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ETHOSOMES- AN EFFECTIVE DERMAL DRUG DELIVERY

K. Kartheswari, G. Akhila and B. Venkata Phani Deepthi*

Joginapally B.R.Pharmacy College, Yenkapally, Moinabad, Hyderabad, Telangana.

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***Corresponding Author**
B. Venkata Phani Deepthi
Joginapally B.R.Pharmacy College, Yenkapally, Moinabad, Hyderabad, Telangana.

ABSTRACT

Ethosomes are the ethanolic phospholipid vesicles which are used mainly for transdermal delivery of drugs. Ethosomes are soft, malleable vesicles composed mainly of phospholipids, ethanol (relatively high concentration) and water. Several approaches have been developed to weaken this skin barrier. One of the approaches for increasing the skin penetration of drugs and many cosmetic chemicals is the use of vesicular systems such as liposomes and ethosomes. Ethanol is known as an efficient permeation enhancer and has been added in the vesicular systems to prepare elastic nanovesicles. Ethosomes have various applications in the pharmaceutical, biotechnology, veterinary, cosmetic, and nutraceutical markets. Ethosomes became the new trend because of its enhanced skin permeation, improved drug delivery, increased drug entrapment efficiency etc. Ethosomes 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 present review focuses mainly on the various aspects of ethosomes including their mechanism of penetration, preparation, composition, characterization, advantages, applications and marketed product of ethosomes.

KEYWORDS: Ethosomes, Phospholipid Vesicles, Penetration, Ethanol, Transdermal drug delivery.

INTRODUCTION

The transdermal drug delivery is a non-invasive procedure for drug delivery[1] as it overcomes a number of limitations of oral drug delivery such as degradation of drugs by digestive enzymes, irritation of gastrointestinal mucosa[2] and first pass effect[3] but the main drawback of TDDS is it encounters the barrier properties of the stratum corneum i.e. only the lipophilic drugs having molecular weight < 500 Da can pass through it.[4] Transdermal drug

delivery (TDD) is the potential route for delivering systemic drugs. But the greatest challenge is the barrier nature of stratum corneum.[5]

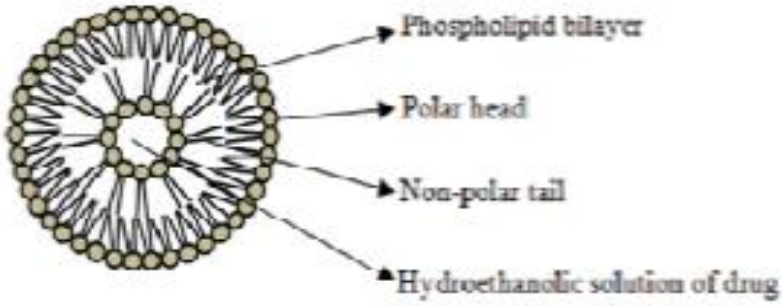
The human skin is a readily accessible surface for delivery of drugs through transdermal layers of skin. Human skin consists of epidermis, dermis, hypodermis. Stratum corneum is the outermost layer of skin which is flexible, relatively impermeable acting as a principal barrier for penetration of drug. Viable epidermis is situated beneath the stratum corneum. Dermis has essential function in regulation of body temperature as it provides nutrients and oxygen to the skin while removing toxins and waste products. Hypodermis serves as a fat storage area.[6]

ETHOSOMES

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.[7] Ethosomes are soft malleable vesicles[2] composed mainly of phospholipid[8] (phosphatidylcholine, phosphatidylserine, phosphatitidic acid), ethanol at relatively high concentration[9] and water.[10] Ethosomes have higher penetration rates when compared to liposomes to efficiently deliver various molecules across the skin.[11] Examples of alcohols used include ethanol (commonly used) and isopropyl alcohol. Glycols can also be used in preparations as a penetration enhancer.[12]

The size range of ethosomes may vary from tens of nanometers to microns (μ).[13]

Ethosomes permeate through the skin layers more rapidly and possess significantly higher tra nsdermal flux in comparison to conventional liposomes.[14] Due to their size (approximately 150–200 nm) and high deformability, they are also referred to as elastic nanovesicles.[15] Soft malleable vesicles consisting of phospholipids and higher concentration of ethanol exhibited synergistic effect of phospholipids and ethanol on permeation proving elastic liposomes (ethosomes) are better carriers for Alfuzosin hydrochloride transdermal delivery.[5] The structure of ethosome[16] is shown in the below figure.



