IJNRD.ORG ISSN : 2456-4184
INTERNATIONAL JOURNAL OF NOVEL RESEARCH AND DEVELOPMENT (IJNRD) | IJNRD.ORG
An International Open Access, Peer-reviewed, Refereed Journal

REVIEW ON TRANSETHOSOMES: NOVEL DRUG DELIVERY SYSTEM

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Abstract

Topical treatment is a safe and efficient therapy choice for skin-related conditions, such as psoriasis, atopic dermatitis, and acne. Topical medication has a number of adverse effects and allergic reactions, which make it difficult for patients to adhere to topical medications. Transethosomes are a new type of surface transethosome that can be applied in the treatment of skin conditions. In this paper, we discuss the development of a transethosomal gel system based on Piroxicam. We also present a review of the current state of the art of drug delivery system

Keywords: Transethosomes, Topical Medications ,Novel Drug Delivery System

Introduction

Research on medication adherence has up until now concentrated on oral medications. The use of topical medications has now been the subject of research. Regarding chronic skin conditions that necessitate long-term usage of topical treatments, such psoriasis, atopic dermatitis, and acne, the issue of patient adherence to topical medications is especially important. (1)

The specifics of topical formulations, drug delivery system fundamentals, and principles are covered in this examination. Topical gel is a safe and efficient therapy choice for skin-related conditions, according to clinical evidence. Applying topical treatments to the skin might have systemic, local, or superficial effects. Because of its emollient, calming, or protecting qualities, the base may occasionally be used on its own. Nonetheless, therapeutically active components found in the majority of topical treatments are dissolved or distributed throughout the base. This is an opportunity for the wide range of topical preparations that are suitable for various forms of therapy and drug administration. Classifying the bases of topical treatments that contain therapeutically active substances using certain keywords may be determined by their content (hydrophilic creams), intended usage (liniments), or physical characteristics (suspension).(2)

The skin is one of the important and legitimate target sites for drug delivery. However, it has its own drawbacks that limit its practical use in this area. Since it is the largest organ in the body, it occupies 16% of the total body weight and has a surface area of 1.8 square meters. Also, the skin contains various derivatives like apocrine glands, sweat glands, hair, nails, and oil glands (as shown in figure). It functions in protecting the body from undesired substances and microbes as it regulates fluids within the body. (3)

Skin layers: Skin contains three structural layers

- Epidermis
- dermis
- Hypodermis

Epidermis:

The epidermis consists of keratinized stratified squamous epithelium. It is a crucial element in drug delivery. The shape and properties of the keratinocytes, which are more than 90% of its cells, change as they move towards the skin surface. The stratum corneum is about 100-150 mm thick and does not contain blood vessels. It forms the outermost layer of the epidermis. The layer underneath contains the dermis with an intricate network of blood vessels that transport blood all around. If a drug penetrates the stratum corneum, it might be transferred to the bloodstream. This phenomenon of passive diffusion is the only one that allows for the transportation of drugs in the right direction across this layer. Secondly, the epidermis harbors melanocytes, Langerhans cells, and Merkel cells

Basement membrane

A physical boundary is therefore created between the dermis and epidermis layers due to the multilayered structure that makes up the dermo-epidermal junction known as the basement membrane. This limits large drug molecules and cells' ability to pass through this barrier.

Dermis

The dermis comprises the largest portion of the thickness of the skin, almost 90%, and is largely composed of connective tissue to hold the epidermis. It can be classified into two anatomical layers: the papillary dermis at the periphery and the reticular dermis. In the papillary layer, the collagen and elastin fibers are arranged more vertically and attached at the dermal-epidermal junction. On the other hand, in the reticular dermis, they lie more horizontally. Since the skin is a critical determinant in the delivery of drugs, such as permeation and absorption, its structure should be understood.

