Journal of Pharma Research
Available online through
www.jprinfo.com

Review Article
ISSN: 2319-5622

A Review: Ethosomes a Promising Tool for Transdermal Delivery of Drug

Raju. Manda*, Dr. R. Suthakaran, Bonagiri Sreedevi, B. Kusuma pravallika
Teegala Ram Reddy College of Pharmacy, Meerpet Hyderabad-500097, Telangana, INDIA.

Received on: 21-10-2014; Revised and Accepted on: 07-11-2014

ABSTRACT

Ethosomes are soft, malleable vesicles composed mainly of phospholipids, ethanol (relatively high concentration) and water. These "soft vesicles" represents novel vesicular carrier for enhanced delivery to/through skin. The size of Ethosomes vesicles can be modulated from tens of nanometers to microns.Ethosomes are provides a number of important benefits including improving the drug's efficacy, enhancing patient compliance and comfort and reducing the total cost of treatment. The Ethosomes were found to be suitable for various applications within the pharmaceutical, biotechnology, veterinary, cosmetic, and nutraceutical markets.

Key Words: *Ethosomes, soft vesicles, cosmetic.*

INTRODUCTION [5]

Transdermal drug delivery offers many advantages as compared to traditional drug delivery systems, including oral and parenteral drug delivery system. Advantages claimed are increased patient acceptability (non invasiveness), avoidance of gastrointestinal disturbances and first pass metabolism of the drug [1]. The traditional transdermal drug delivery systems involve a patch, in which the drug permeates through various layers of skin, via a passive diffusion pathway. However, this limits the basic potential of these systems, as stratum corneum is the most formidable barrier to the passage of most of the drugs, except for highly lipophilic, low molecular weight drugs. To overcome the stratum corneum barrier, various mechanisms have been investigated, including use of chemical or physical enhancers, such as iontophoresis, sonophoresis, etc.

Liposomes, niosomes, transferosomes and ethosomes also have the potential of overcoming the skin barrier and have been reported to enhance permeability of drug through the stratum corneum barrier. 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*.

Ethosomes are noninvasive delivery carriers that enable drugs to reach the deep skin layers and/or the systemic circulation. These are soft, malleable vesicles tailored for enhanced delivery of active agents. They are composed mainly of phospholipids, (phosphatidylcholine, phosphatidylserine, phosphatitidic acid), high concentration of ethanol and water [3]. 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 vesicle membrane, it gives that vesicle the ability to penetrate the stratum corneum. Also, because of their high ethanol concentration, the lipid membrane is packed less tightly than conventional vesicles but has equivalent stability, allowing a more malleable structure and improves drug distribution ability in stratum corneum lipids.

***Corresponding author:**
Raju. Manda
Department of Pharmaceutics and Drug Regulatory Affairs,
Teegala Ram Reddy College of Pharmacy, Meerpet -500097.
Telangana, INDIA. Cell : 9966288297.
**E-Mail: 0502varma@gmail.com*

Mechanism of Drug Penetration: [4]

The enhanced delivery of actives using ethosomes over liposomes can be ascribed to an interaction between ethosomes and skin lipids. A possible mechanism for this interaction has been proposed. It is thought that the first part of the mechanism is due to the 'ethanol effect', whereby intercalation of the ethanol into intercellular lipids increasing lipid fluidity and decreases the density of the lipid multilayer [5]. This is followed by the 'ethosome effect', which includes inter 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 in deep layers of the skin, shown in **Fig. 1**.

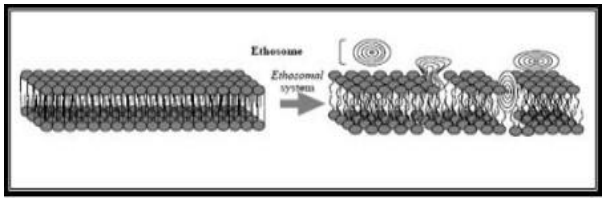

Fig. 1: Mechanism of penetration of ethosomal drug delivery system

Preparation and Characterization:

Ethosomes can be prepared from soybean phosphatidylcholine (Phospholipon 90), ethanol, drug and distilled water. Phospholipon 90 and drug should be dissolved in ethanol. Water has to be added in small quantities and the preparation mixed by mechanical stirring under controlled conditions [6].

Various methods for characterization of Ethosomes:

1. **Visualization:** Visualization of ethosomes can be done using transmission electron microscopy (TEM) and by scanning electron microscopy (SEM).

2. **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).

3. **Entrapment Efficiency:** The entrapment efficiency of drug by ethosomes can be measured by the ultracentrifugation technique.

4. **Transition Temperature:** The transition temperature of the vesicular lipid systems can be determined by using differential scanning calorimetry.

