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Review

A review on transethosomal drug delivery system

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Abstract

The skin has a surface area of 1.8 m^2, and is essential for drug administration because of its enormous surface area for drug dispersion. However, drugs have limitations when it comes to low bioavailability, short residence time, systemic adverse effects, poor skin penetration, and reaching target areas. The goal of novel transdermal medication delivery strategies, including vesicular nano-carrier delivery systems, is to decrease dosage frequency, improve patient compliance, and minimize side effects. Although transdermal medicine distribution is a useful technique, many pharmaceuticals are unable to pass through the main barrier, the stratum corneum. Ethosomes, transferosomes, and transethosomes (TEs) are examples of ultra-deformable vesicles (UDVs) that have been designed to get over this obstacle and deliver medications to the intended location. Transethosomes show promise for transdermal drug delivery because of its ability to accommodate drug molecules with a broad range of solubility because to their lipophilic and hydrophilic areas. Because TEs contain larger amounts of phospholipid, edge activator, and ethanol, they have superior penetration through the stratum corneum. Transethosomes improve the solubility and stability of drugs, which boosts their effectiveness. By administering the medication in a semisolid dosage form, patient compliance is improved.

Keywords: transethosomal drug delivery system

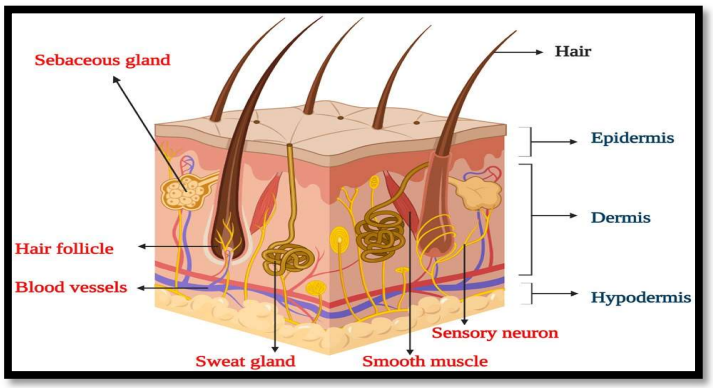
INTRODUCTION

The body's largest multipurpose organ is the skin which effectively protects the body from pathogens and chemicals. Skin diseases are a critical worldwide health issue that may affect anybody, regardless of age or ethnicity, and are brought on by both internal and extrinsic causes. Skin problems can be treated with a variety of therapies, but many of them have drawbacks including side effects or poor penetration. Finding novel, low-cost, extremely effective, and safe chemicals that could be used to treat skin problems is currently of great interest, especially for long-term inflammatory skin conditions like psoriasis and atopic dermatitis [1]. One of the most well-established methods of treating skin issues is the topical administration of drugs, which allows for a direct distribution on the site of action. Topical formulations have several limitations in clinical practice, including poor

skin penetration and localised side effects. Due to these causes, there is currently a need for the development of novel and efficient drug delivery systems.

According to this perspective, the development of nanotechnology has the ability to address these issues and build particular methods for cutaneous delivery [2]. Lipid-based nano-system are capable of dissolving lipophilic active compounds, increasing their bioavailability, delivering them in a regulated way, and reducing the negative effects. Lipophilic nanoparticles, such as liposomes, solid lipid nanoparticles, nanostructured lipid carriers, monoolein aqueous dispersions, ethosomes, and lecithin organogel, have been proposed for cutaneous application; some of them have already found success in the marketplace or are undergoing clinical trials. Throughout history, herbal remedies have been used to treat a variety of pathological problems; in fact, the majority of pharmaceutical products are derived from natural substances or their by-products. But the major pharmaceutical firms prefer to utilize synthetic medications, mostly because natural compounds are rarely bioavailable, which makes it difficult to use them in clinical studies. Natural molecules do undoubtedly have a number of benefits, including less side effects, patient acceptance, a low cost, and low volatility. The idea of using herbal compounds, solubilized in suitable topical vehicles to be applied to the skin, should be examined, especially in the case of treating skin diseases, as synthetic medications have been shown to cause resistance. In light of a safe, non-toxic method, the connection of herbal compounds inside a naturally based delivery system, exemplified by lipid nanocarriers, seems promising. [2]

Structure of skin



The entire body's exterior is covered in skin, the biggest organ in the body. The three layers that comprise the skin are the epidermis, dermis, and hypodermis, and each has a unique structure and function. The skin's intricate network of cells acts as the body's first line of defense against harmful substances, ultraviolet light, infections, and physical trauma. It controls the amount of water released into the environment as well as the temperature. [3]

Epidermis

The epidermis is the uppermost layer of skin. It is resilient and strong. It protects the body from harm, keeps the body moisturized, produces new skin cells, and contains melanin, which regulates skin tone.

Layers of epidermis

The stratum basale, which is the deepest layer of the epidermis, is followed by the stratum spinosum, stratum granulosum, stratum lucidum, and stratum corneum, which is the outermost layer of the epidermis.

Stratum Basale, Or Stratum Germinativum is the lowest layer. Hemidesmosomes bind the stratum basale to the basement membrane, which separates it from the dermis. The cuboidal to columnar mitotically active stem cells that make up this layer are continuously generating keratinocytes. Melanocytes are also present in this stratum.