Hypodermis

The hypodermis, or subcutaneous layer, or superficial fascia, is the layer of tissue directly below the dermis and connects the skin to the underlying fascia surrounding the muscles. Not technically part of the skin, the boundary between the hypodermis and dermis can be hard to define. The hypodermis is composed of dense connective tissue and adipose tissue. It holds the skin to the underlying structures, provides cushioning and insulation, and is closely associated with nerve and vascular systems. The thickness varies depending on the surface of the body. (4)

Transethosomes

Transethosomes are lipid-based vesicular drug carriers which contain phospholipid, ethanol, edge activator, and water. The primary role of phospholipids is acting as a carrier by transferring medication particles directly into the skin. The lipid vesicular system contains hydrophilic head and a hydrophobic tail. The edge activator which is used to make the transethosomes soft the bilayer. It also has the ability to make the vesicle permeable. Adaptability and flexibility are the most important properties of ethanol for the formation of nano-vesicular systems, which can easily let them perforate inside the stratum corneum through very small openings due to the process of fluidization. On reaction, the edge activator mixed with ethanol results in a transposition of the lipid bilayer and may give a more deformation structure easily penetrating into the deeper layer of the skin.(5)

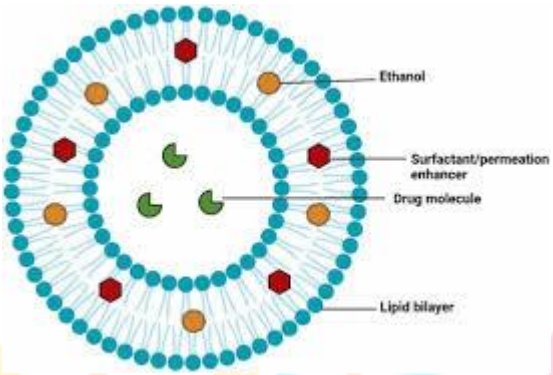
Transethosomes" is the term that has surfaced or acquired significance in pharmaceutical sciences, chemistry, or similar branches of study after my last update, I suggest searching in the most recent scientific journals, research papers, and reputable online resources for updated information. You can even try to get the support from experts of respective field and contact with the academic and research institutions for getting updated news. (6)

Transethosomes Content: high amount of ethanol content, about 30%. It consists of merits of Transferosomes as well as Ethosomes. Transethosomes indicate presence of phospholipids, including phosphatidylcholine, presence of a significant quantity of ethanol, and an edge activator causing enhancement of permeation. Shape of the vesicles: irregular spherical. Transethosomes: The diameter range of these vesicles differs between 40 nm to 200 nm based on the type of drug used. Absorption: Absorption of drugs from transethosomes probably occurs through both ethanol effect and Transethosomes effect. Advanced drug delivery system With the emergence of modern technology, advanced drug delivery systems have been evolving day by day and overcome problems of conventional and present day drug delivery, thus also providing overcomes of side effects. At initial time, drugs were used orally by humans and subsequently slight advancement resulted in human to take those drugs from a transdermal route by avoiding the first pass metabolism and irritation in stomach. (7)

Lipid-based vesicles called transethosomes are made up of water, phospholipids, ethanol, and edge activator (surfactant). When it comes to transporting medication molecules into the skin, these vesicles are essential. As transporters, the phospholipids make it easier to connect with the stratum corneum, the skin's outermost layer.(8) They combine with the lipid layer of the skin and improve tissue hydration. The head of a transethosome is hydrophilic (polar), while the tail is hydrophobic (non-polar). The bilayer structure is weakened by the edge activator, a biocompatible surfactant. Usually, it is used to increase permeability and flexibility One of the main

elements that distinguishes the transethosomal system as a vesicular system is ethanol. (9)Because ethanol distorts the epidermis, these nanosystems become more pliable and flexible, which enables them to pass through microscopic holes in the stratum corneum because of fluidization When coupled with phospholipids, water is necessary for the formation of the bilayer and adds to the system's flexibility. Combining ethanol with edge activator causes the lipid bilayer to reorganize, increasing its deformability and allowing for deeper dermal penetration.(10)

Fig.1. Structure of Transethosomes.



