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Ethosomes: A Novel approach in the design of transdermal drug delivery system

Syeda Shabana Sultana and Krishna Sailaja A*

RBVRR Women's College of Pharmacy, Affiliated to Osmania University, Department of Pharmaceutics, Barkatpura, Hyderabad, India.

Abstract: - 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 and biochemical means using liposomes, niosomes, transferosomes and ethosomes also have been reported to enhance permeability of drug through the stratum corneum⁵⁵. 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 tag the vesicle for cell specificity. One of the major advances in vesicle research was the finding of vesicle derivatives, known as ethosomes. In this review the importance of ethosomes in the design of transdermal drug delivery system was discussed in detail with respect to the preparation methods, characterization parameters and their applications.

Keywords: Ethosomes, Transdermal drug delivery system.

Introduction

Transdermal drug delivery system can be used as an alternative delivery of drug into the systemic circulation^{1,2}. Transdermal drug delivery offers many advantages as compared to traditional drug delivery to achieve constant plasma levels for prolonged periods of time, which additionally could be advantageous because of less frequent dosing regimens.

In the last few years, the vesicular systems have been promoted as a mean of sustained or controlled release of drugs. These vesicles are preferred over other formulations because of their specific characteristics such as lack of toxicity, biodegradation, capacity of encapsulating both hydrophilic and lipophilic molecules, capacity of prolonging the existence of the drug in the systemic circulation by encapsulation in vesicular structures, capacity of targeting the organs and tissues, capacity of reducing the drug toxicity and increasing its bioavailability.^{3,4}

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. 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). Ethosomes are the modified forms of liposomes that are high in ethanol content.

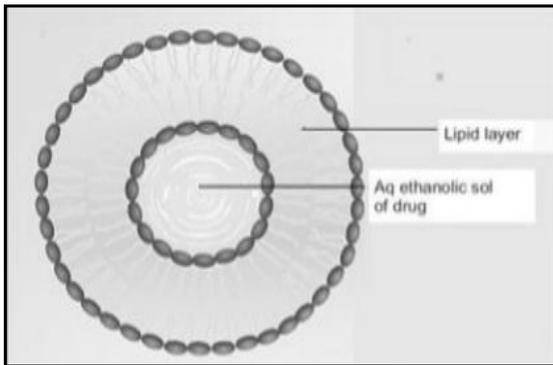


Figure 1: Representation of ethosome contents

The ethosomal system is composed of phospholipid, high concentration of 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^{5, 6}.

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. The various type of additives used in the ethosomes preparations are represented in table.

Table 1: Different additives employed in formulation of ethosomes

| Class | Example | Uses |
|-------------|---|--|
| Phospolipid | Soya phosphatidylcholine Egg phosphatidylcholine Dipalmityl phosphatidylcholine Disteryl phosphatidylcholine | Vesicles forming component. |
| Polyglycol | Propylene glycol Transcutol RTM | As a skin penetration enhancer. |
| Alcohol | Ethanol Isopropyl alcohol | For providing the softness for vesicle membrane As a penetration enhancer |
| Cholesterol | Cholesterol | For providing the stability to vesicle membrane |
| Dye | Rhodamine-123, Rhodamine Red fluorescense isothiocynate 6- carboxy fluorescense | For characterization study. |
| Vehicle | Carbopol D 934 | As a gel former. |

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.
- Ethosomes contain non-toxic materials in formulation, ethosomal drug is administered in semisolid form 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^{7,8}

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 .

