Recent Advances in Transethosomal Drug Delivery System to Enhance the Accuracy and Efficacy in Medical System

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Abstract: Transethosome is one of very recent advancement in the ever-changing field of drug delivery system. It is a vesicular carrier system which transdermally delivers the drug and is thus an alternative for oral drug delivery system. TDDS consists of adhesive devices (or vesicles) which contain a predetermined amount of drug in enclosed area. It uses skin an entry port which permeates the drug to directly enter the blood stream. As skin has stratum corneum (SC) – a layer of dead cells – it is considered as rate limiting barrier for permeation of drug transdermally. Transethosomes help in overcoming this problem as they are ethanol based lipophilic carriers which then fluidizes the SC layer which then allows the drug penetration through the skin. Along with this transethosome also contain edge activator which helps in enhanced skin permeation. This article reviews the various properties, methods of preparation and advantages and disadvantages that transethosome have over other drug delivery system.

Keywords: Transethosome, Vesicular carriers, Transdermal drug delivery system, Stratum corneum, Ethanol based lipophilic carriers, Edge activator.

1. INTRODUCTION

In a world, where almost every single person is suffering from one disease or another, the scope of development of drugs is also increasing exponentially. This calls for advancements in the drug delivery systems as well, because effectiveness of drug and patient compliance is one of the very important aspects of development of drug. The conventional methods of drug administration generally include oral route, parenteral route (via injections) or by inhalations. Though most of the drugs are being administered by these routes, there are several shortcomings of these methods of administration.

The major problems associated with oral method of drug delivery are:

The drugs have to pass through GI tract and are thus exposed to chemical and enzymatic degradation of enzymes present in GI.

These drugs are required to be taken in frequent dosing which leads to a peak and trough profile of drug concentration and may cause problem for patient compliance.

Also, the drugs pass through hepatic elimination (HEPE) which can cause liver damage or cirrhosis.

Though these disadvantages can be overcome through the injectable route of drug delivery, it is an invasive technique.

A more radical approach towards the drug delivery system includes Transdermal Drug Delivery System (TDDS). TDDS is a drug delivery system wherein the route of delivery is the skin. This method aims to deliver the drug in at controlled rate through the skin route directly into our systemic circulation system.

Thus, this route avoids the drug entering the GI tract. Due to this TDDS has an edge over its other contemporary drug delivery systems, i.e. Oral routes and Intravenous routes as it bypasses the HEPE, avoids enzymatic degradation which occurs in gastrointestinal tract, attainment and maintenance of drug concentration within therapeutic effective range and decreases the toxicity caused by the drug and, therefore, increases patient compliance. Drugs having poor oral bioavailability,

short half-life and narrow therapeutic range can be best administered via TDDS.

Though there are many advantages of this method of drug delivery, it also comes with few disadvantages which are mentioned briefly in Table 1.

Table 1: Advantages and disadvantages of TDDS

Advantages	Disadvantages
Continuous and self-administration of drug is possible as it is used as topical application	Only small lipophilic molecules can be delivered through TDDS
As drugs administered through oral route have to go through trough and peak levels, TDDS doesn't undergo through this.	TDDS can be affected by type of skin and environmental conditions
Bypasses the first – pass hepatic metabolism.	Skin allergy and hypersensitivity reactions can occur
Vomiting and diarrhoea do not affect drug dose.	Skin changes from site to site and from person to person and with age, and thus with the change of site of application, drug delivery may also be affected.

As TDDS is generally achieved through topical application on the skin, it is very important to thoroughly understand the skin.

Skin is one of the largest organs of human body covering upto 1.8-meter square surface area. It is the integument or covering which shields the body organs from various biotic and abiotic stress factors like temperature, parasites, radiation, etc.