Stratum spinosum, 8-10 cell layers, also known as the prickle cell layer contains irregular, polyhedral cells with cytoplasmic processes, sometimes called “spines”, that extend outward and contact neighbouring cells by desmosomes. Dendritic cells can be found in this layer.

Stratum granulosum, 3-5 cell layers, contains diamond shaped cells with keratohyalin granules and lamellar granules. Keratohyalin granules contain keratin precursors that eventually aggregate, crosslink, and form bundles.

The lamellar granules contain the glycolipids that get secreted to the surface of the cells and function as a glue, keeping the cells stuck together.

Stratum lucidum, 2-3 cell layers, present in thicker skin found in the palms and soles, is a thin clear layer consisting of eleidin which is a transformation product of keratohyalin.
Stratum corneum, 20-30 cell layers, is the uppermost layer, made up of keratin and horny scales made up of dead keratinocytes, known as anucleate squamous cells. This is the layer which varies most in thickness, especially in callused skin. Within this layer, the dead keratinocytes secrete defensins which are part of our first immune defense. [3]

Cells of epidermis

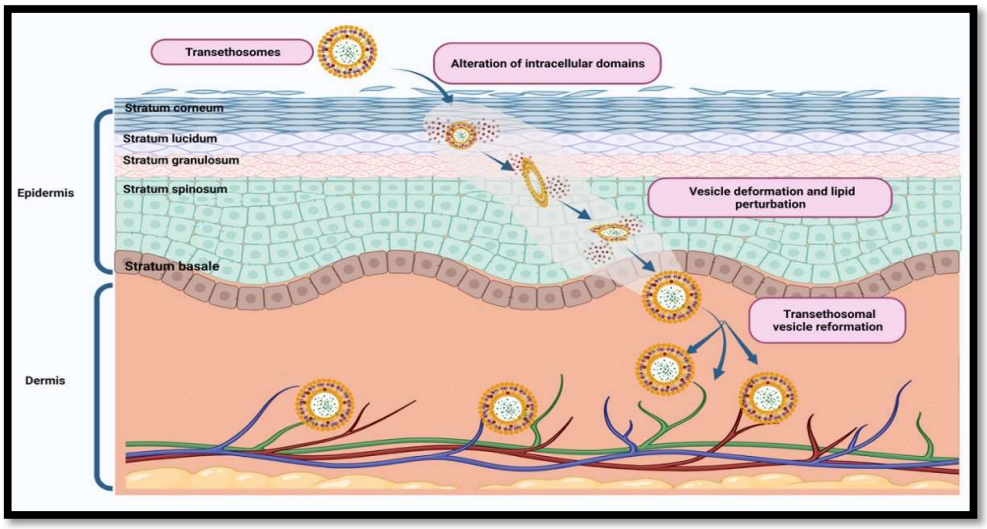
- Keratinocytes
- Melanocytes
- Langerhans' cells
- Merkel's cells

Dermis

The two layers of connective tissue that make up the dermis—the reticular and papillary layers—merge seamlessly with the epidermis at the level of the basement membrane. The thinner top layer, known as the papillary layer, is made up of loose connective tissue that connects the epidermis. The thicker, less cellular, deeper layer is called the reticular layer, and it is made up of bundles of collagen fibers and dense connective tissue. Sweat glands, hair follicles, muscles, sensory neurons, and blood arteries are all located in the dermis.

Hypodermis

The hypodermis is deep to the dermis and is also called subcutaneous fascia. It is the deepest layer of skin and contains adipose lobules along with some skin appendages like the hair follicles, sensory neurons, and blood vessels. [3]



Transferosomes

Transferosomes are vesicles composed of phospholipids with surfactant and ethanol as well as ultra formable vesicle possessing an aqueous core surrounded by the complex lipid bilayer. Higher membrane hydrophilicity and flexibility of transferosomes tend to avoid aggregation and fusion. Transferosomes were introduced for the effective transdermal delivery of number of low and high molecular weight drugs. It can penetrate the intact stratum corneum spontaneously along two routes in the intracellular lipid that differ in their bilayer properties. It consists of both hydrophilic and hydrophobic properties; high deformability gives better penetration of intact vesicles.

Advantages

- Contain hydrophobic and hydrophilic moieties together and as a result can accommodate drug molecules with wide range of solubility.

- Transferosomes can deform and pass-through narrow constriction (from 5 to 10 times less than their own diameter) without measurable loss.
- Possess high entrapment efficiency, in case of lipophilic drugs near to 90% o Used for both systemic as well as topical delivery of drug.

Limitations

- Transferosomes are chemically unstable because of their predisposition to oxidative degradation.
- Purity of natural phospholipids is another criterion militating against adoption of transferosomes as drug delivery vehicles

Ethosomes

Ethosome is another novel lipid carrier, recently developed by Touitou et al. (2000), showing enhanced skin delivery. The ethosomal system is composed of phospholipid, ethanol and water. The size of ethosomes varies from few nanometres to micrometres depending on method of preparation and application of techniques like sonication. Several studies investigated the effect of ethanol on physicochemical characteristics of the ethosomal vesicles. One reported characteristic of ethosomes is their small size relative to liposomes, when both are obtained by preparation methods not involving any size reduction steps. This reduction in vesicle size could be explained as a result of incorporation of high ethanol concentration. Ethanol confers a surface negative net charge to the liposome which causes the size of vesicles to decrease. The size of ethosomal vesicles was reported to increase with decreasing ethanol concentration in the ethanol concentration range of 20–45%. The effect of phospholipid concentration on the size of ethosomal vesicles was also investigated. [8]

Advantages of ethosomes

- The permeation of drug through skin is high for transdermal drug delivery.
- Avoidance of first pass metabolism.
- The stability of formulation is high.
- The delivery of sustain release and control release drug is possible.
- Reduced side effects like gastric irritation, vomiting.
- Can be administered in the form of semisolid dosage form.
- It is suitable for the drugs with short half-life and narrow therapeutic range.
- Controlled plasma level can be maintained.

