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TRANSETHOSOMES; AN EFFECTIVE TOOL IN BYPASSING BARRIERS FOR TOPICAL ADMINISTRATION OF FORMULATION.

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ABSTRACT:

The complex stratum corneum barrier is the main obstacle to the transdermal administration of medicines. Modern lipid-based nanosystems, in particular transethosomes, have the capacity to penetrate the stratum corneum's dense network. They have demonstrated to be an effective technique for the transportation of medicines. Transethosomes(TELs) are composed of phospholipid, ethanol, water and edge activator(surfactants) or permeation enhancer(oleic acid). Delivering medication molecules into the circulation is made possible by the softness and flexibility that ethanol and edge activator both offer. Various techniques involved in the formulation of transethosomes are Cold method, Hot method, Thin film hydration method and Mechanical dispersion method. Compared to other vesicular systems, transethosomes have small particle sizes and are easily able to change the shape of vesicles, allowing them to pass through the layers of skin. The characterization of vesicles include Size of the particle and surface charge, Trasmission Electron microscopy, determination of entrapment efficiency, surface morphology study, interaction study by DSC and FTIR, drug content and stability of vesicles. These vesicular system can be used for transdermal delivery of various drugs such as NSAIDS, antifungal, antibiotics, antiparkinsonism, antiviral etc., In this review, the applications, challenging problems, and potential future developments of transethosomes were examined along with their nature, methods of preparation, and evaluation parameters.

Keywords: *Vesicular system, Liposome, Ethosomes, Transferosomes, Transethosomes.*

INTRODUCTION:

There are various routes of drug delivery systems(DDS), among which the oral route of administration is the most commonly used. However, the oral route of DDS has several drawbacks such as presystemic elimination, first pass metabolism, and are prone to various drug interactions, as a result of which various alternatives for this route of drug delivery have evolved[1]. Transdermal drug delivery systems(TDDS) are a suitable alternative route for oral DDS as they have various advantages over other routes of drug delivery. TDDS is a self-contained, discrete dosage form that is applied to intact skin to deliver the drugs through the skin at a controlled rate to the systemic circulation[2].TDDS will provide a leading edge over the injectable and oral routes as it has good patient compliance and can bypass first-pass metabolism[3].

ADVANTAGES OF TRANSDERMAL DRUG DELIVERY[3]:

The advantages of transdermal delivery over other delivery systems are as follows:

- Transdermal drug delivery system enables the avoidance of first pass metabolism.
- Reduced side effects when compared to the conventional drug delivery.
- Constant plasma drug concentration is achieved.
- Drug candidates with short half-life and low therapeutic index can be chosen.
- In case drug toxicity the patches can be removed at any time.
- Reduction of dosing frequency.
- Enhancement of patient compliance.
- It is possible that an equivalent therapeutic effect can be elicited via transdermal drug input with a lower daily dose of the drug that is necessary.

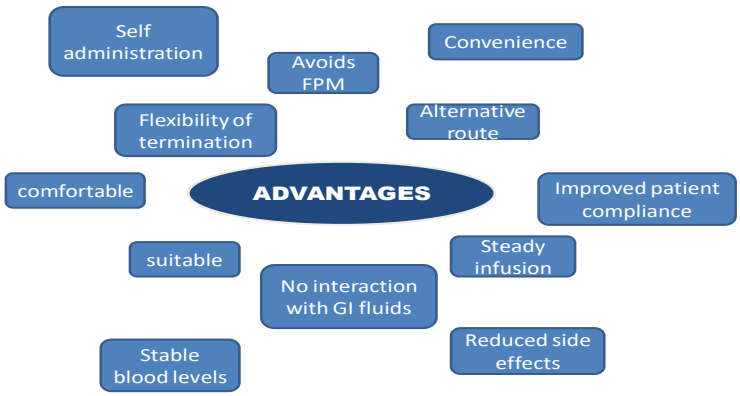

Fig 1: Advantages of Transdermal Drug Delivery System(TDDS)

MECHANISM OF TRANSDERMAL DRUG DELIVERY[5]:

