Indian J. Applied & Pure Bio. Vol. 39(3), 1541-1546 (2024). **ISSN: 0970-2091**
A web of Science Journal

Transethosomes: Revolutionizing transdermal drug delivery through innovative Formulation strategies

Manish Mohan Ghadage and Naina Dubey*

Department of Pharmaceutics, Acropolis Institute of Pharmaceutical Education and Research, Indore - 453771 (India)
*Address for correspondence:
Naina Dubey, Acropolis Institute of Pharmaceutical Education and Research, Indore - 453771 (India)
E-mail: nainadubey@acropolis.edu.in

Abstract

In recent years, transdermal medication delivery has gained popularity for circumventing oral administration challenges. Despite skin penetration difficulties, researchers have devised a solution by encapsulating medication into vesicles that penetrate deeper. Examples such as liposomes, niosomes, ethosomes, and transferosomes tend to aggregate within skin layers. Transethosomes, comprising phospholipids, ethanol, and an edge activator, have emerged as promising alternatives, effectively addressing issues like poor bioavailability and organ toxicity. They enhance skin penetration, facilitating the delivery of various medications including analgesics, proteins, corticosteroids, and anticancer agents. This review provides comprehensive insights into transethosomes, their applications, and preparation methods.

Key words : Transethosomes (TES), edge activator, transdermal medication delivery, enhance skin permeation.

Oral drug administration is the most convenient method of administration; however, many oral formulations may have major side effects, such as decreased bioavailability as a result of first-pass metabolism, gastrointestinal distress, and unappealing taste[5]. Nowadays, a variety of vesicular carrier systems, including liposomes, ethosomes, transferosomes, niosomes, and transethosomes, are accessible. (Figure 1) Drugs are delivered to the skin via liposomes, yet their tendency to stay in the upper stratum corneum limits the amount of medication that can penetrate the skin[14].

Structure of Transethosome :

Transethosomes (Fig. 1) are lipid-based vesicles that are made up of phospholipids, water, ethanol, and edge activator (surfactant). Phospholipids, also known as non-ionic surfactants, are used as medicine molecule carriers when they are applied topically. They can readily combine with the lipids in the stratum corneum, improve tissue hydration, and interact with it[6]. Their heads are hydrophilic (polar), and their tails are hydrophobic (non-polar). Edge activator (biocompatible surfactant) is typically included to increase permeability and flexibility[4].

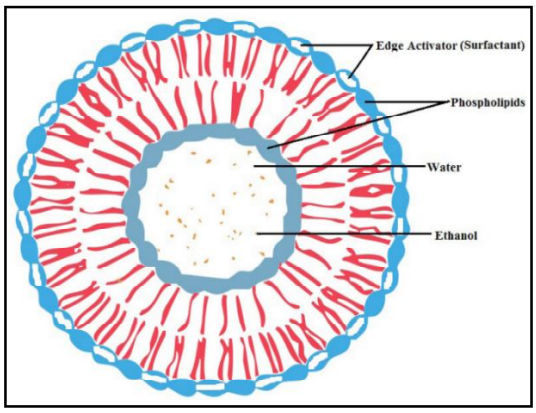

Figure 1. Structure of Transethosome

Preparation of Transethosomes :

In order to promote skin penetration, various techniques are employed to produce tiny vesicles, which are then added to gels or creams. Some frequently employed techniques are listed below.

a. *Cold method :*

The formation of TEs using a low temperature approach is known as the "cold method". This widely used and convenient approach prepares the organic and aqueous phases independently. Phospholipid, penetration enhancer, and to obtain the organic phase, additional lipid components are completely combined in organic solvents in a closed vessel at room temperature[17]. Next, the aqueous phase, which might be buffer solution, plain saline solution, or bidistilled water, is continually added dropwise to the organic phase using a syringe pump.

b. *Hot method :*

The "hot method" refers to the application of heat during the TE formulation

Table-1. Composition of Transethosomes

Component	Examples	Uses	References
Phospholipids	Lecithin, soybean, lecithin, phosphatidy-lcholine, sunflower phospholipids	Vesicle forming agent	(Kabil *et al.*,[7])
Surfactant	Tweens, Spans, oleyl alcohol, Sodium deoxycholate, oleic acid, diacetyl phosphate,	Edge activator	(Kabil *et al.*,[7])
Alcohol	Ethanol, isopropyl alcohol	Penetration enhancer	(Wang *et al.*,[9])
Stabilizer	Hydroxypropyl β cyclodextrin	Imparts stability	(Wang *et al.*,[19])

process. This technique is utilized to increase the drug's EE inside, promote lipid fusion, and increase its solubility in lipids. In this procedure, To make a colloidal dispersion, the phospholipid is dissolved in water at 40°C. A mixture of ethanol and polyol is simultaneously heated to 40°C in another container. The organic phase is added to the water phase and continuously agitated until both components reach a temperature of 40°C in order to form a vesicle suspension[10].