Major types of ethosomes based on composition

Classical ethosomes

They are actually modification of classical liposomes with high alcohol content(45%w/w). They have enhanced entrapment efficiency and higher negative zeta potential compared to classical ethosomes. Molecular weight ranges from 130.07Da to 24kDa.Thus have greater stability as well as increased permeation.

Binary ethosomes

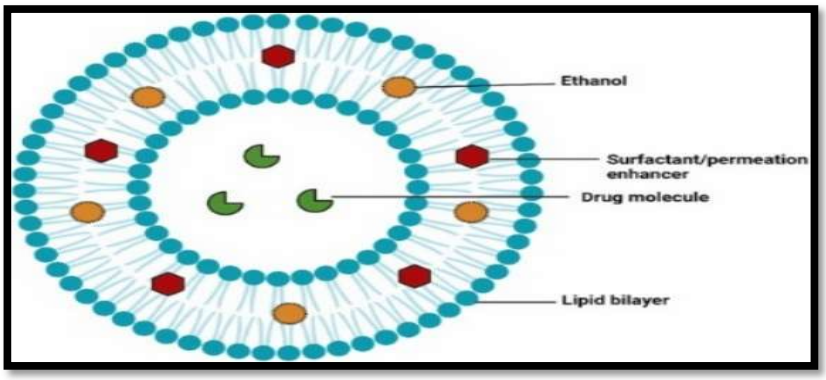
They were introduced first by Zhou et al. They are binary because they are made by adding another alcohol in to the formulation for enhancement of ideal properties. The commonly added alcohols include propylene glycol (PG) and isopropyl alcohol (IPA).

Transethosomes

The new generation of vesicular systems developed by song et al in 2012.They are similar to classical preparations but contains an additional component in the form of an edge activator (surfactant mostly) and/or penetration enhancer. The novel delivery system combines the ideal properties of classical ethosomes as well as the elasticity and deformability of transferosomes as in one formulation known as transethosomes. They were reported to have superior and beneficial characteristics compared to classical ethosomes. They are capable of entrapping drug which have a molecular weight ranging from 130.077Da to 200-235kDa.

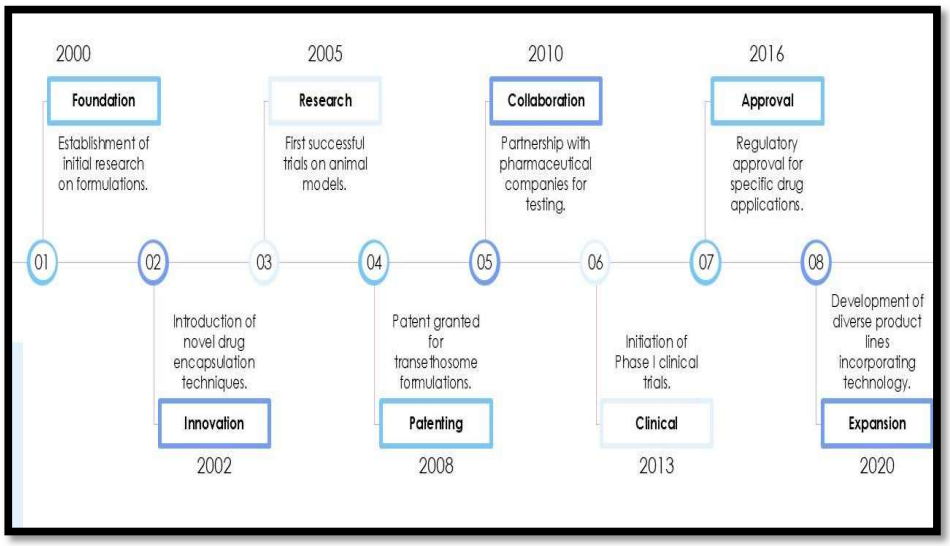
S.NO	Parameter	Classical ethosomes	Binary ethosomes	Transethosomes
1.	**Composition**	1. Phospholipids 2. Ethanol 3. Stabilizers 4. Charge inducer 5. Water 6. Drug/agent	1. Phospholipids 2. Ethanol 3. Propylene glycol or other alcohol 4. Charge inducer 5. Water 6. Drug/agent	1. Phospholipids 2. Ethanol 3. Edge activator or Penetration enhancer 4. Charge inducer 5. Water 6. Drug/agent
2.	**Skin Permeation**	Higher than classical liposomes.	Equal to or higher than classical ethosomes.	Typically, higher than classical ethosomes.
3.	**Entrapment efficiency**	Higher than classical liposomes.	Usually higher than classical ethosomes.	Mostly higher than classical ethosomes.
4.	**Potential**	Negatively charged	Negatively charged	Positively or negatively charged
5.	**Size**	Smaller than classical ethosomes	Equal to or smaller than classical ethosomes	Based on edge activator or penetration enhancer concentration.

