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TRANSETHOSOMES: INNOVATIVE VESICULAR TOOL FOR TOPICAL DRUG DELIVERY

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ABSTRACT

The increasing demand for novel medication delivery methods has prompted a great deal of research to overcome the drawbacks of conventional dosage forms. Drug delivery occurs via liposomes however, these particles usually stay in the upper stratum corneum of the skin, preventing drug penetration. Ultra-deformable vesicles (UDV) are a type of new lipid vesicles that have been designed to enhance medication delivery. Transethosomes have drawn interest in this context as a potential remedy because they provide unique benefits above conventional formulations. Transethosomes reduce poor bioavailability, organ toxicity, first-pass metabolism, and plasma variations. An extensive examination of transethosomes is given in this review and how formulation elements affect the agent characteristics and efficient targeting. This article explores the properties of production and assessment used to guarantee effective drug delivery. By this review substantial contribution by analyzing the different transethosome administration routes, such as transdermal, transvaginal, pulmonary, and ocular delivery. Overall, this work highlights transethosome's tremendous promise as a practical drug delivery technique that can overcome the drawbacks of traditional drug delivery methods.

KEYWORDS: transethosomes, conventional drug delivery, liposomes, ethosomes.

INTRODUCTION

Transdermal drug delivery is a non-invasive technique for delivering a drug formulation to intact, healthy skin in order to disperse medication throughout the body. The drug enters the stratum corneum first, then proceeds to the deeper layers of the epidermis and dermis without building up in the dermal layer. Once the medication reaches the dermal layer, it can be absorbed systemically through the dermal circulatory system.[1]

The traditional approach of administering medication orally is difficult due to the harsh environment of the gastrointestinal tract (GIT) and other physiological barriers, such as factors related to gastrointestinal anatomy, biochemistry, and physiology. Several regions of the gastrointestinal tract (GIT) are important for food digestion and medicine absorption, including the stomach, esophagus, colon, small intestine, and mouth cavity. Drug absorption can also be limited by other anatomical features such the stomach's mucin-bicarbonate barrier, the mouth cavity's small surface area, and enteral enzymes. Much work has been done to solve these problems, which are mostly related to a better understanding of the physiological characteristics of the GIT in both diseased and healthy states. Conventional drug delivery techniques, like ordinary tablets, capsules, or sterile drug formulations, have these disadvantages.[2]

When drug delivery takes into account variables like the target of action, route of administration, and carrier system, it can improve the effectiveness of medications through controlled release. Therapeutic index, bioavailability, and patient compliance are all enhanced by drug delivery techniques. Researchers are actively attempting to deliver the active pharmaceutical ingredient through the transdermal approach, despite the fact that it is still difficult to administer drugs effectively through this route. In the United States, the transdermal medication delivery technique was created in 1950. Medication is absorbed into the bloodstream through the skin's outer layer when using the transdermal technique.[3] It is difficult for medications with high and low partition coefficients to enter the bloodstream Ultra-deformable vesicles (UDV), such as transferosomes, etho somes, and transethosomes, have been designed to overc ome these limitations. Recently, the vesicular system were created to administerdrugs through skin in a targeted manner. The ultradeformable vesicular structure can capture medications that are ampiphilic, hydrophilic, and hydrophobic. In addition vesicular forms of proteins, peptides, and herbal remedies can be applied topically.[4]

Liposomes

Liposomes are colloidal and vesicular structure with one or more lipid bilayer having a diameter range of 15nm to 1000nm. These vesicles are mainly made up of phospholipid and cholesterol. Liposomes being low soluble, short half-life, degradation and leakage of phospholipids make them not suitable for a targeted drug delivery system.[5] Liposomes are unstable in the dispersed liquid state due to the inherent thermodynamic instability accompanied by particle size change and drug leakage during storage. In addition, the liposomal structure is not resistant to the acidic environment of the stomach. In the same manner as various nanoparticles, it is difficult for the intact liposomes to permeate freely across intestinal barriers due to their relatively large size.[6] One of the biggest limitations of liposomes as a drug delivery system has been the difficulty in continuous mass production and quality control because the liposomal system is very complex. Lipid degradants such as lysolipids can be formed during manufacturing or storage. Lysolipids have been known to be associated with toxicity such as hemolysis and apoptosis and thus, the content should be monitored.[7]

