists of corneocytes surrounded by lipid layers, which play an essential role in the barrier properties of the stratum corneum (Wertz, 2000; Williams and Elias, 1987; Pilgram *et al* 1999).

In order to increase the number of drugs administered via transdermal route, novel drug delivery systems have to be designed. These systems include use of physical means, such as

iontophoresis, sonophoresis, microneedles, etc. and chemical means like penetration enhancers (surfactants and organic solvents) and biochemical means using liposomes, niosomes, transferosomes and ethosomes also have been reported to enhance permeability of drug through the stratum corneum (Merdan *et al* 1998).

The vesicles have been well known for their importance in cellular communication and particle transportation for many years. Researchers have understood the properties of vesicles structure for use in better drug delivery within their cavities, which would to tag the vesicle for cell specificity.

One of the major advances in vesicle research was the finding a vesicle derivatives, known as an ethosomes (Elsayed *et al* 2006).

Ethosomes

They are mainly used for the delivery of drugs through transdermal route. Drug can be entrapped in ethosomes which have various physicochemical characteristics *i.e.* hydrophilic, lipophilic, or amphiphilic (Verma and Fahr, 2004; Bhalaria *et al* 2009). Ethosomes are soft, malleable vesicles used for delivery of drugs to reach the deep skin layers and/or the systemic circulation. The size range of ethosomes may vary from tens of nano meters to microns (μ) (Patel, 2007). Ethosomes are the modified forms of liposomes that are high in ethanol content (**Figure 1**). The ethosomal system is composed of phospholipid (Phosphatidylcholine, phosphatidylserine, phosphatitidic acid), high concentration of alcohol (ethanol and isopropyl alcohol) and water.

The high concentration of ethanol makes ethosomes unique because ethanol causes disturbance of skin lipid bilayer organization, hence when incorporated into a vesicle membrane, it enhances the vesicles' ability to penetrate the stratum corneum (Ceve, 2004).

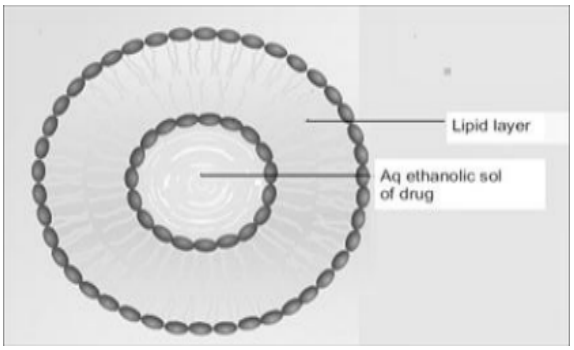

Fig. 1. Representation of ethosomes contents

Ethosomes composition

Ethosomal drug delivery can be modulated by altering alcohol:water or alcohol:polyol:water ratio. Ethosomes are vesicular carrier comprising of hydro alcoholic or hydro/ alcoholic/glycolic phospholipid in which the concentration of alcohols or their combination is relatively high (Friend *et al* 1988). The various type of additives used in the ethosomes preparations are represented in **Table 1**.

Table 1. Different additives employed in formulation of ethosomes

Additives	Uses	Examples
Phospholipid	Vesicles forming component	Soya phosphatidyl choline, Egg phosphatidyl choline, Dipalmityl phosphatidyl choline, Distearyl phosphatidyl choline.
Polyglycol	Skin penetration enhancer	Propylene glycol, Transcutol
Cholesterol	Stabilizer	Cholesterol
Alcohol	For providing the softness for vesicle membrane as a penetration enhancer	Ethanol Isopropyl alcohol
Vehicle	As a gel former	Carbopol 934
Dye	For characterization study	6-Carboxy Fluorescence, Rhodamine-123, Rhodamine red, Fluorescene Isothiocynate.

Advantages of ethosomal drug delivery

Ethosomal drug delivery system has much advantage as compared to other transdermal and dermal delivery systems. These advantages include enhanced permeation of drug through skin for transdermal drug delivery; ethosomes provide platform for the delivery of large and diverse group of drugs across the skin

(peptides, protein molecules); ethosomes contain non-toxic materials in formulation, ethosomal drug is administered in semisolid form (gel or cream) hence producing high patient compliance; ethosomal drug delivery system can be used widely in pharmaceutical, veterinary, cosmetic fields; ethosomal system is passive, non-invasive and is available for immediate commercialization; ethosomal drug delivery is very simple in comparison to iontophoresis and phonophoresis and other complicated methods.

