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Transethosomes: Novel Ultradeformable Lipid Vesicles for Enhanced Skin Permeation: An Overview

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ABSTRACT

Transethosomes, a novel approach in drug delivery systems, offer promising advantages for enhancing skin permeation of various medications. This innovative technology involves the use of ultra-deformable lipid vesicles that can improve drug absorption through the skin, bypassing issues related to oral administration such as first-pass metabolism. Phospholipid, ethanol, water and edge activators (surfactants) or permeation enhancers constitute transethosomes. Researchers have explored the application of transethosomes in delivering a range of medications, including anti-hypertensive, anti-arthritis, peptides, antibiotics etc. By incorporating permeability enhancers and optimizing formulations, researchers have shown that transethosomes improve transdermal permeability and efficacy in various studies. The preparation of transethosomes is relatively straightforward, allowing for scalability without the need for complex equipment. Evaluation parameters such as vesicle morphology, size and zeta potential play a crucial role in assessing the effectiveness and stability of transethosome formulations. Despite the promising benefits of transethosomes, further research is needed to address potential drawbacks and optimize their use in drug delivery systems.

INTRODUCTION

The oral route of administration is the most widely utilised among the various drug delivery system (DDS) routes. However, the oral route of DDS has a number of disadvantages, including first pass metabolism, presystemic clearance, and a tendency to interact with other drugs. As a result, different alternatives to this route of drug delivery have emerged. Since transdermal drug delivery systems (TDDS) offer a number of benefits over other drug delivery methods, they are a good substitute for oral DDS. TDDS is a self-contained, discrete dosage form that is applied to intact skin which delivers medications to the systemic circulation at a controlled rate[1]. Since transdermal medication delivery systems avoid the GI tract, the drugs they dispense are not subject to gastrointestinal degradation. Transdermal systems avoid pre-systemic metabolism by delivering medications straight into the bloodstream through epidermal layers.

The vesicular system is now the most researched transdermal medication delivery method. The vesicles that make up the vesicular system are colloids that have both hydrophilic and amphiphilic groups. In a bilayer effusion, the hydrophilic portion forms the core while the amphiphilic portion protects it. It has been observed that the vesicular system transports medicines that are hydrophilic, lipophilic, or amphiphilic. Various types of vesicular carrier systems exist, such as liposomes, ethosomes, transferosomes, niosomes, transethosomes etc as shown in Figure 1.

TRANSETHOSOMES

Liposomes and other lipid-based vesicular systems are unable to penetrate the stratum corneum. They gradually accumulate on the superior layer of the stratum corneum because they show poor penetration into the deeper layers of the skin. When liposomes are combined with edge activators such as Span 80, Span 25, Tween 80, and sodium cholate to enhance skin penetration, they are referred to as transferosomes. Because of their tendency to deform, transferosomes improve skin penetration; yet, they cannot deeply penetrate the stratum corneum. A different type of vesicular system made of phospholipid, ethanol, and water is