c. *Ethanol injection sonication method :*

In this process, ethanol is used to dissolve phospholipids, SA, and the active ingredient. Using a syringe mechanism, this organic phase is injected at a predefined flow rate into an aqueous phase. Next, an ultrasonic probe sonicator is used to homogenize the resulting mixture[13]. To produce a smaller particle size than the stirring-guided injection approach, an ultrasound-guided injection method was devised.

d. *Thin-film hydration technique (TFH) :*

This method involves dissolving medications, phospholipids, and an edge activator (EA) in an organic phase within a round-bottom flask. The mixture undergoes sonication in a water bath until uniform dispersion is achieved. Organic solvents are then gradually evaporated using rotary evaporation above the lipid transition temperature. The flask undergoes vacuum oven treatment overnight to ensure complete solvent removal. The resulting dried layer is diluted with either an aqueous ethanol solution or a saline phosphate buffer-ethanol solution by rotating the lipid film. Finally, the Transethosome (TE) vesicles are refrigerated at 4°C to 8°C after swelling at room temperature[18].

Evaluation parameter of Transethosomes:

a. *Zeta potential :*

A Zetasizer can be used to measure the physical attribute known as zeta potential, which is what determines the stability of the product. In colloidal dispersion, zeta potential is a measure of electrostatic attraction and repulsion. Surface chemistry information can also be obtained from zeta potential[11].

b. *Entrapment efficiency :*

EE can be used to determine the exact amount of drug that is trapped in the vesicle. EE and drug loading are determined by an ultracentrifugation method The drug's concentration is determined using spectrophotometry[3].

c. *In vitro drug release study :*

The amount of drug release can be studied using the dialysis bag approach. The transethosome formulation is put onto the dialysis membrane using this technique. After loading the membrane, it is placed in a conical flask with buffer solution and allowed to incubate. Aliquots are taken out and centrifuged using minicolumn centrifugation at predetermined intervals[12].

d. *In vivo skin deposition :*

Skin disposition studies are conducted on rats and mice to determine how the medicine is distributed through the different

skin layers following transethosomal formulation injection. A fluorescence spectrophotometer is used to measure the quantity of medication placed into the stratum corneum 24 hours after injection. Using Confocal Laser Scanning Microscopy (CLSM), the whole distribution of a medication through the different skin layers can be seen[13].

e. *Stability studies of TE :*

TEs' size and appearance are usually the primary factors used to evaluate their physical stability. This occurrence is related to the tendency toward agglomeration or aggregation. Drug leakage from TEs can occur as a result of vesicular fusion and rupture during storage.Moreover, drug-phospholipid interactions may impair the chemical stability of TEs. Drug-loaded TE that has just been produced is kept for three months at two distinct temperatures: at room temperature, 25 ± 2°C, and refrigerator temperature, 4 ± 2°C, with a relative humidity of 60% ± 5%. To avoid any potential interactions between the glass container and the stability study formulation, the mixture was kept in a borosilicate container for storage. The medication content and physical changes of the formulation were assessed[16].

Applications of Transethosome :

a. *Delivery of antifungal drugs :*

To find out how effective vesicular carriers are for anti-fungal medications, Song et al. created a new carrier based on TEs for voriconazole's enhanced skin penetration when compared to regular liposomes, deformable liposomes, ethosomes, and controlled polyethylene glycol solutions[9].

b. *Delivery of Anti-Inflammatory Drugs :*

The effectiveness of ethosomes and TEs for the solubilization and administration of mangiferin was demonstrated by Sguizzato et al. Data demonstrated that both nanosystems could enter cells without causing damage and distribute magniferin to the targeted cell, increasing the antioxidant protection of the keratinocytes[1].

c. *Delivery of Anticancer drugs :*

With regard to PDT therapy of resistant melanoma, deep tissue localization of the medication in the skin was demonstrated by TEs of about 500 nm. An apigenin-loaded transethosomal gel was developed by Adnan *et al*., to investigate cutaneous delivery and devise an improved skin cancer treatment plan. The drug was administered with prolonged release by the TEs, who also enhanced the drug's skin permeability[2].

d. *Delivery of Anti-hypertensive Drug :*

Anti-hypertensive medications are often administered orally, yet some have reduced bioavailability because to first-pass metabolism. Olmesartan medoxomil was used as the active ingredient in Albash et al.'s transethosomal formulation, which increased the amount of medication that was absorbed through the skin via the transdermal method[15].

e. *Delivery of Anti-arthritis Drugs :*

Song and associates used sinomenine hydrochloride in an experiment. Transethosomes

were loaded with Sinomenine hydrochloride and then coated with ascorbic acid to form antioxidant surface transethosomes. This demonstrated improved medication disposition and transdermal permeability for oxidative stress in rheumatoid arthritis[8].