Mechanism of drug penetration

The main advantage of ethosomes over the liposomes is the increased permeation of the drug into the stratum corneum. The mechanism of the drug absorption from ethosomes is not clear. The drug absorption probably occurs in following two phases - ethanol effect and ethosomes effect.

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 shown in **Figure 2** (Verma and Fahr, 2004).

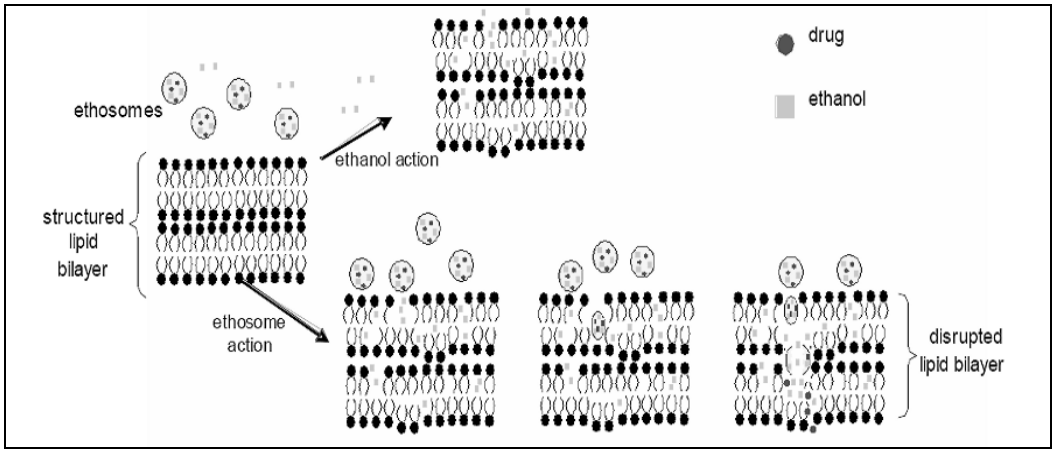

Fig. 2. Drug penetration through ethosomes

Ethosome 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 gets fused with skin lipids and releases the drugs into deep layer of skin (Touitou *et al* 2000).

Method of preparation

Cold method

This is the most common method utilized for the preparation of ethosomal formulation. In this method, phospholipid, drug and other lipid materials is mixed. Propylene glycol or other polyol is added during stirring. This mixture is heated to 300°C in a water bath. The water heated to 300°C in a separate vessel is added to the mixture, which is then stirred for 5 min in a covered vessel.

The vesicle sizes can be decreased to desire extend using sonication or extrusion method. Finally, formulation is stored under refrigeration (Manosroi *et al* 2009).

Hot method

In this method, phospholipid is dispersed in water by heating in a water bath at 400°C until a colloidal solution is obtained. In a separate vessel ethanol and propylene glycol are mixed and heated to 400°C. Once both mixtures reach 400°C, 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 desired extent using probe sonication or extrusion method (Bhalaria *et al* 2009; Touitou, 1998).

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 (Manosroi *et al* 2009).

Mechanical dispersion method
Soya phosphotidylcholine is dissolved in a mixture of chloroform: methanol in round bottom flask (RBF). The organic solvents are removed using rotary vacuum evaporator above lipid transition temperature to form a thin lipid film on wall of the RBF. Finally, traces of solvent mixture are removed from the deposited lipid film by leaving the contents under vacuum overnight. Hydration is done with different concentration of hydroethanolic mixture containing drug by rotating the RBF at suitable temperature (Dubey *et al* 2007).

Characterization of ethosomes

Visualization of vesicles
Transmission electron microscopy (TEM) and scanning electron microscopy (SEM) (Godin and Touitou, 2005).

Vesicle size and zeta potential
Dynamic light scattering (DLS) and photon correlation spectroscopy (PCS). Zeta potential is an important parameter that affects the aggregation of vesicles and depicts the physical stability of vesicular systems and it can be measured by Zeta meter (Rao *et al* 2008).

Entrapment efficiency
Ultracentrifugation technique (Sheer and Chauhan, 2011).

Surface tension activity measurement
Ring method in a Du Nouy ring tensiometer (Cevc, 2004).

Transition temperature
Differential scanning calorimetry (New, 1990).

Penetration and permeation studies
Depth of penetration from ethosomes can be visualized by confocal laser scanning microscopy (CLSM) (Dayan and Touitou, 2002).