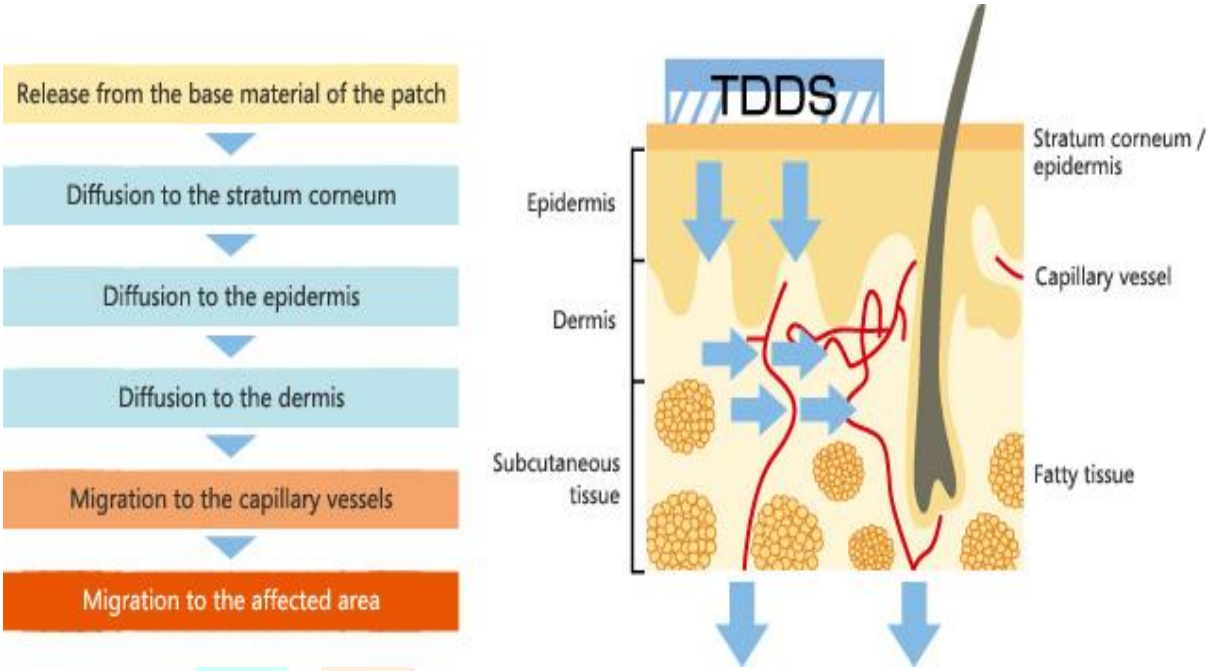

Fig 2: Mechanism of transdermal drug delivery.

TRANSETHOSOMES:

Various vesicular system are being used in delivering the drugs through the skin, among which transethosomes are novel[6]. These are the combination of transferosomes and Ethosomes, and can be used to deliver drugs both topical and systemic route[7].

DIFFERENT VESICULAR SYSTEM AND THEIR PRINCIPAL COMPONENTS:

Transferosomes: phospholipid and edge activator.

Liposomes: phospholipid and cholesterol.

Niosomes: non-ionic surfactant and cholesterol.

Ethosomes: phospholipid and ethanol.

Phytosomes: phospholipid and phytoconstituents.

Pharmacosomes: phospholipid.

Comparision of Ethosomes, Transferosomes and Transethosomes:

Comparison of Ethosomes, Transferosomes and Transethosomes			
Parameters	Ethosomes[8]	Transferosomes[9]	Transethosomes[10]
Composition	Phospholipids, ethanol and water	Phospholipids, edge activator and water.	Phospholipids, ethanol, edge activator and Water.
Entrapment Efficiency	Higher than liposomes.	Higher than Ethosomes.	Higher than ethosomes and transferosomes
Flux rate	More than Liposomes	More or equal to Ethosomes.	Higher flux rate
Skin Permeation	Lipids movement.	Deformation of Vesicles.	Altering the shape of vesicles.

Table 1: Comparision of Ethosomes, Transferosomes and Transethosomes.

Composition of transethosomes[11]:

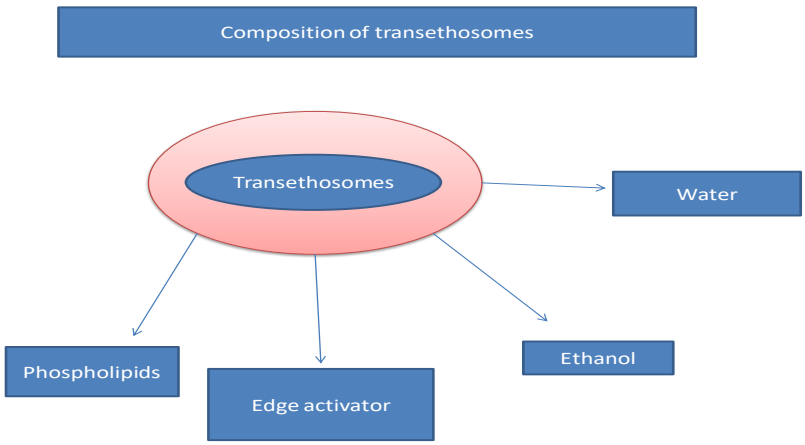

Fig 3: Composition of Transethosomes.

