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Review Article

Transethosomes: A Promising Tool For Transdermal Drug Delivery System

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ABSTRACT

Transdermal drug delivery is an increasingly favoured approach, addressing challenges encountered by oral administration. However, traversing the skin barrier remains a hurdle. Innovative vesicular mechanisms, including liposomes, niosomes, ethosomes, and transferosomes, seek to improve drugs penetration into skin layers. Among these, transethosomes stand out because of their diminutive particle size, deformable nature, and effective skin permeability which is facilitated by ethanol, phospholipids and an edge activator. Transethosomes can be manufactured by utilizing a variety of procedures, including the cold method, hot method, thin film hydration approach and the ethanol injection method. It helps to promote patient adherence and compliance because it is a non-invasive approach for giving medications. The characterization process of transethosomes involves conducting various studies such as pH determination, size and shape analysis, zeta potential assessment, determination of particle size, measurement of transition temperature, evaluation of drug content, examination of vesicle stability, and investigation of skin permeation. The encapsulation of drugs within transethosomes enables targeted delivery to specific skin depths, proving beneficial for various therapeutic categories such as anticancer, corticosteroids, proteins, peptides, and analgesics. The non-invasive nature of transethosomal delivery not only improves patient compliance but also enhances drug entrapment efficiency, showcasing its potential in advancing transdermal therapies.

INTRODUCTION

The oral route is a widely utilized technique method for drug delivery due to its convenience[1]. Formulations administered

through this route often come with notable drawbacks, include GI discomfort, foul taste, and declined bioavailability due to hepatic first-pass metabolism[2,3]. An alternative approach

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involves repeatedly intravenous injection, recognized as a high-dose drug management method to circumvent hepatic 'first pass' metabolism and maintaining an adequate drugs degree over an extended period. However, this necessitates patient hospitalization and vigilant medical supervision[4,5]. Consequently, the healthcare sector is presently benefiting significantly from advancements in transdermal drug delivery technologies[6]. These innovations aim to avoid fluctuations in plasma drug levels during repeated treatments, prevent toxicity to organs and initial metabolism, decrease dose-related adverse effects, and deal with issues including digestive discomfort and minimal the rate of absorption[7,8]. Moreover, transdermal drug delivery offers advantages such as controlled drugs release, reduced dosages, and improved patient adherence[9]. Overcoming challenges associated with drugs featuring low or high partition coefficients in reaching systemic circulation has led to the development of innovative drug delivery vesicles[10]. While conventional topical delivery methods face challenges in reaching deeper layers of the skin, vesicular drug delivery systems offer potential advantages for localized drug activity and effective treatment[11,12]. However, niosomes and liposomes, commonly used vesicles, encounter limitations in penetrating deep skin layers due to their less flexible structure[13]. To overcome these constraints, recent efforts have focused on formulating elastic vesicles[14]. Two main types of elastic vesicles have emerged: transfersomes comprising an edge activator and lipid and ethosomes composed of lipid and ethanol[15-16]. Transfersomes enhance vesicle flexibility by redistributing both the edge activator and lipid within their surroundings. In contrast, ethosomes achieve increased flexibility by fluidizing both the skin and the lipids within the vesicles. A novel vesicle type, known as

transethosomes, has been developed to combine the characteristics of both ethosomes and transfersomes. These unique vesicles contain both lipids and ethanol, aiming to leverage the advantages of both transfersosomal and ethosomal features[17]. These deformable vesicles, incorporating edge activators, exhibit enhanced penetration of drugs through the skin and increased entrapment efficiency. The high elasticity and reduced vesicle size contribute to avoiding fusion and aggregation[10].

Structure of skin:

The corneum layer is the epidermis outermost layer, and it is made up of 10-25 highly keratinized layers made up of continuous, deceased corneal cells. The above layers are firmly incorporated in the double layer of lipid structure. The corneum layer acts as the skin's the primary hurdle, limiting permeation. While using a transdermal preparation on the skin, the therapeutic drugs must pass through the corneum layer. Material dispersion through the skin's decaying keratin layer is slow, which limits these processes. The corneum layer acts as a hydrophobic membrane, regulating the transit rate of both low and large molecular weight organic non-electrolytes[18].