Skin can be anatomically divided into two layers – (i) Dermis (corium) and (ii) Epidermis. Epidermis is the outermost covering whereas dermis lies below the epidermis. In the above mentioned two layers, it is the epidermis that becomes a barrier to the entry of foreign particles. Epidermis is further divided into five layers:

Stratum germinativum (basal layer)

It is the deepest layer of epidermis and consists of many cells which are active and continuously dividing, generally keratinocytes. As it is the basal most layer, it is separated from the dermis with the help of a basement membrane. The keratinocytes are attached to the basement membrane by hemi desmosomes.

Stratum spinosum (spinous layer)

Here keratinocytes are connected through desmosomes which then go on to produce the lamellar bodies. Generally, Langerhans cells and immunologically active cells are present in the middle of this layer.

Stratum granulosum (granular layer)

It is composed of 3-4 layers of cells and appears granular due to absence of nuclei from the keratinocytes. Also, a lipid barrier, formed due to release of lipids from the keratinocytes, is present in this layer.

Stratum lucidum

It is a clear/ translucent layer which is seen only on the soles and palms of the body. Made up of flat and dead cells, it gives the above mentioned two parts, thickened skin.

Stratum corneum (SC)

It is the outermost layer of the epidermis. It is this layer that prevents any foreign particle to enter through the skin and thus, helps it protecting the organs.

It is the SC which is rate limiting barrier of TDDS as it consists of 15- 20 layers of keratin filled corneocytes. Corneocytes under its plasma membrane, contain a protein envelope which are filled with water retaining proteins. Though it was a general belief that SC layer was made up of dead cells, it is now understood to be a live tissue which can perform various physiological functions. Few of the functions performed by SC are:

1. Water flux and hydration regulation
2. Impact resistance

3. Initiation of inflammation through cytokine activation and dendritic cell activity
4. Selective permeability to exclude toxins, irritants, and allergens.

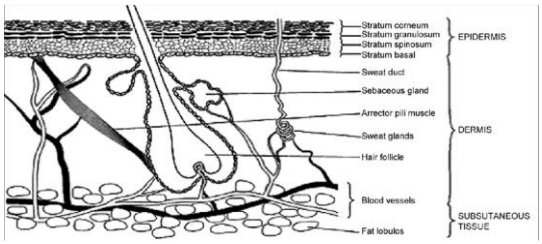

Figure 1: Cross Section view of human skin showing different cell layers [13]

The SC is a very distinctive as the lipids in the layer are in continuous phase and provide diffusion pathway, the composition of the layer is unique and is phospholipid free. Despite this, the layer exists in multilamellar sheets of saturated long chain hydrocarbon tail. This SC layer represents the model of Brick and Mortar, where keratin rich corneocytes - depicting the bricks - are embedded in intracellular lipid rich matrix - depicting the mortar.

Thus, to avail TDDS it is very important to that the drug can easily pass through the SC. This can be achieved via using vesicular system like liposomes, ethosome, transferosome, transethosome, and nanoethosome.

Vesicular systems are a novel drug delivery system. They use vesicles to deliver drug so that it enhances the bioavailability of encapsulated drug and also provide the therapeutic activity in controlled manner for a prolonged period.

Initially, liposomes were introduced as the vesicle for TDDS. Liposomes are structures made up of lipid bilayer, enclosing the aqueous volume completely. They are generally made up of phospholipid and cholesterol. The drug, if hydrophilic, is enclosed in the aqueous volume or, if hydrophobic, then in the lipid bilayer. Though with all of its features, it is not a suitable system for transdermal delivery of drug due to its poor stability and inability to penetrate the SC.

Thus, after liposomes, transferosomes were introduced. These are ultra-deformable vesicles composed of phospholipid, cholesterol and surfactants. Surfactants like Sodium Cholate, Span 80 and Tween 20 have been used as edge activators. These edge activators give the transferosomes the property of being ultra flexible and thus being able to penetrate the mammalian skin without being invasive. Though transferosomes have improved ability to permeate the skin due to its ultra-deformable nature, it is unable to penetrate deep into the SC. Also transferosomes are highly chemically unstable compounds.

