A PROSPECTIVE REVIEW ON TRANSETHASOMAL GEL AS CARRIER FOR ENHANCING TRANSDERMAL DELIVERY

Mohammad amin Yatoo[1], Gururaj S Kulkarni[2], Padmaa M Paarakh[3], Muthukumar A[4]

[1]*Head of the Depament, Department of Pharmaceutics, The Oxford College of Pharmacy, Bangalore, Karnataka, India.*

[2] *Principal, Department of Pharmacognosy, The Oxford College of Pharmacy, Bangalore, Karnataka, India.*

[3] *Assistant Professor Department of Pharmacology, The Oxford College of Pharmacy, Bangalore, Karnataka, India.*

ABSTRACT

Transethosomes are a kind of lipid-based nanosystem that have proven to be useful for for the administration of transdermal drugs because of their capacity to pierce the dense network of the stratum corneum. These soft and flexible nanosystems, which consist of phospholipid, ethanol, water, and an edge activator or permeation enhancer, can transport drug molecules. They can be made in a number of ways, such as hot, cold, thin-film hydration, and ethanol injection procedures. Transethosomes' tiny particle sizes allow them to pass through skin layers and ease of shape modification. Particle size, surface charge, entrapment efficiency, surface shape, drug content, and stability are some of the characteristics that define vesicles. NSAIDS, antifungals, antibiotics, and medications that can all be transdermally delivered using these vesicular systems.

KEY WORDS: *Transethosomes; Analgesic activity; Vesicles; Edge activator*

1. INTRODUCTION

Skin has received a great deal of attention in terms of medication penetration and permeation. Transdermal medication delivery is a well-established approach in the pharmaceutical business[1]. Transdermal drug delivery is a painless way of administering medications that involves putting a drug formulation to the skin. transdermal distribution is superior to traditional methods of drug delivery due to self-medication, excellent safety, higher patient compliance, avoidance of side effects and first pass metabolism, reduced frequency of dose, and more consistent plasma levels. However, The skin is composed of numerous layers, including the subcutaneous, dermal, and epidermal layers.The epidermis contains numerous horny layers composed of fat-based matrices that block the passage of both hydrophilic and heavy in molecular weight medicament molecules into the skin[2].Nanocarriers can be delivered transdermally to improve local dermal effects as well as skin permeation for systemic performance[3]. Because of their closeness to cell membrane structure, vesicular nanocarriers have attracted a lot of interest recently for the administration of transdermal and topical drug applications. They consist of a lipid bilayer around an aquatic core, allowing them to include both hydrophilic and hydrophobic pharmaceutical substances[4]. Furthermore, These nanovesicles enable deep penetration into the epidermal layers and long-term drug release[5]. Researchers have spent decades studying various strategies for weakening or disrupting the permeation barrier and delivering drugs intact through the skinWater, phospholipids, and ethanol are concentrated in high concentrations within vesicular structures known as ethosomal nanocarriers. They are specifically intended for therapeutic agent distribution via the skin or transdermal route[6,7].

2. TYPES OF ETHOSOMES

Ethosomal systems are characterized by their composition into three classes as shown in figure 1

Classical ethosomes, Binary ethosomes and Transethosomes.

2.1 Classical ethosomes

Classical ethosomes are modified liposomes made of phospholipids, a high concentration of ethanol (about 45%w/v), and water. They are thought to be superior to traditional liposomes in transdermal medication delivery because they are smaller in size and so exhibit better skin permeability. Additionally, it exhibited a negative potential and improved entrapment efficiency[8].

2.2 Binary ethosomes

Binary ethosomes were created by adding another form of alcohol to traditional ethosomes, such as isopropyl alcohol (IPA) or propylene glycol (PG)[9].

2.3 Transethosomes

Transethosomes are a new class of ethosomal system that integrates transferosome and ethosome characteristics into one system. Apart from the fundamental elements of traditional ethosomes, this system also incorporates an edge activator or penetration enhancer, like surfactants. Numerous studies have shown how beneficial TEs are for enhancing the dermal and transdermal transport of a range of medications with different physiochemical propertie[9,10].