Structure of transethosomes



Transethosomes are lipid-based vesicles that also include water, ethanol, surfactant, and phospholipids. The phospholipids, also known as non-ionic surfactants, is used to transport medication molecules into the skin. They are easily able to interact with the stratum corneum, enhance tissue hydration, and combine with its lipids. They have a hydrophobic (nonpolar) tail and a hydrophilic (polar) head. Bilayer softener: edge activator (biocompatible surfactant). It is typically included to increase permeability and flexibility. One of the main characteristics of the transethosomal system is alcohol, which gives it a unique identity as a vesicular system. Because of fluidization, ethanol causes the skin's layer to deform and gives these nano systems flexibility and malleability, which allows them to enter the stratum corneum through microscopic gaps. Water is a crucial component because it aids in the formation of a bilayer with the addition of phospholipids and promotes system flexibility. The combination of ethanol and edge activator causes the lipid bilayer to reorganize and become more pliable, allowing it to pierce deeper into the dermis. The innovative delivery method, known as transethosomes, combines the best qualities of traditional ethosomes with the elasticity and deformability of transferosomes. [9]

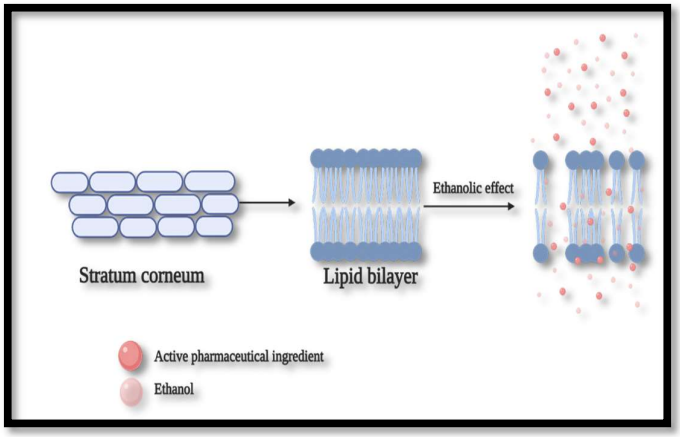
Historical development of transethosomes



Mechanism of action

The mechanism of transethosome involves in two phases:

- Ethanol effect
- Ethosome effect



Ethanol effect

Ethanol effect is considered to be the first mechanism for distribution of drug deeper into the skin layers. This results in reduced transition temperature of lipids in the stratum corneum and increased fluidity in transethosome which penetrates into the lipid layer of the skin by decreasing the density. The presence of alcohol at the surface results in change in membrane shape. It is proved that alcohol breaks the single layer continuity by enhancing the fusion of discontinuous membrane.

Ethosome effect

Transethosome effect is the second mechanism involved. The ethosomal system permeates and penetrates into the lipid layer. The movement of transethosomes through stratum corneum is facilitated by hydration force and bypasses the skin by osmotic theory. Some of the penetration enhancers like (tween 20, tween 60, span 60, span 65, span 80 etc.,) disrupts the intracellular lipid in the stratum corneum layer which facilitates the permeation of drug across the skin.

Salient features of transethosomes

- Due to enhanced biocompatibility and biodegradable nature, their entrapment efficiency is higher.

- They have higher flux rate due to increased flexibility.
- Drugs with low and high molecular weight can be entrapped.
- Transethosome system can be used for both systemic and topical delivery.
- Higher rate of penetration through skin when compared to other vesicular system.

Components of transethosomes

- High concentration of ethanol.
- Phospholipids.
- Cholesterol.
- Edge activators or penetration enhancer
- Drug/active compound.

Ethanol

Ethanol is considered as an efficient penetration enhancer which is characterized in terms of size, stability, entrapment efficiency and skin permeability. The concentration of ethanol in transethosome is up to 10%-20% and also provides softness to the vesicles containing transethosomes. Increased concentration of ethanol results in decrease in size of ethosomes and shifting of vesicular charge from positive to negative which is an important parameter that produces impact on vesicular properties such as stability and vesicle skin interaction. Increase in ethanol concentration will increase the entrapment efficiency. Increase in ethanol beyond the optimal concentration results in leaky bilayer, increased vesicular size and critical decrease in entrapment efficiency. The solubility of hydrophilic and lipophilic drug is increased by ethanol which results in increased drug loading. [11]

Phospholipids

The phospholipid selection is an important parameter to develop an ethosomal system. It has a significant impact on the size of ethosome. The type and the concentration of phospholipid is an important factor which influences the size, entrapment efficiency, zeta potential, stability and penetration and permeation properties of the vesicular system. This helps in formation of vesicles in which the concentration of phospholipids ranges from 0.5% to 5%. Increase in phospholipid concentration results in slight or moderate increase in size of the vesicle. Shen et al., found that the use of Lipoid S100 or SPC50 in preparation of transethosome resulted in smaller size when compared to those produced by Lipoid E80. The use of Lipoid E80 phospholipid resulted in production of stable vesicles due to higher concentration of phosphatidyl choline content. Thereby further increase in phospholipid concentration will have no effect on entrapment efficiency. [12] [13]