Table 2: Composition of different lipid vesicular carrier system [10]

Sl. No.	Additives	Liposomes	Ethosomes	Transethosomes	Examples
1	Phospholipid	Present	Present	Present	SPC
2	Polyglycol	Absent	Present	Present	PG
3	Alcohol	Absent	Present	Present	Ethanol
4	Cholesterol	Present	Present	Present	Cholesterol
5	Vehicle	Present	Present	Present	Carbopol D934
6	Surfactant	Absent	Absent	Present	Sodium Cholate

Due to inability of the transferosomes to penetrate deep into SC, ethosomes were introduced by Touitou et al. in late 1990s. Ethosomes are different from liposome as they contain upto high ethanol concentration along with the phospholipid and water. Due to the presence of high concentration of alcohol, this system

proved to be better TDDS vehicle. The high ethanol concentration helped in increasing the lipid bilayer fluidity, which enhanced the penetration of drug encapsulated in the ethosomal carrier. It also gives unique characteristic to the vehicle in terms of size, zeta potential, stability and entrapment efficacy.

Transethosomes are a variation in ethosomal system. They were introduced by Song et al. in 2012. Transethosomes are combination of transferosomes and ethosomes wherein they contain 30 to 40 percent of ethanol, phospholipid, cholesterol and an edge activator. The edge activator like Span 80, tween 80, etc. enhances the permeation of skin and due to its ultra-deformability, the transethosomes can easily penetrate the SC and thus become a very good drug delivery system. Various edge activators have been mentioned in Table 3.

Table 3: Edge activators or penetration enhancers used in the preparation of transethosomes [1]

Edge activator/penetration enhancer	Type	Concentration
N-Decylmethyl sulfoxide Nonionic surfactant	Nonionic surfactant	0.35%–1% of the total ethosomal system
Dimethyl sulfoxide	Penetration enhancer	10% of the total ethosomal system
Tween 80	Nonionic surfactant	10%–50% of the total phospholipid concentration in the ethosomal system
Tween 60	Nonionic surfactant	Up to 50% of the total phospholipid concentration in the ethosomal system
Tween 20	Nonionic surfactant	15%–50% of the total phospholipid concentration in the ethosomal system
Oleic acid	Penetration enhancer	0.5%–3% of the total ethosomal system
L-Menthol	Penetration enhancer	5% of the total ethosomal system
Sodium stearate	Anionic surfactant	Phosphatidylethanolamine:cholesterol:sodium stearate at a molar ratio of 2:1:2.5
Deoxycholic acid	Bile acid/anionic surfactant	Phosphatidylcholine:cholesterol:deoxycholic acid at molar ratios of 2:1:1 and 6:2:1
Sodium deoxycholate	Bile salt/anionic surfactant	0.8% w/v of the total ethosomal system
Sodium cholate	Bile salt/anionic surfactant	0.66% of the total ethosomal system
Sodium taurocholate	Bile salt/anionic surfactant	0.53% of the total ethosomal system
Polyethylene glycol 4000	Surfactant	Phosphatidylcholine:cholesterol:polyethylene glycol 4000 at molar ratios of 2:1:1 and 6:2:1
Hexadecyltrimethylammonium bromide	Cationic surfactant	1% of the total ethosomal system
Cremophor EL-35	Nonionic surfactant	0.5%–1.5% of the total ethosomal system
Cremophor RH-40	Nonionic surfactant	Up to 50% of the total phospholipid concentration in the ethosomal system
Spans 80, 60, 40, 20	Nonionic surfactant	Up to 50% of the total phospholipid concentration in the ethosomal system
Skin-penetrating and cell-entering (SPACE) peptide	Penetration enhancer	2–10 mg/mL
Sodium dodecyl sulfate	Anionic surfactant	0.8% of the total ethosomal system

2. METHODOLOGY

There are three methods of preparation of transethosomes:

1. Cold Method of Preparation

In this method the phospholipid is dissolved in ethanol and stirred vigorously at room temperature. After this the solution is heated upto °30 C in a water bath.