ADVANTAGES OF TRANSETHOSOME:

Transethosomes has greater efficiency when compared to other liposomes in the transportation of active moieties through the skin.

1. Along 20-50% of ethanol synergic effect is observed hence it is used as a major composition in transethosomes[12].
2. Non invasive approach hence better patient compliance.

3. Can be used to deliver the drugs with larger molecular weight this phenomenon makes it an ideal candidate to deliver protiens and peptides through the skin.
4. Its an effective drug carrier to deliver different dosage form[13].

Mechanism of action:

The vesicular system assists in the transdermal drug delivery of the drug moiety by enhancing the permeation of active drug component. The vesicles gets penetrated into the skin and the drug gets penetrated through it. Presence of permeation enhancer such as Ethanol, Propylene glycol and Isopropyl myristate increases the fluid content in the lipid bilayer along with lipid content that is present in stratum corneum[14].

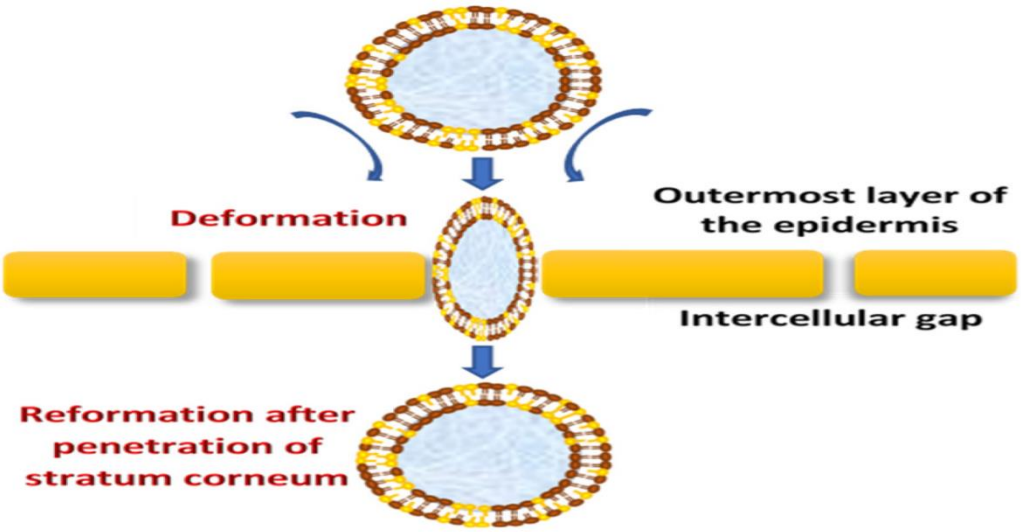

Fig 4: Mechanism of action of Transethosomes.

Methodology:

Different techniques of transethosomes formulation[16]:

- Cold method
- Hot method
- Thin film hydration method
- Mechanical dispersion method

Cold method:

Phospholipid is dissolved in ethanol as solvent system by vigorous shaking. This mixture is heated upto 30°c in a water bath. Water is heated in a separate vessel upto 30°c and added to the alcoholic mixture slowly . During addition of aqueous solution to ethanolic solution magnetic stirrer is used for uniform mixing (700rpm). Probe sonicator can be used in order to modulate the size of vesicles[17].

Hot method:

Phospholipid is dispersed in water and heated upto 40°c. Mixture of ethanol and glycol combination is heated upto 40°c. Mix organic phase with aqueous phase with uniform stirring. Based on solubility of drugs solvent system is chosen (water or ethanol). Constant temperature is maintained throughout the process (40°c). Probe sonication can be used to modulate the vesicular size[18].