Advantages of Transethosomes

When compared to other liposomes, transethosomes are more effective at delivering active ingredients to the skin.
1. Transethosomes use ethanol as a primary component because of the synergistic effect it has when combined with 20–50% ethanol.
2. Better patient compliance due to a non-invasive technique.
3. Capable of delivering medications with higher molecular weights,This phenomenon facilitates the delivery of peptides and proteins through the skin more suitable.
4. It works well as a medication carrier to deliver various dose forms.(11)

Mechanism of Action

One type of vesicular carrier system used for transdermal medication administration is called a transethosome. They fall under the broader heading of lipid-based nanocarriers, which were created especially to enhance drug penetration through the skin. Transethosomes' method of action consists of Phospholipids, edge activators, and occasionally surface-active substances are found in transethosomes. The phospholipids provide the vesicles their fundamental structure and help to replicate the lipid makeup of the stratum corneum, the skin's outermost layer. The vesicle structure is destabilized by the addition of edge activators, such as non-ionic agents or surfactants. They improve interaction and fusion with the skin by lowering the interfacial tension between the stratum corneum and the vesicle.

Transethosomes are expected to be very flexible, deformable, and allow them to pass through even the most restricted intercellular spaces of the stratum corneum. Enhanced flexibility will facilitate transethosomes to penetrate better to the skin barrier. Based on the composition of lipid, edge activators, and flexibility, the capacity of transethosomes to penetrate can be higher than liposomes or other vesicular systems. Therefore, enhanced permeation would mean enhanced drug delivery. The vesicles encapsulate the drug of interest, protecting the same from degradation and delivering the drug through controlled release in the time cycle [7]. The transethosomes, lipid components will interact with skin lipids in order to penetrate the rich lipid layer called stratum corneum of the skin This interaction helps in overcoming the barrier properties of the skin. Since transethosomes enhance drug penetration and reduce the barriers offered by the skin, these vesicles contribute to increased bioavailability of the encapsulated drug. Depending on the particular formulation, transethosomes may be designed to deliver drugs directly to particular layers of the skin or even to systemic circulation .(12)

Method of Preparation

- Cold method
- Hot method
- Reverse phase evaporation method
- Mechanical dispersion method

- Ethanol injection method

- Cold method

This method is generally used in the formation of transethosomes. Its ability lies in such a way that it can be used for thermolabile drugs that are highly sensitive to heat. The method is easily scalable. Solvent system, in which phospholipid is dissolved, is ethanol. These are shaken vigorously. These are heated up to 30°c in the water bath. Water separately is heated up to 30°c and mixed with alcoholic mixture slowly in the vessel. During addition of aqueous solution to ethanolic solution magnetic stirrer is used for uniform mixing (700rpm). Probe sonicator can used in order to modulate the size of vesicles.(13)

- **Hot method**

Using the hot technique, phospholipids are added to water at 400°C to create a colloidal solution. The organic phase is created at 400°C using alcohol (ethanol) and penetration enhancers (glycol). After adding the aqueous phase, the organic phase is continuously stirred for seven to ten minutes [35]. Depending on whether the medicine is hydrophilic or hydrophobic, it dissolves in one of the phases. If hydrophilic, it dissolves in an aqueous phase; if hydrophobic, it dissolves in an organic phase. This combination is then subjected to size reduction via extrusion or sonication.(14)