Separately, water is heated upto 30 °C and then added to the ethanolic mixture in a fine stream. The solution is then stirred for the next 5 to 10 minutes at 700 rpm on magnetic stirrer. Then the suspension is cooled down to room temperature and vesicle size can be modulated using sonicator.

According to the solubility of the drug, it is either mixed with alcoholic solution or water.

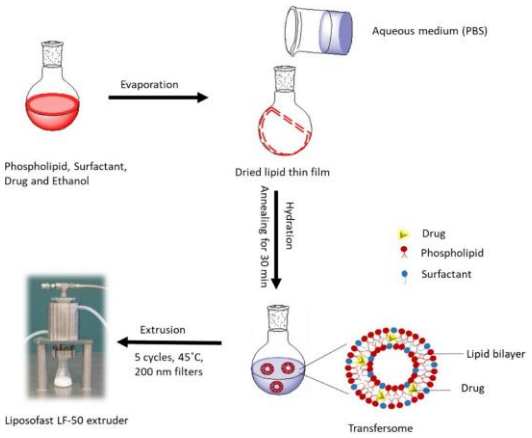

Figure 4: The classical cold method for the preparation of transethosomal systems [1]

Transethosomes are considered to be an effective drug carrier system as they provide better patient compliance due to its semisolid dosage which ensures an enhanced permeation of the drug through the skin.

The mechanism through which the transethosome facilitate skin permeation is explained in brief. Transethosome are mainly made up of phospholipid, ethanol and edge activator. These vesicles gets absorbed by stratum and thus directly reach the blood stream without being invasive which gives them an edge over:

i. Oral route – the drugs undergo the process of metabolism, and hence they are huge amount of drug is lost before it reaches the target organ.

ii. Intravenous route – this is an invasive technique of drug delivery, which though evades the HEPE, can cause damage to the cells surrounding the area through which the injection was given.

Transethosome also contain loosely packed phosphotidyl choline (phospholipid) which helps in giving more flexibility to the vesicles which can then easily cross the skin.

As transethosome contain upto 20 - 50% of ethanol, the fluidity of cell membrane increases. It is so because when ethanol comes in contact with lipid bilayer, the surface density of the lipid decreases leading to a thinner, distention membrane. This in turn leads to accelerated change in shape of membrane in an exocytosis manner. Therefore, presence of alcohol leads to better drug permeation through the skin.

Also, the edge activator helps stabilize these ultra-deformable membranes so that they can contain a certain amount of drug. It is due to its ultra-deformable property, transethosomes are better vesicular systems than the liposomes or ethosomes.

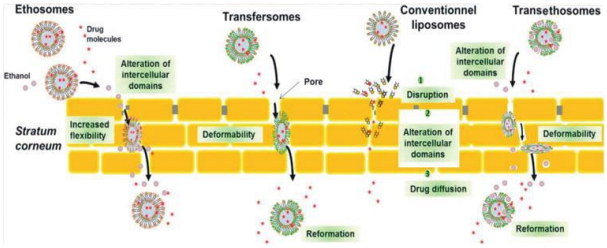

Figure 6: Schematic representation of the main permeation mechanism of lipid based vesicles [10]

Although the transethosomes have many advantages there are a few disadvantages also seen.

Only small lipophilic drugs can be delivered through this system. There are chances of patient getting dermatitis – allergy or hypersensitivity reactions.

Product loss can be there during preparation of the transethosome. Although it is relatively simple to prepare transethosomes, there can be unsuccessful vesicle formation too. Also due to high alcohol content in the vesicle, long term application is not possible as the alcohol can get accumulated over some body parts such as striatum and brain which can have implication on the kinetics of neurotransmission.

Characterization of Transethosomes:

Vesicle Shape: Vesicle shape is the morphological feature of the transethosomes. Generally, SEM and TEM help in characterization of vesicle shape. Transethosomes are regular spherical in shape with an enclosed core. They are soft and flexible. Along with the identification study, detecting the pattern of packing of particles and aggregation, can also be studied via morphological characterization.