An overview of a new medication delivery technology called Transethosome is provided in this paper. Ethanol and an edge activator make up transethosomes. The amount of ethanol grows minimizes particle size and increases the lipid layer's fluidity. Edge activator facilitates penetration into the skin pore and deformation. Transethosomes' small particle size and deformability allow them to go through multiple layers of skin. Furthermore, the vesicular system may easily encapsulate hydrophobic and hydrophilic drugs. Deep research was conducted to get site-specific activity and minimize medication toxicity, and it was determined that photodynamic treatment and surface functionalization of TEs were effective. To make this carrier system profitable, extensive study in this area is needed.

References :

1. Adnan M, Afzal O, S A Altamimi A, MA Alamri, T Haider, and M. Faheem Haider (2023). *Int J Pharm. 631:* 122506. doi: 10.1016/j.ijpharm.2022.122506, PMID 36535455.
2. Albash R, AA Abdelbary, H Refai, and MA El-Nabarawi. (2019). *Int J Nanomedicine. 14:* 1953-68. doi: 10.2147/IJN.S196771, PMID 30936696.
3. Bi Y, H Xia, L Li, RJ Lee, J Xie, and Z Liu *et al*. (2019). *11*(7): 311. doi: 10.3390/pharmaceutics11070311, PMID 31277236.
4. Dhopavkar S, and P. Kadu (2017). Transfersomes-a boon for transdermal delivery. *Indo Am J Pharm Sci. 4*(9): 2908-19.
5. Gayathri P. (2016). A mini review on Oral dosage forms. *Res Rev J Chem. 5*(2): 130-7.
6. Honeywell-Nguyen PL and JA. Bouwstra (2005). *Drug Discov Today Technol. 2*(1): 67-74. doi: 10.1016/j.ddtec.2005.05.003, PMID 24981757.
7. Kabil MF, M Nasr, IT Ibrahim, YA Hassan and IM. El-Sherbiny (2022). *Eur J Pharm Sci. 171:* 106119. doi: 10.1016/j.ejps.2022.106119, PMID 34998905.
8. Kumar L, and P. Utreja (2020). *Micro Nanosystems. 12*(1): 38-47. doi: 10.2174/1876402911666190603093550.
9. Malatesta, M, M *et al*. (2021). *Antioxidants (Basel, Switzerland). 10*(5):768. doi: 10.3390/antiox10050768, PMID 34066018.
10. Mishra KK, and CD. Kaur (2022). *Thai J Pharm Sci. 46*(2): 191-202.
11. Radomska-Soukharev A. (2007). *Adv Drug Deliv Rev. 59*(6): 411-8. doi: 10.1016/j.addr.2007.04.004, PMID 17553589.
12. Rahangdale M, and P. Pandey (2021). Development and characterization of apremilast transethosomal gel for transdermal delivery. PCI- Approved-IJPSN. *14*(3): 5508-18. doi: 10.37285/ijpsn.2021.14.3.8.
13. Salem HF, MM Nafady, RM Kharshoum, OA Abd El-Ghafar and HO. Farouk (2020). *Int J Nanomedicine. 15:* 1517-35. doi: 10.2147/IJN.S238709, PMID 32189966.

14. Samad A, Y Sultana, and M. Aqil (2007). *Curr Drug Deliv. 4*(4): 297-305. doi: 10.2174/156720107782151269, PMID 17979650.
15. Song CK, P Balakrishnan, CK Shim, SJ Chung, S Chong, and DD. Kim (2012). *Colloids Surf B Biointerfaces. 92:* 299-304. doi: 10.1016/j.colsurfb.2011.12.004, PMID 22205066.
16. Song H, J Wen, H Li, Y Meng, Y Zhang, and N Zhang *et al*. (2019). *Int J Nanomedicine. 14:* 3177-88. doi: 10.2147/IJN.S188842, PMID 31118630.
17. Sundar V. D., D, P, and MD. Dhanaraju (2020). *Indian J Pharm Educ Res. 54*(2): 88-97.
18. Wang FC, PL Hudson, K Burk, and AG. Marangoni (2022). *J Colloid Interface Sci. 608*(2): 1222-8. doi: 10.1016/j.jcis.2021.10.143, PMID 34735856.
19. Wang Y, R Wang, X Qi, W Li, Q Guan, and R Wang *et al*. (2021). *J Drug Deliv Sci Technol. 64:* 102425. doi: 10.1016/j.jddst.2021.102425.