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TRANSETHOSOMES: A NEW PROSPECT FOR ENHANCED TRANSDERMAL DELIVERY

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ABSTRACT: The skin covers a total surface area of approximately 1.8 m² and provides the contact between the human body and its external environment. Transdermal route of drug delivery has gained great interest in pharmaceutical research as it overcomes many problems associated with the oral route of administration. Although the skin, particularly the stratum corneum presents a barrier to most drug absorption, it provides a large (1.2 m²) and accessible surface area for drug diffusion. Recently, various strategies have been used to augment the transdermal delivery of bioactives. Mainly, they include iontophoresis, electrophoresis, sonophoresis, chemical permeation enhancers, magnetophoresis, microneedles, vesicular systems (liposomes, niosomes, elastic liposomes such as ethosomes, transfersomes and transethosomes). Among these transethosomes appear to be more promising as they possess both lipophilic and hydrophilic regions and can accommodate drug molecules with a wide range of solubility. Transethosomes can deform and pass through a narrow constriction that is 5 to 10 times less than its own diameter. This high deformability gives better penetration of intact vesicles. These vesicles can be used for transdermal delivery of various classes of drugs like analgesics, anesthetics, corticosteroids, sex hormones, anticancer agents insulin *etc.*

INTRODUCTION: At present, the most common form of drug delivery is the oral route. While this has the notable advantage of easy administration, it also has significant drawbacks-namely poor bioavailability due to hepatic metabolism (first pass) and the tendency to produce rapid blood level spikes (both high and low), leading to a need for high and/or frequent dosing, which can be both cost prohibitive and inconvenient. Continuous intravenous infusion is recognized as a superior mode of drug administration not only to bypass hepatic 'first pass' metabolism but also to maintain a constant and prolong drug level in the body.

But that requires hospitalization of the patients and close medical supervision of administration. At the same time transdermal route offers number of advantages over conventional delivery systems such as lower fluctuations in plasma drug levels, gastrointestinal side effects and high patient compliance. Stratum corneum is the most difficult barrier which does not allow passage of most of the drugs; except lipophilic and low molecular weight drugs^{1, 2}.

Ultra deformable vesicles (UDV) have recently become a promising tool for the development of improved and innovative dermal and transdermal therapies³. Deformable vesicles like transethosomes present the advantages of being nontoxic and thermodynamically stable formulations. They have been used for dermal and transdermal delivery of many molecules including peptides and proteins. In addition, their production is relatively simple and easy to scale up.

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Currently, there are various types of UDV that have been successfully developed for both pharmaceuticals and cosmeceuticals, particularly transfersomes, ethosomes, and, more recently, transethosomes⁴. The term transethosomes and the underlying concept were introduced by Song *et al.*, in 2012, and are characterized by having a high content of ethanol (upto 30%) together with an edge activator. Transethosomes may contain advantages of both transfersomes and ethosomes. The mechanism of skin penetration might be a fusion of both mechanisms.

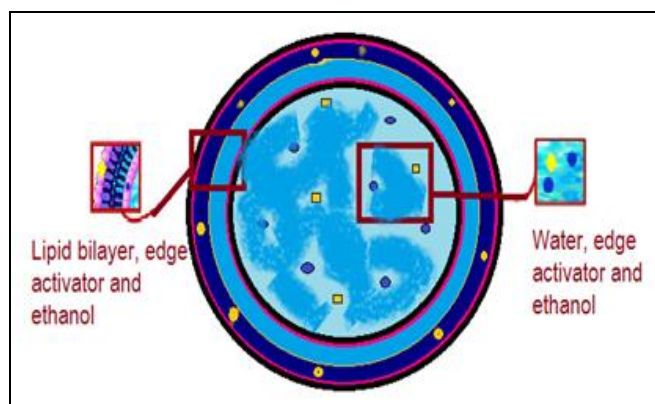


FIG. 1: TRANSETHOSOMES

Transethosomes and its Mechanism: Transethosomes represent novel lipid formulation which contains phospholipids, ethanol in high conc. of 30 to 40%, edge activators like tween 20, tween 60, tween 80, span 60, span 65, span 80, sodium cholate or sodium deoxycholate and water. They show the advantages of both ethosomes and transfersomes. The size range lies between 40 nm to 200 nm depending upon the drug. Ethanol is a central character of transethosomal system giving unique identity to it as a vesicular system. It is thought that the first part of mechanism is due to 'ethanol effect', whereby intercalation of the ethanol into intercellular lipids increasing lipid fluidity and decreases the density of the lipid bilayer.