Particle Size and Zeta Potential: Particle size analyzer, dynamic light scattering and photon correlation spectroscopy help in analysing particle size of transethosomes whereas Zeta potential is measured by zeta meter.

Zeta potential is the degree of electrostatic repulsion and attraction in colloidal dispersion. Stability of the product depends on the presence of charge on the surface of the vesicle. The presence of negative and positive charge on vesicular carrier depends upon the excipient used in the formulation. It also provides information regarding every component of formulation and interaction among them, surface chemistry and the interaction between vesicles and membrane

Entrapment Efficiency: It is be measured by ultra-centrifugation technique. The entrapment efficiency is expressed as the percentage entrapment of the drug added.

% EE can be expressed as: [Qt-Qs/Qt] x 100

Where Qt is total theoretical amount of drug added and Qs is the amount of drug found in supernatant.

Transition Temperature: Differential scanning calorimetry (DSC) determines the transition temperature of transethosomes.

Drug Content: It is done to ascertain if there is required active ingredient in given amount entrapped in the vesicle. Drug content of transethosomes can be determined using U.V spectrophotometer. HPLC can also help in determining the drug content.

Vesicle Stability: The size and structure of vesicles over time determine the vesicle stability.

Surface Tension: The surface tension activity of drug in aqueous solution is measured by the ring method in a Du Nou ring tensiometer.

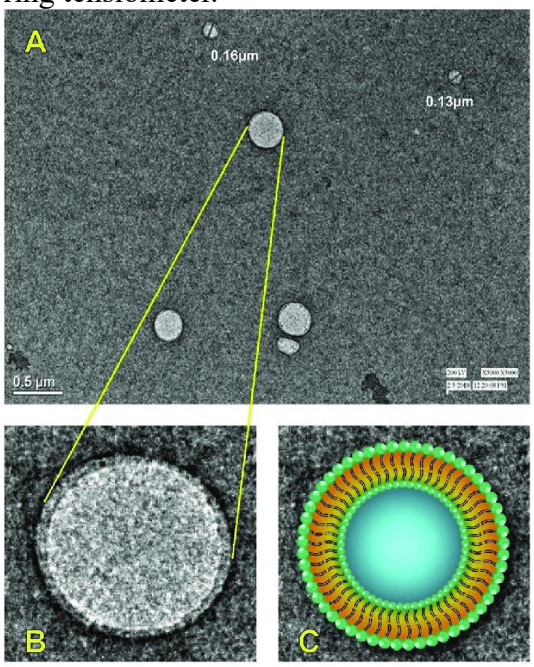

Figure 7: (A). Transmission electron microscopy of transethosome (Scale 0.5 µm); (B) Enlarged view of transethosomes vesicle showing clear lipid bilayer characteristic. (C) Schematic presentation of vesicle made up of concentric hydrophilic heads, lipid bilayer and an inner core containing ethanol [3]

Penetration and Permeation: Depth of penetration from transethosomes is visualized by confocal laser scanning microscopy (CLSM).

In-vitro Drug Release: This is performed for determining the permeation rate. Time needed to attain steady state permeation and the permeation flux at steady state and the information from *in- vitro* studies are used to optimize the formulation before more expensive *in-vivo* studies are performed.

Applications of Transethosomes

1. Delivery of Non – Steroidal Anti – Inflammatory Drug (NSAIDs)

Various GI side effect is associated with the oral administrations of NSAIDs. Hence transdermal delivery using alter-deformable vesicle is preferred. Transethosomes containing ketorolac tromethamine show enhanced penetration than drug containing ethosomes.

liposomes, deformable liposomes and ethosomes.

Table 4 mentions various other drugs which show positive result when are used with transethosome as their carrier.

2. Delivery of anti-cancer drugs

Transethosome vesicles containing imiquimod were investigated for transdermal delivery. The result was positive and provided a new approach for skin cancer treatment. Better penetration and increased transdermal flux were seen using transethosomes. Even after storage the transethosomes retained their penetration power.