Transethosomes:

Transethosomes represent lipid-based vesicles designed for drug delivery, comprising phospholipids, ethanol, an edge activator and water. The main important role of phospholipids is to serve as carriers, facilitating the direct delivery of medication particles into the skin. These lipid vesicles exhibit a hydrophilic head and a hydrophobic tail in their structure. The inclusion of an edge activator serves to soften the bilayer, enhancing the vesicle's permeability properties[19]. Notably, the edge activator can contribute to the flexibility and adaptability of transethosomes. Ethanol, another crucial component, plays a pivotal role in the formulation of nano-vesicular systems. Its key properties of



adaptability and flexibility enable these systems to easily penetrate the stratum corneum through minute openings, facilitated by the fluidization process[20]. The combination of the edge activator and ethanol induces the transposition of the lipid bilayer, resulting in a more deformable structure[21]. This structural change facilitates penetration into deeper skin layers, highlighting the effectiveness of transethosomes in drug delivery applications[22].

ADVANTAGES OF TRANSETHSOMES

1. Enhancement of drug penetration through the skin in transdermal drug delivery (TDD).
2. Utilization of non-toxic raw materials.
3. Non-invasive in nature.
4. Avoids the hepatic first-pass metabolism, which minimizes the risk of adverse effects[23].
5. Exhibits greater stability compared to alternative ultra-deformable vesicles.
6. Facilitates easy penetration through the skin layers[24].
7. Administration of transethosomal drugs in a semi-solid dosage form.
8. Biocompatible and biodegradable characteristics[25].

DISADVANTAGES OF TRANSETHSOMES

1. Product loss during transition between an alcoholic to water medium.
2. May cause skin irritation or allergic responses, not suited for people with sensitivedermatitis.
3. The drug must be sufficiently soluble in both lipophilic and aqueous conditions to enter the cutaneous microcirculation and systemic circulation.
4. The drug must have a reasonable molecular size to facilitate percutaneous absorption[25].
5. Incomplete vesicle production can cause transethosome coalescence[26].

MATERIALS AND METHODS

Ethanol/Alcohol:

The characteristics of ethanol, such as stability, size, entrapment effectiveness, and skin permeability, contribute to its role as an effective penetration promoter. Topical formulations, known as Transethosomes (TEs), often contain 10–20% ethanol, rendering these vesicles soft and elastic. The entrapment efficiency (EE) of TEs is directly influenced by ethanol concentration; higher concentrations enhance the entrapment ability. Ethanol also boosts the solubility of both hydrophilic and lipophilic drugs, facilitating their loading into TEs. However, exceeding the optimal ethanol concentration can lead to lipid bilayer leakage, causing an increase in vesicle size and a subsequent reduction in entrapment efficacy[28].

Phospholipid:

The selection of phospholipids is a crucial factor in the development of ethosomal systems, significantly affecting the size of the ethosomes. Both the type and concentration of phospholipids play a vital role in determining the size, entrapment efficiency, zeta potential, stability as well as the penetration and permeation properties of the vesicular system. The concentration of phospholipids typically falls within the range of 2% to 5%, contributing to the formation of vesicles. An increase in phospholipid concentration tends to result in a slight or moderate increase in the size of the vesicles[29].

Edge activators/penetration enhancer :

Selecting an appropriate edge activator is a critical step in transethosomal (TE) production as it significantly influences their characteristics. Edge activators from all three surfactant types—anionic, cationic, and non-ionic—can be employed in transethosomal systems[30]. Anionic surfactants like sodium stearate, sodium cholate, and deoxycholic acid, as well as non-ionic surfactants like cremophor RH-40 and cremophor EL-35, are examples used in TE formulation. Polyethylene glycol is one option for surfactant use in TE preparation, but commonly, tweens and spans



serve as preferred edge activators. Studies suggest that Tween 80, in particular, enhances stability and reduces vesicular size in transethosomal systems[31].

