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An overview of Transethosomes: Novel nanocarrier for transdermal drug delivery system

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Abstract

The Human skin is made of different layers and the skin will act as a barrier `and it allows the delivery of the drugs through it which is known as TDDS. The delivery of the drug through the epidermis layer of the stratum corneum is difficult as it never allows large particle-sized molecules through it. So there is a need to decrease the particle size and it can be done with new advancements in transdermal delivery by preparing Deformable vesicles which act as a nanocarrier to deliver the drug by changing their shape while transferring from the epidermis to hypodermis. The most advanced Nanocarriers are Ethosomes, Transferosomes, and transethosomes. In this article we will discuss about the transethosomes and their advancement in the TDDS, The transethosomes are prepared by the use of Phospholipids, Ethanol, Edge activators, and penetration enhancers used to make the deformable vesicles. They are prepared by Cold method, hot method, and thin film hydration methods. Their characterization studies include particle size, Shape, PDI, and entrapment efficiency, drug content, *and in vitro* evaluation studies. The applications of transethosomes are studied.

Keywords: TDDS; Transethosomes; Hydrogenated Soybean Phosphatidylcholine (HSPC); Ethanol; Classic method; Edge activator

1. Introduction

The oral route is the most desirable and easy to administer for drug delivery. Due to first-pass metabolism, the formulations show significant drawbacks like unpleasant taste, gastrointestinal discomfort, and decreased bioavailability. An intravenous injection is an alternative strategy regarded as a high-dose drug management approach for avoiding hepatic 'first pass' metabolism and maintaining a highly efficacious, plasma drug level in blood. However, this necessitates hospitalization of patients and careful monitoring under medical supervision. Transdermal drug delivery technologies minimize dose-dependent side effects, prevent gastrointestinal discomfort and poor bioavailability, avoid organ toxicity and early metabolism, and reduce fluctuations in plasma drug levels for repeated treatment. It shows advantages like reduced dosages, better patient compliance, and controlled drug delivery [1]. The stratum corneum (SC), the topmost layer of the epidermis, has tight junctions that are still a major obstacle to drugs entering the body freely, which lowers the bioavailability of transdermal medications. The use of liposomes in the topical delivery of therapeutic agents has sparked a new wave of drug delivery research. Their erratic behaviour in combining with the lipids in the skin, drying out, and staying close to the skin's surface meant that the permeability of the skin was inadequate. Transethosomes also improve bioavailability and drug penetration through ocular barriers for targeted delivery to particular ocular tissues. They offer sustained drug release, which lowers the need for frequent administration and lowers the possibility of side effects in Ocular tissue. They provide a quick and painless way for patients to self-administer, making them patient-friendly, to target delivery to particular areas of the pulmonary system, TEs can also be created [1, 2]. Their purpose is to improve therapeutic efficacy by increasing drug penetration through

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lung tissues. Direct drug delivery to the lungs is made possible by inhalation, as the organs' abundant blood supply and wide surface area promote quick bloodstream absorption.

Transethosomes" is a term that has emerged or gained significance in the fields of pharmaceuticals, chemistry, or related sciences after my last update, I recommend checking the latest scientific literature, research papers, and reputable online sources for the most recent and accurate information. You may also consider consulting with experts in the respective fields or reaching out to academic and research institutions for the latest developments. Transethosomes content of the high level of ethanol (up to 30%). It contains the advantages of both Transferosomes and Ethosomes. Transethosomes show the presence of phospholipids like phosphatidylcholine, high amounts of ethanol, permeation enhancement, or edge activator. Vesicles have an irregular spherical shape. Depending upon the drug their size lies between 40 nm to 200 nm. The drug absorption through transethosomes probably occurs in the Ethanol effect and Transethosomes effect. With the help of new technologies, the most advanced drug delivery systems have been developing day by day and they help to overcome the problems associated with conventional and current drug delivery and to overcome the side effects. Initially, people used to take the drugs through the oral drug delivery systems, and then a little advancement they started taking them through transdermal delivery to avoid the first-pass metabolism and gastric irritation. If you have any additional context or details about transethosomes, feel free to provide them, and I'll do my best to assist based on the information available up to my last update [1, 3].