3. Delivery of anti-fungal drugs

Various anti – fungal drugs like terbinafine, amphotericin B, and ketoconazole showed enhanced permeation when encapsulated in transethosomes. also, transethosomes containing voriconazole showed enhanced skin permeation and deposition as compared to that of conventional

Table 4: Applications of transethosomes for transdermal delivery of some miscellaneous drugs [10]

Drug	Excipients	Sophisticated techniques used	EE (%)	Size/PDI	Animal model	Key findings
Voriconazole	Lipoid S100, cholesterol, Tween80, taurocholic acid sodium, ethanol	TEM, HPLC	96.6 ± 2.7	191.9 ± 41.5 nm/–	Male albino mice	Prepared transethosomes showed high elasticity, high *in-vitro* skin permeation, and high *in-vivo* skin deposition of voriconazole compared to nanoethosomes and conventional liposomes
Ketorolac tromethamine	Phospholipon 90G, sodium deoxycholate,	TEM, FT-IR	82.08 ± 4.5%/	180 ± 70 nm/–	Male albino rats	Transethosomes showed 3-fold more elasticity compared to

	propylene glycol, ethanol					ethosomes and transethosomal gel 3-fold increase in transdermal flux compared to conventional ethosomes
Vitamin E	Soybean phosphatidyl choline, sodium cholate, ethanol	TEM, HPLC	76.689 ± 2.942	154.73 ± 1.89 nm/0.428 ± 0.020	Pig ear skin	For transdermal flux and stability, order obtained was: transethosomes (TE) > ethosomes (E) ≥ transferosomes (T) for vitamin E
Caffeine	Soybean phosphatidyl choline, Sodium cholate, ethanol	TEM, HPLC	3.376 ± 0.812	116.60 ± 2.25 nm/0.133 ± 0.015	Pig ear skin	For transdermal flux and stability, order obtained was: transethosomes (TE) > ethosomes (E) ≥ transferosomes (T) for caffeine
Griseofulvin	Phospholipon 90G, Carbopol 980 NF,	TEM, HPLC fluorescence microscopy, reverse phase	72.94 ± 0.80	148.5 ± 0.48 nm/0.203	Laca mice	Griseofulvin-loaded ethosomes completely cured fungal infection in guinea pigs in 8 days upon twice daily topical applications

Scope for Further Enhancement

Although transethosomes are a very good alternative to conventional drug delivery system, many of limitations of transethosomes can be overcome.

To mention a few would be:

a. If transethosomes could be designed in such a manner where they could not only carry the small lipophilic drugs but all kinds of drug.

b. If application of transethosome would not cause any allergic reaction or would not change from person to person or people with varying age and environment.

c. If long time storage of transethosome would be possible without altering its composition or drug level so that it can be also used in cosmetic industry.

3. CONCLUSION

With rapid development in novel drug delivery system, transethosomes open up a new window to deliver the drugs transdermally. Transdermal route of drug administration is one of the most preferred routes as it overcomes various limitations like administration of the drug which has poor bioavailability, enhances patient compliance and also avoids hepatic metabolism all the while being a non – invasive method.

Although TDDS has several benefits, one of the major limitation while administering rugs transdermally is passing the barrier, i.e., the Stratum Corneum. SC is one of the major rate limiting which the foreign molecules face while trying to penetrate the skin.

Thus, transethosomes help us overcome this limitation. As they contain high ethanolic content along with addition of edge activators, it gets unique characteristics that involves being ultra-deformable along with ethanol increasing the lipid bilayer's fluidity. These two properties together help the transethosome penetrating the SC successfully and thus being able to deliver the drugs transdermally.

As there is no such thing as being an ideal drug delivery system, along with its various benefits, there are also few limitations of transethosomes like, they can carry only small lipophilic molecules, there are chances of product being lost while being transferred from alcoholic to aqueous media and also chances of the patient having hypersensitivity reactions.

So, to conclude, transethosomes can be used as drug delivery system for transdermal drug delivery but one has to be careful while preparing them and also while applying them.

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