Transferosomes

Transferosomes were developed by Cevc et al.16 in the 1990s containing surfactant (SA) or edge activator (EA) to impart elasticity to the prepared vesicles.[8] Transferosomes are elastic vesicular carriers in which edge activator (biocompatible surfactant) is incorporated in to lipid bilayer structure. Even after evaporation of water from the formulation, edge activator remains in the formulation. The major disadvantage with such formulation is that it is difficult to load hydrophobic drugs in these vesicles without compromising the elastic properties.[9,10]

Ethosomes

Ethosomes are prepared which eliminates the disadvantage of transferosomes. Ethosomes are vesicular carriers consisting of hydro-alcoholic phospholipids in which concentration of alcohol is high.[9] The major disadvantage of ethosomes is that it causes dehydration of skin due to evaporation of ethanol from the formulation as soon as it is applied on skin under non-occlusive condition.[12] On the other hand, ethosomal systems were introduced in 1998 containing high levels of ethanol in their formula, which resulted in improved drug absorption through the skin due to the result of ethanol mixing in lipid bilayer vesicles and enhancing saturation of SC lipids. In case if shell locking is ineffective then the ethosomes may coalescence and fall apart on transfer into water. Loss of product during transfer form organic to water media.[13]

Transethosomes

Lipid vesicles called transethosomes are derived from transfersomes and ethosomes. These unique ultra deformable vesicles were first reported by Song et al. in 2012 and are distinguished by possessing an edge activator and a high ethanol concentration (up to 30%).[14] Phospholipids, ethanol in high concentrations of 30 to 40%, edge activators such as tween 20, tween 60, tween 80, span 60, span 65, span 80, sodium cholate or sodium deoxycholate, and water are all present in transethosomes. The influence of ethanol with high concentration in vesicles fluidizes the stratum corneum's lipid layer, promotes system malleability and flexibility that facilitates their penetration through the microscopic pores created by fluidization in the stratum corneum. The amount of alcohol in the vesicular system controls its diameter as well since it reduces the size of the vesicle surface by providing a net negative charge. The ideal range of ethanol concentrations for the creation of stable ethosomes is between 30 and 40%. A 20% reduction in ethanol concentration may cause vesicular size to rise. Phospholipids, which are composed of a hydrophilic head and a hydrophobic tail, are essential for the production of bilayers. This can incorporate both hydrophilic and hydrophobic drugs.[15]

Table 1: Composition of Transethosomes.[23,17]

Sl.no	Composition	Ingredients	Role
1.	Phospholipids (2%-5%)	Soya phosphatidyl choline, lipoid S100, phospholipon 90G	helps in formation of vesicles
2.	Edge activator	Oleic acid, span 80,tween 80, sodium deoxycholate, sodium cholate	Provides elasticity and permeation enhancer
3.	Alcohol (30%-40%)	Ethanol, isopropyl alcohol, propylene glycol	Provides softness to vesicle membrane
4.	Water qs	water	Vesicle forming agent

Skin Structure

Skin structure is well known and has been extensively investigated. The dermis contains a variety of structures, including pilosebaceous units, blood vessels, lymphatic vessels, nerve terminals (sensory receptors), and sweat glands. Based on keratinocyte growth and differentiation, the stratified squamous epithelial tissue that makes up the epidermis can be divided into five distinct layers. These layers are the Stratum Spinosum, Stratum Lucidum (SL), Stratum Granulosum (SG), Stratum Corneum (SC), and Stratum Basale (SB), in order of outermost. The end result of the epidermal cell differentiation process is the SC, and the entire structure of the SC creates a natural barrier that limits the use of

the transdermal route as a systemic drug delivery method by preventing excessive water loss and entry of exogenous chemicals, including drugs.[16] Despite its thinness of only 15-20 µm, the SC plays a key role in the skin's barrier function. Below the SC, the epidermis is made up of keratinocytes and has a thickness of around 100 µm. The SC is formed by these cells' continuous proliferation, which pushes older cells to the surface where they endure programmed cell death and keratinization.