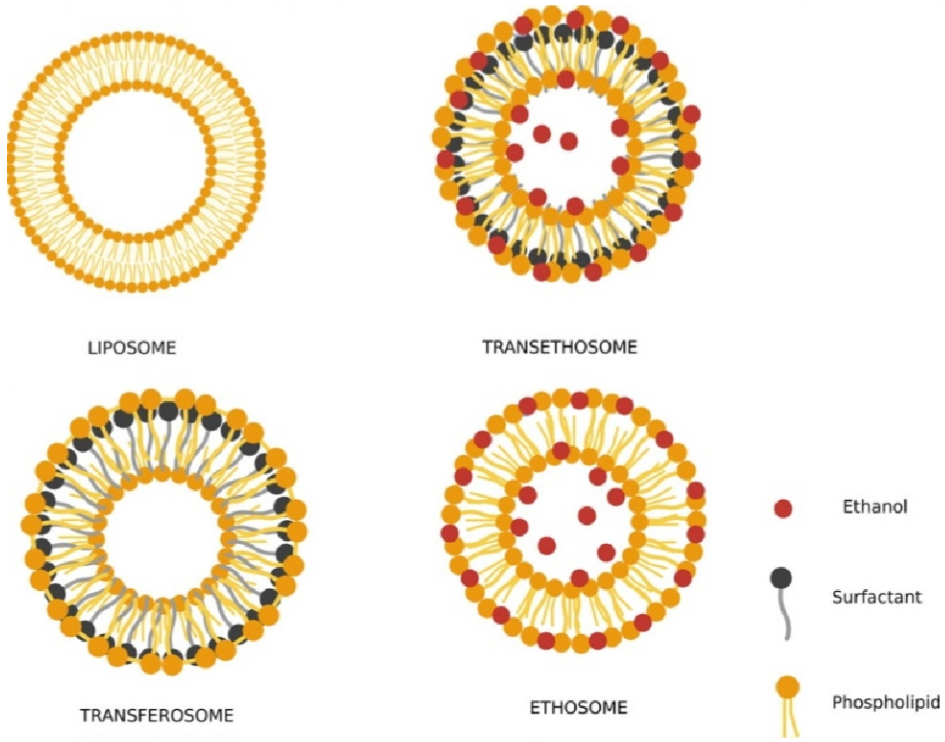

Figure 1 : Schematic illustration of various lipid-based nanocarriers

known as an ethosomes. The intercellular gap between corneocytes expands when ethanol is present, increasing penetration[2-4].

The combination of ethosomes and transferosomes is known as transethosomes. Transferosomes exhibit skin penetration as well as the ability to become malleable. The vesicular system was first described by Song et al. in 2012. Transethosomes can be administered systemically or topically. This mechanism is easily capable of entrapping drugs with molecular weights ranging from low to high. The bioactive agent releases its contents gradually and extremely slowly because it is protected by encapsulation. Because they are biodegradable and biocompatible, they have a very effective encapsulating capacity. There is no need for excessive medicinal additions in this preparation, and it does not need any laborious steps.

ADVANTAGES OF TRANSETHOSOMES

- Better patient compliance due to a non-invasive approach
- Capable of delivering medications with a higher molecular weight.
- Useful drug carrier for delivering various dosage forms.
- Better skin permeation.
- Avoidance of first-pass metabolism.

DISADVANTAGES OF TRANSETHOSOMES

- Potential to cause dermatitis, allergic reaction or skin irritation in some patients.
- Product loss may occur when transferring from an alcoholic to an aqueous medium.

STRUCTURE OF TRANSETHOSOMES

Phospholipids, ethanol, edge activator (surfactant) and water are the constituents of transethosomes. Phospholipids serve as the carrier when it comes to delivering drug molecules into the skin. The stratum corneum can readily interact with them, enhance tissue hydration and combine with the lipids in the stratum corneum. The edge activator (biocompatible surfactant) works as a bilayer softening agent. The main purpose of its addition is to increase flexibility and permeability [5].

One of the main characteristics of the transethosomal system is alcohol, which gives it a unique identity as a vesicular system. Due to fluidization, ethanol causes the skin's layer to deform and gives these nanosystems flexibility and malleability, allowing them to enter the stratum corneum through tiny gaps. Water is a crucial component because it aids in the formation of a bilayer with the addition of phospholipids and promotes flexibility of the system. The combination of ethanol and edge activator causes the lipid bilayer to reorganize and become more pliable, enabling it to penetrate deeper into the dermis.

MECHANISM OF PERMEATION

Stratum corneum is a significant medication absorption barrier. There are three possible routes via which a medication can get through the stratum corneum: intracellular, intercellular, and follicular pathways. There are two routes via which the transethosomes can pass through the stratum corneum.

