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Transethosomes: A Promising Carrier for Enhanced Transdermal Drug Delivery System

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A B S T R A C T

Transethosomes represent a novel and versatile vesicular drug delivery system designed to enhance transdermal and dermal drug permeation. By combining the advantages of ethosomes and transferosomes, transethosomes exhibit improved skin penetration, flexibility, and drug encapsulation efficiency. This article explores the fundamental aspects of transethosomes, beginning with an overview of their origin and significance in overcoming the barriers of traditional topical delivery systems. The composition typically includes phospholipids, ethanol, surfactants, and edge activators, each playing a crucial role in vesicle formation and function. Various preparation methods, such as the thin-film hydration technique and cold method…etc. are discussed with emphasis on their suitability for different drug types. Additionally, the wide range of applications, from delivering transdermal drug delivery and antifungal agents and cosmetic drug delivery system underscores the potential of transethosomes as an effective platform in pharmaceutical and therapeutic development..

Keyword: transethosomes, edgeactivator, ethanol, phospholipids

Introduction

The most popular method of administration is oral. The most convenient way to administer medication is orally, although some oral treatments may have significant drawbacks, including reduced bioavailability due to hepatic first-pass metabolism, stomach irritation, and unpleasant taste and the ability to cause fluctuations in the plasma drug concentration and thus, there will be the need of frequent dosing which may cause patient Incompliance.transdermal drug delivery system offers several advantages to the drug, including the fact that it bypasses first- pass metabolism, maintains a controlled level of drug in plasma, reduces drug toxicity, provides a larger surface area for dosage administration, requires no skill for use, and allows for the discontinuation of drug administration.[3]

Transethosomes are innovative, lipid-based vesicular systems specifically designed to improve drug delivery through the skin. These vesicles are made up of four main components: phospholipids, ethanol, an edge activator, and water. Phospholipids act as the primary carriers, helping to transport drug molecules directly into the skin. Their structure includes a hydrophilic (water-attracting) head and a hydrophobic (water-repelling) tail, which together form a bilayer capable of encapsulating the drug. The edge activator plays a crucial role by softening this lipid bilayer, increasing the vesicle's flexibility and enhancing its ability to pass through the skin. Ethanol plays an important role by loosening or fluidizing the lipid bilayer, which makes the vesicles more flexible and better able to adapt as they pass through the tiny openings in the skin's outermost layer, the stratum corneum. When ethanol is used together with an edge activator, the two work in synergy to disrupt and reorganize the structure of the bilayer. This makes the vesicles more flexible, helping them pass through the layers of the skin more easily. As a result, transethosomes can reach deeper into the skin, improving how effectively and precisely they deliver the medication.[1][2]

COMPOSITION OF TRANSETHOSOME

1.Ethanol

Ethanol is a key ingredient that makes transethosomes work so well. It helps keep these tiny carriers stable, controls their size, improves how much medication they can hold, and makes it easier for the drugs to pass through the skin. Transethosomes usually contain 10–20% ethanol, which is what gives them their soft and flexible texture. What's really interesting is that higher ethanol levels actually help them hold more of the drug—so the more ethanol, the better their entrapment efficiency. Additionally, when hydrophilic and lipophilic medicines are loaded into TEs, ethanol makes them more soluble. If the ethanol is used beyond the optimum concentration, it will result in the leakage of lipid bilayer which will cause an increase in the size of vesicle and ultimately the entrapment efficacy will be significantly reduced[13][9]

2. Phospholipids

For making transethosomes, the ideal phospholipid concentration usually ranges from 2% to 5%, as this helps ensure optimal stability and performance.the size, zeta potential, entrapment effectiveness, stability, penetration, and permeation properties of the TEs are all influenced by the kind and quantity of phospholipid used and thus selection of a suitable phospholipid is a significant factor in the formation of stable TEs.

