ETHOSOMAL DRUG DELIVERY SYSTEM: A REVIEW


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ABSTRACT
The vesicles have been well known for their important in cellular communication and particle transportation for many years. Researchers have understood the properties of vesicle structures for use in better drug delivery within their cavities, that would allow to tag the vesicle for cell specificity. Vesicles would also allow to control the release rate of drug over an extended time, keeping the drug shielded from immune response or other removal systems and would be able to release just the right amount of drug and keep that concentration constant for longer periods of time. One of the major advances in vesicle research was the finding a vesicle derivative, known as an ethosomes. Ethosomes are modified lipid carriers that enable drugs to reach into deeper skin layers and/or systemic circulation, and represent a lipid vesicular carrier system embodying ethanol in relatively high concentration and are very effective in delivering drugs into and across the skin.

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INTRODUCTION

In the past decade, topical delivery of drugs by liposomal formulations has evoked considerable interest. Recently, it has value as carriers for transdermal drug delivery, because they do not deeply penetrate skin but remain confined to upper layers of the stratum corneum. Confocal microscopy studies have shown that intact liposomes are not able to penetrate into the granular layers of the epidermis [1]. Recent approaches to modulating drug delivery through skin have resulted in the design of a novel vesicular carrier, ethosomes. Ethosomes were developed by Touitou et al as additional novel lipid carriers composed of ethanol, phospholipid, and water. Ethosomes were reported to improve the skin delivery of various drugs [2]. Ethanol is known as an efficient permeation enhancer that is believed to act by affecting the intercellular region of the stratum corneum. Its inclusion in liposomes to form ethosomes has already been investigated [3].

Transdermal drug delivery systems offer many advantages over their corresponding classical oral, injectable, and inhaler systems, including (1) improving the systemic bioavailability of drugs because the first-pass metabolism by the liver and digestive system is avoided, and (2) achieving a controlled constant drug delivery profile, which is especially important for those suffering from nocturnal attacks and need a longer duration of therapeutic action from a single application [4].

Despite the many advantages of the skin as a site of drug delivery, only few drugs are currently in the market for transdermal delivery system. The primary reason for this is the low permeability of drugs in the stratum corneum, as stratum corneum (outermost layer) acts as the main barrier in the skin. In general the highly organized crystalline lipid lamellae play an essential role in the barrier properties of the stratum corneum [5]. Many techniques have been aimed to disrupt and weaken the highly organized intercellular lipids in an attempt to enhance drug transport across the intact skin or to increase the driving force for permeation of drugs across this skin barrier. The vesicles have been well known for their important in cellular communication and particle transportation for many years. Researchers have understood the properties of vesicle structures for use in better drug delivery within their cavities that would allow for tagging the vesicle for cell specificity [6]. The ethosomes more advantages when compared to transdermal and dermal delivery. It delivers large molecules such as peptides, protein molecules. Simple method for drug delivery in comparison to Iontophoresis and Phonophoresis and other complicated methods. 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. High patient compliance as it is administrated in semisolid form (gel or cream) and various application in Pharmaceutical, Veterinary, Cosmetic field [7].

COMPOSITION OF ETHOSOMES:

Ethosomes are composed mainly of phosphatidylcholine, high concentration of hydroalcohols or hydroalcohols, glycols and water (Figure 1). Phosphatidylcholine can be: phosphatidyl soya phosphatidylcholine, egg phosphatidylcholine, dipalmityl phosphatidyl choline, hydrogenated phosphatidylcholine. As alcohols, we can use ethanol or isopropyl alcohol, and as poliglicols propylene glycol and transcutol [8].

ETHANOL- AS PENETRATION ENHANCER:

Substances that reversibly reduce the barrier resistance of the stratum corneum are known as chemical penetration enhancers. Ethanol is one of the most commonly used permeation enhancers. A number of mechanisms have been proposed for permeation enhancing action of ethanol. As a solvent, ethanol can be included in the formulation to enhance the solubility of the drug. This is particularly important for poorly soluble permeants, as they are prone to depletion in the donor vehicle. Ethanol is a relatively volatile solvent and will rapidly evaporate at skin temperature. Ethanol loss from a formulation may lead to the drug becoming supersaturated, which will influence drug
flux across the membrane. In addition, ethanol is thought to alter the solubility properties of the stratum corneum, facilitating improved drug partitioning [9].