Lipid layer of stratum corneum is fluidized by impact of ethanol and its high concentration in transethosomes that promote malleability and flexibility of these systems enhancing their penetration through tiny openings formed in stratum corneum due to fluidization. Alcohol amount in vesicular system also control its diameter as it provides net negative charge to vesicle surface reducing its size. 30 - 40% is optimum concentration range of ethanol for the

formation of stable ethosomes. Reducing ethanol concentration to 20% may lead to increase in vesicular size. Phospholipids have an integral role in bilayer formation; consisting of hydrophilic head and hydrophobic tail⁵.

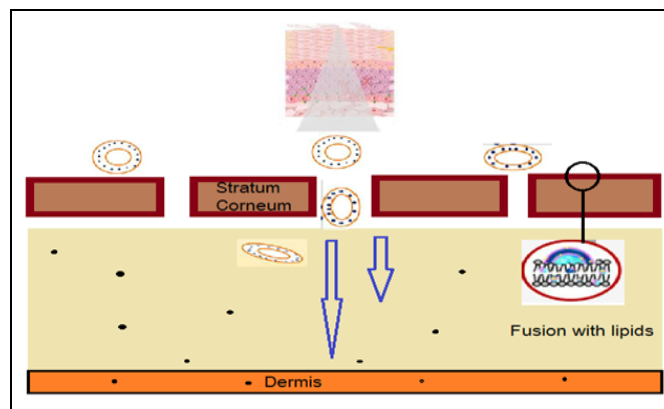


FIG. 2: PERMEATION AND PENETRATION OF TRANSETHOSOMES THROUGH SKIN

Advantages of Transethosomal Drug Delivery: In comparison to other transdermal and dermal delivery systems

- The transethosomal system is passive, non-invasive and is available for immediate commercialization⁸.
- It contains non-toxic raw materials in the formulation⁸.
- Transethosomal drug delivery can be applied to many fields including veterinary and cosmetic fields.
- It shows high patient compliance as it is administered in semisolid gel or cream form.
- Contrary to deformable liposomes, transethosomes improve skin delivery of drugs both under occlusive and non occlusive condition¹¹.
- This drug delivery system shows better stability as compared to other conventional vesicles.
- Simple method of drug delivery as compared to iontophoresis, laser surgery, cryo surgery and other complicated methods.

Disadvantages of Transethosomal Drug Delivery:

- Adequate solubility of the drug in both lipophilic and aqueous environments to reach dermal microcirculation and gain access to the systemic circulation.
- The molecular size of the drug should be reasonable that it should be absorbed percutaneously¹¹.

TABLE 1: SHOWS THE COMPARISON BETWEEN ETHOSOMES AND TRANSETHOSOMES¹²

Parameter	Ethosomes	Transethosomes
Composition	1. Phospholipids 2. Ethanol 3. Propylene glycol or other alcohol 4. Charge inducer 5. Water	1. Phospholipids 2. Ethanol 3. Edge activator (surfactant) or penetration enhancer 4. Charge inducer 5. Water
Morphology	Spherical	Regular or irregular spherical shape
Entrapment efficiency	Higher than classical ethosomes	Higher than ethosomes
Skin permeation	Typically equal to or higher than classical ethosomes	Higher than ethosomes
Size	equal to or smaller than classical ethosomes	Size based on type and concentration of penetration enhancer or edge activator used
Stability	Stable than classical ethosomes	Stable than ethosomes

Methods of Preparation: Mechanical dispersion, cold method and hot method are the methods used for the preparation of transethosomes. Cold method is the most commonly used method.