Table 1 Differences between Ethosomes, Transferosomes, and Transethosomes [2]

Ethosomes	**Transferosomes**	**Transethosomes**
Third-generation elastic lipid vesicle	Second-generation elastic lipid vesicle	Use as 3rd generation vesicle
20 – 45 % ethanol within Multiple bilayers	Double bilayer	Multiple bilayer
Made up of Ethanol and phospholipid	Made up of Edge activator and phospholipids	Made up of Phospholipid, ethanol, edge activator, and water
Appear as Elastic liposome	Ultra-flexible liposome	Ultra-flexible elastic liposome
Flexibility is High elasticity and deformable	High deformability	Ultra-deformable because of the ethanol and surfactant
Permeation due to Lipid perturbation	Permeation due to Deformation of vesicle	Permeation due to Deformation and lipid perturbation
Easy Skin penetration because of ethanol	Easy penetration due to flexibility	Easy penetration through Para cellular space because of flexibility and ethanol effect.
Topical and transdermal route of administration	Topical and transdermal route of administration	Topical and transdermal route of administration

Transethosomes are a type of novel drug delivery system designed to enhance the transdermal delivery of drugs. They are lipid-based vesicles that offer several advantages for drug delivery through the skin. Here are some potential advantages of transethosomes [2,3]:

- **Enhanced Permeation:** Transethosomes can improve the permeation of drugs through the skin due to their flexible and deformable nature. This allows them to squeeze through the tight junctions of the stratum corneum, the outermost layer of the skin, facilitating drug absorption [4].
- **Increased Drug Bioavailability:** The enhanced permeation of drugs achieved by transethosomes can lead to increased bioavailability. This means that a higher percentage of the administered drug can reach the systemic circulation, improving the overall effectiveness of the treatment [2].
- **Improved Drug Stability:** Transethosomes can protect drugs from degradation, denaturation, or inactivation. The lipid bilayer of transethosomes can shield the encapsulated drug from environmental factors, contributing to improved stability and shelf life [3].
- **Targeted Delivery:** Transethosomes can be engineered to target specific tissues or cells, allowing for targeted drug delivery. This can minimize systemic exposure and reduce the risk of side effects by directing the drug to the desired site of action [5].

- **Versatility:** Transethosomes can encapsulate a wide range of drugs, including hydrophobic and hydrophilic compounds. This versatility makes them suitable for delivering various types of therapeutic agents [2].
- **Patient Compliance:** The transdermal route of drug delivery is often preferred by patients because it is non-invasive and avoids issues associated with oral administration, such as gastrointestinal irritation or first-pass metabolism. This can lead to improved patient compliance with the treatment regimen [3].
- **Reduced Side Effects:** Targeted delivery and controlled release provided by transethosomes can help minimize systemic exposure to drugs, reducing the likelihood of adverse effects and enhancing the safety profile of the treatment [3].

It's important to note that while transethosomes offer these potential advantages, their effectiveness can depend on factors such as the specific formulation, the characteristics of the drug being delivered, and the intended therapeutic application. Additionally, further research and clinical studies are needed to fully understand the potential of transethosomes in various medical contexts [5, 29].

2. Mechanism of action of transethosomes for transdermal drug delivery

Transethosomes are a type of vesicular carrier system designed for transdermal drug delivery. They belong to the broader category of lipid-based nanocarriers, specifically developed to improve the penetration of drugs through the skin. The mechanism of action of transethosomes involves Transethosomes typically consist of phospholipids, edge activators, and sometimes surface-active agents. Phospholipids form the basic structure of the vesicles and help in mimicking the lipid composition of the stratum corneum, the outermost layer of the skin. Edge activators, such as surfactants or non-ionic agents, are included to destabilize the vesicle structure. They reduce the interfacial tension between the vesicle and the stratum corneum, leading to better interaction and fusion with the skin [2, 3].