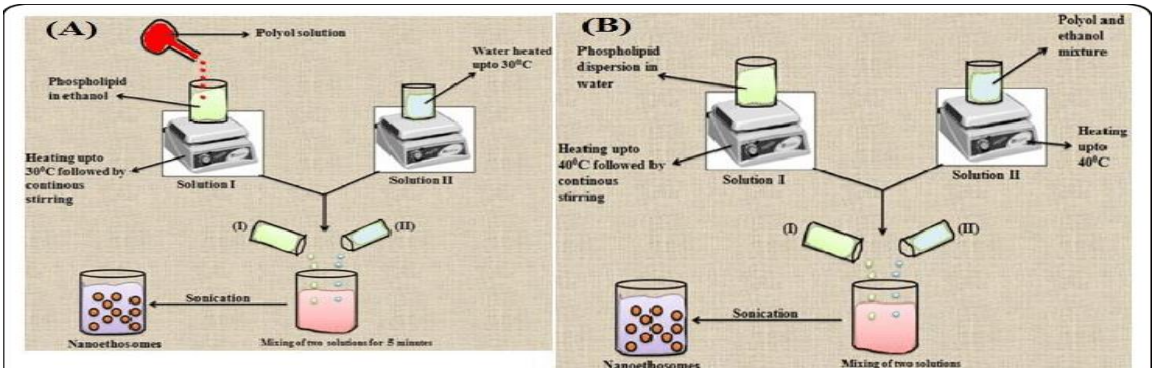

Fig 5: (A) Cold technique (B) Hot technique

Mechanical dispersion technique:

Round Bottom flask is used in this technique, Liquid and surfactant mixture is dissolved in ethanol. Efficiency of this technique can be enhanced by combination of hydrated thin film and ultrasound homogenization. Using rotary evaporator thin lipid film can be produced, the excess of organic solvent can be removed by keeping it overnight under vaccum. 10%v/v ethanol in phosphate buffer(6.5pH) atm60rpm is used in hydration process. Sonication technique can be employed to modify the vesicular size[19].

Reverse phase evaporation:

Lipid is dissolved in ethanol , edge activators are added to aqueous phase. Aqueous phase is added into organic phase, and ultrasonication technique is used in separation of two phases at 0°c .Formation of gel occurs under pressure upon removal of organic solvent[20].

