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Review

Transethosomes Novel Carrier: Promising Ultra deformable system for topical drug delivery

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Abstract:

Lipid nanoparticles have been the subject of much investigation as frontline nanocarriers for medication and vaccine formulations due to the growing demand for novel drug delivery strategies. With benefits over conventional formulations such as reduced plasma fluctuations, first-pass metabolism, organ toxicity, and low bioavailability, transethosomes have come to light as a potentially effective treatment. This thorough analysis looks at manufacturing methods and assessment attributes for effective drug delivery, as well as the effects of formulation elements on the characteristics and efficient targeting of transethosomes. In order to demonstrate the adaptability and possibility for controlled release of transethosomes, the review also looks at their numerous routes of administration, such as transdermal, transvaginal, pulmonary, and ocular delivery. The review also looks at how photodynamic treatment and functionalization could improve the effectiveness of medication delivery.

Keywords: *Lipid nanoparticles, low bioavailability, transethosomes, medication delivery*

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Introduction

At the moment, oral administration is the most used method of administering medication. Although this has the benefit of being easy to administer, it has several disadvantages as well, such as poor bioavailability because of hepatic metabolism (first pass) and the potential for both high and low blood level spikes that require high and/or frequent dosage, which can be expensive and inconvenient. Continuous intravenous infusion is thought to be a better way to administer drugs because it prevents the liver from doing a "first pass" metabolism and maintains a stable, long-lasting medication level in the body.[01 to 05] But this means that the patients must be admitted to the hospital, and the administration must keep an eye on their health. In addition, the transdermal methodology has several advantages over traditional distribution techniques, such as high patient compliance, gastrointestinal adverse effects, and less volatility of plasma drug levels.[06, 08 09]

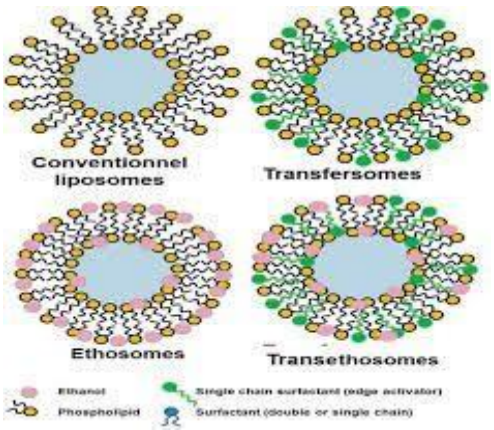

Figure 1 Transethosomal

Advantages of Transethosomal Drug Delivery

i. The transethosomal system is passive, non-invasive and is available for immediate commercialization.
ii. It contains non-toxic raw material in the formulation.[10]
iii. The Transethosomes drug is administered in a semisolid form.[11]
iv. Transethosomes drug delivery can be applied to many fields including veterinary andcosmetic fields.

Disadvantages of Transethosomes Drug Delivery

i. The molecular size of the drug should be reasonable that it should be absorbed percutaneously.[12]
ii. Skin irritation or allergic reaction on contact dermatitis.
iii. Product loss during transfer from alcoholic and water media.
iv. Unsuccessful vesicles formation can coalesce transethosome.[11]

Salient features of Transethosomes

i. They have high entrapment efficacy, as they are biocompatible and biodegradable innature.
ii. Encapsulation drug is protected from the degradation as due to which they their contentslowly and gradually.
iii. Easy to prepare, does not involve tedious process and also avoids the unnecessary use of pharmaceutical additives, can be used for both systemic as well as topical delivery.[17 to 20]

The Impact of Formulation Components on Transethosome Properties

Assimilation of the function and influence of formulation components is essential for building transethosomal formulations that can maximize drug distribution across the biological barrier, and for examining the impact of these components on TE preparation.

1. **Phospholipids**

   The essential components and vesicle-forming agents that come from various sources are called phospholipids. Phospholipids can be classified as natural or synthetic based on their origins. A variety of foods and goods, such as sunflower seeds, egg yolks, and soybeans, naturally contain phospholipids. The SC fluidizes when natural unsaturated phospholipids are used, enabling APIs to penetrate deeper levels. Saturated (hydrogenated) phospholipids, on the other hand, enhance or reinstate the skin's barrier function, allowing APIs to stay in place for an extended period of time. Phosphatidylcholine (PC), phosphatidylinositol, phosphatidylserine, phosphatidylethanolamine, phosphatidic acid, and phosphatidylglycerol are the different types of phospholipids.[11, 13, 14, 33, 34]

2. **Ethanol**

   Ethanol softens the membrane of the vesicle and promotes penetration. The concentration of ethanol affects the size, stability, zeta potential, improved skin permeability, mucosal permeability, and effectiveness of entrapment of vesicles. 10% to 50% of the TE is made up of ethanol. When ethanol concentration rises from 10% to 30% w/v, the size of the vesicle falls and surpasses the optimal level, resulting in a leaky bilayer and a minor increase in vesicle size. The interaction between the lipid layer and ethanol may be the reason why phospholipid dissolves in ethanol more readily as ethanol concentration rises, leading to a notable reduction in entrapment effectiveness.