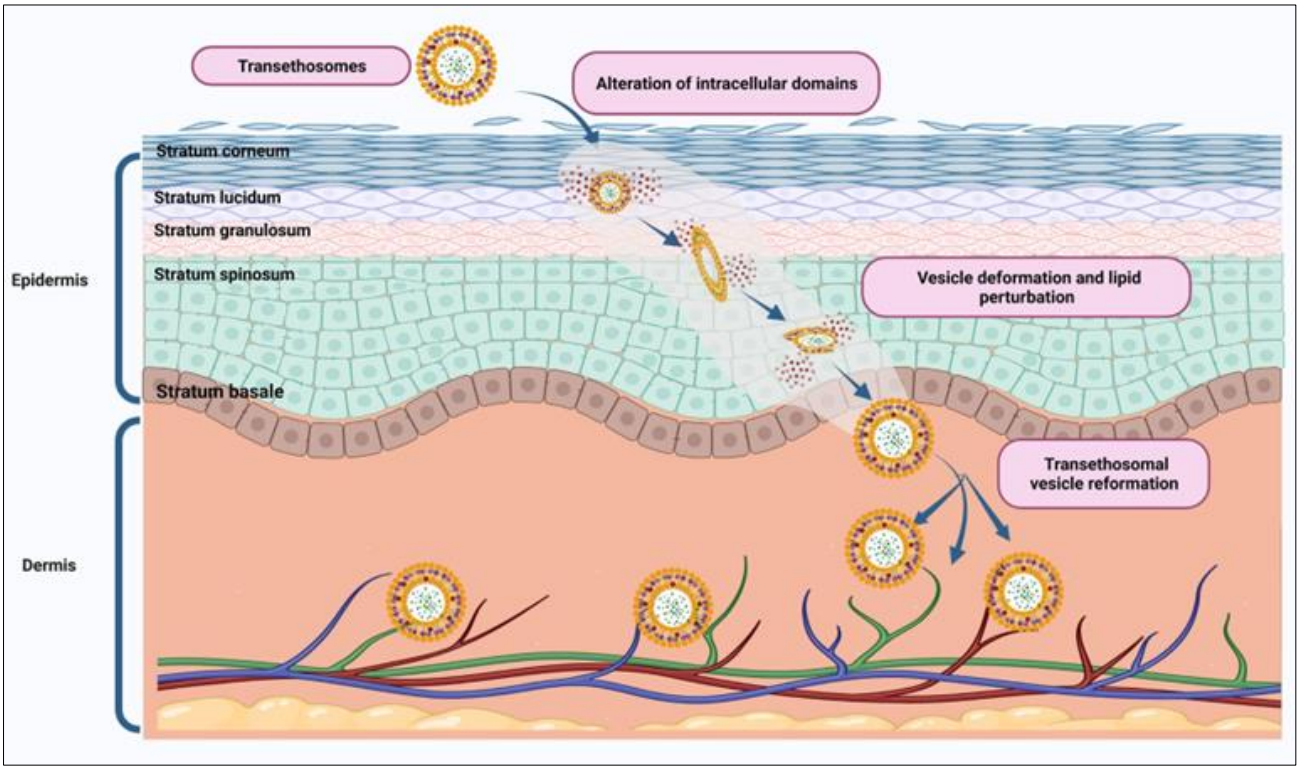

Figure 1 Mechanism of Permeation of Transethosomes is Through The Transdermal Route [7]

Transethosomes are designed to be highly flexible and deformable, allowing them to squeeze through the tight intercellular spaces of the stratum corneum. This flexibility enhances their ability to penetrate the skin barrier. The combination of lipid composition, edge activators, and flexibility enables transethosomes to penetrate the skin more effectively than traditional liposomes or other vesicular systems. This improved penetration allows for better delivery of drugs through the skin. The drug of interest is encapsulated within the vesicles. This encapsulation protects the drug from degradation and facilitates controlled release over time [7]. The lipid components of transethosomes interact with the skin lipids, facilitating the passage of the vesicles through the lipid-rich stratum corneum. This interaction helps in

overcoming the barrier properties of the skin. By enhancing drug penetration and reducing the barriers presented by the skin, transethosomes contribute to improved bioavailability of the encapsulated drug. Depending on the specific formulation, transethosomes can be engineered to provide targeted delivery of drugs to specific layers of the skin or even to systemic circulation [7, 8].