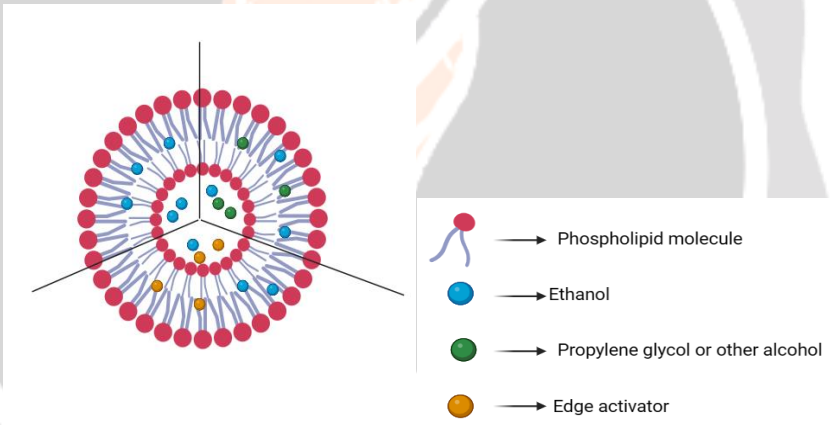

Fig-1: Ethosomes system

3. ADVANTAGES AND DISADVANTAGES

3.1 ADVANTAGES

- ✓ The raw components employed in the formulation are not harmful in nature.
- ✓ Passive, non-invasive, and ready for rapid commercialization.
- ✓ Avoidance of the first pass effect.
- ✓ The transethosomal medication is given in a semisolid dose form.
- ✓ It improves medication penetration through the skin, enabling transdermal drug delivery.
- ✓ Transethosomal drug delivery is applicable to various industries, including cosmetics and veterinary medicine.
- ✓ It has great patient compliance.

3.2 DISADVANTAGES

- ✓ Drug permeation through the skin depends on several factors.
- ✓ A few recipients may have skin discomfort.
- ✓ Drugs that require blood volume cannot be delivered.

- ✓ It may not be affordable for some folks[11].

4. APPLICATION

4.1 Delivery of Anti-inflammatory drugs:

Oral administration of NSAIDs (Nonsteroidal Anti-inflammatory Drugs) has been associated to gastrointestinal side effects. The Transethosomal formulation showed improved penetration[12].

The recipe with 45% ethanol and a reduced lecithin content yielded the best results Percutaneous permeability and tolerability were improved in the in vitro investigation. In the in vivo experiment, volunteers showed higher levels of anti-inflammatory activity[13].

4.2 Hormone delivery:

Hormone administration orally has been linked to a number of issues, including increased FPM, many dose-dependent side effects, as well as limited oral bioavailability. Incorporating hormones such as testosterone in transethosomal formulations resulted in roughly 30 times more skin penetration than other marketed oral preparations[14].

4.3 Delivery of Antibiotics:

Topically administered antibiotics have a higher therapeutic efficacy. The usage of oral medication has previously resulted in a number of negative outcomes, including allergic reactions. Transethosomes eliminate the risk of reduced permeability to subdermal tissues and deeper skin layers, which is often used in conventional external preparations Ethosomes rapidly penetrate the epidermis, transporting numerous treatments reaching the skin's deepest layers and eliminating sickness at its cause[15].

4.4 Delivery of Antifungal drugs:

Transethosomes carrying amphotericin B, terbinafine, ketoconazole, and other medications demonstrated skin permeability and deposition as compared to ordinary liposomes and ethosome[16].

4.5 Delivery of an Anti-Parkinsonian medication:

The transethosomal version of the psychoactive medication trihexyphenidyl hydrochloride demonstrated higher skin penetration capability than its liposomal variant[17].

4.6 Application of ethosomes in cosmetics:

Transethosomes have been effectively included into cosmetic compositions for a range of advantages, including transdermal penetration and stability, as well as reduced severe cosmetic ingredients causing skin irritation. Curcuma longa extract-containing transethosomal creams have also been developed and investigated for their photoprotective and anti-aging qualities. Use of transethosomal creams containing Curcuma longa extract on human volunteers as a photoprotective and anti-wrinkle therapy[18].