3. **Edge activator**

   The deformability and flexibility of phospholipid vesicles are imparted by adding an edge activator. The type and quantity of EA can alter the drug's permeability profile. Surfactants employed in the formation of TEs include Tween 20, sodium cholate, dipotassium glycyrrhizinate, bile salts, Span 80, oleic acid, and Tween 80. The transethosomal systems containing tween and oleic acid resulted in increased size, and the sodium deoxycholate system remained virtually unchanged. Still, the zeta potential value is increased, indicating stability and a threefold increase in EE, which may be due to reduced polarity by combining deoxycholate anion and drug cation.[11, 18, 12, 33, 34]

4. **Stabilizer**

   To stop them from aggregating, keep them in their proper size and structure, and extend their shelf life, stabilizers are frequently added to TE formulations. It gives the TE system stability. The most often used stabilizer is cholesterol. At greater ethanol concentrations, the TE formulation's stability and deformability were enhanced by the addition of cholesterol. Because cholesterol is poorly soluble, a rise in cholesterol concentration causes

the EE to decrease. the impact of varying hydroxypropyl-β-cyclodextrin concentrations as a stabilizer on the drug release characteristics and stability of TEs containing metronidazole, a hydrophilic antibiotic. The results of the investigation showed that the stability and drug-release characteristics of the TEs were considerably enhanced by the addition of hydroxypropyl-β-cyclodextrin. Furthermore, metronidazole's skin penetration was improved in the TEs with greater hydroxypropyl-β-cyclodextrin concentrations. The exact medication and formulation determine which stabilizer is best, because using too much of one can compromise the integrity and stability of TEs.[12, 15, 19, 33, 14]

5. **Drug or active compound**

Without changing the dispersity index, a medication added to the transethosomal system affects the mean diameter and zeta potential of the vesicle. Straightforward the nanovesicles' surface displayed a negative charge. When the medication was added, the surface of the vesicles showed a positive charge. The impact of drug loading on the lipophilic drug curcumin's stability and drug release characteristics of TEs the investigation discovered that the use of curcumin raised the zeta potential of TEs while reducing their particle size. In addition, compared to a traditional cream, the TEs demonstrated improved skin penetration of curcumin and sustained drug release over 48 hours. Nevertheless, the stability and integrity of TEs may be adversely affected by the addition of a medication, and excessive drug loading may result in drug leakage and aggregation.[14, 17, 19,34]

6. **Surface functionalization of TE**

Targeting ligands, peptides, and antibodies are a few examples of chemical moieties that may be added to the vesicles' surface to functionalize TEs. These alterations may increase the TEs' selectivity and specificity, enabling them to target particular tissues or cells. For instance, it has been demonstrated that functionalizing TEs with folic acid increases their absorption by cancer cells that overexpress folate receptors. Comparably, it has been demonstrated that using transferrin-conjugated TEs improves medication absorption into cells that exhibit transferrin receptors. The effect of functionalization on the effectiveness of TEs' medication delivery has been the subject of several investigations. A peptide that binds the vascular endothelial growth factor receptor (VEGFR) was discovered by Ellis and Hicklin. In vitro experiments utilizing breast cancer cells revealed that VEGFR-targeted treatment had better anticancer efficacy and greater cellular absorption than non-functionalized therapy.[15, 26 , 28, 33]

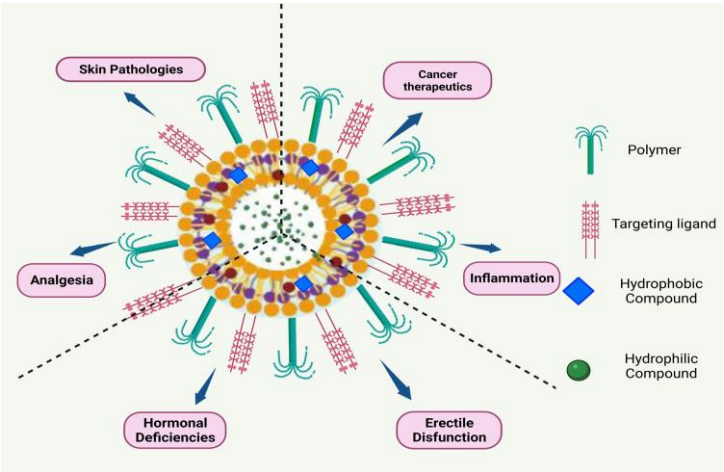

Figure 2: Schematic representation of the applications of surface functionalized transethosomes.