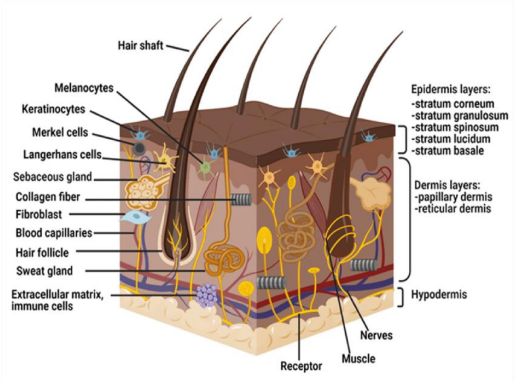

Fig. 1: Structure of skin.[50]

Advantages of Nanotransethosomes[17,15,19,20,21]

1. The flexibility of transethosomes is very high and has a very high skin permeation rate and high flux rate compared to other vesicular systems.
2. The main advantage of transethosomes is that they can easily deform and easily move through the narrow obstructions.
3. Biocompatible and biodegradable transethosomes can be easily formulated with the help of natural phospholipids.
4. It is much more stable than another vesicular system.
5. It has very high entrapment efficiency, and the drug can be easily incorporated and also protected from metabolic degradation.
6. The preparation method of transethosomes is easy and it has high penetration power.
7. After preparing transethosomes they can be easily administered in transdermal dosage forms such as cream, gel, and in a patch.
8. Transethosomes prepared with small size known as nano-transethosomes can easily hit the target site.

Disadvantages of Transethosomes[22]

1. Sufficient solubility of the medication in aqueous and lipophilic conditions to enter the systemic circulation and reach the cutaneous microcirculation.
2. The drug's molecular size should be reasonable enough for it to be absorbed via the skin.

Method of Preparation of Transethosomes

Ultra-Deformable Vesicles are simple to formulate and easy to scale-up. Transethosomes are one such among them which includes; ethanol injection, cold method, direct method, reverse phase evaporation, thin film hydration method.

Ethanol Injection Method[24,25]

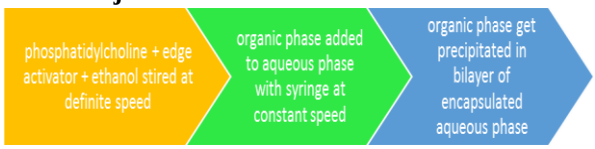

Fig. 2: Ethanol injection method.[14]

In ethanol injection method of preparation, phospholipid, surfactant and active ingredient are dissolved in ethanol. The organic phase is injected into aqueous phase at predetermined speed by using a syringe, then by using an ultrasonic probe sonicator resultant mixture was homogenized. The particle size is affected by ultrasound, injection time, and probe ultrasound. Using the ethanol injection method followed by the hot procedure (probe sonication).

Thin Layer Film Hydration Method[26,27,28,29,30]

In this method, phospholipid, surfactant, drug are dissolved in the organic phase which is taken in the rotary evaporator flask. A homogenous mixture can be obtained when kept in water bath sonicator. Organic solvents in excess will be removed above the lipid transition temperature at low pressure and produce thin lipid film on the wall of flask. The lipid film will be kept under vaccum over night that ensures the complete removal of organic solvents. Dried film then will be diluted with ethanol or buffer solution. The formed transethosomes will keep at room temperature to swell and store at refrigerated temperature. average size of vesicles produced by this method can be of 62.85nm.

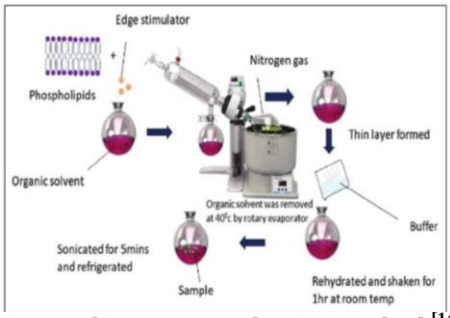

Fig. 3: Thin Layer Hydration Method.[14]

Cold Method[31,32,33,34]

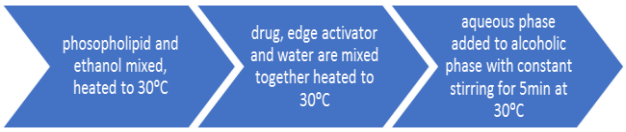

Fig 4: Cold method.[14]

Cold methods can be used to create thermolabile drugs. This approach, which prepares the organic and aqueous phases independently, is easy to use and convenient. Phospholipids, surfactant, and other lipid components are vigorously mixed with an organic solvent at room

temperature in a closed vessel to create the organic phase. Buffer solution is continuously added dropwise to this. This mixture was stirred at 700–2000 rpm for 5–30 minutes using a magnetic stirrer. The amount of stirring time can change the size of the vesicle, and the drug can dissolve in the organic or aqueous phase depending on the physicochemical properties of the molecule.