Mechanism Of Action

The transethosome mechanism involves in two phases:

Ethanol effect:

The ethanol effect is considered the primary mechanism for enhancing drug distribution deeper into the skin layers. This leads to a reduction in the transition temperature of lipids within the stratum corneum and an increased fluidity in transethosomes. The result is improved penetration into the lipid layer of the skin by reducing density. The presence of alcohol at the surface induces a change in membrane shape, breaking the continuity of the single layer by promoting the fusion of a discontinuous membrane[29,26].

Ethosomes effect:

The transethosome effect represents the second mechanism at play. The ethosomal system effectively permeates and penetrates the lipid layer. The movement of transethosomes through the stratum corneum is facilitated by hydration force and they navigate through the skin via osmotic theory. Certain penetration enhancers such as Tween 20, Tween 60, Span 60, Span 65, Span 80, among others, disrupt the intracellular lipid structure in the stratum corneum, facilitating the permeation of drugs across the skin[27].

METHOD OF PREPARATION

Cold Method:

The cold approach is the most often used method for manufacturing transethosomes. In this method, phospholipids are introduced into ethanol, well blended, and then heated to 30°C (Organic Phase). In a separate container, the edge activator, drug and water are mixed and heated to 30°C (Aqueous Phase). The drug's hydrophilic or hydrophobic nature determines whether it may be dissolved in

water or ethanol. The mixture is held on a magnetic stirrer at 700 rpm while the aqueous solution is added to the alcoholic solution in a fine stream and the temperature is kept at 30°C throughout the operation. The resultant mixture is then sonicated in a sonicator to minimize the size of transethosomes[41].

Hot Method:

1. To create a colloidal solution, distribute phospholipid in water and heat in a water bath to 40°C.
2. Maintain ethanol and glycol mixture at 40°C. The phase containing ethanol and glycol is added to the aqueous phase and stirred for 7–10 minutes.
3. The drug's hydrophilic or hydrophobic characteristics determine whether it can dissolve in water or ethanol. The temperature is maintained at 40°C during the operation.
4. Sonication reduces the size of transethosomes[39].

Ethanol Injection Method:

1. Phospholipid + edge activator + drug dissolved in organic solvent (ethanol) with mixing at appropriate
2. Rapidly injection of above solution in small stream through a fine needle into water with constant stirring
3. Lipid molecule precipitate and form bilayer planar fragments encapsulating aqueous phase
4. Sample is centrifuged and filtered analysis of transethosomes is done[41].

Thin Film Hydration method:

1. In this method accurately weighed drug, lipid and edge activator are dissolved in a mixture containing organic mixture.
2. A rotary evaporator can be used which forms a thin film on evaporation under reduced pressure.
3. The film is then hydrated using pH 7.4 buffer with different concentration of ethanol.



4. The mixture is then left overnight for hydration[43].

CHARACTERIZATION PARAMETERS OF TRANSETHOSOMES

Morphology of Transethosomes :

The morphology of Transethosomes can be investigated through visual imaging using transmission electron microscopy (TEM) and scanning electron microscopy (SEM). Observation under electron microscopy reveals that Transethosomes have a vesicular size ranging from 300 to 400 nm in diameter. These vesicles exhibit flexibility, attributed to their irregularly round shape[44].

Vesicle size and Zeta potential:

Particle Size Analyzer and Light Scattering Technique are employed for identification. In the light scattering technique, particles of varying sizes scatter light. Vesicular diameter is determined using photon correction spectroscopy or dynamic light scattering (DLS)[36]. Zeta potential serves as a gauge for electrostatic repulsion and attraction within colloidal dispersions. Additionally, it offers insights into the surface chemistry of the system. This parameter plays a crucial role in determining the stability and firmness of colloidal dispersion systems[46].

Entrapment Efficiency:

To assess the entrapment efficiency of formulations, the ultracentrifugation method was employed. Approximately 2 ml of the formulations underwent ultracentrifugation in an Ultracentrifuge at 15,000 rpm for 60 minutes at a temperature of 4°C, separating the untrapped drug from the dispersion. The resulting supernatant, containing the free drug, and the transethosomal pellets were collected. Subsequently, the transethosomal pellets were washed with PBS (pH 7.4) through centrifugation to eliminate any remaining untrapped drug. The combined supernatant was then diluted with PBS

(pH 7.4) and quantified spectrophotometrically using a UV spectrophotometer[47].