Hot Method: Disperse phospholipid in water by heating in a water bath at 40 °C to obtain a colloidal solution. Ethanol and glycol are mixed and heated upto 40 °C. Organic phase is added to aqueous phase. Stir for 7 to 10 min. Depending on its hydrophilic/hydrophobic properties, drug can be dissolved in water or ethanol. Temperature is maintained at 40 °C throughout the preparation. Size of the vesicles is reduced by probe sonication¹³.

Cold Method: Dissolve phospholipid in ethanol by vigorous stirring. This mixture is heated upto 30 °C in water bath. Water is heated upto 30 °C in a separate vessel and added to the alcoholic mixture slowly in a fine stream. Depending on drug solubility, it can be dissolved in water or ethanol. The mixture is kept on magnetic stirrer at 700 rpm during the addition of the above aqueous solution to ethanolic solution. Modulation of vesicle size can be done using probe sonicator.

Mechanical Dispersion Method: Lipid and surfactant is taken in clean, dry, round bottom flask. Lipid mixture is dissolved in solvent mixture of chloroform and methanol mixture. A thin film of lipid is obtained using rotary evaporator above the lipid transition temperature. It is kept overnight under vacuum to remove traces of organic solvent. The deposited film is hydrated with 10 % v/v ethanol in phosphate buffer pH 6.5 by rotation at 60 rpm. Drug is added to the formulation. The vesicles are sonicated for desired size.

Various methods for Characterization of Trans ethosomes:

Vesicle Shape: Vesicle shape can be determined by transmission electron microscopy (TEM) and by scanning electron microscopy (SEM).

Particle Size and Zeta Potential: Particle size of transethosomes can be done by particle size analyzer, dynamic light scattering and photon correlation spectroscopy. Zeta potential of the formulation can be measured by zeta meter.

Entrapment Efficiency: The entrapment efficiency is expressed as the percentage entrapment of the drug added. This can be measured by ultracentrifugation technique. % EE can be expressed as: $[\frac{Q_t - Q_s}{Q_t}] * 100$

Where Q_t is total theoretical amount of drug added and Q_s is the amount of drug found in supernatant.

Transition Temperature: The transition temperature of transethosomes can be determined by using differential scanning calorimetry (DSC).

Drug Content: Drug content of transethosomes can be determined using U.V spectrophotometer. This can also be quantified by a modified high performance liquid chromatographic method.

Vesicle Stability: The stability of vesicles can be determined by assessing the size and structure of vesicles over time.

Surface Tension: The surface tension activity of drug in aqueous solution can be measured by the ring method in a Du Nou ring tensiometer¹⁵.

Penetration and Permeation: Depth of penetration from transethosomes can be visualized by confocal laser scanning microscopy (CLSM) ¹⁷.

In-vitro Drug Release: ¹⁸ 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.

Materials Commonly Used in Preparation of Transethosomes: ¹⁴

TABLE 2: MATERIALS USED IN TRANSETHOSOMES

Class	Examples	Role
Phospholipid	Soya phosphatidyl choline	Vesicle forming unit
	Hydrogenated soy phosphatidyl choline	
	Egg phosphatidyl choline	
	Distearyl phosphatidyl choline	
Alcohol	Ethanol	Imparts softness and act as a penetration enhancer
Surfactant	Sodium deoxycholate	Flexibility to the vesicles
	Sodium cholate	
	Tween 80 Span 80	
Dye	Rhodamine 123	Characterization
	Rhodamine-DHPE	
	Fluorescein-DHPE	
	Nile-red	
Buffering agent	Saline phosphate buffer pH 6.4	As a hydrating agent

Application of Transethosomes:

Delivery of Non-steroidal Anti-inflammatory Drugs (NSAIDs): Oral administration of NSAIDs are associated with number of GI side effects. Hence transdermal delivery using ultradeformable vesicles is preferred. Transethosomes containing ketorolac tromethamine show enhanced penetration than drug containing ethosomes.

Garg V *et al.*, recently proved that transethosomal gel of piroxicam was found to be superior in all aspects as compared to other vesicular systems with improved stability and highest elasticity ²².