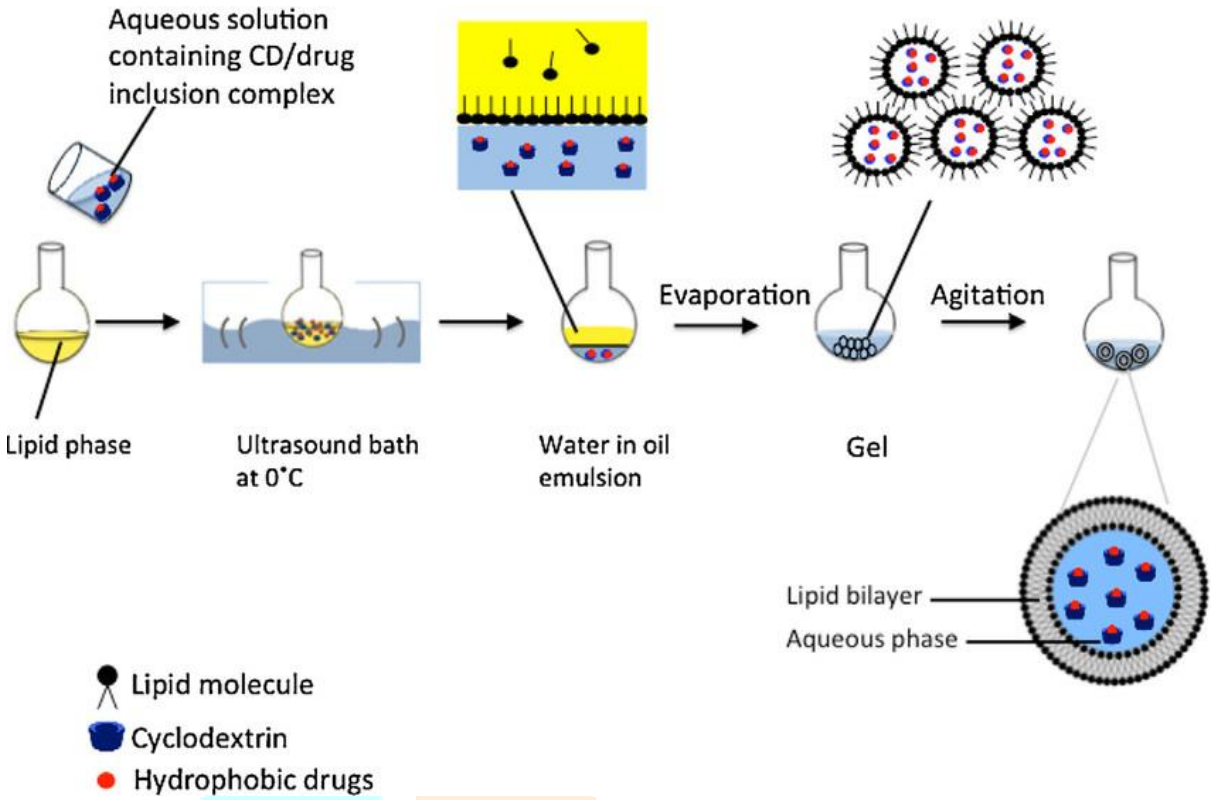

Fig 6: Formulation of Transethosomes by Reverse Phase Evaporation.

EVALUATION OF TRANSETHOSOMES:

Size of the particle and surface charge:

Size of the particle can be determined using laser scattering particle size distribution analyser. Zeta potential analyser the surface charge can be determined[21].

Transmission electron microscopy (TEM)

Visualization of the vesicles can be done using TEM. Conventional negative staining is performed using 1 % PTA(Phosphotungistic acid), dried later is visualized[22].

Determination of entrapment efficiency

Ultracentrifugation technique is used to determine the entrapment efficiency of transethosomes. Ultracentrifugation is performed at 1500rpm for 60 min at 4°c. Sediment and supernatant liquid is separated and the amount of sediment was determined and drug entrapment efficiency was calculated using the equation:

% Entrapment efficiency = Amount entrapped API x 100[23].

Surface morphology study:

Transethosomes are made up of lipids. Different type of lipids influence the surface morphology/ shape of the particles. SEM is used in determining the surface morphology[24].

Interaction study by using DSC and FTIR:

DSC is used to conduct study for the interaction between lipid and drug. Mettler DSC can be used in determination of the transition temperature(Tm) of the vesicular lipid system. The transition temperature is measured using aluminium crucibles at a heating rate 10°/min within a temperature ranging between 200-300°c. FTIR technique can also be used for conduction the interaction study[25].

Drug Content:

UV spectrophotometer can be utilized in studying the drug content present in the transethosomes. HPLC can be used for quantification[16].

Stability of Ethosome:

The ability of transethosomal formulations to retain the drug is checked by keeping the preparations at different temperatures, i.e.25±2°C(room temperature), 37±2°C and 45±2°C for different periods of time. The stability of ethosomes can also be determined quantitatively by monitoring size and morphology of the vesicles using DLS and TEM[14].

Drug Content:

The % drug content of ethosomal preparation was determined by using following formula

%drug content = Sample absorbance /standard absorbance[14].

Application:

When compared to liposomes, ethosomes and nanoethosomes; transethosomes are more effective. They distribute drugs 65% more effectively than liposomes do because they can pass through more layers of human skin with ease. The effectiveness of these vesicular systems is being investigated using a small number of bioactive compounds[27].

Delivery of NSAIDs (Non-steroidal Anti-inflammatory Drugs):

NSAIDs taken orally are linked to gastrointestinal adverse effects. Transethosomal formulation of ketorolac tromethamine demonstrated improved penetration. Piroxicam transethosomal gel recently demonstrated greater stability and elasticity compared to other deformable vesicle systems, according to Garg V et al[19].

In an experiment, Paolina et al. gave humans ethosomes that had been ammonium glycyrrhizinate-entrapped. The formulation with 45% ethanol and a lower proportion of lecithin produced the better results. The in vitro study produced improved tolerability and percutaneous permeability. Volunteers in the in vivo trial had increased anti-inflammatory activity[11].

Delivery of hormones:

Hormone administration orally has been associated with a number of problems, including high first-pass metabolism, poor oral bioavailability, and a range of dose-dependent side effects. Touitou et al., compared a commercially available testosterone transdermal patch (Testoderm® patch, Alza Corporation, California) to the skin penetration capacity of testosterone ethosomes through rabbit pinna skin. The ethosomal formulation's testosterone skin penetration was around 30 times greater than that of a commercially available transdermal patch. Also, it was discovered that the ethosomal system's AUC and Cmax were larger than those of Testoderm®[28].

