Transdermal drug delivery is the movement of drug formulation from the healthy and intact stratum corneum layer of skin to the systemic circulation of the body [1]. Transdermal drug delivery has more advantages than the oral route and hypodermic injections, as it is non-invasive, painless, and eliminates the risk of transmission of disease by the reuse of needles. It bypasses the first-pass effect, is easier to self-administer, prolonged and improved therapeutic effect, enhanced bioavailability, ensures a sustained release of drugs from the drug formulation, and is inexpensive [2]. This route not only bypasses the first-pass-effect but also provides a large surface area for absorption and improves efficacy [3]. Despite all the benefits, it has some challenges, the most common of which is skin acting as a barrier for drug penetration due to its organized structure [4]. The barrier properties of skin are due to the outermost layer of the epidermis called the stratum corneum. The stratum corneum consists of corneocytes, proteins and is enveloped in a lipid bilayer that prevents the absorption of drugs. It allows the entry of molecules having lipid solubility, and lower molecular weight[5].

**DRUG DELIVERY PATHWAYS THROUGH SKIN**

There are basically three main routes for the drug penetration through the layers of skin, which include transcellular, intercellular, and appendageal routes [6].
The transdermal drug administration through the appendageal route is the least used route due to low diffusion rate and small area for absorption [7]. The transcellular routes are the major pathway for polar drugs during the percutaneous absorption of the drug and for hydrophilic compounds[8].

**TRANSETHOSOMES**

Transethosomes are lipid-based, elastic, Ultra-Deformable Vesicles(UDV). These are uneven spherical shaped carriers that have the ability to encapsulate low as well as high molecular weight drugs [9]. After the discovery of transfersomes and ethosomes, the transethosomal system of drug delivery was first introduced in 2012 [10]. The novel transethosomes contain the major benefits of ethosomes and transfersomes i.e., vesicle elasticity and skin permeation. The structure of transethosomes mainly consists of phospholipids along with ethanol, edge activator (surfactant), and water. Phospholipids being amphiphilic perform the main role in bilayer formation [9]. Edge activators like tween 20, tween 60, tween 80, span 60, span 65, span 80, and sodium cholate or sodium deoxycholat, among others, improves the permeability and the flexibility of the vesicle [11, 12]. However, Ethanol (used in concentration up to 30%) is the penetration enhancer and water is the vesicle forming agent [13].

Permeation mechanism of transethosomes through skin barrier; transethosomes assist in the drug delivery by enhancing the permeability of the components of the free drug through the skin with the help of vesicle components. Ethanol is the major constituent responsible for the penetration of transethosomes as edge activators alone are not sufficient to penetrate into the lower layers of the skin [14,15]. Ethanol present in transethosomes causes disruption of the phospholipids in the stratum corneum causing fluidization [16]. Increased fluidization results in increased intracellular space which in turn increases the penetration. Transethosomes instigate hydration that broadens the pore size. This allows the edge activator to utilize its deforming properties to help squeeze the molecule through the stratum corneum despite the smaller diameter of the pores [17]. Subsequent to passing through corneum, it goes through feasible epidermis and arrives at the dermis[18].

<table>
<thead>
<tr>
<th>Therapeutic agent</th>
<th>Title of the study</th>
<th>Major findings</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brucine-strychnine</td>
<td>Novel transethosomes for the delivery of brucine and strychnine: Formulation optimization, characterization and in vitro evaluation in hepatoma cells</td>
<td>Hematoma cells took up the brucine-strychnine transethosome formulation making the long-term, potent inhibition of proliferation possible to achieve.</td>
<td>[19]</td>
</tr>
<tr>
<td>Paeonol</td>
<td>Evaluation of paeonol-loaded transethosomes as transdermal delivery carriers</td>
<td>Bioavailability of paeonol can be increased by using paeonol transethosomes</td>
<td>[20]</td>
</tr>
<tr>
<td>Coenzyme Q10</td>
<td>Coenzyme Q10 phospholipid vesicular formulations for treatment of androgenic alopecia; ex vivo permeation and clinical appraisal</td>
<td>CoQ10-loaded transethosomes enhanced the therapeutic efficiency to help treat androgenic alopecia and other topical diseases.</td>
<td>[22]</td>
</tr>
<tr>
<td>Medoxomil</td>
<td>Use of transethosomes for enhancing the transdermal delivery of medoxomil: in vitro, ex vivo, and in vivo evaluation</td>
<td>Transethosomes have proved to be a successful carrier for medoxomil</td>
<td>[25]</td>
</tr>
<tr>
<td>Olmesartan</td>
<td>Systematic Development of Transethosomal Gel System of Olmesartan: Formulation Optimization, In Vitro Evaluation, and Ex Vivo Assessment</td>
<td>Olmesartan-loaded transethosomes showed high elasticity and improved stability.</td>
<td>[28]</td>
</tr>
</tbody>
</table>

**Table 1:** Summarized list of therapeutic agents delivered through transethosomes.

Transethosomes are easy to manufacture and simple to scale up without contribution of refined apparatus at both pilot plant and modern level. Various strategies are utilized to accomplish smaller vesicular size and these vesicles are fused into gels or creams to increment skin infiltration. The commonly used methods are; a) Cold method, b) Hot method, and c) Mechanical Dispersion method. Transethosomes have the combined properties of both transfersomes and ethosomes exhibiting properties of both skin permeation and deformability, this help to bypass the presystemic metabolism, transethosomes provide a non-invasive route of administration and in diseases or conditions, where patients cannot take drugs orally transethosomes can be an effective route of delivery. Skin allergies or contact dermatitis can be a possibility, reasonable molecular size of the drug is needed for absorption and incomplete formulation of vesicles can lead to coalescence.

**CONCLUSION**

Ultra-deformable Vesicles (UDVs) have been developed to improve the transdermal drug delivery by augmenting the penetration of the drug molecules through the stratum corneum. Transethosomes have proved to be more effective drug carrier as they have enhanced permeability properties. Transethosomes have combined the
penetration abilities of transfersomes and ethosomes by incorporating the edge activator with the ethanol in the vesicle. More advancement in this area may lead to further innovations creating betterment in the field of pharmaceutics.

REFERENCES