4.7 Delivery of Anticancer drugs:

Conducted study on cutaneous melanoma using dual drug loading and transethosomal formulation. They selected two drugs, dacarbazine and tretinoin, since they had less cytotoxicity and performed better in concert than the other formulations. Transethosomes with dual loading beat single-loaded medicines in terms of anticancer activity. Skin penetration can be improved, they discovered[19].

5. TRANSETHOSOMES COMPOSITION

High levels of phospholipids, ethanol, edge activators, and active ingredients make up the transethosomes. These ingredients along with their functions are shown in Tabel:1

Table-1: Composition of transethosomes

Class	Example	Uses
Phospholipids (2-5%)	Soya phosphatidyl choline (S-75), Lipoid S100, Phospholipon 90G.	Vesicles forming component

Edge activator	Oleic acid, Span 80, Tween 80, Tween 20, sodium deoxycholate, sodium cholate.	It uses as elasticity and acts as penetration enhancer
Alcohol (30%-40%)	Ethylene glycol.	It provides softness to the vesicle membrane
Cholesterol	Cholesterol	Provides stability to the vesicle membrane
Water (q.s 100)	Water	Used as a vesicle forming agent

5.1 Ethanol

Because of its size, stability, entrapment effectiveness, and skin permeability, ethanol has the potential to be a formidable penetration promoter. 10-20% ethanol is added to TEs to soften and elasticize the vesicles.
Higher ethanol concentrations increase entrapment ability, as does The effectiveness of entrapment (EE) in thermoelectric plants. The solubility and loading of both lipophilic and hydrophilic medications into Transethosomes are improved by ethanol. Excessive ethanol usage can promote lipid bilayer leakage, increasing vesicle size and decreasing entrapment efficiency[20].

5.2 Phospholipids

There are just a few of the characteristics that the TEs display. Selecting the appropriate phospholipid is essential for the formation of stable TEs since it affects the kind and amount used. Phospholipid concentrations between 2-5% are ideal for TE production[21].

5.3 Cholesterol

Once cholesterol is integrated into the TE, they develop greater stability and efficient at entrapping medicinal molecules. It is also said that the addition of cholesterol causes the vesicles to enlarge. It was found that the amounts of cholesterol employed in certain formulations were less than 3%. According to reports, cholesterol stabilises in these vesicle systems and keeps the particles from clumping together[22].

5.4 Edge activators / penetration enhancers

Choosing the right edge activator is critical for producing TEs as it affects their properties. Transethosomal system edge activators can be triggered by surfactants of any kind, including cationic, anionic, and non-ionic ones. TEs may be made with anionic surfactants such as deoxycholic acid, sodium cholate, and sodium stearate. Two examples of non-ionic surfactants are Cremophor EL-35 and RH-40. One way to produce TEs is by using a surfactant, like polyethylene glycol. Often utilised edge activators are spans and tweens. Tween 30 may decrease vesicular size and enhance TE stability, according to studies[23,24].

6. METHODS

There are four easy and practical ways to generate transethosomes:

Cold technique,

Hot method,

Ethanol injection method, and

Thin film hydration method which are shown as;