Delivery of Antibiotics:

The therapeutic efficacy of antibiotics can be increased more effectively when applied topically. The use of oral medication in the past has had a number of adverse consequences, including allergic reactions. Concerns about restricted permeability to subdermal tissues and deeper skin layers, which are frequent with conventional external preparations, can be avoided with ethosomes. Ethosomes rapidly penetrate the epidermis, carrying several medications to the skin's deeper layers and squelching infection at its root. For this objective, Godin and Touitou developed an ethosomal formulation for cutaneous and intracellular administration containing bacitracin and erythromycin.The results of this study showed that an ethosomal antibiotic formulation could be very powerful and circumvent the shortcomings of conventional treatment[28.]

Delivery of antifungal drugs:

Terbinafine, amphotericin B, and ketoconazole-containing transethosomes had better penetration. Voriconazole transethosomes demonstrated skin penetration and deposition when compared to regular liposomes, deformable liposomes, and ethosomes[28].

Delivery of Anti-parkinsonism agent:

Trihexyphenidyl hydrochloride (THP), a psychoactive drug, was made into an ethosomal formulation by Dayan and Touitou, and they compared it to conventional liposomal formulations. Parkinson's disease is managed with THP, an M1 muscarinic receptor antagonist. The results indicated that the ethosomal-THP formulation had a greater capability for skin penetration and may be used to more effectively manage Parkinson's disease[20].

Cosmeceutical application of ethosomes:

Ethosomes have been effectively included into cosmetic formulations for a number of advantages, such as improved transdermal penetration and increased stability, as well as less skin irritation from harsh cosmetic chemicals. Ethosomal creams containing curcuma longa extract have also been created and studied for their

potential to have anti-aging and photoprotective properties. The use of C.longa extract-loaded ethosomal creams as a photoprotective and antiwrinkle treatment on human volunteers produced good results in both studies. A transethosome-based hair dye developed by Yeh et al., has been demonstrated to be more effective than a hydroethanolic solution at delivering and enhancing the absorption of black tea extracts to the hair surface[29].

Delivery of Anticancer drugs:

While treating cutaneous melanoma, Lei et al., conducted experiments using dual drug loading and transethosomal formulation. They settled on two drugs, dacarbazine and tretinoin, because they worked better together than the other formulations and had less cytotoxicity. Dual loaded transethosomes showed improved antitumor efficacy as compared to a single loaded drug. Skin penetration can be increased, they found. Shaji et al. discovered that encapsulating 5-Fluorouracil into a transethosomal gel led to improved deformability, higher skin penetration, and deeper skin targeting as compared to ethosomes[28].

FUTURE PROSPECT:

Transethosomal vesicular carriers are among the innovative medication delivery technologies now being studied by researchers. The creation, production, importation, exportation, and distribution of drugs should be regulated to adhere to set standards, which makes the future look promising. Transethosomal formulation should be checked by the manufacturer to make sure it satisfies the required standards. Excipients employed by researchers are "Generally regarded as Safe" and clinically non-toxic (GRAS)[29]. It offers a superior carrier system to guarantee the stability of various proteins and medications. Both hydrophilic and hydrophobic medicines can be loaded with it. Transethosomes can be used to deliver many drug types, including antivirals, anti-diabetics, and anticoagulants. Transethosomal administration of an anticancer medication combination is possible with minimal cytotoxicity To boost a drug's efficacy, combinations of different medications can be given as transethosomes. There isn't a lot of clinical trials literature available because it's not commercially available. As a result, transethosomes have a lot of potential for usage as a delivery system for topical or transdermal drugs[30].

CONCLUSION:

Barriers prevent some bioactive chemicals from penetrating the skin. Greater skin penetration is made possible by the development of ethanol-based ultradeformable vesicular (UDV) systems. Ethosomes, transferosomes, and transethosomes are components of the new vesicular system. Due to its improved compatibility with both hydrophilic and hydrophobic therapeutic molecules, this transethosomal vesicular system can offer enhanced solubility, penetration, and flexibility. Alcohol and edge activators make up the transethosomal system, which aids in improved topical medication administration to the intended spot. Transethosomal system has the ability to deliver medications with enormous molecular weight, such as peptides and protein molecules, due to high carrier capacity. High patient compliance is achieved when

transethosomal gel or cream is used topically. Moreover, ethosomal systems are employed to deliver cosmeceuticals, anticancer, antiviral, antifungal, and anticancer medications. The transethosome vesicular system is more effective than other traditional transdermal permeation approaches because it delivers safety, efficacy, and patient compliance.

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