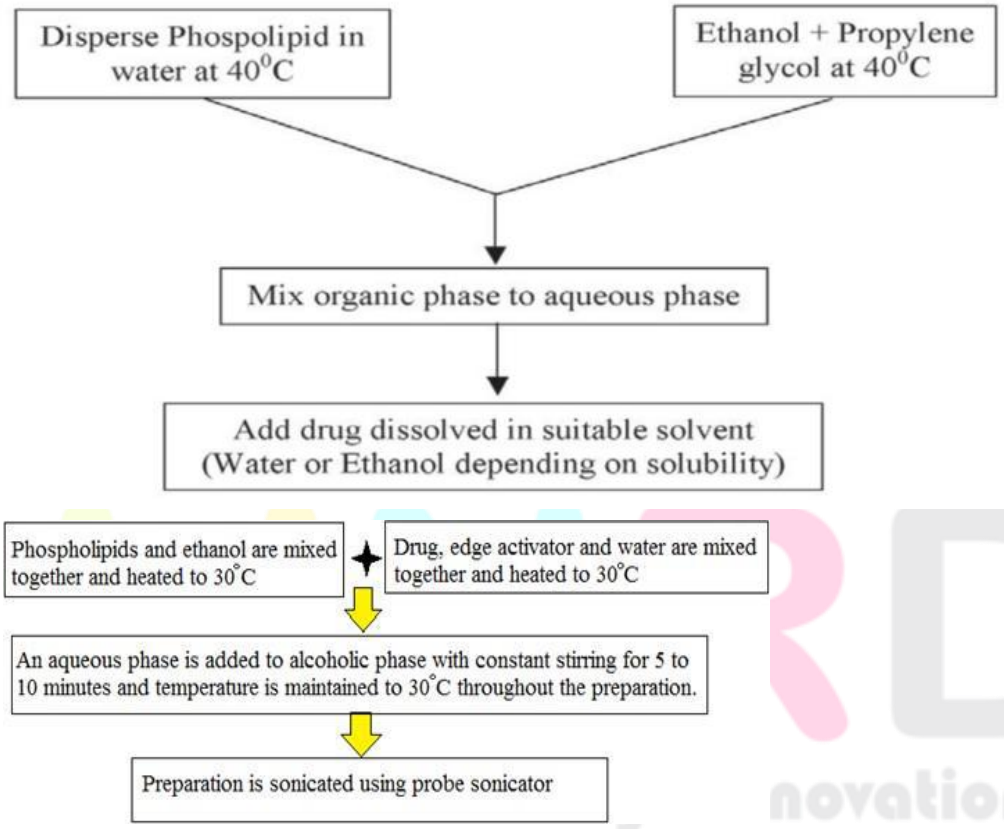


Figure : Hot method.

Figure 6: Cold method

- **Reverse phase evaporation method**

This approach may also be the best choice for creating nanotransethosomes. With this specific technique, the medication and edge activator can be dissolved in an aqueous solvent, while the phospholipids can be dissolved in an organic solvent. Following the addition

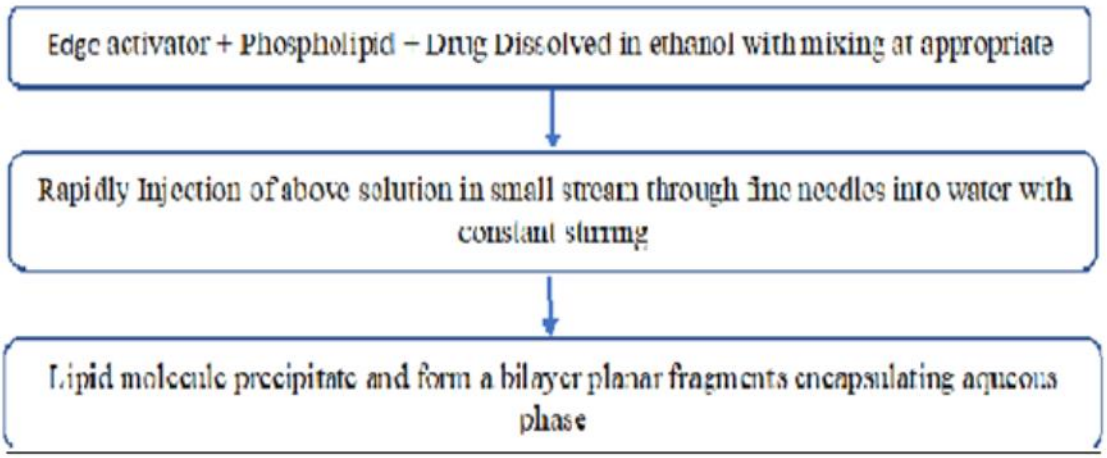
of an aqueous phase to the organic phase, the mixture is kept at 0°C in an ultrasonic bath until the two-phase separation occurs. After the organic phase is eliminated, gel formation takes place under low pressure. The lipid layer integrates into the aqueous layer after further agitation, and the sample is now filtered.(15)

- **Mechanical dispersion method**

The mechanical dispersion approach involves dissolving the phospholipids and penetration enhancers in organic solvents in a Round Bottom Flask (RBF). Ethanol and chloroform are organic solvents with a 2:1 ratio. The rotary evaporator is used to evaporate organic solvents by creating a thin lipid layer above the lipid transition temperature at a pressure of 35+10 C. The medication is added to the lipid layer after 10% v/v ethanol is added and it is hydrated at 60 rpm with phosphate buffer pH 6.5 present. Reduce the size of the transethosomes by sonicating the liquid, then filter and refrigerate.(16)

- **Ethanol injection method**

This technique works well with hydrophobic medications. The medication, edge activator, and phospholipids are dissolved in ethanol while being continuously stirred at 350C to create the organic phase. With constant stirring, an injection of the organic phase is made into a water medium at a rate of 1 milliliter per minute. The aqueous phase precipitates the bilayered lipid vesicles that have formed.(17)



Gelling Agent(18)

The gelling agents are polymers used in the preparation of transethosomes, which stabilizes the vesicular structure and increase the viscosity of the gel base. The following are common gelling agents:

1.Carbopol 934: These are synthetic polymers and provide a thickening effect and maintain the gel structure.