Cholesterol

The incorporation of cholesterol into ethosomal system resulted in enhanced stability and entrapment efficiency. It is reported that cholesterol increases the vesicular size. The concentration range of cholesterol used were found to be <3% in some formulation. Increased concentration of cholesterol at the range of 0% to 0.15% w/w resulted in increased vesicular size from 102± 13 nm to 152± 12 nm. It is found that cholesterol stabilizes into the ethosomal system and prevents the aggregation of the particles. [12]

Oleic acid

Oleic acid improves the vesicle size, elasticity, zeta potential, and skin permeability by changing the characteristics of the stratum corneum, which increases the layer's fluidity. When administered at a low dose of 0.5%, it often acts as a penetration enhancer. According to completed investigations, transethosomes containing oleic acid have a negative zeta potential, increased skin penetration, and more drug disposition in the dermis and epidermis of rats. [13].

Edge activator or pentration enhancers

The proper selection of edge activator is a critical step in the formulation of transethosomes as they influence the properties of the ethosomal system. The most commonly used edge activators are tweens and spans.

Surfactant

The most commonly used surfactants for the transethosomal system include the anionic and non-ionic surfactants. The non-ionic surfactants include Cremophor EL-35, Cremophor RH-40 etc., and some of the anionic surfactants used are Sodium cholate, Deoxycholic acid, Sodium stearate. The surfactant like Polyethylene glycol can be used in the preparation of transethosomes.

Tweens and spans

Tweens and Spans like Tween 80, Tween 60, Tween 20, Span 20 Span 40, and Span 60 are used in the formulation of transethosomal system. It is reported that Tween 80 in ethosomal system resulted in increased

stability and reduction in vesicular size. This resulted in enhanced skin permeation property. This resulted in smaller vesicle size (258.4±3.3 nm), enhanced Ex vivo skin penetration through the human skin and enhanced entrapment efficiency compared to ethosomal system containing Tween 80. The addition of Tween 60 to the transethosomal formulation of artesunate and febrifugine resulted in unstable formulation due to formulation of crystals after 5 days. Another study resulted that use of Span 20 in transethosome formulation containing caffeine and vitamin E was successful. [15]

Cremophor

Cremophor is an ethoxylated detergent. Shu Meng et al., used cremophor EL-35 in the preparation of testosterone propionate ethosomal system at the concentration range of 0.5%-
1.5 %. The use of cremophor EL35 resulted in increased solubility of drug which further resulted in enhanced entrapment efficiency and reduction in vesicular size.

Propylene glycol

Transethosome formulation containing propylene glycol provides enhanced distribution of the drug through the vesicles. This resulted in increased drug solubility and higher entrapment efficiency of drugs. The propylene glycol is most used in the preparation of binary ethosomes. It is used in concentration range of 5%-20%. PG in ethosomal system resulted in increased fluidity of ethosomes than liposomes and the In vitro diffusion of drug from ethosomes was twice than the liposome. [16] [17] [18]

Polyethylene glycol 4000:

The studies that were conducted using transethosomes containing mycophenolic acid revealed a major result that they have a very positive impact on essentially increasing the vesicular size while it produced no visible effect on other properties like entrapment efficiency, permeability and vesicular stability. [19]

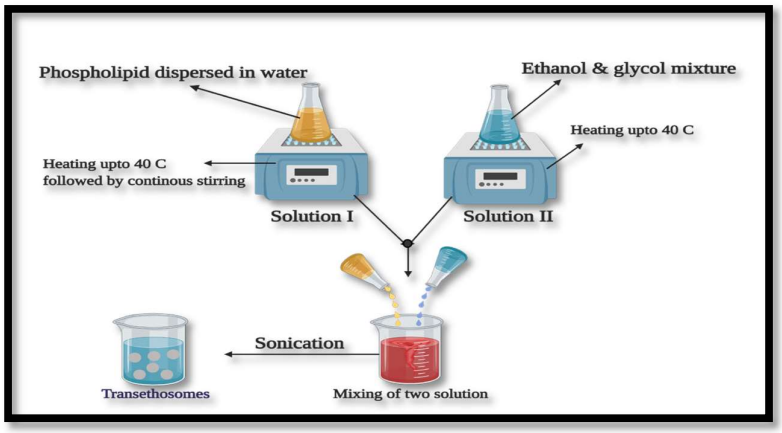
S.NO	Edge activators	Concentration	Type
1.	Tween 80	10%-50%	Non-ionic surfactants
2.	Tween 60	1%-50%	Non-ionic surfactants
3.	Tween 20	15%-50%	Non-ionic surfactants
4.	Span 20,40,60,80	1%-50%	Non-ionic surfactants
5.	Cremophor EL-35	0.5%-1.5%	Non-ionic surfactants
6.	Polyethylene glycol 4000	1%	Anionic surfactants
7.	Sodium deoxycholate	0.8%	Bile acid /anionic surfactant

Methods of preparation of transethosomes

Transethosomes are simple to prepare and easy to scale up without involvement of sophisticated equipment's at both pilot plant and industrial level. Different methods are used to achieve small vesicular size and these vesicles are incorporated into gels or creams to increase skin penetration.
The following are some of commonly used methods.