Ethosomes Effect

Ethanol is known as an efficient permeation enhancer and has been added in the vesicular systems to prepare elastic nanovesicles.[17] The ethanol present in ethosomes increases cell membrane fluidity of lipids causes increased skin permeability.[18] So the ethosomes permeates very easily inside the deep skin layers, where it got fused with skin lipids and releases the drugs into deep layer of skin.[10]

Composition of Ethosomes

Ethosomes are composed mainly of phosphatidylcholine, phosphatidyl soya phosphatidylcholine, egg phosphatidylcholine, dipalmityl phosphatidyl choline, hydrogenated phosphatidylcholine, high concentration of hydroalcohols. Examples of alcohols include ethanol or isopropyl alcohol and as poliglicols propylene glycol and transcutol.[19]

Mechanism of Penetration

At physiological temperature, the stratum corneum lipid multilayer are densely packed and highly conformationally ordered. The high concentration of ethanol causes disturbance of skin lipid bilayer organization such that the vesicles have the ability to penetrate the stratum corneum. The rigidity of the stratum corneum lipids is reduced because of ethanol interacts with lipid molecules in the polar hard group region, thereby increasing their fluidity which in turn increases the membrane permeability. In addition to this, the ethanol may also interact with the stratum corneum barrier.

Advantages of Ethosomal Drug Delivery

1. Ethosomes enhances the permeation of the drug through skin transdermal and dermal delivery.[10]
2. Ethosomes are platforms for the delivery of large macromolecular drugs like peptides, protein molecules.

3. Ethosomal systems are much more efficient at delivering a fluorescent probe (quantum dots) to the skin in terms of quantity and depth[20] It contains non-toxic raw material in formulation.[4]
4. 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.
5. High patient compliance–The ethosome drugs are administrated in a semisolid form like gel or cream[10] producing high patient compliance.
6. The products have high market attractiveness with proprietary technology.
7. Relatively simple to manufacture with no complicated technical investments required for the production of ethosomes.
8. The ethosomes system is passive, non-passive and available for immediate commercialization.
9. Ethosomal drug delivery system has various applications in the pharmaceutical, veterinary, and cosmetic fields.[20]
10. Ethosomes improve skin delivery of drugs both under occlusive and non-occlusive conditions.
11. The composition and components of ethosomes are safe.
12. Better stability and solubility of many drugs as compared to conventional vesicles.
13. Relatively smaller size as compared to conventional vesicles.[10]

DISADVANTAGES/LIMITATIONS OF ETHOSOMES

1. Poor yield
2. In case if shell locking is ineffective then the ethosomes may coalescence and fall apart on transfer into water.
3. Loss of product during transfer from organic to water media.

METHODS OF PREPARATION OF ETHOSOMES

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.[9] This method is used for preparation of ethosomal gel of Clotrimazole for Fungal Infection.[7]

Ethosomes can be prepared by two very simple and convenient methods that are hot method and cold method.

1. Cold Method

This is the most common method utilized for the preparation of ethosomal formulation. In this method phospholipid, drug and other lipid materials are dissolved in ethanol in a covered vessel at room temperature by vigorous stirring with the use of mixer.[20] 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. Finally, the formulation is stored under refrigeration.[4]

2. 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 desire extent using probe sonication or extrusion method.[21] The formulation is then homogenized at 15,000 psi pressure, in three cycles, using a high pressure homogenizer to get nano-sized ethosomes.[20]

CHARACTERIZATION OF ETHOSOMES

1. Visualization: Visualization of ethosomes can be done using transmission electron microscopy (TEM) and by scanning electron microscopy (SEM).[22] The colour, texture, physical appearance and homogeneity of the gels were evaluated by visual observations.[2] Ethosomes vesicles were visualized using TEM, with an accelerating voltage of 100 kV.[1]

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)(4). Turbidity of all ethosomal vesicular suspensions was measured by ELICO-CL 52D Nephalometer. In this method, 500 NTU (Nephalometric Turbidity Units) range is set. Then zero reading is set with Millipore water. After this,

formulation is transferred to glass cuvettes of capacity 50 ml and placed in the holder inside the instrument. The method is repeated for each formulation and measurement of turbidity is displayed on the screen and expressed as NTU. Zeta potential of the vesicles was determined using Zetasizer (Nano-ZS, Malvern, U.K.). The measurements were made in triplicate.[1] Particle size was measured using the laser dynamic scattering mastersizer 3000 (Malvern, England) immediately after diluting the ethosomes with phosphate buffer saline solution. The average particle size of ethosomes was calculated based on the measurements of 5 batches of ethosomes.[23]

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

4. 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.

5. Entrapment Efficiency The entrapment efficiency of drug by ethosomes can be measured by the ultra centrifugation technique.[4] One ml of the formulation was centrifuged at 4ºC at 14,000 rpm for 1 hr. The supernatant containing the unentrapped drug was decanted. The vesicles lyses was done using Triton-X 100 (0.1%v/v) and after further dilutions it was analyzed for drug content using UV Spectrophotometer at 228nm.

