REVIEW ARTICLE

Transethosomes: An Innovative Approach for Drug Delivery

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Abstract

Since a few years ago, the delivery of drugs through the skin has gained popularity. By doing so, it gets around problems with the oral route. Despite the fact that only a few pathways are as appealing as the transdermal route, it is difficult to deliver drugs through the skin. Researchers have developed a technique that allows the medicine to be encapsulated into vesicles, which may then go deep into the layer of skin to reach the target spot. Consequently, bioactive agents can penetrate the skin more effectively. Liposomes, niosomes, transethosomes, and transferosomes are vesicular systems that frequently remain collected in the skin layers. Transethosomes can pass through multiple layers of skin because they have tiny particle sizes and can change the form of vesicles more easily than another vesicular system. Transethosomes allow the medicine to be conveniently delivered to the target place. Ethanol, phospholipids, and an edge stimulator make up transethosomes. Transethosomes' ability to penetrate the skin is improved by ethanol and edge stimulators. It increases patient cooperation because it is a non-intrusive procedure. It also improves the effectiveness of drug entrapment. These vesicles can hold a wide range of medications, including pain relievers, antitumor medicines, steroids, proteins, and peptides.

Key words: Drug delivery, encapsulation, skin, transdermal, transethosomes

INTRODUCTION

The most popular method of administration is oral. The oral route of medication administration is the most practical, although some oral medications may have serious disadvantages, such as decreased bioavailability caused by hepatic first-pass metabolism, stomach irritability, and unpleasant taste. A transdermal strategy has been tried as a solution to these problems because it offers advantages such as skipping the hepatic first-pass metabolism. When it comes to medications with a high first-pass metabolism, topical formulations can demonstrate greater bioavailability than oral routes.[1] It has some restrictions, such as the fact that medications with greater molecular weights cannot reach the horny layer. Drugs with greater or lesser distribution coefficients have trouble entering the bloodstream.[2] Drugs are delivered into the skin using liposomes, but their penetration is limited by their propensity to stay in the upper stratum corneum.[3,4] New lipid vesicles called highly-deformable vesicles have been created to enhance medication delivery. There are many different forms of this type of vesicle, including ethosomes, transferosomes, and transethosomes, that are created for the administration of cosmetics and medications.[5] Transferosomes are flexible vesicular transporters with a lipid dual-layer architecture and an edge stimulator. Edge stimulator is still present in the formulation in spite of the water which has evaporated. This formulation's principal drawback is that it is challenging to load hydrophobic medicines in this vesicular system with retaining their elastic characteristics.[5,6] As a result of this, ethosomes are created. Ethosomes are vesicular transporters made of phospholipids that have a high alcohol content and are hydro-alcoholic.[7] The main drawback of ethosomes is that when applied to surface under non-occlusive state, the ethanol in the mixture evaporates, leading to skin dryness.[5] Thus, transethosomes, a combination of transferosomes and ethosomes, are created. It is extremely

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elastic and has non-uniformly spherical form. It is simple to load pharmaceuticals with low and high molecular masses.

SIMILARITIES BETWEEN ETHOSOMES, TRANSFEROSOMES, AND TRANSETHOSOMES

The distinction between ethosomes, transferosomes, and transethosomes is shown in Table 1 below. Transethosomes have been found to have a higher drug encapsulation efficiency and transdermal flux rate than other formulations, making them comparably better. It has the power to enter deep layers of skin and change shape.

FRAMEWORK OF TRANSETHOSOMES

As seen in Figure 1, transethosomes are phosphatidylcholine-based vesicles that include phosphatides, ethanol, edge stimulator, and water. Phosphatides, often known as non-ionic surfactants, operate as a vehicle for transporting medication molecules to the surface. Transethosome can effortlessly combine with horny layer, enhance tissue moistening, and combine with fats of stratum corneum.[18] Both a hydrophilic head and a hydrophobic tail are present in them.[19] An effective dual-layer softening agent is edge stimulator. Usually, it is included to increase permeation and mobility.[20] The transethosomal system's fundamental element is alcohol, which gives it a distinctive identity as a vesicle. Because ethanol disrupts the topmost layer of the skin and makes these tiny structures flexible and versatile through fluidization, they can enter the stratum corneum through extremely small openings.[21] Water is a crucial component because it aids in the formation of a bilayer when phospholipids are introduced and promotes system flexibility.[4] The lipid bilayer is altered and made flexible as ethanol and edge stimulator are combined, allowing for deeper penetration into the dermis.