Stability of ethosomes
The ability of ethosomal formulations to retain the drug was checked by keeping the preparations at different temperatures, *i.e.* 25±2°C (room temperature), 37±2°C and 45±2°C for different periods of time. The stability of ethosomes can also be determined quantitatively by monitoring size and morphology of the vesicles using DLS and TEM (Toll *et al* 2004).

Degree of deformability and turbidity
The degree of deformability of the ethosomal preparation can be performed by extrusion method and the turbidity of the preparation can be performed by using nephelometer (Cevc *et al* 1995).

Applications of ethosomes

Transdermal delivery of hormones
Oral delivery of hormones is associated with problems like high first pass metabolism, low oral bioavailability and several dose dependent side effects, increased risk of failure of treatment if the pill is missed. The skin permeation potential of testosterone ethosomes across rabbit pinna skin with marketed transdermal patch of testosterone (Testoderm patch, Alza) compared and it was observed nearly 30 times higher skin permeation of testosterone from ethosomal formulation as compared to that of marketed formulation of testosterone. Both *in vitro* and *in vivo* studies demonstrated improved skin permeation and bioavailability of testosterone from ethosomal formulation. Further, testosterone non patch formulation was designed to reduce the area of application. With the ethosomal testosterone formulation, area of application required to produce the effective plasma concentration was 10 times less than that required by commercial gel formulation (Ainbinder and Touitou, 2005).

Delivery of anti-parkinsonism agent
Dayan and Touitou (2002) prepared ethosomal formulation of psychoactive drug trihexy-phenidyl·HCl (THP) used in treatment of parkinson disease and compared its delivery with that from classical liposomal formulation. THP ethosomal formulation when visualized under TEM and SEM, found to consists of small phospholipid vesicles.
The value of 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. At the end of 18 h, quantity of drug remaining in skin was significantly higher after application of ethosomes as compared to that of application of liposome or hydroethanolic solution. The results showed the better skin permeation potential of trihexylphenidyl hydro-chloride (THP) ethosomal formulation and its

use for better management of parkinson disease.

Pilosebaceous targeting

In percutaneous drug delivery the hair follicles and sebaceous glands are potentially significant elements for permeation of drug. Pilosebaceous units has been interestingly used particularly for the treatment of follicle-related disorders such as acne or alopecia.

Minoxidil ethosomal formulation has been developed which is used topically on the scalp for the treatment of baldness. The conventional topical formulation has very poor permeation via skin and poor 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 as compared to ethanolic phospholipids dispersion, hydroethanolic/ethanolic solution of drug (0.5%) respectively. Results showed possibility of using ethosomes for pilosebaceous targeting of minoxidil to achieve its better clinical efficacy (Lauer *et al* 1999).

Transcellular delivery

The efficiency of transcellular delivery of ethosomes in Swiss albino mice 3T3 fibroblast has been investigated. The three probes chosen for study were D-289 [4-(4-(diethyl amino) styryl-*N*-methylpyridinum iodide], rhodamine red [dihexadecanoylglycero phosphorethanol amine] and fluorescent phosphatidylcholine. The penetration of these probes into fibroblasts and nude mice skin was examined by CLSM (Confocal Laser Scanning Microscopy) and FACS (Fluorescent Activated Cell Sorting) techniques Fibroblasts viability tests result showed that the ethosomal carrier was not toxic to the cultured cells (Touitou *et al* 2001).

Delivery of anti-arthritis drug

Topical route is a better option for site-specific delivery of anti-arthritis drug and overcomes the problem associated with conventional oral therapy. Cannabinol (CBD)-ethosomal formulation for transdermal delivery were prepared because its oral administration is associated with a number of problems like low bioavailability, first pass metabolism and GIT degradation. *In vivo* study of the skin deposition showed significant accumulation of CBD in skin and underlying muscles after application of CBD ethosomal formulation to the abdomen of ICR mice. The plasma concentration study showed that steady state level was reached in 24 h and maintained through 72 h.

A significant increase in biological anti-inflammatory activity of CBD ethosomal formulation was observed when tested by 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 (Lodzki *et al* 2003).

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 (Chetty and Chien, 1998). The effect of ethosomal insulin delivery in lowering blood glucose levels (BGL) *in vivo* in normal and diabetic rats have been investigated. Cyclosporin ethosomal formulation has been reported for the treatment of inflammatory skin disease like psoriasis, atopic dermatitis and disease of hair follicle like alopecia areata (Verma and Fahr, 2004). The potential application of the ethosomes for dermal delivery of ammonium glycyrrhizinate have been investigated (Paolino *et al* 2007). Ammonium glycyrrhizinate is naturally occurring triterpenes obtained from *Glycyrrhiza glabra* and useful for the treatment of various inflammation based skin diseases.

