TRANSETHOSOMES: A NEW PROSPECT FOR ENHANCED TRANSDERMAL DELIVERY

Jessy Shaji* and Rinki Bajaj

Department of Pharmaceutics, Principal K. M. Kundnani College of Pharmacy, Cuffe Parade, Mumbai - 400005, Maharashtra, India.

ABSTRACT: The skin covers a total surface area of approximately 1.8 m² and provides the contact between the human body and its external environment. Transdermal route of drug delivery has gained great interest in pharmaceutical research as it overcomes many problems associated with the oral route of administration. Although the skin, particularly the stratum corneum presents a barrier to most drug absorption, it provides a large (1.2 m²) and accessible surface area for drug diffusion. Recently, various strategies have been used to augment the transdermal delivery of bioactives. Mainly, they include iontophoresis, electrophoresis, sonophoresis, chemical permeation enhancers, magnetophoresis, microneedles, vesicular systems (liposomes, niosomes, elastic liposomes such as ethosomes, transfersomes and transethosomes). Among these transethosomes appear to be more promising as they possess both lipophilic and hydrophilic regions and can accommodate drug molecules with a wide range of solubility. Transethosomes can deform and pass through a narrow constriction that is 5 to 10 times less than its own diameter. This high deformability gives better penetration of intact vesicles. These vesicles can be used for transdermal delivery of various classes of drugs like analgesics, anesthetics, corticosteroids, sex hormones, anticancer agents insulin etc.

INTRODUCTION: At present, the most common form of drug delivery is the oral route. While this has the notable advantage of easy administration, it also has significant drawbacks—namely poor bioavailability due to hepatic metabolism (first pass) and the tendency to produce rapid blood level spikes (both high and low), leading to a need for high and/or frequent dosing, which can be both cost prohibitive and inconvenient. Continuous intravenous infusion is recognized as a superior mode of drug administration not only to bypass hepatic ‘first pass’ metabolism but also to maintain a constant and prolong drug level in the body. But that requires hospitalization of the patients and close medical supervision of administration. At the same time transdermal route offers number of advantages over conventional delivery systems such as lower fluctuations in plasma drug levels, gastrointestinal side effects and high patient compliance. Stratum corneum is the most difficult barrier which does not allow passage of most of the drugs; except lipophilic and low molecular weight drugs 1, 2.

Ultra deformable vesicles (UDV) have recently become a promising tool for the development of improved and innovative dermal and transdermal therapies 3. Deformable vesicles like transethosomes present the advantages of being nontoxic and thermodynamically stable formulations. They have been used for dermal and transdermal delivery of many molecules including peptides and proteins. In addition, their production is relatively simple and easy to scale up.
Currently, there are various types of UDV that have been successfully developed for both pharmaceuticals and cosmeceuticals, particularly transfersomes, ethosomes, and, more recently, transethosomes. The term transethosomes and the underlying concept were introduced by Song et al., in 2012, and are characterized by having a high content of ethanol (upto 30%) together with an edge activator. Transethosomes may contain advantages of both transfersomes and ethosomes. The mechanism of skin penetration might be a fusion of both mechanisms.

**Advantages of Transethosomal Drug Delivery:**
- The transethosomal system is passive, non-invasive and is available for immediate commercialization.
- It contains non-toxic raw materials in the formulation.
- Transethosomal drug delivery can be applied to many fields including veterinary and cosmetic fields.
- It shows high patient compliance as it is administered in semisolid gel or cream form.
- Contrary to deformable liposomes, transethosomes improve skin delivery of drugs both under occlusive and non-occlusive condition.
- This drug delivery system shows better stability as compared to other conventional vesicles.
- Simple method of drug delivery as compared to iontophoresis, laser surgery, cryo surgery and other complicated methods.

**Disadvantages of Transethosomal Drug Delivery:**
- Adequate solubility of the drug in both lipophilic and aqueous environments to reach dermal microcirculation and gain access to the systemic circulation.
- The molecular size of the drug should be reasonable that it should be absorbed percutaneously.