3. Materials /components of transethosomes

Transethosomes are a type of advanced lipid-based drug delivery system designed to enhance the permeation of therapeutic agents through the skin. Excipients play a crucial role in the formulation of transethosomes, contributing to the stability, bioavailability, and overall performance of the delivery system. The selection of excipients depends on the specific characteristics of the drug, the intended application, and the desired properties of the transethosomal formulation. Here are some common excipients used in the formulation of transethosomes [2, 8]:

Table 2 Materials /Components of Transethosomes

Sr No	Excipients	Role	Example
1	Phospholipid	Forming the lipid bilayer structure that encapsulates the drug	Phosphatidylcholine, phosphatidylethanolamine, and phosphatidylserine.
2	Edge activators	Disrupt the lipid bilayer structure, improving the deformability and flexibility of the vesicles. enhance the penetration of transethosomes through the skin	Tween 80, Span 80, and sodium cholate
3	Surfactants	Stabilize the formulation and improve its dispensability	Non-ionic surfactants like polylobate 80 and polyoxyethylene (20) sorbitan monolete.
4	Cholesterol	To enhance membrane stability and reduce permeability. It helps maintain the structural integrity of the vesicles	Cholesterol
5	Hydration medium	Used during the preparation of transethosomes, may contain water or a combination of water and organic solvents	alcohol (ethanol)
6	Co-surfactants	Used to optimize the formulation by improving the vesicle size, stability, and drug entrapment efficiency	Transcutol
7	Preservatives	To prevent microbial growth and increase the shelf life of the transethosomal formulation	Methyl paraben , Propyl paraben
8	Gelling Agent	to provide a more controlled release of the drug and improve skin adhesion	Carbopol D934

It's important to note that the specific excipients and their concentrations may vary based on the nature of the drug, the targeted application, and the desired characteristics of the transethosomal formulation. Formulation development is a complex process that requires consideration of various factors to achieve the desired therapeutic outcome [37, 40].

4. Method of preparation of transethosomes

4.1. Cold Method

It is the most commonly used method for transethosomes preparation. The organic phase is prepared by dissolving the phospholipids in ethanol at a temperature of 30^0C and adding the edge activator to it with constant stirring. The aqueous phase of water is heated at 30^0C for 5 min. Then slowly add the aqueous phase to the organic phase with continuous

stirring for 10-15min. Sonicate the mixture to reduce the size of transethosomes. Store the prepared transethosomes in the refrigerator [8, 9].

4.2. Hot method

The hot method involves the preparation of the colloidal solution by adding phospholipids in water at 40^0C. By using penetration enhancers (glycol) and alcohol (ethanol) organic phase is prepared at 40^0C. The aqueous phase is added to the organic phase followed by continuous stirring for 7-10 minutes [35]. The drug is dissolved in one of the phases, based on its nature either hydrophilic or hydrophobic, if it is hydrophilic it dissolves in an aqueous phase, and if it's hydrophobic it dissolves in an organic phase. The mixture undergoes size reduction either by sonication or extrusion [10].

4.3. Ethanol Injection Method

This method is suitable for the hydrophobic drugs. The organic phase is prepared by dissolving the drug, edge activator, and phospholipids in the ethanol with continuous stirring at 35^0C temperature. The organic phase is taken into an injection and injected it into the water medium at a rate of 1ml/min with continuous stirring. The formed bilayered lipid vesicles get precipitated in the aqueous phase [11].