1. Ethanol effect
2. Transethosome effect

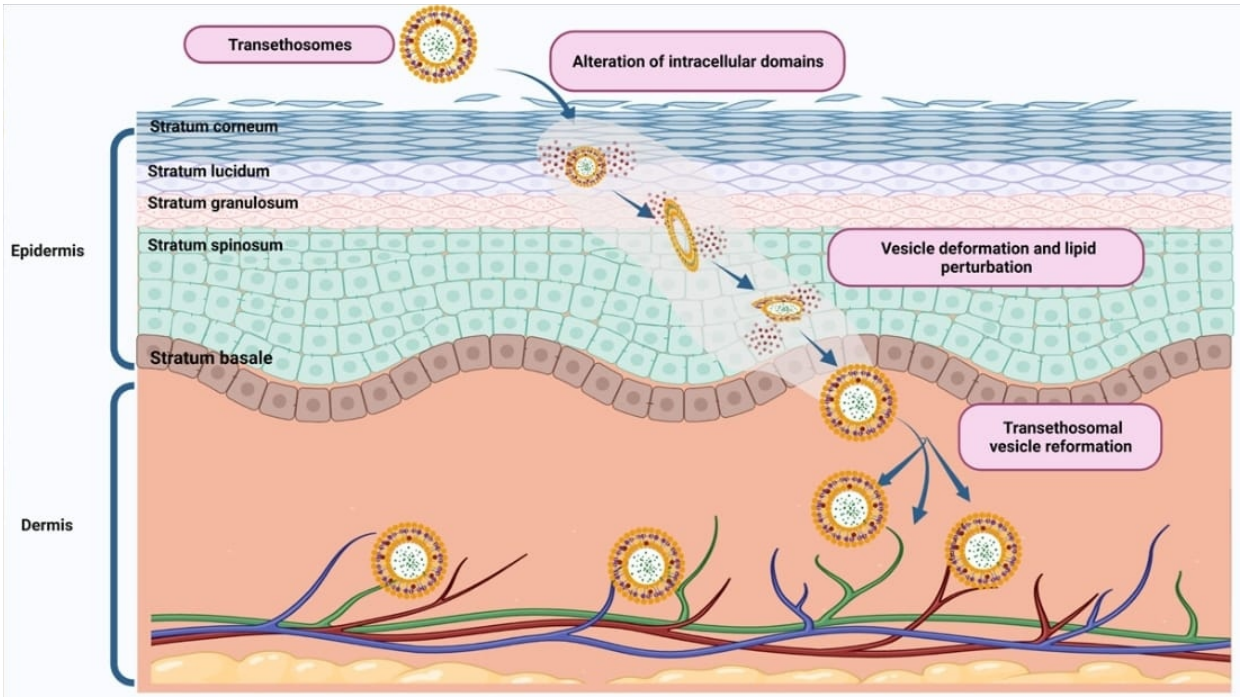

Figure 2 : Primary mechanism of permeation of transethosomes through transdermal route

Ethanol effect:

About 20-50% of transethosomes are made of ethanol. Ethanol breaks down the phospholipids and fluidizes the lipid layer of stratum corneum when it comes into contact with it. Ethanol produces empty space, lowers density, and finally thins and softens the membrane, increasing penetration and allowing the medicinal substance to be released gradually into the layers of the skin[6].

Transethosome effect:

The intracellular lipids in the stratum corneum are disrupted by permeability enhancers found in the transethosome. When intracellular lipids are disrupted, the skin's pores enlarge and make it easier for systems to penetrate the skin[7].

METHOD OF PREPARATION

Different techniques are employed to produce vesicles with small sizes, which are then added to gels or lotions to improve skin penetration. Here are a few of the often employed techniques.

Cold method:

The cold method, which prepares the organic and aqueous phases independently, is a popular and convenient procedure. Phospholipid, penetration enhancer, and other lipid components are thoroughly mixed in organic solvents at room temperature in a closed vessel to obtain the organic phase. Then, a syringe pump is used to continuously introduce the aqueous phase to the organic phase dropwise. The mixture is agitated for 5 to 30 minutes at a speed of 700 to 2000 rpm using a magnetic stirrer. The finished product is kept cold and stored for later use. By using this method, the heat stress that can cause medication degradation is avoided [8].

Hot method:

The application of heat during the TE formulation process is known as the "hot method." This approach involves heating phospholipid and water dispersion to 40°C. Heating at the same temperature is done step by step until a colloidal solution forms. Glycol and ethanol are added to a different vessel simultaneously and heated to 40°C. The organic phase is added to the aqueous phase once the temperatures of both mixes progressively rise to 40°C. Following five more minutes of stirring, the resulting vesicle suspension is allowed to cool to room temperature. The medication dissolves in ethanol or water, depending on its affinity and capacity to bind with hydrophilic and hydrophobic solvents. Sonication or extrusion are simple ways to produce vesicles to the desired size [9].

Ethanol injection method:

Phospholipids are dissolved in ethanol in a glass bottle which is sealed, equipped with a syringe so that ethanol can be added without evaporation. Double-distilled water is used to dissolve drug separately. Following the addition of the ethanolic lecithin solution to the aqueous drug solution at a predetermined flow rate, the mixture is homogenised using an ultrasonic probe sonicator. The concentration of lipid content and injection rate, both affect the actual size of transethosomes[10].