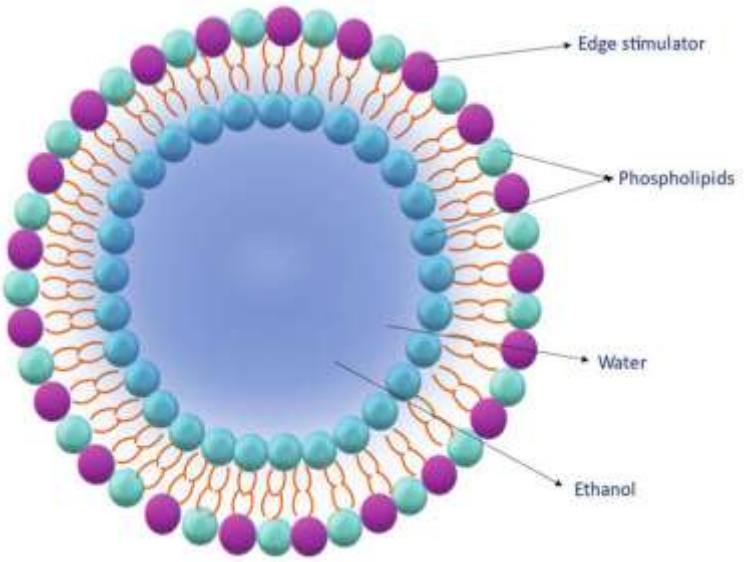
3.Cholestrol

The cholesterol is used in the concentrations of less than 3% or less. Cholesterol is reported to stabilize into this vesicle system and prevent the particles from agglomeration.[6]

4.Edge activator

Edge activator also called permeation enhancer Surfactants of all three types– anionic, cationic, and non-ionic can be used as transethosomal system edge activators. Sodium stearate, sodium cholate, and deoxycholic acid are some of the anionic surfactants which can be used for making TEs, while Cremophor RH-40 and Cremophor EL-35 are non-ionic surfactants. The preparation of TEs can be done using a surfactant such polyethylene glycol.[6][7]

Figure1:Transethosomes[16]



Mechanism of action of Transethosomes

Transethosomes are tiny, flexible droplet that help medicine get through the skin more easily. They're made from ingredients like phospholipids (similar to what's already in our skin), a bit of alcohol(ethanol), edge activator, and water. This combination makes them super soft and stretchy, so they can squeeze through the little spaces between skin cells. The alcohol helps by gently loosening up the outer layer of the skin, making it easier for the medicine to slip inside. Once these droplets reach deeper layers of the skin, they mix in with the skin's own fats, which helps the medicine spread and absorb better. They also release the medicine slowly, so it keeps working for a longer time without needing constant reapplication. Because of their smart design, they can carry both watery and oily medicines, which makes them more effective than regular creams. They're safe, non-invasive, and a great option for treating skin problems or even delivering medicine into the body through the skin.[6][3]

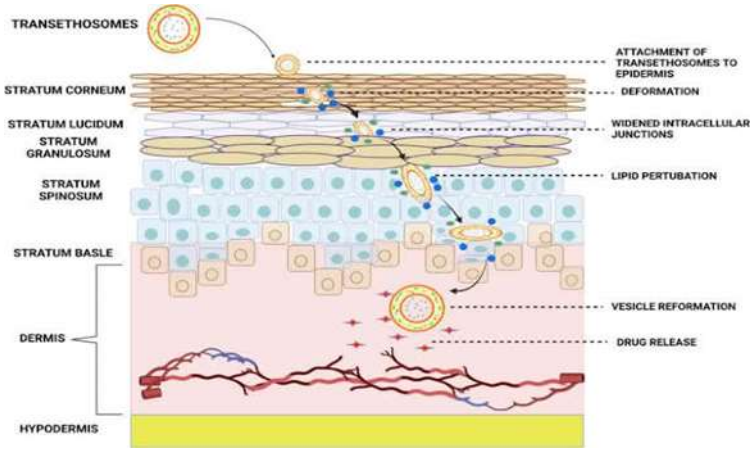


Figure 2: Mechanism of transethosome-mediated skin Penetration[7]

Methods of preparation of transethosomes

1.Cold method

This method useful for the heat sensitive or thermolabile drugs.in this method lipids have been mixed in the ethanol at room temperature and then followed by the addition of edge activator this mixture is heated to 30^{o}c under constant stirring upto 5minutes in enclosed container. The water is heated in a different container to 30^{o}c before being added to the alcoholic mixture. Then, sonication is done to minimize the size of TEs. Finally, the prepared formulation is kept under refrigeration.

2. Hot method

The hot method involves immersing phospholipids in water and heating them in a water bath at around 40 °C until they form a colloidal (cloudy) solution. Simultaneously, a mixture of ethanol and a co-solvent, often propylene glycol, is heated separately to the same temperature. Once both phases reach ~40 °C, the ethanol/glycol solution is slowly added to the heated lipid dispersion while stirring continuously for 7–10 minutes. The drug, depending on whether it's water-soluble or oil-soluble, is dissolved appropriately in either the aqueous or alcohol/glycol phase before mixing. Finally, the vesicle suspension is sonicated or extruded to reduce particle size and achieve uniformity.