4.4. Mechanical Dispersion Method

In the mechanical dispersion method, a Round Bottom Flask (RBF) is taken and the Phospholipids along with the penetration enhancers are dissolved in the organic solvents. The organic solvents of chloroform and ethanol are used in the ratio of 2:1. By using the rotary evaporator at a pressure of 35 ± 1^0 C, the organic solvents are evaporated by forming a thin lipid layer above the lipid transition temperature. Then hydrate the lipid layer by adding 10% v/v ethanol to it at 60 rpm in the presence of Phosphate buffer pH 6.5 and add the drug to it. Next, sonicate the mixture to form a reduced size of the transethosomes, filter it, and store it in the refrigerator [12].

4.5. Thin-film hydration technique (TFH)

The thin film hydration technique is used to prepare multila0mellar vesicles and this method is also called the Rotatory Evaporation Sonication method. In this method, Phospholipids, drugs, and edge activators are dissolved in the organic solvents of chloroform and ethanol in a 2:1 ratio. A thin film was formed upon the evaporation of solvents at a phase transition temperature under reduced pressure. The thin film was hydrated using a saline phosphate buffer of pH 6.5 by rotation of 60 rpm for 1 hour and kept overnight for complete hydration of the vesicles [6, 11].

Table 3 Different Method of Preparation for Transethosomes [19, 33, 41]

S.No	Method of preparation	Drug	Characterization(Size/EE%/zeta potential/morphology)	Application
1	Cold Method	Tramadol, Hydrochloride, Cholecalciferol (vitamin D3), Colchicine, Irbesartan	149.34 to 278 nm , 79.37% and −22 mV	TE is a suitable carrier for poorly soluble drugs. TE is proven to be an alternative route to the oral route to overcome bioavailability problems and other side effects
2	TFH technique	Voriconazole, Ketoconazole, Luliconazole, Flurbiprofen, Apremilast, Brucine-strychnine, Rolapitant, Niacinamide Coenzyme Q10	152.06 ± 5.10 to 215.2 ± 0.53 nm 76.0 ± 0.53% −30.09 ± 0.46 mV Irregular spherical shape	TFE Use as an effective carrier for the management of antifungal, Anti-inflammatory, arthritis, anti-cancer, Anti-hypertensive etc.
3	Ethanol injection method	Paeonol, Naproxen sodium	133.3 ± 3.42 to 349.5 ± 1.24 nm 23.5 ± 3.84 to 74.6 ± 4.97 mV	The paeonol TE demonstrated narrow size distribution, high EE,

		Luliconazole, Progesterone	Spherical Nano vesicle	prolonged residence in the plasma, and a remarkable increase in bioavailability
4	Homogenization method	Propranolol Hydrochloride	182.7 ± 5.4 nm −21.91 ± 0.65 mV Spherical shape	TE can Avoid the disadvantages associated with oral propranolol, like the first-pass effect, high dosing frequency, and organ toxicity

5. Characterization of transethosomes [2, 3, 14]

5.1. Morphology (Particle Shape)

The vesicles are flexible in nature with regular or irregular shapes with a diameter of 300-400nm. The vesicle morphology can be studied by using a Scanning electron microscope (SEM) and a Transmission Electron microscope (TEM) [2, 30].

5.2. Particle Size and Zeta Potential

The smaller the particle size the greater the efficiency of the transethosomes. The particle size can be determined by using Differential Scanning Calorimetry (DSC) and Photon Correlation Spectroscopy (PCS). The surface charge of the vesicle can be determined by the Zeta sizer. The surface charge provides the information related to formulation components, their interactions, and surface chemistry. The transethosomes are diluted by using Milli–Q water and measuring the zeta potential [11, 34].

5.3. pH

The pH of the transethosomes is measured by using a digital pH meter. It is important to measure the pH because the pH if it's too low or too high will cause skin irritation and affect the skin penetration [12].