The entrapment efficiency was expressed as percentage of total drug entrapped using the following formula.

$$\text{Percentage Entrapment} = C/T \times 100.....$$

Where, T = theoretical amount of drug that was added, and C = amount of T drug detected after dissolving the vesicles.[1]

6. Penetration and Permeation Studies Depth of penetration from ethosomes can be visualized by confocal laser scanning(4). The in vitro skin permeation of a drug was studied using locally fabricated Franz diffusion cell or modified Franz diffusion cell with egg membrane(24) with an effective permeation area and receptor cell volume of 1.0 cm^2 and 20 ml respectively. The temperature was maintained at 32 ± 1ºC. The receptor compartment

contained 10 ml PBS (pH 7.4).[1] The formulation was placed (equivalent to 2.5 mg of drug) on the upper side of skin in donor compartment. The temperature of the assembly was maintained at 37±2°. Samples were withdrawn after every hour from the receptor media through the sampling tube and at the same time, same amount of fresh receptor media was added to make sink condition. Withdrawn samples were analyzed for drug content using UV/Vis spectrophotometer.[24]

7. 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 dynamic light scattering (DLS) and structure changes are observed by transmission electron microscopy (TEM).[4]

8. Elasticity: Elasticity of vesicle membrane is a unique parameter of ethosomal formulations because it differentiates ethosomal from other vesicular carriers like liposomes that are unable to cross the stratum corneum intact. The deformability study was done for the ethosomal formulation against the standard liposome preparations. In this study the flux of vesicle suspensions through a large number of pores of known size (a sandwich of polycarbonate filters with pore diameter between 50 and 200 nm depending on the starting vesicle suspension), was driven by an external pressure of 2.5 bars. The amount of vesicle suspension, which was extruded during 5 min, was measured and vesicle size and size distribution were monitored by DLS measurement before and after filtration. The experiment was performed in triplicate and each sample was analyzed twice.

The elasticity of vesicle membrane was calculated by using the following formula

D = ... (1)

Where D is the elasticity of vesicle membrane;

J is amount of suspension, which was extruded during 5 min;

rv = size of vesicles (after passes); and

rp= pore size of the barrier (1).

93 In-vitro drug release- through cellophane membrane

Suitable size of membrane (Molecular weight cut of 12,000-14,000, HI Media, Ltd.) was cut and was kept in saline solution for 1 hour before dialysis to ensure complete wetting of the membrane. One ml of the drug-loaded vesicles was placed in the dialysis bag, which was then transferred into 50 ml of phosphate buffer saline (PBS) (pH 6.8). The receiver medium was stirred with a magnetic stirrer which is thermostatically controlled. Sample was

withdrawn after 0.5-, 1.0-, 1.5-, 2.0-, 3-, 4-, 6-, and 12-hour time intervals and replaced with equal volumes of PBS(1).

APPLICATIONS OF ETHOSOMES

1. Delivery of Anti-Viral Drugs

Zidovudine is a potent antiviral agent used in the treatment of acquired immunodeficiency virus. Oral administration of zidovudine is associated with strong side effects, ethosomes increases the transdermal flux, prolong the release rate of drug thereby acting as a effective route for sustained delivery of zidovudine. Acyclovir is another anti-viral drug that widely used topically for treatment of Herpes labialis. The conventional marketed acyclovir external formulation is associated with poor skin penetration of hydrophilic acyclovir to dermal layer resulting in weak therapeutic efficiency. The problem can be overcome by acyclovir ethosomal formulation for dermal delivery.

2. Topical Delivery of DNA

Another important application of ethosomes is to use them for topical delivery of DNA molecules to express genes in skin cells.[20] Better skin permeation ability of ethosomes opens the possibility of using these dosage forms for delivery of immunizing agents.[4] Ethosomes are used for transcutaneous immunization, and antigen-loaded ethosomes for transcutaneous immunization against Hepatitis B.[20]

3. Transdermal Delivery of Hormones

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.[4] Higher skin permeation of testosterone from the ethosomal formulation as compared to the marketed formulation.