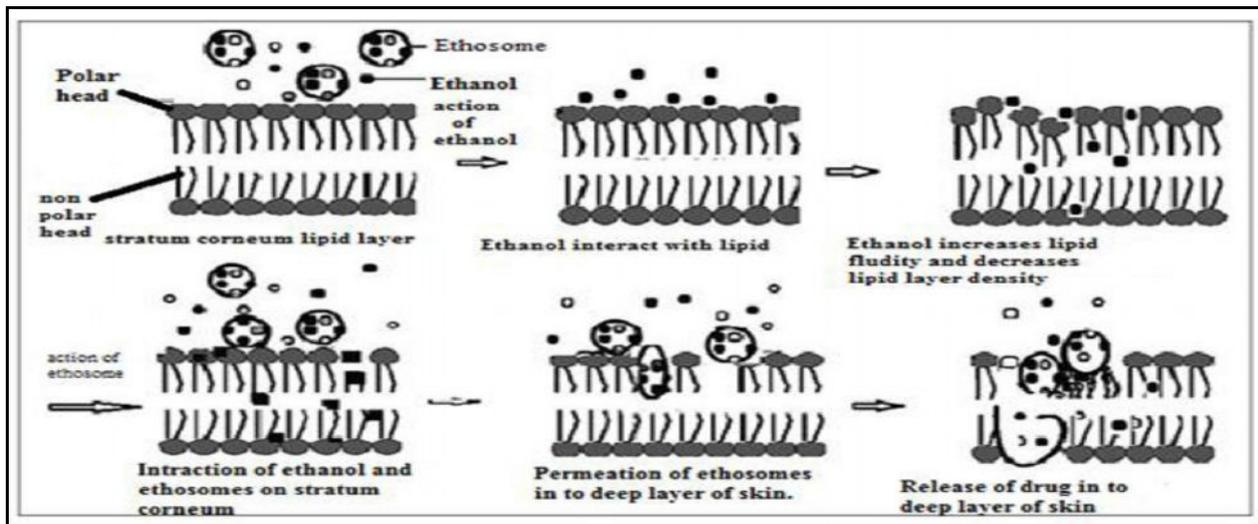


Fig 2 :Drug penetration through ethosomes

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.

Methods 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 30°C in a water bath. The water heated to 30°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 extent using sonication or extrusion method. Finally, formulation is stored under refrigeration.

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.

Classic method

The phospholipid and drug are dissolved in ethanol and heated to $30^{\circ}\text{C}\pm 1^{\circ}\text{C}$ 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.

Mechanical dispersion method

Soya phosphatidylcholine is dissolved in a mixture of chloroform: methanol in round bottom flask. 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^{9,10}.

Characterization Of Ethosomes

Visualization of vesicles

Vesicles are visualized by Transmission electron microscopy (TEM) and scanning electron microscopy (SEM).

Vesicle size and zeta potential

Vesicle size is measured by 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 meter⁶⁷.

Entrapment efficiency¹¹

Entrapment efficiency is determined by Ultracentrifugation technique.

Surface tension activity measurement

It is measured by Ring method in a Du Nouy ring tensiometer.

Transition temperature

It is determined by means of Differential scanning calorimetry.

Penetration and permeation studies

Depth of penetration from ethosomes can be visualized by confocal laser scanning microscopy (CLSM).

Stability of ethosomes

The ability of ethosomal formulations to retain the drug was checked by keeping the preparations at different temperatures, *i.e.* $25\pm 2^{\circ}\text{C}$, $37\pm 2^{\circ}\text{C}$ and $45\pm 2^{\circ}\text{C}$ 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.

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.

Therapeutic Applications of Ethosomes¹²

1. In the treatment herpetic infection- 5% Acyclovir ethosomal preparation compared to the 5 % acyclovir cream showed significant improvements in treatment of herpetic infections.

2. Transcellular Delivery- Ethosomes- as compared to the marketed formulation suggested ethosomes to be an attractive clinical alternative for anti-HIV therapy.

3. Ethosomes are used in pilosabeceous targeting-Ethosomes, the high ethanol containing vesicles are able to penetrate the deeper layers of the skin and hence appear to be vesicles of choice for transdermal drug delivery of hydrophilic and impermeable drugs through the skin.

4. Transdermal Delivery of Hormones- Oral administration of hormones is associated with problems like high first pass metabolism, low oral bioavailability and several dose dependent side effects. The risk of failure of treatment is known to increase with each pill missed.

5. Delivery of Anti-Arthritis Drug- Topical delivery of anti-arthritis drug is a better option for its site-specific delivery and overcomes the problem associated with conventional oral therapy.

Marketed products of ethosomes

In 2000, the ethosomes technology began to commercialize. There are only two companies which developed ethosome products.

Table :- 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 3years | Trima, Israel |

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