5.4. Entrapment Efficiency

Entrapment efficiency is used to estimate the efficacy of a nanocarrier to retain the drug/active ingredient to ensure the delivery of an adequate amount of active component to the target site. Ultracentrifugation is the technique used to determine the entrapment efficiency of transethosomes. The transethosomes were separated by ultracentrifugation at 15000 rpm at 4^0c for 60 min. After centrifugation, the sediment and supernatant liquids were separated and The amount of the drug entrapped was determined by rupturing the vesicles in the sediment by dissolving them in methanol and measuring the drug concentration through UV spectrophotometry. The Percentage of Entrapment efficiency (%EE) can be determined by using the following formula [14, 15]:

$$\% \text{ EE } = \frac{\text{Total drug added} - \text{Free unentraped drug}}{\text{Total drug added}} \times 100\%$$

5.5. Phase Transition Temperature

Phase Transition temperature is used to measure the amount of drug release from the vesicle. It can be identified by using Differential Scanning Calorimetry (DSC). Each sample is analyzed under constant nitrogen steam at different temperatures. The thermal curves of samples are compared [16, 28].

5.6. Vesicular Stability Study

The vesicular stability of transethosomes was measured by exposing them to various temperature conditions. The stability can be achieved by keeping the samples at different temperatures that 25 ± 2^0C, 35 ± 2^0C and 45 ± 2^0C at different time periods. The vesicular stability of the transethosomes was determined by observing the vesicle shape and size by TEM and DLS [12, 17].

5.7. Drug Content

The drug content of transethosomes can determined by analytical methods of UV spectrophotometry and High-Performance liquid chromatography. The percentage of drug content can be determined by the formula [18].

%Drug content =Sample absorbance/Standard absorbance

5.8. Elasticity Measurement

Elasticity measurement is one of the important factors for penetration into the skin. The extrusion method is used to find out the elastic properties of vesicles. The vesicles were extruded through the cellulose membrane filter pores by applying suitable pressure. Extruded vesicle dispersion is calculated by the following formula [19]

$$E = J * (rv/rp)2$$

Whereas E = Elasticity index of the vesicle membrane
J = Rate of penetration through a membrane filter
rv = Vesicle size after extrusion
rp = Pore size of membrane

5.9. *In-Vitro* Drug Release Studies

The *In-Vitro* drug release studies were performed by dialysis bag method in which the transethosomes were loaded and kept in the buffer solution. At regular intervals of time, the samples were withdrawn into aliquots and centrifuged and concentrations were measured in a UV spectrophotometer or HPLC [6].

5.10. *In-Vitro* Skin Permeation Studies

In-vitro skin permeation studies were performed to determine the transport efficiency of the transethosomes. It is found to be an alternative to in-vivo skin permeation studies. In this Franz-diffusion cell was used and the egg membrane acted as a transporter. The Franz-diffusion cell has two compartments and they were filled with phosphate buffer solution. The donor compartment was applied with the transethosomes formulation. A magnetic bar was placed in the buffer solution to stir at 100 rpm in the receptor compartment. To maintain the sink conditions the aliquots of receptor medium samples were withdrawn at regular intervals and replenished with the same amount of saline phosphate buffer solution of pH 6.4. The collected samples are analyzed by the UV spectrophotometer [11].