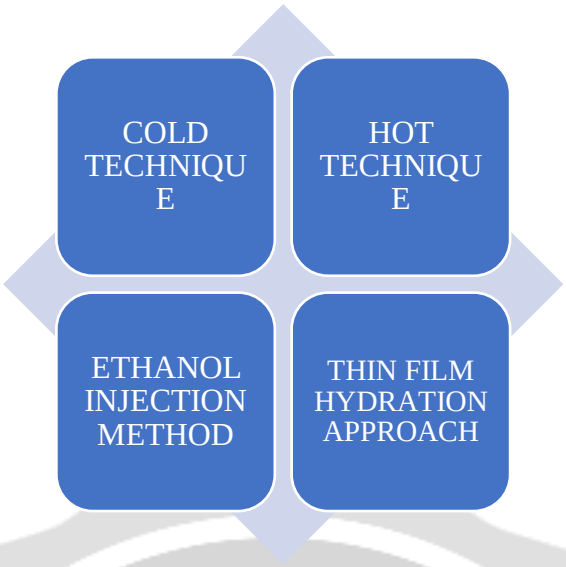

Fig-2: Different types of methods

6.1 Cold method

Transethosomes are typically formed using this technique. Because of its capabilities, medications that are heat-sensitive and thermolabile can be treated with it. It can be scaled up with ease. By vigorously shaking the ethanol solvent system, phospholipid is dissolved. In a water bath, this combination is heated to 30°C. After being heated to 30°C in a separate jar, water is gradually added to the alcoholic mixture. For even mixing while adding an aqueous solution to an ethanolic solution, a magnetic stirrer running at 700 rpm is utilised. Vesicle size may be modulated with the use of a probe sonicator.25

6.2 Hot method

Water is used to scatter phospholipid, which is then heated to 40°C. Heating a mixture of ethanol and glycol to 40°C is done. Combine the aqueous and organic phases while stirring continuously. The solvent system (ethanol or water) is selected based on how soluble the medication is. Throughout the procedure, a constant temperature of 40°C is maintained. The vesicular size can be modulated using probe sonication.26

6.3 Thin film hydration method

The transethosomes were prepared using the conventional thin-film hydration technique. Drug, oleic acid, and lecithin were combined in a 3:1 ratio with a combination of chloroform and methanol in a dry round-bottom flask. After permitting the organic solvents to evaporate via a rotary evaporator set at 60 rpm, under low pressure at 55 °C, a thin lipid layer was created on the wall of the round-bottom flask. For a full night, the last solvent remnants were removed under hoover. The film was then hydrated for one hour at room temperature with ethanol and phosphate buffer solution (pH 5.5) spinning at 100 revolutions per minute. The preparation was sonicated for 15–20 minutes to reduce the particle size, and then kept at 4 °C for additional research.27

7. MECHANISM OF TRANSETHOSOMES

Phospholipids, ethanol at a high concentration, edge activators and water are the ingredients of transethosomes, a special lipid formulation. They illustrate the benefits of transfersomes and ethosomes. Depending on the drug, the size range is 40 nm to 200 nm. One important characteristic of the transethosomal system that sets it apart from other vesicular systems is ethanol[12]. The ethanol impact is the result of ethanol intercalating into intercellular lipids, increasing the fluidity of lipids and decreases lipid bilayer density, is thought to be connected to the first part of the mechanism. Ethanol and other molecules work together to fluidize the stratum corneum's lipid layer its high conc. in Transethosomes, which encourage the systems ability to adapt and change, allowing them to penetrate via tiny gaps generated in the layers of corneum due to fluidization. Alcohol content in the transethosomes also influences its diameter because it imparts a net negative charge to the vesicle surface, lowering its size. The ideal ethanol concentration range is 30-40% for the generation of consistent ethosomes. A 20% reduction in ethanol level might result in larger vesicles[13]. Phospholipids play an important part in bilayer formation, with a hydrophobic tail and a hydrophilic head[28].

8. EVALUATION

8.1 Transethosome determination using surface morphology:

A transmission electron microscope was used to investigate the morphology of liquid dispersion. The thin film of vesicular dispersion was deposited on the copper grid that was coated with carbon, and the vesicles were stained before being examined and photographed[30].

8.2 pH measurement

A digital pH metre can be used to assess the transethosomal formulation's pH[31].

8.3 Entrapment efficiency determination

The suggested formulations' entrapment efficiency assessed using ultracentrifugation. To test the formulation, 1 mL was rotated for 3 hours at 25,000 rpm at 4°C by using a centrifuge. After centrifugation, the supernatant was diluted with methanol. Using the same procedure, UV spectroscopy was used to analyse the free HTC at 224 nm, using a blank formulation as a reference. To determine the concentration, we employed the following formula[32].

8.4 Determination of particle size

Transethosome vesicles were examined by using a Malvern zeta sizer. These measurements define the vesicles size and uniformity. The transethosome vesicles were also detected with a trinocular microscope prior to sonication[33].

8.5 Determination of stability studies

To examine the vesicular stability of transethosomal vesicles, deposit them at different temperatures (25±20C, 37±20C, 45±20C).TEM and DLS can be used to determine the size and shape of transethosomes[34].

