Review Article

Innovative Approach to Enhance Permeation of Drug Through Ethosomal Patch: A Review

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ABSTRACT

Since many years, vesicles have been well known and are widely used for their importance in cellular communication and particle transportation. One of the major advances in vesicle research was finding a vesicle derivative, known as ethosomes. Ethosomes are the ethanolic phospholipid vesicles which are mainly used for transdermal delivery of drugs. Ethosomes are advancing, because of its enhanced skin permeation, improved drug delivery, increased drug entrapment efficiency etc. Skin is one of the most extensive and readily accessible organs of the human body which provides a route of drug delivery and offers many advantages over conventional formulation including low plasma drug levels, avoidance of gastrointestinal disturbances and first-pass metabolism of the drugs, and high patient compliance. Flexible liposomes are most commonly used drug carriers in transdermal drug-delivery systems, with relatively good liquidity and deformability. Currently there are three types of flexible liposomes, i.e., transferosomes, ethosomes, and niosomes. Presently, ethosomes have become new liposome carriers with high deformability, high entrapment efficiency, and a good transdermal permeation rate in the drug-delivery system, and are suitable for transdermal administration. Current article reviews about introduction, mechanism of drug penetration, method of preparation of ethosomes, evaluation, preparation and evaluation of ethosomal patch.

Keywords: Ethosomes, vesicles, ethosomal patch.

INTRODUCTION

Skin is regarded as the principal organ of human body, its use for topical delivery of medicine has been well documented. Skin, an external multi-layered organ, functions as a permeability barrier, preventing penetration of foreign matter from the exterior environment into the body. The outermost layer of the skin, stratum corneum (SC) is itself multi-layered and contains relatively low concentrations of water. It is so-called ''brick and mortar'' organization consists of corneocytes, flattened nonnucleated terminally differentiated keratinocytes, embedded in a multilamellar, ordered lipid domain. The cell walls are strengthened by covalently bound lipids and crosslinked proteins, bound to neighbouring cells by protein structures called desmosomes. In contrast to other biological membranes, which are composed primarily of phospholipids, the SC contains mainly ceramides, cholesterol, free fatty acids, and cholesteryl sulphate. Immediately under the SC lies the viable epidermis containing keratinocytes, melanocytes, Merkel cells, and Langerhans cells, the latter of which are important for antigen presentation and the immune response. Below the epidermis is the dermis, embodying structured elements such as collagen fibres and elastin in a mucopolysaccharide network. Fibroblasts, fibrocytes, and histiocytes are embedded in this network of connective tissue, which has the ability to slowly regenerate. In addition, the epidermis and horny layer are interspersed with hair follicles and sweat gland ducts, which originate in the dermis blood supply and fat underneath Topical drug delivery systems, from a pharmaceutical point of view offer several advantages compared with other routes of administration, including avoidance of first-pass metabolism, fewer administration frequency, smaller fluctuations in plasma drug profile, and good patient compliance[1].

Transdermal drug delivery system (TDDS) established a promising result in assessment to oral drug transport system, as it gets rid of gastrointestinal interferences and primary bypass metabolism of the drug but the primary disadvantage of TDDS is, it encounters the barriers of the Stratum Corneum i.e. the lipophilic drugs having molecular weight < 500 Da can only pass through it [2,3].

"Ethosomes are ethanolic liposomes." Ethosomes can be defined as non-invasive delivery carriers that enable drugs to reach deep into the skin layers and/or the systemic circulation. These are soft, malleable vesicles tailored for enhanced delivery of active agents [4].

Ethosomal drug delivery system has numerous benefits in comparison to different transdermal transport systems. These include enhanced permeation of drug via skin pores; ethosomes provide platform for the transport of huge and diversified group of drugs through the pores of skin (peptides, protein molecules); ethosomes contain non-toxic materials in formulation, ethosomal drug is administered in semisolid form (gel or cream) therefore producing high patient compliance. Ethosomal drug delivery system can be used widely in pharmaceutical, veterinary and cosmetic fields. The system is passive, non-invasive and is available for immediate commercialization also, ethosomal drug transport is quite simple in

comparison to iontophoresis and phonophoresis and other complicated methods [5].

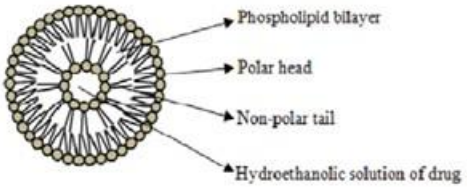

Figure 1: Structure of ethosome[6]

MECHANISM OF DRUG PENETRATION

The main advantage of ethosomes over liposomes is increased permeation of the drug. The drug absorption probably occurs in following two phases:

1. Ethanol effect

Ethanol is major ingredient and acts as a penetration enhancer through the skin. The mechanism of its penetration enhancing effect is well known. Ethanol interacts with lipid molecules in the polar head group region, resulting in reducing rigidity of the stratum corneum, increasing their fluidity. The intercalation of ethanol into the polar headgroup environment can result in an increasing membrane permeability.

2. Ethosomes effect

Increased cell membrane lipid fluidity caused by the ethanol of ethosomes results in increased skin permeability. So, the ethosomes permeates very easily inside the deep skin layers, where it got fused with skin lipids and releases the drugs into deeper layers of skin[7].