6. Future outcomes and challenges

To enhance the penetration of drugs through biological barriers, the Transethosomes drug delivery system has transformed drug delivery. However, there are important obstacles that must be overcome as Transethosomes move from laboratory-scale production to large-scale manufacturing. The main difficulty lies in the raw material selection process, which is essential to the production of Transethosomes [18, 19]. It is essential to choose premium phospholipids, edge activators, and ethanol to guarantee the product's effectiveness, stability, and repeatability. Quality control procedures that guarantee the steady supply and calibre of raw materials can be used to overcome this difficulty. Furthermore, the large-scale production of Transethosomes can be complicated and expensive, which makes it challenging to transfer formulations developed in laboratories to commercial manufacturing. It is imperative to guarantee both cost-effectiveness and reproducibility to promote their broad usage in pharmaceutical applications. It is crucial to create reliable manufacturing procedures that preserve Transethosomes' integrity and quality on a bigger scale. Transethosomes vesicles must be homogenized, mixed, and heated with efficiency if they are to be repeatable and consistent. Process analytical techniques (PAT) and automation in Transethosomes manufacturing process optimization can increase reproducibility, lower production costs, and enable scalability. Transethosomes are also prone to instability and degradation when stored [20]. Temperature, light exposure, pH, and other variables can alter their physicochemical characteristics, which can alter the effectiveness of drug encapsulation and the integrity of the vesicle. To assess the shelf-life of TE formulations and optimize storage conditions, long-term stability studies are required. To increase stability and prolong shelf-life, tactics like adding antioxidants, using lyophilization techniques, and using protective packaging can be used. Furthermore, following quality control procedures and legal requirements is necessary when producing Transethosomes for commercial use. The development of suitable quality control techniques and the application of good manufacturing practices (GMP) are imperative in guaranteeing batch-to-batch uniformity, product safety, and effectiveness. These techniques can be used to optimize Transethosomes manufacturing, which will increase productivity, enhance product quality, and ensure regulatory compliance [21, 22].

7. Therapeutic application [23, 25]

7.1. Delivery of NSAIDS

Ketorolac transethosomal formulations show greater penetration when compared to conventional preparations. The transethosomal gel of Piroxicam shows greater stability and elasticity when compared with other vesicular systems. Mefinamic acid shows better effects when prepared through a thin film hydration technique [3, 22].

7.2. Delivery of Anti-fungal drugs

Transethosomes, a novel vesicular carrier was used for the transdermal delivery of Voriconazole. Transethosomal formulation showed higher elasticity, permeability, and skin deposition due to the synergistic effect of ethanol in conjunction with ethanol, edge activator, or permeation enhancer and it was found to be more effective when compared with deformable liposomes and conventional liposomes [17, 24].

7.3. Delivery of Anti-Hypertensive drugs

Propranolol hydrochloride has 23% of bioavailability when administered through the oral route due to hepatic first-pass metabolism and degradation of drugs by GI enzymes. The transdermal route of drug delivery is considered one of the effective delivery paths for transferring the drugs, as it avoids the GI side effects [25]. Transethosomes loaded propranolol hydrochloride by homogenization method and converted into the gel using carbopol® 934 polymers and *In-Vitro* drug release study showed sustained release of drug with maximum stability for up to 5 months at a temperature of 25 ± 1.5 °C, 4 ± 1.5 °C with 75% relative Humidity in the dark environment [27].

7.4. Treatment of Gout

To overcome the side effects, and poor bioavailability of colchicine through the oral route, transethosomes are used as a potential carrier for transdermal delivery of colchicine. The optimized transethosomal-loaded colchicine gel was characterized by the amount of colchicine permeated (after 24 h) through the skin of rats from the transethosomal gel was significantly higher than the NE gel [28].

8. Conclusion

The epidermal barrier of the skin is the major limiting factor for the transdermal drug delivery system, and to overcome these barrier problems ethosomes and transethosomes were showing significant effects. With the help of the transethosomes, we can deliver the drug molecules that are unable to cross the barrier of the skin. The transethosomes are made up of ethanol and edge activators in their preparation. The ethanol will increase the fluidity of the lipid bilayer and reduce the particle size and the edge activators help in the deformation and penetration into the skin layers. The transethosomes can deliver the drugs easily into the skin layers because of the lipid deformability and reduce the particle size. When compared to the ethosomes, the transethosomes are more efficient in terms of drug delivery through the skin as they can entrap the drug molecules of larger sizes such as peptides and proteins. More research work needs to be done to utilize the full efficacy of the transethosomes.

Compliance with ethical standards

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Disclosure of conflict of interest

No conflict of interest to be disclosed.

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