Delivery of antibiotics

Conventional oral therapy of antibiotics causes several allergic reactions along with several side effects. Topical delivery of antibiotics is a better choice for increasing the therapeutic efficacy of these agents. Conventional external formulations possess low permeability to deep skin layers and sub-dermal 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 roots.

There are reports of preparation of bacitracin and erythromycin loaded ethosomal formulation for dermal and intracellular delivery in literature (Godin and Touitou, 2005). CLSM experiments revealed that ethosomes facilitated the co-penetration of antibiotic and phospholipid into cultured 3T3 Swiss albino mice fibroblasts. He found that ethosomes penetrated the cellular

membrane and released the entrapped drug molecules within the cells.

Delivery of anti-viral drugs

Ethosomal formulation of zidovudine have been developed to increase the transdermal flux, prolong the release because the oral administration of zidovudine is associated with strong side effects (Jain *et al* 2004). Therefore, an adequate zero order delivery of zidovudine is desired to maintain expected anti-AIDS effect.

Acyclovir ethosomal formulation has been formulated for dermal delivery (Horwitz *et al* 1999). They have clinically evaluated its performance in a double blind, randomized study with marketed formulation of acyclovir (Zovirax, Glaxo-Wellcome) in terms of time to crust formation, time to loss of crust and proportions of lesions not progressive beyond the popular stage (abortive lesions). Significant improvement in all evaluated clinical parameters was observed when disorder was treated with ethosomal formulation in comparison to marketed formulation. The average time to crusting of lesions was 1.6 *vs* 4.3 days in the parallel arm and 1.8 *vs* 3.5 days in the crossover arm ($P<0.025$) for ethosomal acyclovir and zovirax, respectively. Hence, shorter healing time and higher percentage of abortive lesions were observed when acyclovir was loaded into ethosomes.

Ethosomes used for cosmetics

The advantage of ethosomes in cosmeceuticals is not only to increase the stability of the cosmetics and decrease skin irritation from the irritating cosmetic chemicals, but also for transdermal permeation enhancement, especially in the elastic forms.

Topical administration of many antioxidants is one of the several approaches to diminish oxidative injury in the skin for cosmetic and cosmeceutical applications. A USA company, Osmotics Inc., reported new cellulite cream called lipoduction prepared by using ethosome technology that penetrated the skin lipid barrier and delivered ingredients directly into the fat cells (Verma and Pathak, 2010).

Marketed product of ethosomes

In 2000, the ethosomes technology began to commercialize. There are only two companies which developed ethosome products (Verma and Pathak, 2010) (**Table 2**).

Table 2. Marketed products based on ethosomal drug delivery system

Name of product	Uses	Manufacturer
Cellutight EF	Topical cellulite cream, contains a powerful combination of ingredients to increase metabolism and break down fat	Hampden Health, USA
Decorin cream	Anti-aging cream, treating, repairing, and delaying the visible aging signs of the skin including wrinkle lines, sagging, age spots, loss of elasticity, and hyperpigmentation	Genome Cosmetics, Pennsylvania, US
Nanominox	First minoxidil containing product, which uses ethosomes. Contains 4% Minoxidil, well-known hair growth promoter that must be metabolized by sulfation to the active compound	Sinere, Germany
Noicellex	Topical anti-cellulite cream	Novel Therapeutic Technologies, Israel
Skin genuity	Powerful cellulite buster, reduces orange peel	Physonics, Nottingham, UK
Supravir cream	For the treatment of herpes virus, formulation of acyclovir drug has a long shelf life with no stability problems, stable for at least three years, at 25°C. Skin permeation experiments showed that the cream retained its initial penetration enhancing properties even after three years	Trima, Israel

CONCLUSION

The main disadvantage of transdermal drug delivery is the poor penetration of most compounds into the human skin. The main barrier of the skin is located within its uppermost layer, the stratum corneum. Ethosomes has initiated a new area in vesicular research for transdermal drug delivery which can provide better skin permeation than liposomes or hydroalcoholic solution. Ethosomes are soft, malleable vesicles and potential carrier for transportation of drugs. Ethosomes have been tested to encapsulate hydrophilic drugs, cationic drugs, proteins and peptides. Further, research in this area will allow better control over drug release *in vivo* and long term safety data, allowing the therapy more effective.

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