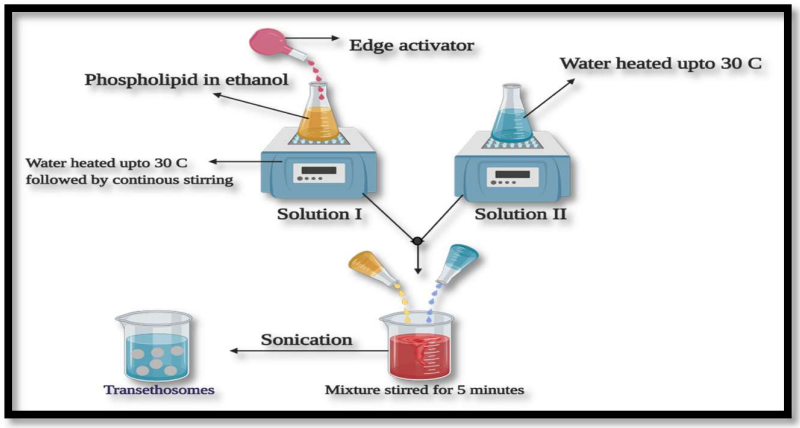
- Hot method
- Cold method
- The Ethanol injection -Sonication method
- The Reverse phase evaporation method
- Transmembrane pH gradient method
- Thin film hydration method. [9]

Hot method



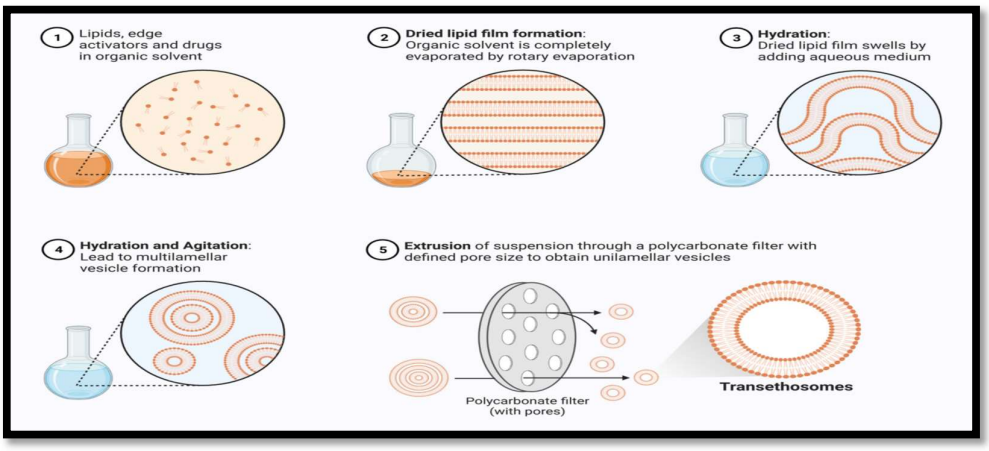
Touitou first developed the hot technique in 1996. The dispersion of phospholipid through heating in a water bath at 40ºC in a beaker filled with water. In one water bath, ethanol and propylene glycol are combined and heated to 40ºC. The aqueous phase is subsequently combined with the organic phase. The medication dissolves in either ethanol or water, depending on its hydrophobic/hydrophilic characteristics. To the required extent, the ethosomal formulation's vesicle size can be reduced using the probe sonication or extrusion approach. [1]

Cold method



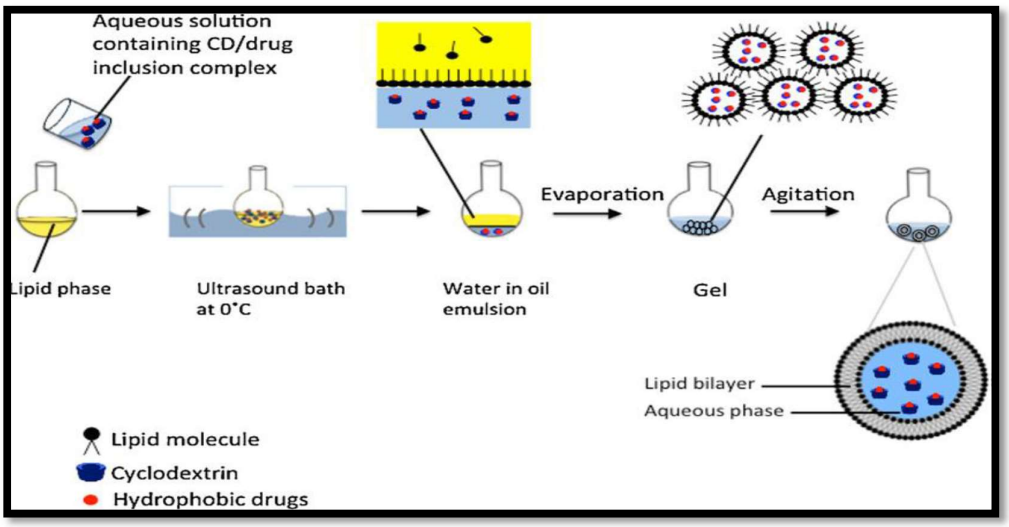
This is the most widely used method of all. Drugs, phospholipids, and other lipid ingredients are dissolved in room-temperature alcohol (usually ethanol) in a covered vessel, and the mixture is vigorously stirred afterward. At 40°C, polyols such as polyethylene glycol are added while the mixture is being stirred. The setup is permitted to be warmed to 30°C in a water bath.Water that has been heated to 30°C separately. is added to a covered vessel and stirred for five minutes. the method of using extrusion and sonication to reduce vesicles' size to the appropriate levels. It is crucial to use the right temperature to meet the requirements of the preparation. It suggests that cold storage is required. The aqueous phase used can be water, buffer solution or normal saline. [21]