5. **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.

6. **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.

7. **Drug Content**: Drug can be quantified by a modified high performance liquid chromatographic method.

8. **Penetration and Permeation Studies:** Depth of penetration from ethosomes can be visualized by confocal laser scanning microscopy (CLSM).

Advantages of Ethosomal Drug delivery: [8]

In comparison to other transdermal & dermal delivery systems,

1. Ethosomes are enhanced permeation of drug through skin for transdermal and dermal delivery.
2. Ethosomes are platform for the delivery of large and diverse group of drugs (peptides, protein molecules)
3. Ethosome composition is safe and the components are approved for pharmaceutical and cosmetic use.
4. Low risk profile- The technology has no large-scale drug development risk since the toxicological profiles of the ethosomal components are well documented in the scientific literature.
5. High patient compliance- The Ethosomal drug is administrated in semisolid form (gel or cream), producing high patient compliance by is high. In contrast, Iontophoresis and Phonophoresis are relatively complicated to use which will affect patient compliance.
6. High market attractiveness for products with proprietary technology. Relatively simple to manufacture with no complicated technical investments required for production of Ethosomes.
7. The Ethosomal system is passive, non-invasive and is available for immediate commercialization.
8. Various application in Pharmaceutical, Veterinary, Cosmetic field.

Therapeutic Application of Ethosomes: [12]

Horwitz et al. reported that a 5 % acyclovir ethosomal preparation compared to the 5 % acyclovir cream showed significant improvements in treatment of herpetic infections.

Jain et al. prepared zidovudine ethosomes and characterized in vitro and in vivo. The effect of different formulation variables on skin permeation of zidovudine was studied using locally fabricated Keshry-Chien type of diffusion cell. To understand the mechanism of better skin permeation of ethosomes, vesicle skin interaction study was carried out. To confirm the better skin permeability of ethosomes, fluorescence microscopy using rhodamine 123 as fluorescence probe was performed. The optimized ethosomes showed transdermal flux of 78.5± 2.5 $\mu g/cm^2/h$ across the rat skin. Vesicle skin interaction study showed that ethosomes affected the ultrastructure of the stratum corneum as distinct regions with lamellar stacks derived from 5the vesicles were observed in the intercellular spaces of the stratum corneum. Thus ethosomes can increase the transdermal flux, prolong the release and present an attractive route for sustained delivery of Zidovudine.

Dayan et al. investigated the delivery of trihexyphenidyl HCl (THP) from ethosomes versus classic liposomes. As the THP concentration was increased from 0 to 3%, the size of the vesicles decreased from 154 to 90 nm. This is most likely due to the surface activity of THP (critical micelle concentration of 5.9 mg/ml), as measured in this work. In addition, the ethosome zeta potential value increased as a function of THP concentration, from -4.5 to +10.4 when the THP concentration was increased from 0 to 3%. In contrast, THP liposomes were much larger and their charge was not affected by THP. When compared with standard liposomes, ethosomes had a higher entrapment capacity and a greater ability to deliver entrapped fluorescent probe to the deeper layers of skin. The flux of THP through nude mouse skin from THP ethosomes (0.21 mg/cm2 h) was 87, 51 and 4.5 times higher than from liposomes.

Godin et al. investigated a new approach to treat deep skin and soft tissue bacterial infections by dermal application of erythromycin in an ethosomal carrier. The efficiency of ethosomal erythromycin applied to the skin-infected site was compared with intraperitoneal erythromycin administration and with local application of hydroethanolic erythromycin solution. Bacterial counts and histological evaluation of the skin treated with ethosomal antibiotic revealed no bacterial growth and normal skin structure. On the contrary, no subdermal healing was observed in infected animals treated with topical hydroethanolic erythromycin solution.

Donatella et al. studied in vitro percutaneous permeation of ammonium glycyrrhizinate/ethosomes through human stratum corneum and epidermis membranes by using Franz's cells and compared with the permeation profiles of drug solutions either in water or in a water–ethanol mixture. The ethosomal suspension showed very good skin tolerability in human volunteers, also when applied for a long period (48 h). Ethosomes elicited an increase of the in vitro percutaneous permeation of both methylnicotinate and ammonium glycyrrhizinate. Ethosomes were able to significantly enhance the anti-inflammatory activity of ammonium glycyrrhizinate compared to the ethanolic or aqueous solutions of this drug.

Touitou et al. experimentally tested the effect of an ethosomal insulin formulation that was applied to the skin on blood glucose level. The ethosomal formulation caused much as a 60% decrease in blood glucose levels in both normal and diabetic rats and kept the level constant for at least 8 hours.