ARCHITECTURE AND FUNCTION OF TRANSETHOSOME

Transethosome components are under the category of "Generally Recognized as Safe" (GRAS)[22] listed compounds. Table 2 lists excipients that are often used and have GRAS approval.

FORMULATION APPROACHES FOR TRANSETHOSOME

Without the need for complex machinery, transethosomes can be prepared and scaled up easily at both the commercial and experimental plant levels. To improve skin penetration, tiny vesicles are created using a variety of techniques and then added to topical gels or creams. The techniques discussed below are some of the more popular ones.

Ethanol injection technique

Due to its simplicity in preparation and scaling up, this technique has many benefits over other approaches. The fact that ethanol is safe makes it a popular choice for organic solvents.[26,27] Figure 2 gives a good explanation of this technique.

Thin-layer hydration technique

Preparation is simple where one can obtain lipid and aqueous substance encapsulated. Its time-consuming process makes scaling up difficult, which is a significant drawback.[28] Figure 3 shows this approach.[27,29]

Cold technique

Transethosomes are frequently developed with ease using this procedure.[30] Drugs that are thermo-sensitive can be encapsulated. Figure 4 clearly explains this technique.

Direct technique

In an organic part, the quantity required of phosphatides, edge stimulator, and medicament is dissolved. The organic part is mixed with aqueous part. For 10 min, the mixture is homogenized. Then, the preparation is filtered. It is simple to execute and scale up.[31]

Table 1: Similarities between ethosomes, transferosomes, and transethosomes

Variables	Ethosomes	Transferosomes	Transethosomes
Constitution	Phosphatides, ethyl alcohol and water.[8]	Phosphatides, edge stimulator, and water.[9]	Phosphatides, ethyl alcohol, edge stimulator and water.[10]
Encapsulation efficiency	High than liposomes.[11]	High than ethosomes.[12]	High than both ethosome and transferosomes.[5]
Transdermal flux rate	Greater than liposomes.[13]	High or equal to ethosomes.[14]	Highest flux rate.[15]
Permeation mechanism	Fat perturbation[16]	Distortion of vesicles.[17]	Transformation in structure of vesicles.[10]

Table 2: GRAS approved list of excipients

Architecture	Excipients	Function
Phosphatides (2–5%)[23]	L-α-Lecithin, Phospholipon, and Phospholipon 90NG[24]	Vesicle formation
Edge stimulator[25]	Oleic acid, cholalic acid sodium salt, Tween 80, Tween 20, desoxycholic acid sodium salt, and Span 80[12]	It gives the vesicle flexibility and improves penetration.
Alcohol (40%)[11]	Ethanol, isopropanol, methyl glycol, and carbitol[24]	It makes the vesicle envelope supple.
Water (qs)	Water	Vesicle synthesizing agent