Hot Method[35,36]

It is a technique that involves the application of heat during the formulation of transethosomes. To enhance lipid solubility, facilitate lipid fusion, and also to improve the encapsulation efficiency of the drug, hot method can be used. Phospholipid dispersed in water at 40°C to form a colloidal dispersion. Simultaneously in a different container, a mixture of polyol and ethanol is heated to 40°C. The organic phase is then added to the water phase by continuous stirring until both components reach a temperature of 40°C to form a vesicle suspension. Based on drug type (hydrophilic or lipophilic), it can be dissolved in water or ethanol.

Reverse Phase Evaporation Method[37,38,39]

Using this method, transethosomes are made by water in oil emulsion, and then letting the organic solvent evaporate to form vesicles. This method was developed specifically to produce uni-lamellar vesicles and is the least used technique. Using this technique, a thin lipid film is formed in a round-bottom flask by evaporating the phospholipid, stabilizer, and organic solvent solution under vacuum. Nitrogen gas is used to dry a thin lipid layer in order to extract the residual solvent. Next, at room temperature, the lipid film is suspended in a solvent or solvent mixture and agitated. To create a stable emulsion, the produced formulation is sonicated for 10 minutes at 5°C–6°C in a sonication bath. A gel can be formed by removing the solvent under reduced pressure by mechanical agitation.

Evaluation of Transethosomes

Vesicular Shape[40]

Transmission electron microscopy (TEM) can be used to observe vesicular shape. Samples are arranged in a thin-film copper grid that has been coated with carbon. Phosphotungstic acid produces a negatively discolored mark on it. Transethosomes were present in an irregularly spherical shape.

Drug Entrapment Efficiency[41]

Mini column centrifugation method can be used for studying entrapment efficiency. Vesicle suspension loaded with 0.2 ml of the drug was placed in the column containing Sephadex G-50, and the column was centrifuged at 2000 rpm. The column was allowed to elute. The eluted vesicles were collected and observed under a microscope for the absence of any crystal. The column was eluted four times with 0.2 ml distilled water. These eluted vesicles were digested, ruptured with methanol, and analyzed spectrophotometrically at 365 nm.

$$\text{Percentage drug entrapment} = \frac{\text{amount drug entrapped}}{\text{total amount of drug}} \times 100$$

When comparing the entrapment efficiency among the ultra-deformable vesicles it shows following order: transethosomes > transfersomes > ethosomes > liposomes.

Vesicular Size and Zeta Potential[42]

Particle size and zeta potential can be determined by dynamic light scattering (DLS) using a computerized inspection system and photon correlation spectroscopy (PCS).

Elasticity Measurement[43,44]

Extrusion method is used to find elasticity of the vesicular bilayer. The prepared vesicles can be extruded through a nylon membrane filter of pore size 0.1 mm under reduced pressure of 2.5 bar.

$$\text{Elasticity (\%)} = \frac{\text{vesicle size before extrusion} - \text{vesicle size after extrusion}}{\text{vesicle size before extrusion}} \times 100$$

Edge activator and ethanol concentration will increase the elasticity of membranes. A vital aspect of the lipid bilayers' elasticity is their ability to enhance the lipid vesicles' ability to permeate. There is no benefit in terms of transcutaneous permeation efficiency when the concentration of the edge activator is increased above a particular concentration in vesicle membranes. It has been proven that ethanol increases the lipid bilayers' flexibility in the vesicles.

In-Vitro Drug Release Study[44]

The dialysis bag technique was employed to determine the transethosome release pattern. Transethosomes were put in dialysis bags with the same amount of each formulation—three milligrams of the medication and then put in beakers with 50 ml of phosphate buffer solution (PBS). Subsequently, the beakers were placed in a water bath that was shaking, with a temperature maintained at 37 ± 0.5 °C and a speed of 100 rpm. An in vitro drug release research was carried out at pH values of 5.5 and 7.4. The dialysis bag was fully moistened before the test soaking it in the phosphate buffer solution (PBS) for 30 minutes. The samples were taken out after a set period of time, and the same amount of PBS was added again promptly to maintain sink conditions. The shaker's speed was adjusted to 100 rpm. A UV visible spectrophotometer was used to measure the drug's concentration in the samples at a specific wavelength. the ultra-deformable lipid-based nanoparticles exhibit a sustained drug release profile.