Kaplun and Touitou et al. have demonstrated in-vitro and in-vivo delivery of testosterone. Testosterone delivery from Testosterone® versus Testoderm® was in-vitro for skin permeation and in-vivo in animals for percutaneous absorption. The results of the in-vitro experiments showed that the amount of testosterone permeating into the skin from Testosome® patch was significantly higher than from Testoderm®. The in-vivo results presented as AUC of serum testosterone indicated that Testosome® was able to systemically deliver increased amounts of testosterone.

Lodzki et al. designed a transdermal delivery system for cannabidol by using ethosomal carriers. Transdermal application of ethosomal cannabidol prevented the inflammatrion and edema induced by sub-plantar injection of carrageenan in the same animal model. Thus, ethosomes enabled cannabidol skin permeation and its accumulation in a depot at levels that demonstrated.

Esposito et al. investigated basic properties and the *in vitro* release rate kinetics of azelaic acid, alternatively vehiculated in different phospholipid-based vesicles such as ethosomes or liposomes. Diffusion of azelaic acid from ethosomal or liposomal dispersions and from ethosomes and liposomes incorporated in a viscous gel was investigated by a Franz cell assembled with synthetic membranes. The release rate was more rapid from ethosomal systems than from liposomal systems.

Kim et al. prepared three kinds of topical dosage forms of minodixil, namely, vesicle, double emulsions, and an inclusion complex with Hydroxypropyl-g-cyclodextrin (HP-g-CD). The skin retention of minodixil in the preparations was evaluated in-vitro using hairless mouse skins. Retention was highest when the drug was encapsulated in cationic vesicles. Nonionic vehicle, the double emulsion and HP-g-CD left no significant amount of drug penetrated through the skin. In-vivo hair growth promotion effect of each dosage form was investigated, in which the sample application on to clipped back of female mice and the subsequent rinsing of the backs was done once a day for 30 days. Only minodixil in the cationic vesicles demonstrated hair growth promotion effect, possibly due to significant skin retention.

Osmotics Inc., USA, reported a new cellulite cream called *Lipoduction*, Which smooth the skin and has a break through permeation technology called ethosomes that penetrate skin lipid barrier and deliver ingredients directly into fat cells. Flexible nanospheres (ethosomes) in lipoduction cream have been introduced that allow a cocktail of fat-metabolizing ingredients to reach the fat cells 700 % more effectively that the current cream. Ingredients in lipoduction improved the appearance of cellulite by up to 80 percent in less than 60 days.

Godin et al. studied the dermal and intracellular delivery of bacitracin from ethosomes. Efficient delivery of antibiotics to deep skin from ethosomal application was reported to be highly beneficial, reducing possible side effects. Transdermal absorption of polypeptides is currently under investigation. The high interest of ethosomes in the design of new therapies has been investigated

with other drugs such as propranolol; in this respect ethosomes showed their potential as transdermal dosage forms for prophylaxis of migraine. Moreover the ability of ethosomes to deliver compounds to cells in culture was investigated.

Table No. 1: Ethosomes as a carrier of various drug molecules has been listed below [13-19]

Drug	Applications	Comments
Acyclovir	Treatment of Herpetic infection	Improved drug delivery
Zidovudine	Treatment of AIDS	Improved transdermal flux
Trihexypenidyl HCl	Treatment of Parkinsonian syndrome	Increased drug entrapment efficiency, reduced side effect & constant systemic levels
Erythromycin	Efficient healing of *S. aureus* - induced deep dermal infections	Improved drug penetration and systemic effect.
Insulin	Treatment of Diabetes	Improved therapeutic efficacy of drug
Testosterone	Treatment of male hypogonodism	Enhance skin permeation
Cannabidol	Prevents inflammation and edema	Significant accumulation of the drug in the skin
Minodixil	Hair growth promotion effect	Higher skin retention
Bacitracin	Treatment of dermal infections	Reduced drug toxicity

CONCLUSION

Ethosomes are soft, malleable vesicles and potential carrier for transportation of drugs. Ethosomes are characterized by simplicity in their preparation, safety and efficacy and can be tailored for enhanced skin permeation of active drugs. Ethosomes have been found to be much more efficient at delivering drug to the skin, than either liposomes or hydroalcoholic solution. Ethosomes have been tested to encapsulate hydrophilic drugs, cationic drugs, proteins and peptides. Ethosomal carrier opens new challenges and opportunities for the development of novel improved therapies.

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How to cite this article:

Raju. Manda et al.,: A Review: Ethosomes a Promising Tool for Transdermal Delivery of Drug. J. Pharm. Res., 2014; 3(11): 220-222.

Conflict of interest: The authors have declared that no conflict of interest exists.

Source of support: Nil