Entrapment Efficiency formula

Amount of drug added initially - Amount of drug determined in the filtrate by spectrophotometry X 100

Amount of drug added initially

=Represents the amount of drug entrapped in the formulation.

Stability:

Transethosomal formulations are evaluated for drug retention at various temperatures, including room temperature ($25\pm 2^\circ\text{C}$), $37\pm 2^\circ\text{C}$, and $45\pm 2^\circ\text{C}$, during varying time periods. The stability of ethosomes may be quantitatively assessed by monitoring the size and appearance of the vesicles using DLS and TEM[48].

In vitro skin permeation study:

The Franz diffusion cell may be used to conduct in-vitro skin permeability studies on transethosomes. Confocal Laser Scanning Microscopy can be used to assess transethosomes' capacity to penetrate deeper into the skin for targeted medication administration. Maintain the instrument temperature at $32^\circ\text{C} \pm 10^\circ\text{C}$. There is a receptor compartment cell that holds 10 ml of PBS. The skin on which the permeation investigation may be performed is located between the donor and receptor compartment. Now apply the transethosomal vesicles to the skin's outermost surface. Samples can be discarded after a set period of time, such as 1, 2, 3, 4, 8, 12, 16, 20, or 24 hours. The samples are removed at a certain time interval are analysed by using HPLC[49].

In-vitro Drug Release Study:

An in-vitro investigation with the Dialysis bag method may simply assess the quantity of medication release from the transethosomes.

1. Firstly the transethosomal formulation loaded in dialysis bag.
2. Transfer the transethosome-loaded membrane to a conical flask containing buffer solution.



3. Then it is incubated for particular period of time.
4. After some time interval the aliquots are withdrawn and then it is centrifuged using column centrifugation method[49].

Surface Tension:

The surface tension activity of drug in aqueous solution can be measured by the ring method in a Du Nou ring tensiometer[40].

Drug Content:

The drug content of transethosomes can be evaluated using an ultraviolet spectrophotometer. This can also be measured using a modified high-performance liquid chromatography approach[49].

APPLICATIONS OF TRANSETHOSOMAL VESICULAR SYSTEM.

Delivery of Anticancer Drugs:

Researcher conducted an investigation wherein they optimized nanotransethosomal vesicles loaded with fisetin, a natural flavonoid prevalent in numerous fruits and vegetables, using Box-Behnken design software. The experiment revealed that the nanotransethosomal vesicles exhibited good entrapment efficiency (EE) and demonstrated a reasonable flux[49]. Researcher formulated involving the dual loading of drugs into a transethosomal formulation for the treatment of cutaneous melanoma. The selected drugs, dacarbazine and tretinoin, were chosen for their synergistic action, effectively eliminating cytotoxic effects in comparison to alternative formulations. The dual-loaded transethosomes exhibited heightened anticancer activity when compared to single-loaded drugs. The study revealed that an enhanced skin penetration capability could be achieved through this approach[51]. Researchers observed that encapsulating 5-Fluorouracil into transethosomal gel demonstrated enhanced deformability, higher skin penetration, and deeper skin targeting as compared to ethosomes[52].

Delivery of Antiarthritic Drug:

Researcher have developed an experiment involving the development of a piroxicam-loaded transethosomal hydrogel for the treatment of Rheumatoid Arthritis. In this study, the transethosomal hydrogel was prepared using lipid, ethanol, an edge activator, and comprehensive characterization was performed. The results clearly demonstrate that the formulated piroxicam transethosomal hydrogel possesses the capability to penetrate deeply into the skin, facilitating targeted drug delivery[41]. A study showcasing the formulation of flurbiprofen-loaded transethosomes for arthritis treatment. The research highlighted that transethosomes exhibited the highest ethanol percentage. Consequently, the findings suggest that the flurbiprofen-loaded transethosomal gel may serve as a promising carrier for the dermal delivery of the hydrophobic drug, flurbiprofen[53].