4. Delivery of anti-parkinsonism agent

Trihexyphenidyl (THP) is a M1 muscarinic receptors antagonist and used in the treatment of Parkinson disease.[20] Its ethosomal formulation shows better skin permeation potential and its use for better management of Parkinson disease.[4]

5. Transcellular Delivery

Ethosomal delivery of anti HIV drugs like zidovudine and lamivudine is an attractive clinical alternative for anti-HIV therapy.[4] 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. Ammonium glycyrrhizinate ethosomal formulation is used to treat various skin diseases.[20]

6. Delivery of Anti-Arthritis Drug

Topical delivery of anti-arthritis drug is a better option for its site-specific delivery. CBD-ethosomal formulation for transdermal delivery of cannabiol[4] is used for the treatment of rheumatoid arthritis.[20]

7. Delivery of Problematic drug molecules

The oral delivery of large macromolecules such as peptides or proteins is difficult because they are completely degraded in the GI tract. Non-invasive delivery of proteins including ethosomal formulation of proteins is a better option for overcoming the problems. For example ethosomal insulin delivery in lowering blood glucose levels (BGL) in vivo in normal and diabetic SDI rats. Ammonium glycyrrhizinate is naturally occurring triterpenes obtained from Glycyrrhizinate Glabra and useful for the treatment of various inflammatory based skin diseases.[4] Minoxidil is a lipid-soluble drug its ethosomal formulation is used topically on the scalp for the treatment of baldness.[20]

8. Delivery of Antibiotics

Conventional oral therapy 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. Ethosomes penetrate rapidly through the epidermis and deliver appreciable amount of drugs into the deeper layer of skin. Bacitracin and erythromycin loaded ethosomal formulation are used for dermal and intracellular delivery.[4]

9. Cosmetic applications of ethosomes

Ethosomes are used in cosmeceuticals to decrease skin irritation from the irritating cosmetic chemicals. In order to deliver vitamin E into the deeper layer of skin, formulation of 'Anti-oxidant Ethosomes for Topical Delivery Utilizing the Synergistic Properties of Vitamin A Palmitate, Vitamin E, and Vitamin C,' was made. Ethosomes and liposomes of azelaic acid (Anti-keratinizing agent used in the treatment of acne) were prepared as a topical vehicle. New cellulite cream called lipoduction, which used ethosome technology that penetrated the skin lipid barrier and delivered ingredients directly into the fat cells.[20]

Stability of ethosomes

Stability of the formulations was evaluated in terms of the entrapment capacity and the particle size for a specified period. The lipid composition is properly selected in obtaining stable ethosomes dispersions with optimum pharmaceutical and therapeutic characteristics. The increase in concentration of ethanol from 15 to 45% increases the entrapment efficiency owing to an increase in the fluidity of the membranes. Further increase in the concentration of ethanol (>45%) makes the vesicle membrane more leaky, thus leading to a decrease in entrapment efficiency causes destabilization of the ethosomes. The lipid portion of the ethosomes containing unsaturated fatty acids are known to undergo oxidative reactions. The reaction products cause permeability changes in the ethosomes bilayers. Oxidative degradation of the lipids can be minimized by adding antioxidants such as α-tocopherol. Hydrolysis of lipids leads to the formation of lyso-PC enhances the permeability of ethosomes, to keep its level to a minimum in a given preparation.[20] Optimized ethosomal formulations were stored at 2^{o}C, 8^{o}C and at room temperature. Percent drug entrapment was determined at different time intervals (1, 15, 30 and 45 d).[24]

Marketed formulations of ethosomes

Nanominox

First minoxidil containing product which uses ethosomes contains 4% Minoxidil, well known hair growth promoter that must be metabolised by sulfation to the active compound.

Supravir cream

It is used for the treatment of herpes virus, formulation of acyclovir drug has a long shelf life with no stability problems, stable for atleast three years, at 25C. Skin permeation experiments showed that the cream retained its initial penetration enhancing properties even after three years.

Cellutight EF

It is a topical cellulite cream, contains a powerful combination of ingredients to increase metabolism and break down fat.

Decorin cream

It is an anti aging cream, used for treating , repairing and delaying the visible aging signs of the skin including wrinkle lines, sagging, age spots, loss of elasticity and hyperpigmentation.

Noicellex

It is a topical anti cellulite cream.

Skin genuity

It is a powerful cellulite buster, reduces orange peel.

Experimental design

A three-factor, three-level Taguchi L9 orthogonal array experimental design was constructed using MINITAB 16 software (Minitab Inc., PA, U.S.A). The independent variables selected were the type of phospholipid, concentration of phospholipid and concentration of ethanol(5).

CONCLUSION

Though these vesicular systems offer a good potential for rational drug delivery, a thoughtfully designed process is required to optimize the process variables involved. Industrial scale production of efficacious, safe, cost effective and stable formulations of both these delivery systems appears to be a pre-requisite to ensure their utility as the trans-dermal vehicles.[25]

Future perspectives

Introduction of ethosomes in transdermal drug delivery is one of the promising approach. Ethosomes offers a good opportunity for the non-invasive delivery of small, medium, and large-sized drug molecules. The results were supported by the acyclovir-ethosomal formulation. Studies will continue to further improve the skin delivery of drugs using lipid vesicles. It seems to be a challenging task for transdermal delivery of proteins and other macromolecules.[20]

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