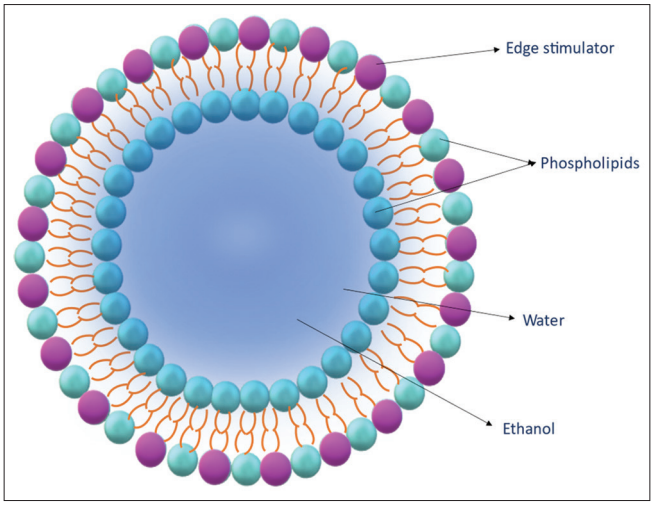

Figure 1: Structure of transethosomes

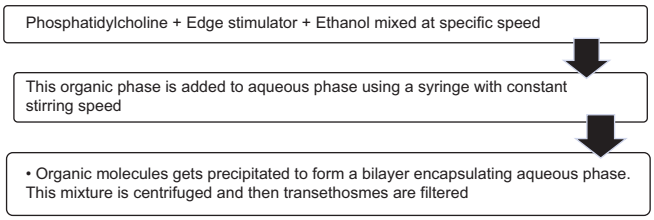

Figure 2: Ethanol injection technique

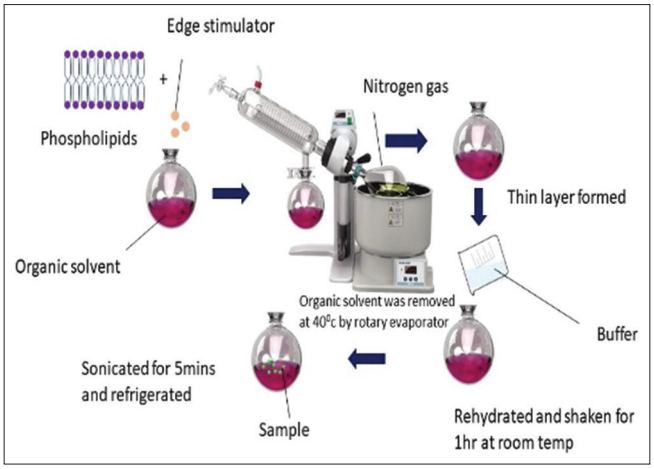

Figure 3: Thin-layer hydration technique

Reverse phase evaporation technique

It is an efficient approach with 50% of encapsulation rate.[28] Figure 5 explains the procedure.

OPTIMIZATION OF TRANSETHOSOMAL FORMULATION

Transethosome preparation and characteristics are influenced by a number of process variables, including drug concentration, edge stimulator proportion, lipid proportion, and ethanol proportion. To get desired encapsulation efficiency, flux rate, vesicle size, and drug transport, these independent factors can be tuned. Other factors are tuned to produce the goal product profile during the manufacture of a specific system, for instance, medication concentration and stimulation agents are kept constant.[23,27]

STRUCTURE OF SKIN

The three layers of skin are epidermis, dermis, and hypodermis.

Epidermis

Epidermis is composed of keratinocytes and makes up the top layer of skin.[32] It has both non-viable and viable epidermis layers, which are two different types. Stratum corneum (horny layer), which means the non-viable epidermal layer: It is the skin's outermost layer. It is made up of tightly packed lipid bilayers that are found in the spaces in between corneocytes.[33] It serves as a crucial barrier to medication absorption. It stops an outside material from entering the body.

Dermis

The connective tissue matrix that makes up this layer is where the medication is absorbed. From the dermis, hair cavities, sebum glands, and sweat glands ascend to the epidermis, which also participates in drug transport.

Hypodermis

It is made up of subcutaneous fat tissue, which cushions blood capillaries and nerve endings from shock. It serves as a nourishing and protecting covering.[22]

CONCEPT OF DRUG PERMEATION

The stratum corneum is a significant medication absorption barrier. Drugs can be transported through the stratum corneum