Delivery of Antifungal Drugs: Transethosomes containing terbinafine, amphotericin B, ketoconazole showed enhanced permeation. Also voriconazole transethosomes showed skin permeation and deposition as compared to that of conventional liposomes, deformable liposomes and ethosomes ²³.

Delivery of Anticancer Drugs: Imiquimod was investigated for transdermal delivery using transethosome technology. The results were favorable and provided a new approach for skin cancer treatment. Transethosomes showed better penetration and increased transdermal flux. Even after storage transethosomes retained its penetration power.

Issues and Future Progress Related to Ethanol Based Vesicles for Transdermal Drug Delivery:

Most of the active molecules do not pass through stratum corneum barrier. Ethanol based nanocarriers have opened a new window to deliver various bioactive molecules transdermally as they have capability to fluidize and disturb the rigid lipid system of stratum corneum. These systems represent an efficient non-invasive drug delivery approach for medium and large sized bioactive molecules along with high patient compliance and low cost treatment. However, effective clinical exploration of the ethanol based nanocarrier system is still a challenge. It is necessary to evaluate them clinically to check their potency. Ethanol based nanocarriers need safety exploration in some specific clinical conditions like their application to open areas of eczema as ethanol show irritant effect to skin. So, further research in this field will promote effective drug release *in-vivo* and make transdermal therapy ²⁴.

CONCLUSION: Skin permeation enhancement technology is a rapidly growing field which will significantly increase the number of drugs for transdermal delivery. As a result skin may become major route of delivery in the coming decade ²⁵. Transethosomes provide the highest flexibility to the formulator to change the ethosomal properties according to the required research criteria by changing the edge activators and/or penetration enhancers ²⁶. Ultra deformable vesicles like transethosomes have the ability to deliver larger range of molecules like peptides, drugs with poor penetration, drugs for quicker and targeted action, hormones and antibiotics *etc.*

They offer safety, efficacy and patient compliance hence are more superior to other conventional transdermal permeation techniques. Transethosomes have become promising carriers not only for topical treatment of local but also for systemic

disorders. They can be explored in the future for delivery of various drugs through transdermal delivery. Formulation of these vesicles in gel form may improve their viscosity and hence increase their residence time on the site of action.

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REFERENCES:

1. Article, R. Proniosomes And Ethosomes: New Prospect In Transdermal And Dermal Drug Delivery System Nidhi Pandey KIET School of Pharmacy, Ghaziabad, Uttar Pradesh, India. 2011; 2(8): 1988-1996.
2. Akiladevi D and Basak S: Ethosomes - A Noninvasive Approach for Transdermal Drug Delivery. 2010; 2(4): 2-5.
3. Ascenso A, Raposo S, *et al.*, Development, characterization, and skin delivery studies of related ultra deformable vesicles: transfersomes, ethosomes, and transethosomes. Int J Nanomedicine. 2015; 10: 5837-5851.
4. Bhana R, Verma A and Jain S: Development and characterization of ethosomes bearing losartan potassium for transdermal drug delivery. Int J Pharm Pharm Sci. 2013; 5(1): 35-40.
5. Ibrahim NA, Darwis Y, *et al.*, Ethosomal nanocarriers: the impact of constituents and formulation techniques on ethosomal properties, *in-vivo* studies, and clinical trials. Int. J. Nanomedicine. 2016; 11: 2279-2304.
6. Cevc G: Lipid vesicles and other colloids as drug carriers on the skin. 2004; 56: 675-711. Doi: 10.1016/j.addr. 2003. 10.028.
7. Goindi S, Dhatt B and Kaur A: Ethosomes-based topical delivery system of antihistaminic drug for treatment of skin allergies. J Microencapsul. 2014; 31(7): 716-724.
8. Dianzani C, Zara GP, Maina G, Pettazzoni P, Pizzimenti S, Rossi F, Gigliotti CL, Ciamporcerio ES, Daga M and Barrera G: Drug delivery nanoparticles in skin cancers. 2014.
9. Ascenso A, Raposo S, *et al.*, Development, characterization, and skin delivery studies of related ultradeformable vesicles: transfersomes, ethosomes, and transethosomes. Int J Nanomedicine. 2015; 10: 5837-5851.
10. Filipe V, Hawe A and Jiskoot W: Critical evaluation of nanoparticle tracking analysis (NTA) by nanosight for the measurement of nanoparticles and protein aggregates. Pharm Res 2010; 27: 796-810.
11. Goindi S, Dhatt B and Kaur A: Ethosomes-based topical delivery system of antihistaminic drug for treatment of skin allergies. J Microencapsul. 2014; 31(7): 716-724.
12. Honeywell-nguyen PL and Bouwstra JA: Vesicles as a tool for transdermal and dermal delivery. 2005; 2(1): 67-74. Doi: 10.1016/j.ddtec.2005.05.003.
13. Nandan D and Shivalik P: Ethanol based vesicular carriers in transdermal drug delivery: Nanoethosomes and Transethosomes in Focus. NWJ 2016; 1-30.
14. Karim NA: Ethosomal nanocarriers: the impact of constituents and formulation techniques on ethosomal properties, *in-vivo* studies and clinical trials. 2016; 2279-2304.
15. Lalit K, Verma S, Singh K, Prasad D and Jain A: Ethanol based vesicular carriers in transdermal drug delivery: Nanoethosomes and Transethosomes in Focus. Nano World Journal 2016; 30: 41-51.
16. Rigon RB, Oyafuso MH, Fujimura AT, Gonçalez ML, Haddad A, Palmira M, Gremião D and Chorilli M: Nanotechnology-based drug delivery systems for melanoma antitumoral therapy: A review. Biomed research international. 2015.
17. Romero EL: Highly deformable and highly fluid vesicles as potential drug delivery systems-theoretical and practical consideration. Int. J. Nanomedicine 2013; 8: 1-16.
18. Rigon RB, *et al.*, Nanotechnology-based drug delivery systems for melanoma antitumoral therapy: A review. Biomed research international. 2015; 2(5): 34-39.
19. Sathya Prasad S, *et al.*, Ethosomes as drug carrier: A novel approach. Int Journal of Innovative Drug Discovery. 2013; 3(2): 55-66.
20. Song CK, Balakrishnan P, Shim C, Chung S, Chong S and Kim D: A novel vesicular carrier, transethosome, for enhanced skin delivery of voriconazole: characterization and *in-vitro/in-vivo* evaluation. Colloids Surf 2012; 92: 299-304.
21. Shaji J and Garude S: <http://www.iajpr.com>. 2014; 4(08).
22. Touitou E, Dayan N, Bergelson L, Godin B and Eliaz M: Ethosomes-novel vesicular carriers for enhanced delivery: characterization and skin penetration properties. J Controlled Release 2000; 65: 403-18.
23. Garg V, *et al.*, Systematic development of transethosomal gel system of piroxicam: Formulation optimization, *in-vitro* evaluation, and *ex-vivo* assessment. AAPS Pharm Sci Tech. 2017; 18(1): 58-71.
24. Walve JR, Bakliwal SR, Rane BR and Pawar SP: Transfersomes: a surrogated carrier for transdermal drug delivery system. 2011; 2(1): 204-213.
25. Wo Y, Zhang Z, Zhang Y, Zhang Z, Wang K and Mao X: Enhanced *in-vivo* delivery of 5-fluorouracil by ethosomal gels in rabbit ear hypertrophic scar model. 2014; 22786-22800. Doi: 10.3390/ijms151222786.
26. Wong CSM, Strange RC, Lear JT: Clinical review Basal cell carcinoma. 2003; 327.
27. Vikas S, Seema S, Gurpreet S, Rana C and Baibhav J: Penetration enhancers: a novel strategy for enhancing transdermal drug delivery. Int. Res. J. Pharm. 2011; 2(12): 32-36.
28. Hussain A, Samad A, Ramzan M, Ahsan MN, Rehman U and Ahmad FJ: Elastic liposome-based gel for topical delivery of 5- fluorouracil: *in-vitro* and *in-vivo* investigation. 2016; 7544: 1-15.

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