8.6 Drug content determination

A modified HPLC technique and UV spectrophotometer are used to quantify drugs[35].

9. CONCLUSIONS:

Skin permeation improvement technology has the potential to expand transdermal drug delivery options. They provide safety, efficacy, and patient compliance, making them preferable to traditional transdermal permeation methods. The main challenge in creating a transdermal medicine delivery device is overcoming the epidermal barrier.Transethosomes, which contain alcohol and edge activator have superior skin permeation than other new vesicles such as liposomes and niosomes.These formulations are easy to prepare, effective, safe, and suitable for both topical and systemic drug administration. Incorporating transethosomal incorporation into transdermal patches or topical formulations enhances medication skin permeability. The use of ethanolic vesicular carriers in formulation has the potential to deliver medications with solubility issues via transdermal route.

10. REFERENCES

1.Teaima MH, Alsofany JM, El-Nabarawi MA. Clove oil endorsed transdermal flux of dronedarone hydrochloride loaded bilosomal nanogel: Factorial design, in vitro evaluation and ex vivo permeation. AAPS PharmSciTech. 2022 Jul 1;23(6):182.

2. Rakesh R, Anoop KR. Ethosomes for Transdermal and Topical Drug Delivery. Int J Pharm Sci 2012;4:17–24.

3. Rodríguez-Luna A, Talero E, Ávila-Román J, et al. Preparation and in vivo evaluation of rosmarinic acid-loaded transethosomes after percutaneous application on a psoriasis animal model. AAPS PharmSciTech. 2021;22:1–18.

4. El-Mahdy MM, Hassan AS, El-Badry M, El-Gindy GE-DA. Performance of curcumin in nanosized carriers niosomes and ethosomes as potential anti-inflammatory delivery system for topical application. Bull Pharm Sci. 2020;43:105–122.

5. Hassan AS, Hofni A, Abourehab MA, Abdel-Rahman IA. Ginger extract–loaded transethosomes for effective transdermal permeation and anti-inflammation in rat model. International Journal of Nanomedicine. 2023 Dec 31:1259-80.

6. Tiwari RK, Chauhan NS. Ethosomes: A potential carries for transdermal drug delivery. Int J Drug Dev Res 2010;2(2):448–52.

7. Touitou E, Dayan N, Bergelson L, Godin B, Eliaz M. Ethosomes - novel vesicular carriers for enhanced delivery: characterization and skin penetration properties. J Control Release 2000;65(3):403–18.

8. Sudhakar CK, Jain S, Charyulu RN. A Comparison Study of Liposomes, Transfersomes and Ethosomes Bearing Lamivudine. Int J Pharm Sci Res 2016;7(10):4214–21.

9. Maxwell A, Priya S. Nanosized ethosomes-a promising vesicular drug carrier for transdermal drug delivery. Research Journal of pharmacy and technology. 2019;12(2):876-80.

10. Abdulbaqi IM, Darwis Y, Assi RA, Khan NA. Transethosomal gels as carriers for the transdermal delivery of colchicine: statistical optimization, characterization, and ex vivo evaluation. Drug design, development and therapy. 2018 Apr 9:795-813.

11. Shilpa Shyam M, Shammika P. A REVIEW OF FLUCONAZOLE LOADED TRANSETHOSOMAL GEL FOR CANDIDIASIS.

12. Nicolini C. Ethanol based vesicular carriers in transdermal drug delivery: nanoethosomes and transethosomes in focus. NanoWorld journal. 2016 Oct 26;1(2).

13. Zhaowu Z, Xiaoli W, Yangde Z, Nianfeng L. 2009. Preparation of matrine ethosome, its percutaneous permeation in vitro and anti inflammatory activity in-vivo in rats. J Liposome Res 19(2): 155-162.

14. Ainbinder D, Touitou E. Testosterone ethosomes for enhanced transdermal delivery. Drug Deliv 2005;12:297–303.

15. Aggarwal R, Sahoo PK. Ethosome: The novel drug delivery carriers. Sch Acad J Pharm. 2018;7(6):266-273.

16. Puneet Utreja, Lalit Kumar. Formulation and Characterization of Transethosomes for Enhanced Transdermal Delivery of Propranolol Hydrochloride. Micro and Nanosystems, 2020; 12(1): 38-47.