Thin-film hydration technique (TFH):

In a round bottom flask, the phospholipids, drugs and edge activators are dissolved in the organic phase. Then, the mixture is held in a water bath sonicator until a uniform dispersion is achieved. After that, organic solvents are gradually eliminated by rotary evaporator at decreasing pressure above the lipid transition temperature to leave a thin lipid film on the flask wall. The flask is

Figure 3 : Ethanol injection method

kept in a vacuum oven for the entire night in order to guarantee complete elimination of the organic solvents. The dried layer is diluted with either an aqueous ethanol solution or a saline phosphate buffer-ethanol solution by rotating the lipid film. After allowing the vesicles to grow at room temperature and stored at 4°C - 8°C for further use[11].

EVALUATION PARAMETERS

Vesicle morphology

The study of vesicular carriers' size and shape is known as morphology. Vesicular carriers typically have an enclosed core, a consistent spherical form, and are physically soft and flexible. Since the majority of the vesicles are nanoscale, the morphology may be viewed by both transmission and scanning electron microscopy. Morphology not only explains identification studies but also explains how particle packing and aggregation patterns are detected.

Vesicle size

The Particle Size Analyser and the Light Scattering Technique may both identify the vesicle size. Dynamic light scattering (DLS) or photon correction spectroscopy can be used to determine the vesicular diameter [12].

Zeta potential

The zeta potential measures the strength of electrostatic attraction and repulsion in colloidal dispersion. It is possible to employ photon correlation spectroscopy (PCS) and dynamic light scattering (DLS).

One of the main factors influencing the product's stability is the existence of charge on the surface of the nanoparticle. The high zeta potential of dispersion medium indicates strongly charged particles, which inhibit flocculation, aggregation, and coagulation. Coagulation happens when the zeta potential is low, favouring attraction over repulsion.

Phase transition temperature

The drug release from the vesicles depends on the temperature at which the phase shift takes place. It can be analysed by using a Differential Scanning Calorimeter (DSC). Every sample is tested within a specific temperature range while under steady nitrogen flow. Thermal differential curves are used to compare the samples.

Entrapment efficiency

The precise amount of drug trapped in the vesicle can be obtained via entrapment efficiency. There are two ways to find the unentrapped drug: membrane dialysis and ultracentrifugation method. According to Zhu et al., the ultracentrifugation method is not as suitable as the membrane dialysis method for determination of entrapment efficiency.

To prevent the vesicles from rupturing, the drug-TE solution is centrifuged at a controlled speed and temperature using the ultracentrifugation technique to extract the unentrapped drug[42]. Using an appropriate solvent to burst the vesicles, sediment and supernatant liquid are separated, and the number of drug molecules in the sediment is calculated. The drug concentration is determined by using spectrophotometry[13]. Equation can be used to compute the EE.

$$\%EE = \frac{\text{Total drug added} - \text{Free unentraped drug}}{\text{Total drug added}} \times 100$$

Degree of deformability

One of the unique characteristics of TE is their deformability, which allows them to move freely across the skin membrane. The nano carrier's deformability is characterised by the deformability index, which is determined by:

$$E = j\left(\frac{rv}{rp}\right)^2$$

E = the deformability index of the vesicle bilayer

j = the penetration rate through a membrane filter

rv = vesicle size (after extrusion)

rp = the membrane's pore size.

Drug content

The vesicles are lysed to release the substance in order to determine whether the preparation has the active component in the necessary amount in the vesicles. The content that has been

liberated is added to the solution and subjected a chromatographic assay or spectrophotometric analysis. Solvents such as methanol, isopropyl alcohol, etc. are used in the lysis of vesicles [14]. Equation used to determine the percentage of drug content in transethosomal preparation:

$$\% \text{ Drug content} = \frac{\text{Sample absorbance}}{\text{Standard absorbance}}$$

***In vitro* drug release study**

The dialysis bag method can be used to study the amount of drug release. The transethosome formulation is put onto the dialysis membrane. After loading the membrane, it is placed in a conical flask with buffer solution and allowed to incubate. Aliquots are taken out at predetermined time intervals and centrifuged using mini column centrifuge. A relevant method is used to evaluate the free drug[15].

Skin permeation Studies

Studies on skin permeation use the skin of fresh animals, such as rat, goat. A Franz diffusion cell with phosphate buffer saline in the receptor compartment is used to mount the skin sample. The formulation is administered on the donor side of the diffusion cell that faces the stratum corneum. Sample is taken out of the receptor compartment at various time interval while maintaining a steady temperature. HPLC is used to analyse the sample while maintaining the sink condition[16].