**FIG. 1: TRANSETHOSOMES**

**FIG. 2: PERMEATION AND PENETRATION OF TRANSETHOSOMES THROUGH SKIN**
TABLE 1: SHOWS THE COMPARISON BETWEEN ETHOSOMES AND TRANSETHOSOMES

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Ethosomes</th>
<th>Transethosomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Composition</td>
<td>1. Phospholipids</td>
<td>1. Phospholipids</td>
</tr>
<tr>
<td></td>
<td>2. Ethanol</td>
<td>2. Ethanol</td>
</tr>
<tr>
<td></td>
<td>3. Propylene glycol or other alcohol</td>
<td>3. Edge activator (surfactant) or penetration enhancer</td>
</tr>
<tr>
<td></td>
<td>4. Charge inducer</td>
<td>4. Charge inducer</td>
</tr>
<tr>
<td></td>
<td>5. Water</td>
<td>5. Water</td>
</tr>
<tr>
<td>Morphology</td>
<td>Spherical</td>
<td>Regular or irregular spherical shape</td>
</tr>
<tr>
<td>Entrapment efficiency</td>
<td>Higher than classical ethosomes</td>
<td>Higher than ethosomes</td>
</tr>
<tr>
<td>Skin permeation</td>
<td>Typically equal to or higher than classical ethosomes</td>
<td>Higher than ethosomes</td>
</tr>
<tr>
<td>Size</td>
<td>equal to or smaller than classical ethosomes</td>
<td>Size based on type and concentration of penetration enhancer or edge activator used</td>
</tr>
<tr>
<td>Stability</td>
<td>Stable than classical ethosomes</td>
<td>Stable than ethosomes</td>
</tr>
</tbody>
</table>

Methods of Preparation: Mechanical dispersion, cold method and hot method are the methods used for the preparation of transethosomes. Cold method is the most commonly used method.

Hot Method: Disperse phospholipid in water by heating in a water bath at 40 °C to obtain a colloidal solution. Ethanol and glycol are mixed and heated up to 40 °C. Organic phase is added to aqueous phase. Stir for 7 to 10 min. Depending on its hydrophilic/hydrophobic properties, drug can be dissolved in water or ethanol. Temperature is maintained at 40 °C throughout the preparation. Size of the vesicles is reduced by probe sonication.

Cold Method: Dissolve phospholipid in ethanol by vigorous stirring. This mixture is heated up to 30 °C in water bath. Water is heated up to 30 °C in a separate vessel and added to the alcoholic mixture slowly in a fine stream. Depending on drug solubility, it can be dissolved in water or ethanol. The mixture is kept on magnetic stirrer at 700 rpm during the addition of the above aqueous solution to ethanolic solution. Modulation of vesicle size can be done using probe sonicator.

Mechanical Dispersion Method: Lipid and surfactant is taken in clean, dry, round bottom flask. Lipid mixture is dissolved in solvent mixture of chloroform and methanol mixture. A thin film of lipid is obtained using rotary evaporator above the lipid transition temperature. It is kept overnight under vacuum to remove traces of organic solvent. The deposited film is hydrated with 10 % v/v ethanol in phosphate buffer pH 6.5 by rotation at 60 rpm. Drug is added to the formulation. The vesicles are sonicated for desired size.

Various methods for Characterization of Transethosomes:

Vesicle Shape: Vesicle shape can be determined by transmission electron microscopy (TEM) and by scanning electron microscopy (SEM).

Particle Size and Zeta Potential: Particle size of transethosomes can be done by particle size analyzer, dynamic light scattering and photon correlation spectroscopy. Zeta potential of the formulation can be measured by zeta meter.

Entrapment Efficiency: The entrapment efficiency is expressed as the percentage entrapment of the drug added. This can be measured by ultracentrifugation technique. % EE can be expressed as: [Qt-Qs/Qt]* 100

Where Qt is total theoretical amount of drug added and Qs is the amount of drug found in supernatant.

Transition Temperature: The transition temperature of transethosomes can be determined by using differential scanning calorimetry (DSC).

Drug Content: Drug content of transethosomes can be determined using U.V spectrophotometer. This can also be quantified by a modified high performance liquid chromatographic method.

Vesicle Stability: The stability of vesicles can be determined by assessing the size and structure of vesicles over time.