3.Thin film hydration method

The thin-film hydration method prepared by using phospholipids, edge activators (like Tween 80 or Span 80), and the drug are first dissolved in a mixture of organic solvents, such as chloroform and methanol. This solution is then evaporated using a rotary evaporator to form a thin, dry film of lipids on the wall of a flask. Next, this film is hydrated with a buffer solution containing ethanol, which helps form tiny, flexible vesicles called transethosomes. The mixture is stirred or shaken to help the lipids absorb the water and form vesicles. To make them smaller and more uniform, the vesicles are often sonicated or passed through filters.[10]

4. Ethanol injection method

The phospholipid, edge activator, and drug are mixed together in ethanol to form a uniform solution. This mixture is then quickly injected in a thin stream through a fine needle into water while stirring continuously. As soon as the solution hits the water, the lipids start to come out of the mixture and arrange themselves into thin layers, trapping some of the water inside. These tiny structures, called transethosomes, are then collected by spinning the sample in a centrifuge and filtering it. After that, the final product is ready to be studied and analysed.[6][7][5]

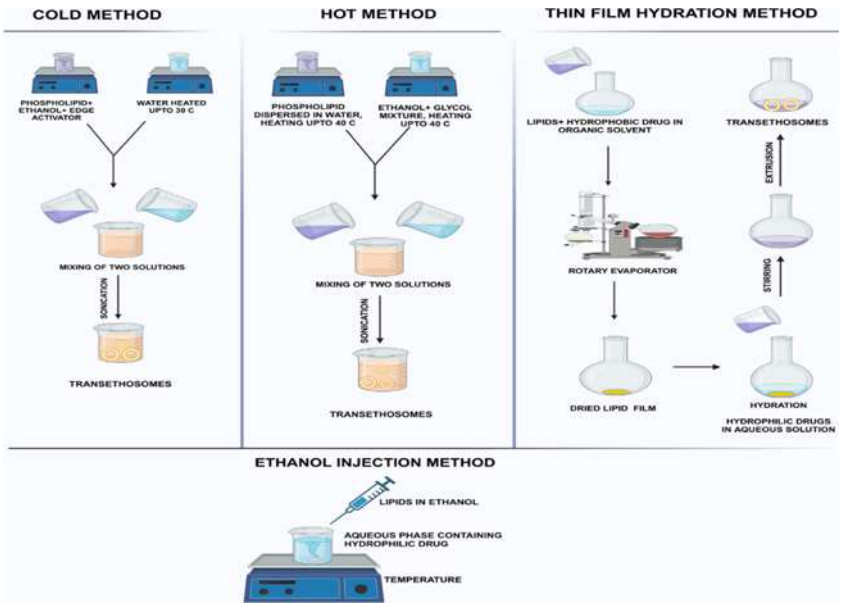


Figure 3: Methods of preparation of transethosomes [7]

Evaluation test of transethosomes

1.Morphology of transethosomes

The structure and morphology of transethosomes can be examined using advanced imaging methods such as scanning electron microscopy (SEM) and transmission electron microscopy (TEM).

2.Entrapment efficiency

The amount of drug entrapped inside transethosomes can be determined using the centrifugation method. In this process, the drug-loaded vesicular suspension is placed in a small column and centrifuged at a controlled speed and temperature to prevent damage to the vesicles. This separates the free (unentrapped) drug in the supernatant from the drug contained within the vesicles. The vesicles are then broken open using solvents like menthol or Triton X in 2-propanol to release the entrapped drug. The drug content is measured using UV–visible spectrophotometry, and the entrapment efficiency (EE%) is calculated using the formula **[1]**

$$\% = [(\text{Total drug} - \text{Free drug}) / \text{Total drug}] \times 100.$$

3. Invitro drug release study

The dialysis bag method can be used to measure the amount of drug released through the vesicle. The TE formulation is introduced into the dialysis membrane. The loaded membrane is placed into the conical flask containing buffer solution and then subjected to the incubation. Aliquots are taken out and centrifuged using small column centrifugation at predetermined intervals.[9][11]

4.Determination of pH

Measuring the pH of transethosomes (TEs) incorporated into a gel using a digital pH meter is important. The pH of a transdermal delivery system can affect how well the drug permeates through the skin. If the pH is too acidic or too alkaline, it may cause skin irritation, which can reduce the effectiveness of the drug delivery and lower patient compliance.[10]