Stability study

Long-term usage of lipid-based vesicles slows down their popularity due to their physical instability. It is therefore difficult to keep the vesicles from degrading, particularly lipid-based vesicles. Degradation by chemicals, physical agents, and biological agents may have an impact on stability. The ethanol content allows it to resist microbial contamination. Zeta potential is a crucial metric for evaluating stability[17].

Drug-loaded TE that has just been produced is kept for three months at two different temperatures: room temperature at 25 ± 2°C, and refrigerator temperature, 4 ± 2°C, with a relative humidity of 60% ± 5%. TEM and DLS can be used to assess the physical changes associated with TE.

APPLICATIONS OF TRANSETHOSOMES

Delivery of Non-Steroidal Anti-Inflammatory Drugs (NSAIDS)

Although NSAIDS are often taken orally, there are a number of gastrointestinal adverse effects that are linked to them. In an attempt to get around this issue, researchers attempted to use highly deformable vesicles to administer the drug transdermally. The experiment was carried out by Garg V et al. utilising piroxicam as the active ingredient, which was subsequently blended into transethosomal gel. Compared to other vesicular carriers, this formulation was found to exhibit higher levels of elasticity and stability.

In an experiment, Shaji et al. developed a transethosomal gel and compared it to ethosomes using ketorolac tromethamine as the active ingredient. The experiment yielded favourable results, as the gel's elastic behaviour allowed it to penetrate the skin more deeply than the ethosomes.

Delivery of Antifungal drugs

Song et al. originally reported using transethosomes as a transdermal drug delivery technique to administer the antifungal drug voriconazole. They made comparison between the transethosomes, ethosomes, liposomes, and deformable liposomes. Transethosomes performed better in the skin deposition study than other vesicles. The dermis/epidermis area exhibits a high concentration of drug due to the high vesicle flexibility. It can therefore readily pass through the skin and reach deeper cells.

Delivery of Anticancer drugs

In order to treat cutaneous melanoma, Lei et al. conducted tests using dual loading of drugs in a transethosomal formulation. They selected two drugs, namely tretinoin and dacarbazine, because they show synergistic action and lower the risk of cytotoxicity when compared to other combinations. 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.

Delivery of Anti-hypertensive Drugs

Anti-hypertensive medications are often administered orally, yet some have reduced bioavailability because of first-pass metabolism. Albash et al. created a transethosomal formulation using olmesartan medoxomil as the active ingredient, which increased the amount of medication absorbed through the skin via the transdermal route.

Delivery of Anti-arthritis Drugs

To create antioxidant surface-transethosomes, Song et al. loaded Sinomenine hydrochloride into transethosomes and subsequently coated them with ascorbic acid. This demonstrated improved drug disposition and transdermal permeability for treating oxidative stress in rheumatoid arthritis.

Delivery of peptide drugs

Peptides cannot cross the stratum corneum because of their bigger size. So delivery of peptides via transdermal route is so challenging. To enhance transdermal distribution, Kim et al. conducted an experiment wherein they encapsulated palmitoyl pentapeptide in a transethosomal formulation. They came to the conclusion that adding palmitoyl pentapeptide to the transethosomal formulation enhanced its flexibility and boosted skin penetration.

Delivery of antibiotics

Topical antibiotic therapy may be able to lessen the side effects and severe allergic responses linked to oral antibiotic therapy. By dispersing a significant amount of drug into the skin's deeper layers, ethosomes can prevent these problems. E. Touitou et al. created erythromycin ethosomes, which showed a better inhibitory impact on Staphylococcus aureus than conventional oral antibiotic formulations.

CONCLUSION

Transethosomes represent a promising advancement in drug delivery technology, offering a novel approach to enhancing skin permeation of various medications. By utilizing ultra-deformable lipid vesicles, transethosomes offer a solution to overcome the limitations of traditional drug delivery systems, such as first-pass metabolism and gastrointestinal degradation. The advantages of transethosomes, including better patient compliance, the ability

to deliver medications with higher molecular weights, and improved skin permeation, make them a valuable option for delivering a wide range of drugs.

Researchers have explored different methods of formulating transethosomes, such as the thin-film hydration technique and the ethanol injection method, to optimize drug absorption through the skin. Studies on *in vitro* drug release, skin permeation, and stability have offered valuable insights into the effectiveness and reliability of transethosome formulations.

Overall, the potential applications of transethosomes in delivering various dosage forms and their ability to bypass first-pass metabolism make them a promising alternative to traditional drug delivery methods. Continued research and development in this field are essential to fully harness the benefits of transethosomes and to pave the way for innovative drug delivery solutions in the future.

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