Surface Tension: The surface tension activity of drug in aqueous solution can be measured by the ring method in a Du Nou ring tensiometer.
Penetration and Permeation: Depth of penetration from transethosomes can be visualized by confocal laser scanning microscopy (CLSM)\textsuperscript{17}.

In-vitro Drug Release:\textsuperscript{18} This is performed for determining the permeation rate. Time needed to attain steady state permeation and the permeation flux at steady state and the information from in-vitro studies are used to optimize the formulation before more expensive in-vivo studies are performed.

Materials Commonly Used in Preparation of Transethosomes:\textsuperscript{14}

<table>
<thead>
<tr>
<th>TABLE 2: MATERIALS USED IN TRANSETHOSOMES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class</td>
</tr>
<tr>
<td>Phospholipid</td>
</tr>
<tr>
<td>Alcohol</td>
</tr>
<tr>
<td>Surfactant</td>
</tr>
<tr>
<td>Dye</td>
</tr>
<tr>
<td>Buffering agent</td>
</tr>
</tbody>
</table>

Application of Transethosomes:

Delivery of Non-steroidal Anti-inflammatory Drugs (NSAIDs): Oral administration of NSAIDs are associated with number of GI side effects. Hence transdermal delivery using ultraformable vesicles is preferred. Transethosomes containing ketorolac tromethamine show enhanced penetration than drug containing ethosomes.

Garg V et al., recently proved that transethosomal gel of piroxicam was found to be superior in all aspects as compared to other vesicular systems with improved stability and highest elasticity\textsuperscript{22}.

Delivery of Antifungal Drugs: Transethosomes containing terbinafine, amphotericin B, ketoconazole showed enhanced permeation. Also voriconazole transesthosomes showed skin permeation and deposition as compared to that of conventional liposomes, deformable liposomes and ethosomes\textsuperscript{23}.

Delivery of Anticancer Drugs: Imiquimod was investigated for transdermal delivery using transethosome technology. The results were favorable and provided a new approach for skin cancer treatment. Transethosomes showed better penetration and increased transdermal flux. Even after storage transethosomes retained its penetration power.

Issues and Future Progress Related to Ethanol Based Vesicles for Transdermal Drug Delivery:
Most of the active molecules do not pass through stratum corneum barrier. Ethanol based nanocarriers have opened a new window to deliver various bioactive molecules transdermally as they have capability to fluidize and disturb the rigid lipid system of stratum corneum. These systems represent an efficient non-invasive drug delivery approach for medium and large sized bioactive molecules along with high patient compliance and low cost treatment. However, effective clinical exploration of the ethanol based nanocarrier system is still a challenge. It is necessary to evaluate them clinically to check their potency. Ethanol based nanocarriers need safety exploration in some specific clinical conditions like their application to open areas of eczema as ethanol show irritant effect to skin. So, further research in this field will promote effective drug release in-vivo and make transdermal therapy\textsuperscript{24}.

CONCLUSION: Skin permeation enhancement technology is a rapidly growing field which will significantly increase the number of drugs for transdermal delivery. As a result skin may become major route of delivery in the coming decade\textsuperscript{25}. Transethosomes provide the highest flexibility to the formulator to change the ethosomal properties according to the required research criteria by changing the edge activators and/or penetration enhancers\textsuperscript{26}. Ultra deformable vesicles like transethosomes have the ability to deliver larger range of molecules like peptides, drugs with poor penetration, drugs for quicker and targeted action, hormones and antibiotics etc.

They offer safety, efficacy and patient compliance hence are more superior to other conventional transdermal permeation techniques. Transethosomes have become promising carriers not only for topical treatment of local but also for systemic...
disorders. They can be explored in the future for delivery of various drugs through transdermal delivery. Formulation of these vesicles in gel form may improve their viscosity and hence increase their residence time on the site of action.

**ACKNOWLEDGEMENT:** Authors are thankful to Naprod Life Science Pvt. Ltd. (Mumbai, India) for the gift sample of 5-Fluorouracil.

**CONFLICT OF INTEREST:** The authors declare no conflict of interest.

**REFERENCES:**