5.Vesicle size and Zeta potential:

Particle size analysis and light scattering techniques are commonly used for particle identification. In light scattering, particles of different sizes scatter light uniquely. The vesicular diameter is measured through photon correlation spectroscopy, also known as dynamic light scattering (DLS). Zeta potential is an important indicator of the electrostatic forces—both repulsive and attractive within colloidal dispersions. It also provides valuable information about the surface chemistry of the system. This parameter is essential for assessing the stability and integrity of colloidal dispersion systems.[15][4][12]

Application of Transethosomes

1.Transdermal drug delivery system

Transethosomes are highly effective in transdermal drug delivery systems due to their unique ability to penetrate the stratum corneum and deliver drugs deeply into or across the skin. Their ultra-deformable vesicular structure, made of phospholipids, ethanol, and edge activators, allows them to squeeze through tiny skin pores and enhance drug permeability. This makes them ideal for delivering hydrophilic and lipophilic drugs transdermally, improving bioavailability and reducing the need for oral or injectable routes. Transethosomes are used to deliver drugs such as diclofenac (anti-inflammatory), testosterone (hormone therapy), and insulin (for diabetes) through the skin. Their use leads to controlled both release, reduced systemic side effects, and improved patient compliance, making them a promising carrier in modern transdermal drug delivery systems.[8]

2.Cosmetic drug delivery system

Transethosomes are special carriers used in skincare products to help ingredients go deeper into the skin. This makes the products work better than regular creams or lotions. Because they are soft and flexible, they can pass through the skin’s outer layer easily. These are used to deliver ingredients like retinol and coenzyme Q10 for anti-aging, kojic acid and niacinamide for skin brightening, and hyaluronic acid for hydration and also help improve skin moisture, softness, and appearance. These can also be really helpful for treating acne, fading dark spots, and reducing the appearance of wrinkles. They are made from safe ingredients like phospholipids, ethanol, and surfactants, which also make the product feel nice on the skin. Overall, they make skincare products more effective and gentler.

3. Anti-fungal drug delivery system

Transethosomes are emerging as a highly promising approach for treating fungal skin infections, offering improved effectiveness and skin penetration compared to traditional methods. because of their soft, flexible structure, they can carry antifungal drugs deep into the skin reaching the layers where the infection actually lives. This helps them work better than regular creams, which often stay on the surface.

Medications like fluconazole, itraconazole, clotrimazole, and amphotericin B have been successfully used in transethosome-based treatments. These advanced carriers help the drug stay longer at the infection site, boost its effectiveness, and reduce the chance of unwanted side effects that can happen with traditional treatments.[14][16]

Current challenges

Transethosomes face several challenges, including poor stability, as they can break down when exposed to heat, pH changes, or light. Large-scale production is difficult due to issues with maintaining consistent quality. There's also limited clinical research, so their real-world effectiveness is still

uncertain.[7] Skin absorption can vary between individuals, and some ingredients like ethanol or surfactants may cause irritation or side effects, especially with long-term or sensitive use.

Future prospective

Transethosomes are primarily used for transdermal drug delivery, but recent studies show they can also be effective through other routes, such as vaginal and intranasal delivery. For example, drugs like vinpocetine and piracetam have been successfully delivered intranasally using transethosomes to treat neurodegenerative diseases by crossing the blood–brain barrier. In the future, combining transethosomes with physical methods like iontophoresis, sonophoresis, or magnetophoresis may enhance drug delivery to hard-to-reach skin targets, including tumor cells, immune cells (like Langerhans cells), and stem cells in hair follicles. Additionally, modifying the surface of transethosomes with targeting agents such as carbohydrates, antibodies, peptides, or small molecules can improve site-specific delivery and enable administration through various body routes. These advanced modifications also open the door for transethosomes to be used in theranostics, combining drug delivery and disease diagnosis in one platform, making them highly versatile in personalized medicine.[5][6]

Conclusion

Transethosomes are a promising and innovative vesicular drug delivery system that effectively combines the advantages of ethosomes and transferosomes to enhance drug penetration through the skin and other mucosal routes. Their flexible and deformable structure allows for improved delivery of both hydrophilic and lipophilic drugs, overcoming many limitations of traditional topical therapies. Although challenges such as stability, large-scale manufacturing, and potential irritation remain, ongoing research is rapidly advancing solutions to these issues. With their expanding applications, including targeted delivery and potential use in personalized medicine, transethosomes hold great potential to revolutionize drug delivery in pharmaceutical and cosmetic fields.

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