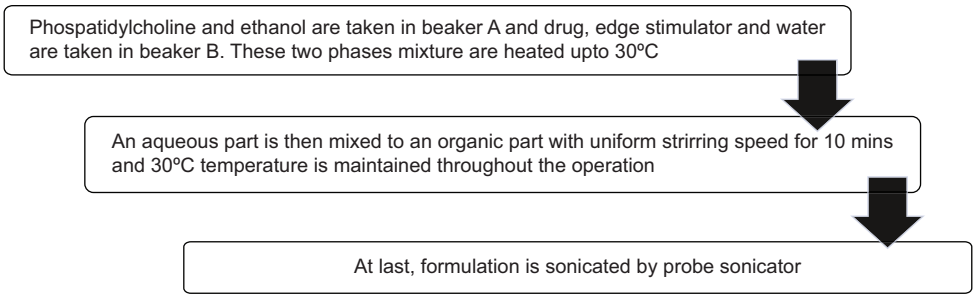

Figure 4: Cold technique

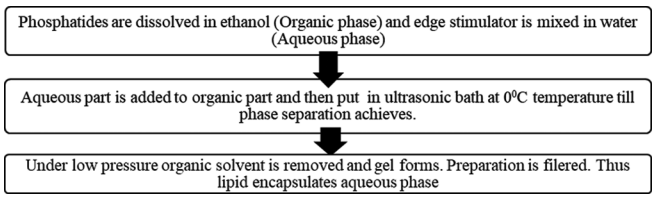

Figure 5: Reverse phase evaporation technique

through three different pathways that are intracellular, intercellular, and follicular.[34]

When ethanol interacts with it, the phosphatides in the stratum corneum are disrupted and becomes fluidized.[35] It expands the intracellular zone between the corneocytes, allowing greater penetration and the medicinal substance to be released more gradually into the epidermal layers.[8,16] Edge stimulators expand the skin's hydrophilic pores and disturb the intercellular lipids. The medication is slowly released through these pores.[36] As a result, there is an increase in molecular interaction and skin penetration.[37] According to several researches, edge activators by themselves are unable to penetrate the deeper layers of skin.[38,39]

Transethosomes become more fluid and elastic as a result of ethanol and edge stimulator. The size of the lipid layer decreases as its fluidity rises.[40] The shape can be changed due to the elastic behavior to fit through the intercellular pathway's constrained spaces. It travels through the epidermis and stratum corneum before entering the dermis.[41]

PROPERTIES OF TRANSETHOSOMES

In comparison with various vesicular structures, it has a substantial flow rate and a high rate of permeation through the skin due to its considerable flexibility.[42] It can bend and squeeze through tight spaces without suffering any significant harm.[36] It is environmentally friendly and biodegradable due to the fact that it is made of organic phospholipids. The encapsulated medication is shielded from metabolic degradations thus has high encapsulation efficiency.[43] Simple to prepare and avoids using extraneous pharmaceutical substances.[13]

MERITS OF TRANSETHOSOMES

It is not intrusive method.[7] It skips the hepatic first-pass metabolism and prevents drawbacks like vomiting due to an unpleasant taste or stomach mucosal irritation. Compared to other vesicular system, it is more stable. It is able to pass through multiple sections of skin.[44] Transethosomes can be utilized to encapsulate drugs, allowing for controlled and sustained release. To ensure good patient compliance, transethosome can be given in semisolid dose formulations such as topical gel or cream.[35]

DEMERITS OF TANSETHOSOMES

Because ethanol is a component of the formulation, it may produce dermatitis, an allergic reaction, and skin irritation.[45] The amalgamation of transethosomes may result from inadequate vesicle production.[10]

EVALUATION OF TRANSETHOSOMES

Shape

Shape of transethosome can be seen under ta transmission electron microscope.[46] Six samples are inserted into a copper grid having carbon coating to create a thin film matrix. Phosphotungstic acid stains it negatively. Transethosomes were found to exist in an atypically spherical shape.[45]

Size distribution and zeta potential

Light scattering method and size analyzer can be used to determine vesicle size. Light scattering technique, particles of various sizes scatter light which is measured. Using quasi-elastic light scattering, the diameter of vesicles can be determined.[47]

In colloidal dispersion, electrostatic attraction and repulsion are quantified by the zeta potential. Zeta potential can also reveal details about the chemistry of a surface.[48] Zeta potential values should be larger, which boosts the vesicle's stability due to higher electrostatic repulsion.

Phase transformation temperature

The temperature at which the phase change occurs is being investigated to better understand drug release from vesicles. It is detectable with a Differential Scanning Calorimeter. Sample is tested at a certain temperature condition using a continuous nitrogen stream. The specimens are compared using differential thermal curves.[19]