Mechanical dispersion or thin film hydration



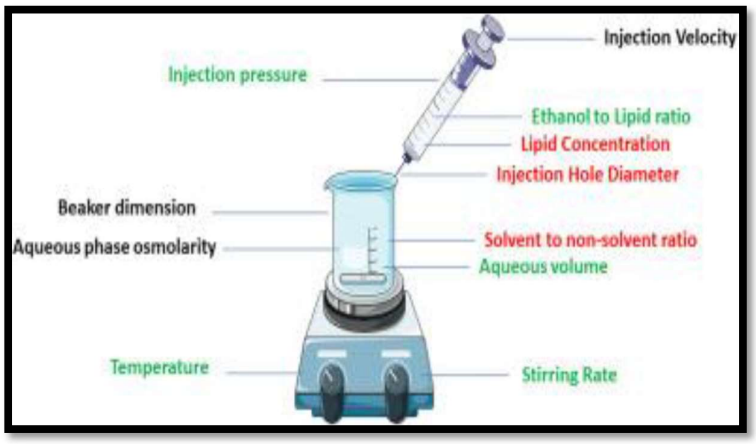
This approach uses a flask with a round bottom. In an appropriate organic mixture-filled round-bottom flask, soya phosphatidylcholine is dissolved. A rotary vacuum evaporator is used to evaporate the organic solvent at a temperature higher than the lipid transition temperature. After that, the flak is left overnight, allowing the lipid film to form on it and for solvent traces to be extracted. To hydrate a drug mixture at varying concentrations, a simple round-bottom flask rotation is performed [20][21]

Reverse phase evaporation technique



This is the least common strategy and is seldom ever used. Its main application is in the synthesis of giant unilamellar vesicles. The organic phase utilized to dissolve the phospholipids is diethyl ether. It is combined with aqueous phase at 3:1 ratio in ultrasonic bath at 0°C for 5 minutes which results to the creation of water in oil emulsion. The organic phase is removed by reducing the pressure to a very low level, which then causes a violent mechanical agitation that forms a colloidal dispersion. [22]

Ethanol injection – sonication method



The phospholipid ethanolic solution is used as the organic phase, and it is subsequently injected into the aqueous phase using a syringe method. A constant flow rate of 200 µL/minute is maintained. In five minutes, homogenization is completed with the use of an ultrasonic probe. [23]

Classic method

Using a water bath, the phospholipids, drug, and ethanol were combined until the drug disintegrated at a temperature of 30°C. In a closed vessel, the mixture was continuously stirred at 700 rpm while a fine stream of double-distilled water was introduced. The homogenization process involved three cycles of the resulting suspension being run through a polycarbonate membrane using a manual extruder. [22]

Transmembrane ph gradient method

Liposome formulation was the initial application of this technique. The medicine is actively loaded in this approach according to the pH gradient difference between the ethosomal formulation's external basic phase and its internal acidic phase. Three phases are involved in this process for formulating the ethosomal system: First, a blank ethosomal system must be prepared. Next, drugs must be actively loaded into the system. Finally, the drug must be incubated at a specific temperature for the unionized drug to actively pass through to the bilayer of the ethosomal vesicle. [10]

Advantages of transethosomes

- Skin permeation of drugs administered transdermally is high.
- Preventing first pass metabolism and having a high formulation stability.
- Delivering medications with both controlled and sustained release is a possibility.
- Decreased adverse effects, like nausea and upset stomach.
- It is perfect for drugs with a brief half-life and a narrow therapeutic window.
- Maintaining a regulated plasma level is possible.

Limitations

- A low yield could result from imprecise transethosomal formulations.
- When switching from organic to aqueous medium, there is a considerable loss of medicine.
- A loss of vital stability and coalescence might result from inefficient shell locking.
- To ensure that the method stops the distribution of all pharmaceuticals, the substance to be loaded needs to have a suitable molecular size.
- They might not be pleasant to wear, which would reduce their usefulness.
- Another key impediment is the uneconomical character of their price.

Characterization of transethosomes

Various characterization methods of transethosomes

- Morphology of transethosomes
- Particle Size and Zeta Potential
- Entrapment Efficiency
- Drug content

- Skin Permeation studies
- Skin Retention

Morphology of Transethosomes

Vesicle shape of transethosomes can be identified. The visual imaging of transethosomes can be done by using optical microscopy, Transmission electron microscopy (TEM) and Scanning electron microscopy (SEM).