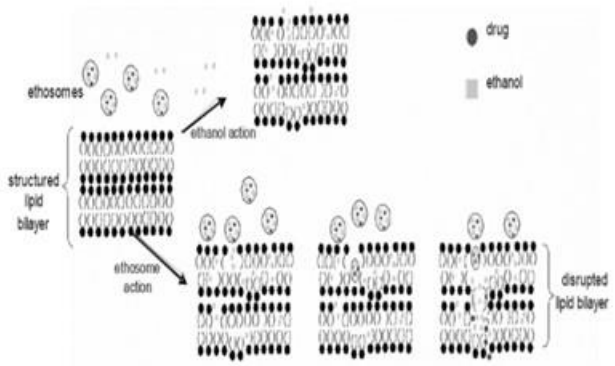

Figure 2: Drug Penetration Through Ethosomes [8]

Methods of preparation of Ethosomes

Ethosomes can be prepared by two very simple and convenient methods that is

1. Cold method[9,10]
2. Hot method

1. Cold Method

This is most widely used method for the preparation of ethosomal formulation. In this method phospholipid, drug and other lipid materials are dissolved in ethanol in a well closed vessel at room temperature by vigorous stirring with the help of mixer. Propylene glycol or another polyol was 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 size of ethosomal formulation can be decreased to desire extend using sonication[11] or extrusion[12] method. Finally, the formulation is stored under refrigeration [13].

2. Hot method

In this method phospholipid and other lipid materials are dispersed in water by heating in a water bath at 40°C until a colloidal solution is obtained. In another vessel, ethanol and propylene glycol are mixed and heated to 40°C. Once the mixtures reach 40°C, the organic phase is added to the aqueous phase. The drug is dissolved in water or ethanol depending on its hydrophilic/ hydrophobic properties. The vesicle size of ethosomal formulation can be reduced to the desire extent using probe sonication or extrusion method [14].

CHARACTERIZATION OF ETHOSOMES

Size and shape of vesicles

Scanning electron Microscopy (SEM) are used to characterize the surface morphology of the ethosomal vesicles. SEM gives a three-dimensional image of the globules. One drop of ethosomal suspension was mounted on a clear glass stub. It was then air dried and gold coated using sodium auro thiomalate to visualize under scanning electron microscope [15].

Zeta Potential

Zeta potential was determined using zetasizer. Measurements were performed on the same samples prepared for size analysis. Zeta potential indicates the degree of repulsion between adjacent, similarly charged particles in dispersion system [15].

Entrapment efficiency

Entrapment efficiency is done by dialysis bag method. The ethosomal suspension was filled in dialysis bag to separate free drug. The dialysis bags were dialyzed for 24h in to 100ml phosphate buffer saline (Ph7.4). After 24h, 0.5ml was taken and isopropanol was added up to 5ml, then the volume was increased to 10ml with respective solvent. The absorbance of the resulting solution was measured using uv-visible spectrophotometry [16].

In vitro drug diffusion study

The in vitro diffusion study is carried out using Franz Diffusion Cell. The semi permeable membrane is mounted between the donor and the receptor compartment. Ethosomal suspension is placed in donor compartment. Suitable buffer is taken in the receptor compartment. The receptor compartment is surrounded by water jacket so as to maintain the temperature at 37°C ± 0.5°C. Samples were withdrawn and replaced by equal volumes of fresh

receptor fluid on each occasion and analysed spectrophotometrically [17].

Preparation of ethosomal patch

- Ethosomal patch was prepared by dissolving the weighed amount of polymer in solvent mixture on magnetic stirrer.
- Ethosomal suspension is added to polymer solution during stirring to get uniform mixing of suspension with polymer solution.
- After formation of homogenous mixture plasticizer was incorporated then continuously mixed to obtain uniform mixture.
- Obtained solution is poured into moulds and allow it to dry for 24 h at room temperature and the obtained patches were stored in desiccators to remove excess moisture in them[18].

CHARACTERIZATION OF ETHOSOMAL PATCH

Tensile strength

The tensile strength of the patch can be evaluated using the tensiometer. It consists of two load cell grips. The lower one was fixed, and upper one was movable. Film strips were fixed between these cell grips, and force was gradually applied till the film broke. The tensile strength was taken directly from the dial reading in kg.[19,20]

Thickness

Thickness of the patch can be measured using digital micro meter screw gauge at three different places, and the mean value was calculated.[19,20]

Uniformity of weight

Patches are randomly collected and the weight is determined. The value reported must be the mean of three sets of experiments. [19,20]

Folding Endurance

The folding endurance was measured manually for the prepared patches. It is expressed as number of times the patch is folded at the same place either to break the patch or to develop visible cracks. This is important to check the ability of sample to withstand folding. This also gives an indication of brittleness. This was determined by repeatedly folding one patch at the same place till it breaks. The number of times the patch could be folded at the same place without breaking/cracking gave the value of folding endurance. [19,20]

Percent moisture content

The films should be weighed individually and kept in desiccators containing calcium chloride at room temperature for at least 24 h. Film was weighed again; the difference in weight (initial and final weight) gives moisture content. [18]

$$\% \text{ Moisture content} = \frac{\text{Initial weight - final weight}}{\text{Initial weight}}$$

***In vitro* drug diffusion study**

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CONCLUSION

Development of vesicular systems such as ethosomes showed enhanced permeability, sustained action and high entrapment of drug. Though ethosomes have drawbacks such as drug leakage in case of incomplete shell-locking, ethosomes act as self-permeating structures through stratum corneum, hence they are considered to be promising topical drug delivery systems. Formulation of ethosomal patch releases the drug at fixed doses.

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