Entrapment efficiency, drug loading, and transethosomal yield

EE can provide data on the original quantity of drug entrapped in the system. The small-column centrifugation approach is an option. A suitable amount of drug is loaded into a vesicular suspension, subsequently placed in a micro column and rotated. The released transethosomes are removed off the microcolumn and examined beneath a microscope. The speed and temperature are both adjusted during centrifugation. As a result, vesicles are not fractured during the procedure. The generated supernatant is separated from the vesicles in the final stage of centrifugation. To be lysed, vesicles must be processed with solvents such as octoxynol and methyl alcohol. The medication concentration is determined using ultraviolet visible spectrometry. Various equations are used to calculate entrapment efficiency, drug loading, and transethosomal yield.[49,50]

$$\%Entrapment\ efficiency = \left(\frac{X_o - X_u}{X_o}\right) * 100$$

$$\%Drug\ loading = \left(\frac{X_o - X_u}{Y}\right) * 100$$

$$\%Transethosome\ yield = \left(\frac{X_v}{X_o + Y}\right) * 100$$

X_o = Original amount of the drug utilized
X_u = Unencapsulated drug
Y = Quantity of lipid taken for formulation
X_v = Amount of transethosome produced

It was discovered that tiny particle size facilitated drug penetration. Hence, in case to increase entrapment, particle size should not increase as it will subsequently affects penetration.

In vitro study for drug release

The dialysis bag technique can be utilized to study the drug release pattern. The transethosome formulation is put onto the dialysis membrane in this approach. Then, this membrane is placed in a conical flask with buffer solution and incubated. Aliquots are extracted and centrifuged employing column centrifugation method at predetermined time intervals. The released drug is evaluated using an appropriate procedure.[51] It was discovered that medication release can be sustained for 24 h. This can minimize dosing frequency, resulting in improved patient comfort.[52]

In vivo permeation study

Skin distribution is performed in rodents such as rats and mice to determine the permeation of medication through different sections of skin following transethosomal injection. The amount of medication accumulated in the horny layer is assessed using a fluorospectrophotometer after 24 h.[53] Wide field fluorescence microscopy is employed to visualize medication distribution through many layers of skin. It was discovered that transethosomes penetrate deeper inside epidermal layers and overcome the stratum corneum barrier.[54]

Ex vivo skin permeation

Fresh animal skin, such as goat or rat skin, is used to study skin permeation. The mucosal sample is placed on diffusion cell with phosphate-buffered saline in the receptor medium. The formulation is applied to the donor compartment of the Franz diffusion cell that is on the side of the horny layer. The sample is withdrawn from the cell's receiver compartment at regular period of time and at a steady temperature. The sink condition is preserved, and the sample is evaluated with High-performance liquid chromatography.[55] It was observed that drug penetration through surface is greater in transethosomal form when compared with other vesicular system. They found that transethosomes had higher flux rates.[56]

The totalquantity of drug penetration through animal's membrane is calculated by[23]

$$Q_A = \left[C_T V_R + \sum C_i V_S\right]$$

C_T= Concentration of drug at particular time
V_R= Volume of receptor compartment of diffusion cell
Cn= Drug Concentration at the *n*th sample
V_S= Volume of sample
Q_A= Total amount of drug per unit area.

Elastic determination

It is a particularly important feature for effective skin penetration. The extrusion method is employed to determine the elasticity of bilayer of vesicles. By applying pressure, vesicles are ejected out through a membrane filter, made up of cellulose with the proper membrane pore diameter.

Dispersion of vesicles which are extruded is calculated by[57]

$$E = J \times \left(\frac{V}{P}\right)^2$$

E = Elasticity of membrane
J = Flux rate through cellulose membrane filter
V = Vesicular size after ejection
P = Membrane pore size

It was observed that transethosomes shows better elasticity index compared with ethosomes. Thus, drug permeation through skin is found to be greater.[19]

Preclinical study

The table presents a summary of preclinical studies focusing on the use of transethosomal preparations as delivery systems for various drugs. The studies investigate the performance of these systems in enhancing drug delivery, particularly through the skin, and highlight their potential therapeutic benefits. Table 3 shows data about preclinical studies of transethosomal preparations.