METHOD OF PREPARATION

- Cold method
- Hot method
- Thin film hydration method
- Mechanical dispersion method

1. **Cold Method:**

Phospholipids were dissolved in ethanol with vigorous stirring. In a water bath, this mixture is heated to 30°C. In a separate container, water is heated to 30°C before being gradually introduced in a fine stream to the alcoholic mixture. The drug's solubility determines whether or not it dissolves in water. When adding the aqueous solution above to the ethanolic solution, the mixture is held on a magnetic stirrer running at

700 rpm. With a probe sonicator, vesicle size may be modulated.[17, 18, 19]

2. **Hot Method**:
   To make phospholipids disperse in water, boil them in a water bath at 400 degrees Celsius to create a colloidal solution. After being combined, ethanol and glycol are heated to 40°C. aqueous phase is supplemented with organic phase. Stir for ten to fifteen minutes. The process of probe sonication reduces the size of the vesicle based on its hydrophilic or hydrophobic qualities.[20, 30, 34]
3. **Thin Film Hydration Method**:
   In 25 milliliters of chloroform-methanol, SPC (final concentration of 36 mg/ml), permeation enhancers, and IM (final concentration of 0.5 mg/ml) were dissolved. In order to guarantee complete elimination of solvent traces, the rotatory evaporation of the chloroform-methanol combination at decreased pressure at 35+1c was performed for one hour, resulting in the lipid mixture being deposited as a thin layer in a round-bottom flask. Using 10 milliliters of phosphate buffer, the lipid film was hydrated and formed within the eluates.[22, 25, 28]
4. **Mechanical Dispersion Method**:
   A clean, dry round-bottom flask is used to take lipid and surfactant. A solvent combination of ethanol and chloroform is used to dissolve the lipid mixture. Above the lipid transition temperature, a rotary evaporator is used to produce a thin layer of lipid. To get rid of any leftover organic solvent, it is vacuum-sealed for the whole night. Vesicles formed from the deposited film are sonicated to the appropriate size.[25 to 29]

Characterization of Transethosomes-

1. **Vesicle Shape**: Both transmission and scanning electronic microscopy are used to identify the form of the vesicle.[04]
2. **Vesicle size and Zeta Potential**: Dynamic light scattering and photon correlation spectroscopy can be used to measure particle size. Transethosomes vary in size from tens of nanometers to microns, and their size is determined by the formulation's composition. A zeta meter may be used to measure the formulation's zeta potential, which can be utilized to forecast and manage stability.[07]
3. **Transition Temperature**: Differential scanning calorimetry may be used to find the transition temperature of transethosomes.
4. **Drug Content**: A UV Spectrophotometer can be used to evaluate the drug content in transethosomes. A modified high performance liquid chromatographic technique may also be used to quantify this.

   %drug content =sample absorbance/standard absorbance.
5. **Surface Tension**: The ring technique in an Ado Noun ring tensiometer can be used to measure the surface tension activity of a medication in an aqueous solution.
6. **Penetration and Permeation Studies**: Confocal laser scanning microscopy can be used to visualize the depth of penetration caused by trans-ethosomes (CLSM).
7. **Vesicle Stability**: Examining the vesicle's size and shape over time will reveal the stability of the vesicle.
8. **Surface Morphology Study:** The particle's shape or surface morphology is influenced by various lipid types. It is examined with a scanning electronic microscope to determine its shape and surface characteristics. [07,31,30]
9. **In-Vitro Drug Release**: The purpose of this is to calculate the penetration rate. The formulation is optimized using data from in vitro investigations, the time required to reach steady state permeation, and the permeation flow at steady state.[09, 33, 34]

Conclusion

Transethosomes (TEs) represent a potentially effective delivery mechanism for a range of bioactive substances, including hormones, antibiotics, peptides, and medications with low penetration. They have been investigated for ophthalmic, transvaginal, and intranasal methods and have the ability to penetrate deeper layers of the skin. Deeper skin layers can be reached by TEs because of their phospholipid, high ethanol concentration, edge activator, and encapsulated medicinal molecules. Drug toxicity has been successfully decreased, and site-specific action has been achieved with surface functionalization and photodynamic treatment.Skin penetration enhancement technology is expanding quickly, and in the next ten years, skin will play a significant role in drug delivery. Transethosomes are better than other traditional transdermal permeation procedures because they provide formulators with the most freedom to modify ethosomal features in accordance with study objectives. They can be investigated for different medications by transdermal administration and are also interesting carriers for topical therapy of local and systemic illnesses. These vesicles' viscosity and duration of stay at the site of action might be increased by formulating them as gels.

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