Optical Microscopy

The optical microscopy of TEs will be measured by spreading the sample on a glass slide with the help of a glass rod and cover with a coverslip. The samples will be observed under a magnification of 40x and 10x. [24]

Scanning Electron Microscopy (SEM)

A scanning electron microscope (SEM) produce images of a sample by scanning the surface with a focused beam of electrons. The sample specimen will be prepared by mounting a drop of dispersion on-air dried-clear glass slide and sputter- coated with gold. Then the slide will be observed under the scanning electron microscope. [24]

Transmission Electron Microscopy (TEM)

Transethosomal vesicles can be examined with transmission electron microscope. The extra material is filtered off using filter paper after that the vesicular suspension is deposited on a grid made of copper or carbon. This is dyed using a phosphotungstic acid aqueous solution or a 2% uranyl acetate solution. The grid is then partially cured and looked at using a transmission electron microscope. [25] [26]

Particle Size and Zeta Potential

- Particle size of the transethosomes can be studied by using
  - Dynamic light Scattering (DLS)
  - Photon correlation spectroscopy (PCS)
- The size of transethosomes ranges from tens of nanometers to microns.
- The surface charge of the particle can be studied using Zeta potential.
- The Stability of the particle can also be predicted by this method. [10]

Entrapment Efficiency[27]

Entrapment efficiency of TEs is determined by ultracentrifugation method. TEs are separated by ultracentrifugation at 12,000 rpm for 90 minutes at a temperature of 4ºC. The
sediment and supernatant liquid are separated, the amount of drug in the sediment will be determined by rupturing the vesicles using methanol and the amount of drug was quantified spectrophotometrically. Entrapment efficiency is determined by the following equation

Drug content

The amount of drug present in transethosomal formulation can be determined by using methods such as Ultra violet (UV) spectrometer and High-performance liquid chromatography (HPLC). [10]

Skin Permeation studies

Using an in-vitro technique, a Franz diffusion cell is used for the skin permeation investigations of transethosomes. The temperature is held at 32°C plus or minus 1°C. The semi- permeable membrane is placed between the donor and the receptor compartment. The semi- permeable membrane is subsequently covered with the prepared formulation of transethosomes. Samples are taken at intervals of 1, 2, 3, 4, 8, 12, 16, and 24 hours. Ultraviolet spectroscopy is used to analyze and measure the withdrawn samples.

Skin Retention studies

At the completion of the invitro permeation experiment, the amount of medication retained in the skin is determined. A cotton soaked with methanol is used to clean the skin. Two approaches are used to determine drug retention.

Skin destruction method:

The skin sample is weighed, sliced with scissors, and placed in a glass homogenizer with 1ml methanol, where it is homogenized for 5 minutes using an electric stirrer. The resultant solution is centrifuged at 7000 rpm for 10 minutes. The drug content of the supernatant is determined using an appropriate analytical method. [28] [29]

b) Skin extraction method

At the termination of the invitro permeation study, the receptor content is fully removed and replaced with 50% v/v ethanol in distilled water for a further 12 hours and the drug content
is calculated. This receptor solution diffused into the skin, destroying any liposome structure and removing the medication deposited on the skin, providing a measure of skin deposition. [30] [31]

Application of transethosomal drug delivery system

Transethosomes are often used to replace liposomes. The dermal and transdermal modes of drug administration are the most common. Transethosomes can be utilized to deliver hydrophilic and impermeable medications to the skin via transdermal administration. The transethosomal carrier has been used with a range of medications.

NSAIDs (Non-steroidal Anti-inflammatory Drugs)

- Ketorolac tromethamine
- Piroxicam
- Flurbiprofen,
- apremilast
- mangiferin,
- naproxen sodium

Antifungal Drugs

- Terbinafine,
- Amphotericin B,
- Ketoconazole
- Voriconazole
- Luliconazole,
- Econazole Nitrate
- Tioconazole
- Miconazole Nitrate
- Itraconazole

Anticancer drugs

- Brucine-strychnine,
- Rolapitant

Antihypertensive drugs

- Olmesartan medoxomil
- Propranolol hydrochloride
- Irbesartan
- Paenol
- Telmisartan

Antiaging drugs

- Cycloastragenol
- niacinamide

Future prospect

Researchers are now studying a number of cutting-edge drug delivery systems, including transethosomal vesicular carriers. The future appears bright since medicine development, manufacture, importation, exportation, and distribution should be controlled to meet predetermined criteria. The manufacturer should verify that the transethosomal formulation meets the necessary requirements. "Generally regarded as Safe" (GRAS) and clinically non-toxic excipients are used by researchers29. It provides an excellent carrier system to ensure the stability of different proteins and drugs. It can be included into hydrophilic and hydrophobic medications. Numerous medication classes, such as antivirals, anti-diabetics, and anticoagulants, can be delivered by transethosomes. It is feasible to provide a combination of anticancer medications transethosomally with little or no cytotoxicity. Transethosomes, or mixtures of multiple drugs, can be administered to increase the efficacy of a drug. Because clinical trial literature is not commercially available, it is not widely accessed. Transethosomes therefore have a great deal of potential for use as a transdermal or topical drug delivery mechanism.

CONCLUSION

Some bioactive substances are blocked from entering the skin by barriers. The creation of ultra deformable vesicular (UDV) systems based on ethanol allows for greater skin penetration. The new vesicular system consists of ethosomes, transferosomes, and transethosomes. greater solubility, penetration, and flexibility can be obtained with this transethosomal vesicular system because of its greater compatibility with hydrophilic and hydrophobic medicinal compounds. The transethosomal system, which helps to improve topical medicine administration to the intended area, is made up of alcohol and edge activators. Because of its great carrier capacity, the transethosomal system can carry drugs with very large molecular weights, like peptides and protein molecules. Topically applied transethosomal gel or cream results in high patient compliance.

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