Ethanol has been employed in vitro to enhance transdermal delivery of levonorgesterol, hydrocortisone and 5-fluouracil across rodent skin, and estradiol across human skin in vivo. Megrab and collaborators noted that the enhancement effect of ethanol was concentration dependent. The authors investigated the effect of ethanol on skin water content and concluded that formulations containing high levels of alcohol were capable of dehydrating the skin, which may explain the concentration dependant action of ethanol.

METHOD OF PREPARATION

There are two methods which can be used for formulation and preparation of ethosomes. Both of these are very simple and convenient and do not involve any sofisticated instrument or complicated process.

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 [10].

Cold Method

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. 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 [11]. The vesicle size of ethosomal formulation can be de-creased to desire extend using sonication or extrusion method. Finally, the formulation is stored under refrigeration.

MECHANISM OF PENETRATION:

The mechanism of penetration of the ethosomes in and through the skin is not yet completely elucidated. Two simultaneous mechanisms of action have been proposed: ethanol has a fluidization effect on the ethosomal lipids and ethanol has a fluidization effect on the stratum corneum lipids. (Figure 2) Because of the use of ethanol in the preparation of the ethosomes, the deformability of the prepared vesicles is increasing. Besides, the high alcohol content is expected to partially extract the stratum corneum lipids. These processes are responsible for increasing inter and intracellular permeability of ethosomes. The ultra deformable vesicles can forge paths in the disordered stratum corneum and finally release drug in the deeper layers of the skin. Therefore, a path through the skin can be expected to result, permitting the fusion of ethosomes with the cells from the deepest skin layers [12]. Flow chart of penetration of ethosomes is as depicted in figure 3.
TABLE 1: Therapeutic Applications of Ethosomal Carrier

<table>
<thead>
<tr>
<th>Sr.No.</th>
<th>Drug</th>
<th>Purpose of Ethosomal Delivery</th>
<th>Therapeutic Application</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Azelaic acid</td>
<td>Improves the sustained release</td>
<td>Treatment of acne</td>
</tr>
<tr>
<td>2</td>
<td>Diclofenac</td>
<td>Selective targeting the cells</td>
<td>NSAIDS</td>
</tr>
<tr>
<td>3</td>
<td>Testosterone</td>
<td>low oral bioavailability, dose dependent side effects</td>
<td>Steroidal hormone</td>
</tr>
<tr>
<td>4</td>
<td>Trihexyphenidyl hydrochloride</td>
<td>4.5 times higher than that from liposome</td>
<td>Treatment of Parkinson’s disease</td>
</tr>
<tr>
<td>5</td>
<td>Zidovudine and lamivudine</td>
<td>Better cellular uptake</td>
<td>Anti HIV</td>
</tr>
<tr>
<td>6</td>
<td>Bacitracin</td>
<td>Better cellular uptake</td>
<td>Antibacterial</td>
</tr>
<tr>
<td>7</td>
<td>Erythromycin</td>
<td>Better cellular uptake</td>
<td>Antimicrobial</td>
</tr>
<tr>
<td>8</td>
<td>DNA</td>
<td>Expression into skin cells</td>
<td>Treatment of genetic disorders</td>
</tr>
<tr>
<td>9</td>
<td>Cannabidiol</td>
<td>low bioavailability</td>
<td>Treatment of rheumatoid</td>
</tr>
<tr>
<td>10</td>
<td>Acyclovir</td>
<td>Poor skin permeation</td>
<td>Treatment of Herpes labialis</td>
</tr>
<tr>
<td>11</td>
<td>Insulin</td>
<td>GIT degradation</td>
<td>Treatment of diabetes</td>
</tr>
<tr>
<td>12</td>
<td>Cyclosporin</td>
<td>GIT degradation, Poor oral</td>
<td>Treatment of Inflammatory skin disease</td>
</tr>
<tr>
<td>13</td>
<td>Ammonium glycyrrhizinate</td>
<td>Poor skin permeation, Poor oral bioavailability</td>
<td>Treatment of inflammatory based skin diseases</td>
</tr>
<tr>
<td>14</td>
<td>Fluconazole</td>
<td>Poor skin permeation</td>
<td>Treatment of candidiasis</td>
</tr>
<tr>
<td>15</td>
<td>Methotrexate</td>
<td>Poor skin permeation</td>
<td>Treatment of psoriasis</td>
</tr>
<tr>
<td>16</td>
<td>Salbutamol</td>
<td>Enhanced drug delivery through skin with ethosomes</td>
<td>Anti asthmatic</td>
</tr>
<tr>
<td>17</td>
<td>Minoxidil</td>
<td>Piloceobaceous targeting, Accumulation in skin increased</td>
<td>Treatment of baldness</td>
</tr>
<tr>
<td>18</td>
<td>Proteins and Peptides</td>
<td>Large molecules</td>
<td>overcoming the problems associated with oral delivery</td>
</tr>
<tr>
<td>19</td>
<td>Enalapril maleate</td>
<td>Low oral bioavailability, Major side effects in oral delivery</td>
<td>Treatment of Hypertension</td>
</tr>
</tbody>
</table>
CHARACTERISATION OF ETHOSOMAL SYSTEM:

Visualization of Vesicles by TEM and by SEM:

Vesicular shape of the ethosome preparations is assessed by using Transmission Electron Microscope (TEM). Samples are dried on carbon-coated grid and negatively stained with aqueous solution of phosphotungstic acid. After drying the specimen is viewed under the microscope at 10–100 k-fold enlargements at an accelerating voltage of 100 Kv [13].

The size and shape of the vesicles are observed in the Scanning Electron Microscopy (SEM). One drop of ethosomal suspension is mounted on a clear glass stub. It is then air dried and gold coated using sodium aurothiomalate to visualize under scanning electron microscope at 10,000 magnifications.

Size Distribution and Vesicular Size:

The size distribution of ethosomal preparation can be measured in a multimodal mode, by Dynamic Light Scattering (DLS) technique using a computerized Malvern Autosizer 5002 inspection system. For vesicle size measurement, ethosomal preparation is mixed with the appropriate medium.[14].

Entrapment Efficiency:

Entrapment efficiency of ethosomal vesicles can be determined by centrifugation method. The vesicles were separated in a high speed cooling centrifuge at 20,000 rpm for 90 minutes in the temperature maintained at 4°C [15]. The sediment and supernatant liquids were separated amount of drug in the sediment can be determined by lysing the vesicles using methanol. From this, the entrapment efficiency can be determined by the following equation,

\[ \text{Entrapment Efficiency} = \frac{\text{DE}}{\text{DT}} \times 100 \]

Where,

DE - Amount of drug in the ethosomal sediment
DT - Theoretical amount of drug used to prepare the formulation (equal to amount of drug in supernatant liquid and in the sediment)

Transition Temperature:

The Transition temperature (T) of vesicular lipids can be measured in duplicate by DSC in an aluminum pan at a heating rate of 10°C per min, under a constant nitrogen stream [16].

Confocal Scanning Laser Microscopy (CSLM):

CSLM can be used to investigate depth and mechanism of skin penetration of ethosomal preparation [17]. The skin thickness can be optically scanned at different increments through the z-axis of a confocal laser scanning microscope.

Drug Content:

Drug content of the ethosomes can be determined using UV spectrophotometer. This can also be quantified by a modified high performance liquid chromatographic method [18].

Surface Tension Measurement:

The surface tension activity of drug in aqueous solution can be measured by the ring method in a Du Nouy ring tensiometer [19].
Phospholipid-ethanol interaction:--
The phospholipid-ethanol interaction was studied by using proton decoupled 31P-NMR and Differential Scanning calorimetry [20].

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 Nephalometer [21].

In vitro drug release study and Drug Deposition study:--
In vitro drug release study and Drug Deposition of ethosomal preparation can be performed by Franz diffusion cell with artificial or biological membrane, Dialysis bag diffusion [22].

ADVANTAGES OF ETHOSOMAL DRUG DELIVERY:--
In comparison to other transdermal & dermal delivery systems
- Enhanced permeation of drug through skin for transdermal drug delivery.
- Delivery of large molecules (peptides, protein molecules) is possible.
- It contains non-toxic raw material in formulation.
- High patient compliance- The ethosomal drug is administrated in semisolid form (gel or cream) hence producing high patient compliance.
- The Ethosomal system is passive, non-invasive and is available for immediate commercialization.
- Ethosomal drug delivery system can be applied widely in Pharmaceutical, Veterinary, Cosmetic fields.
- Simple method for drug delivery in comparison to iontophoresis and phosphophoresis and other complicated methods.

THERAPEUTIC APPLICATIONS:--
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. Various therapeutic applications of ethosomes are as shown in table 1.

REFERENCE:-
10. Touitou E, inventor. Composition of applying active substance to or through the skin. US patent 5 540 934, July 30, 1996.
11. Touitou E, Godin B, Weiss C. Enhanced delivery of drugs into and across the