APPLICATIONS FOR TRANSETHOSOMAL DRUG DELIVERY

Anti-fungal drug delivery

Comparison of econazole nitratite loaded transethosomal gel to commercialized econazole nitratite topical cream to determine the antifungal activity of drug. It was discovered that transethosomal gel had excellent cutaneous upkeep and antifungal property. The drug release is in a regular pattern by the transethosomal gel, which treats cutaneous candidiasis.[61]

NSAIDs drug delivery

NSAIDS is often delivered orally, although they are associated with various gastrointestinal adverse effects. To address this issue, researchers attempted to give the medication through transdermal delivery utilizing extremely deformable vesicles. An experiment was carried out in which ketorolac tromethamine was taken as the active ingredient and created a transethosomal gel that was corelated to ethosomes. This study yielded a good result since the gel penetrated the skin better than the ethosomes due to its elastic nature.[62]

Peptide drug delivery

Peptides cannot pass through the stratum corneum because they are greater in size. As a result, transdermal peptide delivery is tricky. It was observed that transdermal administration of encapsulated palmitoyl pentapeptide as transethosomal formulation. It was concluded that loading of palmitoyl pentapeptide into a transethosomal form improved elasticity, which boosted skin penetration.[29]

Table 3: Data of preclinical studies of transethosomal preparation

S. No	Delivery system	Drug (s)	Key findings	Year of publication	Reference
1	Dermal Delivery	Fistein	Skin treated with transethosomal gel exhibited significantly higher maximum concentration in the skin and area under the curve from 0 to 8 h in both the epidermis and dermis, in contrast to the conventional gel.	2018	[55]
2	Transdermal Delivery	Olmesartan medoxomil	The dermatokinetic study revealed that transethosomes exhibited notably higher maximum concentration and area under the curve from 0 to 10 h in comparison to the drug suspension.	2019	[54]
3	Cutaneous Delivery	Azelaic Acid	Transethosomal preparations show great potential as carriers for augmenting the antidermatophyte effectiveness of azelaic acid by facilitating its deep penetration through the layers of the skin.	2023	[58]
4	Transdermal Delivery	Ginger Extract	The transethosomal hydrogel was deemed suitable for topical skin application, demonstrating enhanced skin permeability and superior anti-inflammatory effects in a rat-paw edema model.	2023	[59]
5	Topical Delivery	Metformin HCl	The transethosmal preparation has substantially improved the transdermal penetration of metformin and has led to a notably variable reduction in fasting blood glucose levels compared to the results achieved with oral metformin.	2023	[60]

Anti-cancer drug delivery

Scientists completed the trials to cure cutaneous melanoma by dual loading medicines into a transethosomal formulation. They chose two medications with synergistic action, such as dacarbazine and tretinoin, that decreased cell toxicity when compared to the other pharmaceutical formulations. When compared to a single drug encapsulated, dual-loaded transethosomes showed augmented anticancer efficacy. They observed that skin permeation can be improved. In other study, it was observed that loading 5-fluorouracil in transethosomal gel formulation resulted in higher superficial permeation and good skin targeting as corelated to ethosomes.[63]

Anti-arthritis drug delivery

To generate antioxidant coated transethosomes, transethosomes were filled with Sinomenine hydrochloride and subsequently coated with ascorbic acid. This resulted in increased transdermal permeability and medication disposition for rheumatoid arthritis oxidative stress.[64]

Anti-hypertensive drug delivery

Antihypertensive medications are often administered orally, but some have decreased bioavailability due to hepatic first-pass metabolism. For e.g when olmesartan medoxomil was given as main ingredient in a transethosomal gel that augmented drug permeation through the surface through the transdermal method.[54]

CONCLUSION

Some active moieties cannot pass through epidermal barriers. Drug encapsulated in transethosomal formulations transports through the horny layer through both inter- and intracellular channels. Transethosomes are composed up of ethanol and an edge stimulator. Ethanol improves the flexibility of the lipid layer while reducing vesicle size. Edge stimulator aids in skin pore distortion and permeation. Transethosomes can penetrate through several sections of skin due to their tiny size of particles and fluidity. Transethosomes have the potential to be employed in the treatment of cancer, particularly skin cancer. As biomolecules are bigger in size, they can permeate deeper into the skin when enclosed in transethosomal formulation. These properties make the transethosome vesicular carrier concept an effective widget in the fields of pharmaceutical nanotechnology and medicinal products. To render this vesicular system work in the marketplace, further study is required.

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CONSENT FOR PUBLICATION

I give my consent for the publication of identifiable details, which include details within the text to be published in the AJP and Article. All authors have read and approved the manuscript for submission to editorial system of Asian journal of pharmaceutics.

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