Delivery of Antihypertensive Drugs:

Researcher conducted an experiment formulating transethosomes as a transdermal delivery system for Olmesartan medoxomil. The findings suggest that transethosomes exhibit promise as effective transdermal delivery systems for Olmesartan medoxomil, offering the potential to circumvent extensive first-pass metabolism of Olmesartan medoxomil[8]. Investigator performed the study in which nanotransethosomes loaded with propranolol hydrochloride demonstrated improved skin in-vitro penetration and high regulated drug release. According to the most current study, nanotransethosomal vesicles can be easily manufactured for antihypertensive medicines[54].

Delivery of Non-steroidal Anti-inflammatory Drugs (NSAIDs):

Investigator conducted an experiment utilizing the key component piroxicam, which was subsequently formulated into a transethosomal gel. The findings revealed that this formulation exhibited superior stability and elasticity



compared to other vesicular carriers[42]. Researcher conducted an experiment with ketorolac tromethamine as the key component, formulating a transethosomal gel that was compared to ethosomes. The results were favourable, indicating that the gel exhibited improved skin penetration attributed to its elastic behaviour in contrast to ethosomes[55].

Delivery of Antifungal Drug:

A study was conducted on experiment wherein they formulated Voriconazole-loaded transethosomes and incorporated them into a hydrogel for antifungal and antileishmanial applications. The results showcased showed that the produced Voriconazole transethosomal hydrogel can be extremely beneficial for treating topical fungal infections[56]. The investigator utilized Econazole Nitrate as the active moiety and conducted a comparative analysis between econazole nitrate loaded transethosomal gel and a commercially available econazole nitrate transdermal cream. Their findings indicated that the transethosomal gel exhibited elevated ex vivo skin retention and significant in vitro antifungal activity. The controlled drug release from the transethosomal gel was observed to effectively eliminate cutaneous candidiasis[57].

FUTURE PROSPECT

Among the emerging novel drug delivery systems, transethosomal vesicular carriers have gathered considerable attention from researchers. This trend holds promise for the future, as the development, production, importation, exportation, and distribution of drugs should be regulated to meet standardized specifications. Manufacturers must ensure that transethosomal formulations adhere to desired specifications, utilizing excipients that are clinically non-toxic and listed as "Generally Recognized as Safe" (GRAS), as detailed in Table 1. Transethosomal vesicular carriers provide an enhanced mechanism for guaranteeing the stability of diverse proteins and medications in the domain

of transdermal drug administration and therapies. They prove suitable for loading both hydrophilic and hydrophobic drugs, opening avenues for exploring diverse drug classes such as antivirals, anti-diabetics, and anticoagulants using transethosomes. Furthermore, the administration of anti-cancer drugs as a combination through transethosomal delivery shows potential for minimal cytotoxicity and efficient skin permeation. The versatility of transethosomes extends to the administration of drug combinations, enhancing the efficacy of medications. Despite the current absence of commercially available transethosomes, limited literature exists on clinical trials. Consequently, transethosomes exhibit significant potential as carriers for transdermal or topical drug delivery.

CONCLUSION:

In recent years, the transdermal route has gained significant favour as a preferred method for drug delivery, overcoming drawbacks associated with oral administration, notably the issue of first-pass metabolism. To tackle the challenge, scientists and investigator have introduced the transethosomes. In this innovative approach, drug molecules, whether synthetic or herbal, are incorporated into vesicles that can penetrate deeply into the skin, facilitating targeted drug delivery. Among the vesicular system, Transethosomes emerge as a novel and promising prospect for enhanced transdermal drug delivery. The effectiveness of transethosomes lies in their composition, including ethanol, edge activators, and phospholipids, which contribute to their enhanced penetrability. The versatility of UDV systems extends to the transdermal delivery of diverse drug classes, including anti-arthritic, analgesic, anticancer, antibiotic, and antiviral drugs. Overcoming the challenge posed by drugs with both high and low partition coefficients, ultra-deformable vesicles, encompassing Transferosomes, Ethosomes, and Transethosomes have developed. Furthermore,



transethosomes can be integrated into novel drug delivery systems, including creams, gels, and patches. The Transethosomal vesicular system demonstrates substantial potential as a carrier for transdermal drug delivery.

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