2.Hydroxyethylcellulose: A natural polymer, increases viscosity and gel stability.

3.Xanthan Gum: Another natural polymer that increases the viscosity and gives a smooth texture to the gel.

4.Sodium Alginate: This is another natural polysaccharide that forms a gel matrix. It helps in drug encapsulation and release.

Preparation of Transethosomal gel

Carbopol 934 was weighed in a beaker and accurately dispensed in deionized water (80ml).The solution was mixed continuously at 800 rpm for 1 hour before adding 10 ml of propylene glycol. For removing air bubbles, the gel must be diluted to 100 mL and sonicated on a bath sonicator for 10 minutes. Finally, the pH of the gel base should be adjusted to 6.8.For attaining the drug concentration that must be reached.in the gel base, a transethosomal preparation equivalent to 0.1 percent w/w of drug is then introduced into the gel base.(19)

Evaluation of Transethosomes gel

- Transmission Electron Microscopy
- Entrapment efficiency
- Optical Microscopy
- Vesicle charge
- Interaction studies by using FTIR spectroscopy
- Drug content
- Stability study:
- Particle Size and Zeta Potential
- In-Vitro Skin Permeation Studies

Transmission Electron Microscopy

TEM was used to image the transethosomes vesicles. Transethosomal dispersion (selected formulation) was diluted ten times using distilled water, then a drop was placed on a copper grid with a 300-mesh carbon coating and was left for a minute to let some of the vesicles stick to the carbon substrate. The grid was rinsed two times in deionized water for 3–5 seconds, and any extra dispersion was removed with a piece of filter paper. The sample was observed under the microscope using 10–100× magnification and accelerating voltage of 100 kV.(20)

Entrapment efficiency (21)

For one hour, a milliliter of transethosome suspension was spun at 15,000 rpm in order to separate the entrapped and unentrapped drugs. Methanol was used to lyse the silt.Following the removal of the supernatant, a UV spectrophotometer (Labindia 3000+) was used to perform a spectrophotometric analysis at 256 nm. The following formula was used to estimate the percentage of drug entrapment efficiency in the transethosomes that were prepared:

% EE =Total drug added−Free unentraped drug/Total drug added ×100%

Optical Microscopy

The transethosomes mounted on a glass slide are viewed on a microscope having 1200X magnification power to observe after proper dilution. Preparation photomicrograph by a digital SLR camera got from a microscope.(22)

Vesicle charge

Zeta potential is measured for morphological observation following appropriate dilution to estimate vesicle charge. Using a digital SLR camera, the preparation's photomicrograph was also taken from the microscope.(23)

Interaction studies by using FTIR spectroscopy

A Fourier transform infrared spectrophotometer (FTIR) was used to investigate the drug-excipient interaction. A Fourier transform infrared spectrophotometer (FTIR 1615, Perkin Elmer, USA) was used to record the infrared spectra of drug and powdered transethosomes using potassium bromide (KBr) pellets. The range of 3600 to 400 cm-1 was used to scan the spectra.(24)

Drug content(25)

This measures quantitatively the amount of drug encapsulated into the transethosomal vesicles. In this,, vesicles are disrupted and the amount of drugin the vesicles measured to release the content of preparation. Released content is left in solution andevaluated onchromatography or tested byspectrophotometry. With a use of a ZORBAXEclipse Plus C18 analytical column and as a mobile phase - a mixture of methanol and a 50mM Phosphate buffer solution, Syed et al.68 established and validated a high-performance liquid

chromatographic method for estimation of the concentration of benidipine hydrochloride in lipid-based formulation. In the validation result, it stated that the process is sensitive, precise, linear, accurate and specific toward quantifying drug concentration. Percentage content of drug in ethosomal preparation was determined:

% Drug content = Sample absorbance/Standard absorbance

Stability study(26)

For three weeks, drug-loaded transethosomes were observed at two different temperatures: chilled temperature(4.0±0.2°C) and room temperature (25-28±2°C). The formulation of stability study was packed in a borosilicate container to ensure no glass container material should contact the formulation.
Physical changes along with the content for pharmacological test of the formulation.