Stability Studies[45]

Short term stability studies were conducted according to ICH GCP guidelines to establish the stability of the optimized TELs. The formulation was stored in glass vials in a humidity control oven at 25±2°C/65±5% RH and refrigerated at 4±2°C/65±5% RH. The sample was

withdrawn at intervals of 30, 60 and 90 days for analysis of particle size and % entrapment efficiency.

Applications of Transethosomes

Antifungal Drug Delivery[46]

Transethosomal preparation containing Terbinafine, Amphotericin B, Ketoconazole, Voriconazole had shown better penetration and deposition in skin. Voriconazole Song *et al* demonstrated that transethosomes when compared with other UDV shown high elasticity, high in-vitro skin permeation, and high in-vitro skin deposition.

Anti-Cancer Drug Delivery[47,48]

In order to treat cutaneous melanoma, Lei *et al*. conducted tests using dual loading of medicines in a transethosome formulation. In contrast to the other formulations, they chose two medications, such as dacarbazine and tretinoin, that worked in concert and reduced cytotoxic effects. Comparing dual loaded transethosomes to single loaded drugs, the former had more anticancer activity. They discovered that it is possible to get improved skin penetration.

Bajaj *et al* also conducted researches for anticancer indicating that new phospholipid carrier transethosomes which consists of high concentration of ethanol and edge activator enhances the permeation of 5- Fluorouracil. They compared the release profile of 5- fluorouracil loaded transethosomes (80.35%) and transethosomal gel of 83.67% with 65% for conventional 1% 5-FU loaded flonida cream.

Anti- Hypertensive Drug[49]

Albash *et al*, created a transethosomal formulation using Olmesartan Medoxomil as the active ingredient, which increased medication penetration through the skin via the transdermal route. Olmesartan that are taken orally reduces the bioavailability because of extensive first pass metabolism. It was found that transethosomal preparation possess entrapment efficiency of 58.50%±1.30%.

Challenges and Future Aspects[50,51,52]

The main difficulty lies in the raw material selection process, which is essential to the production of TE. It is essential to choose premium phospholipids, edge activators, and ethanol to guarantee the product stability, effectiveness, and repeatability. Quality control procedures that guarantee the steady availability and grade of raw materials can be put in place to meet this problem. The majority of active chemicals are unable to cross the stratum corneum barrier. Because ethanol-based nanocarriers can fluidize and disrupt the stratum corneum's hard lipid structure, they have created a novel avenue for the transdermal delivery of numerous bioactive compounds. For medium- and large-sized bioactive compounds, these systems offer an effective non-invasive drug delivery method that also has good patient compliance and inexpensive treatment costs. Effective clinical investigation of the ethanol-based nanocarrier technology is still difficult to accomplish, though. To determine their potency, a clinical evaluation is required. Since ethanol irritates skin, it is necessary to investigate the safety of using ethanol-based on exposed eczema regions, for example. Furthermore, the large-scale manufacturing of TEs can be complicated and expensive, which makes it challenging to transfer laboratory-scale formulations to commercial manufacturing. It is imperative to guarantee both cost-effectiveness and reproducibility in order to promote their widespread use in pharmaceutical applications. It is crucial to create reliable manufacturing procedures that preserve the integrity and caliber of TEs on a bigger scale.

CONCLUSION

An important development in skin penetration enhancing technology is the potential for a large increase in the number of medications that can be applied transdermal. Therefore, in the upcoming ten years, skin may play a significant role as a delivery method. The formulator can modify the ethosomal qualities to suit the needs of the research to the maximum extent possible by adjusting the edge activators and/or penetration enhancers. Transethosomes, for instance, are incredibly malleable vesicles that may carry a variety of substances, including hormones, antibiotics, low-penetration medications, peptides, and pharmaceuticals with a quicker and more focused impact. They perform better than other common transdermal permeation techniques in terms of safety, effectiveness, and patient compliance. Transethosomes have shown great promise as carriers for the treatment of both systemic and local diseases.

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