17. Mohanty D, Mounika A, Bakshi V, Haque MA, Sahoo CK. Ethosomes: a novel approach for transdermal drug delivery. 2018;11(8):219-26.

18. Walve JR, Bakliwal SR, Rane BR, Pawar SP. Transfersomes: a surrogated carrier for transdermal drug delivery system. 2011;2(1).

19. Aggarwal R, Sahoo PK. Ethosome: The novel drug delivery carriers. 2018;7(6):266-273.

20. Hmingthansanga, V., et al., 2022. Improved topical drug delivery: role of permeation enhancers and advanced approaches. Pharmaceutics, 14 (12), 2018.

21. Touitou, E., et al., 2000. Ethosomes—novel vesicular carriers for enhanced delivery: characterization and skin penetration properties. Journal of controlled release: official journal of the controlled release society, 65 (3), 403–418.

22. Pandey, V., Golhani, D., and Shukla, R., 2015. Ethosomes: versatile vesicu lar carriers for efficient transdermal delivery of therapeutic agents. Drug delivery, 22 (8), 988–1002.

23. Mishra, V., et al., 2018. Solid lipid nanoparticles: emerging colloidal nano drug delivery systems. Pharmaceutics, 10 (4), 191.

24. Nayak, D. and Tippavajhala, V.K., 2021. A comprehensive review on prep aration, evaluation and applications of deformable liposomes. Iranian journal of pharmaceutical research, 20, 186.

25. Sravani A, Shyamala SJ. An updated review on transethosomes. World J Pharm Res. 2019;8(13):629-37.

26. Dehaghani MZ, Mahapatra D, Joseph T. Novel vesicular system: an overview. Journal of applied pharmaceutical science. Int J Med Phar Sci. 2021;11(08).

27. Garg V, Singh H, Bhatia A, Raza K, Singh SK, Singh B, Beg S. Systematic development of transethosomal gel system of piroxicam: formulation optimization, in vitro evaluation, and ex vivo assessment. AAPS pharmscitech. 2017 Jan;18:58-71.

28. Bajaj KJ, Parab BS, Shidhaye SS. Nano-transethosomes: a novel tool for drug delivery through skin. Indian J. Pharm. Educ. Res. 2021 Jan 1;55(1):1-0.

29. Shaji J, Bajaj R. Transethosomes: A new prospect for enhanced transdermal delivery. International journal of pharmaceutical sciences and research. 2018 Jul 1;9(7):2681-5.

30. Rahangdale M, Pandey P. Development and characterization of apremilast transethosomal gel for transdermal delivery. International Journal of Pharmaceutical Sciences and Nanotechnology (IJPSN). 2021 May 6;14(3):5508-18.

31. Vijeta B, Namrata M, Alagusundaram M. Ultra Deformable Nanotransethosomes: A Novel Tool to Intensify Transdermal Drug Delivery a Review. Journal of Pharmaceutical Negative Results. 2023 Feb 13:2024-32.

32. Aodah AH, Hashmi S, Akhtar N, Ullah Z, Zafar A, Zaki RM, Khan S, Ansari MJ, Jawaid T, Alam A, Ali MS. Formulation development, optimization by box–behnken design, and in vitro and ex vivo characterization of hexatriacontane-loaded transethosomal gel for antimicrobial treatment for skin infections. Gels. 2023 Apr 11;9(4):322.

33. Yewale C, Baradia D, Patil S, Bhatt P, Amrutiya J, Gandhi R and Kore G (2018). Docetaxel loaded immunonanoparticles delivery in EGFR overexpressed breast carcinoma cells. Journal of Drug Delivery Science and Technology 45: 334-345.

34. Gondkar SB, Patil NR, Saudagar RB. Formulation development and characterization of drug loaded transethosomes for transdermal delivery. Int J Chemtech Res. 2017;10(6):535-44.

35. Teerawan R et al (2012). Comparative study of liposomes, transfersomes, ethosomes and cubosomes for transcutaneous immunisation: characterisation and in vitro skin penetration. J Pharm Pharmacol. 2012:1560-1569.