Particle Size and Zeta Potential(27)

The efficiency of the transethosomes increases with decreasing particle size. Differential Scanning Calorimetry (DSC) and Photon Correlation Spectroscopy (PCS) can be used to measure the particle size. The Zeta sizer can be used to measure the vesicle's surface charge. Information on formulation ingredients, their interactions, and surface chemistry is provided by the surface charge. Milli-Q water is used to dilute the transethosomes, and the zeta potential is measured .

In-Vitro Skin Permeation Studies(28)

A Franz diffusion cell is used to evaluate drug release in vitro.The medication parameters should guide the selection of the dialysis bag membrane. The Commonly employed is a cellophane dialysis membrane with a particular molecular weight that is hydrated with physiological medium, typically phosphate buffer saline with a pH of 7.4. In order to replicate human skin, the donor compartment is filled with formulation, the receptor compartment with a 7.4 pH solution, and both are agitated with magnetic beads at 300–400 rpm and 32 ± 1°C. At regular intervals, a 1 ml aliquot is taken and replaced right away with an equivalent amount of brand-new buffer. Every drug sample is examined using UV spectrophotometry.

Application of transethosomes

Antifungal Drug Delivery: presented an experiment wherein transethosomes loaded with voriconazole were formulated and incorporated into a hydrogel for antifungal and antileishmanial applications. The outcome showed that topical fungal infections may benefit greatly from the use of the developed Voriconazole transethosomal hydrogel.(29)

Antibiotic delivery time:

The best option for boosting the therapeutic effectiveness of antibiotics is topical administration. Traditional oral medication has a number of adverse effects and allergic responses. Traditional external preparations have poor penetration to subcutaneous tissues and deep skin layers. Ethosomes can get around this issue by getting enough antibiotic into the skin's deeper layers. Ethosomes quickly pierce the epidermis, deliver a sizable quantity of medications to the deeper skin layer, and stop infections at their source. Godin and Touitou created a formulation of ethosomes loaded with bacitracin and erythromycin for both intracellular and cutaneous distribution with this goal in mind. The study's findings demonstrated that an antibiotic's ethosomal formulation might be extremely effective and would overcome the problems associated with conventional therapy(30)

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

Non-steroidal anti-inflammatory drugs (NSAIDs) taken orally produce gastrointestinal side effects. In contrast, a transethosomal formulation of ketorolac tromethamine demonstrated enhanced penetration, and piroxicam transethosomal gel displayed higher stability and elasticity compared to the other deformable vesicle systems,In an experiment, conducted human studies using ethosomes containing ammonium glycyrrhizinate. The formulation with 45% ethanol and a lower proportion of lecithin produced better results. The in vitro study showed improved tolerability and percutaneous permeability, while volunteers in the in vivo trial exhibited increased anti-inflammatory activity.(31)

Conclusion

As delivery vehicles for a range of bioactive substances, transethosomes have attracted a lot of interest. Apart from the transdermal approach, scientists have investigated ocular,
TEs have been shown to be viable drug delivery vehicles by transvaginal and intranasal methods for a range of medicinal uses. A TE can penetrate deeper layers of the skin because it contains an encapsulated medicinal molecule, a phospholipid, a high ethanol concentration, and an edge activator. Surface functionalization and photodynamic therapy of TEs were shown to be effective after extensive research was conducted to obtain site-specific activity and lower medication toxicity. To create a final product that is both safe and effective, the complexity involved in the formulation and development of TEs can be controlled by simultaneously optimizing a number of characteristics. Despite more study is required to solve the stability difficulties, however the majority of drug-loaded TEs show deeper skin penetration, prolonged drug release, and targeted administration. To sum up, TEs can support a range of therapeutic applications with site-specific action through a variety of pathways. Therefore, by reducing toxicity levels, TEs should show improved clinical outcomes with fewer side effects.

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