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Transethosomes as Vesicular Drug Delivery : a Modified Form of Ethosomes and Transfersomes

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Abstract: Liposomal vesicle formulations can be classified into two categories, namely rigid hard vesicles such as liposomes and elastic vesicles such as transferosome. One of the shortcomings of conventional liposomes is their permeation strength in the stratum corneum, so that in later generations liposomes are designed to be able to better overcome these obstacles. Deformable liposomes, also known as transfersomes, are liposomes that contain edge activators/surfactants. The combination of phospolipids with membrane softening agents allow the transfersome to penetrate pores that are five times smaller than their own diameter, even after it passes through small pores. Ethosomes are liposomes with modified ethanol that act as reservoir systems and offer the continuous delivery of drugs to the desired site. The high concentration of ethanol content in the manufacture of ethosome systems makes this system different from other vesicle systems, because the ethanol content will interfere with the double layer of skin lipids and thus increase the ability of vesicles to penetrate into the stratum corneum. Phospholipids in ethosomes serve as vesicular-forming components. Phospholipids are also reported to act synergistically with ethanol to improve drug permeation in ethosome formulations. Transethosomes are ethanol-based lipid vesicular systems resulting from modifications of ethosome and transfersome systems that can increase penetration in the skin. It is a new generation of the ethosome system which developed by increasing the flexibility of vesicles by redistributing edge activators and lipids on the skin. The mechanism of action of transethosomes is a combination of advantages of both transferosome systems and ethosomes.

Keyword: Transethosome, transfersome, ethosome, vesicular

INTRODUCTION

In recent years, the vesicle system has been introduced as a controlled drug release system, due to some of its advantages such as lack of toxicity, biodegradation, its ability to encapsulate drugs of a hydrophilic or lipophilic nature, ability to prolong the drug in the circulatory system due to its encapsulation in vesicles, ability to target drugs in organs and tissues, and the ability to reduce drug toxicity and increase bioavailability.

Conventional lipid-based vesicular systems with ethanol bases show the ability to cross the stratum corneal layer. Generally, vesicles consist of phospholipids and nonionic

surfactants. The reason for the use of vesicles in percutaneous drug delivery is because of their composition that is able to penetrate through the skin. Based on this fact, vesicles can be used as drug carriers to deliver drugs that are absorbed through the skin. Therefore, vesicles are also used as depots for the controlled release of active ingredients in topical formulations.

Liposomal vesicle formulations can be classified into two categories, namely rigid hard vesicles such as liposomes and niosomes, as well as elastic vesicles such as transferosome, ethosome and transethosome with fundamental differences in the constituent structure of each vesikel. One of the shortcomings of conventional liposomes is their permeation strength in the stratum corneum, so that in later generations liposomes are designed to be able to better overcome these obstacles. Niosomes (first generation), Transferosomes (second generation), and Ethosomes (third generation) where the last two are generations of flexible liposomes or also called *Ultra Deformable Vesicles* (UDV) with different mechanisms to improve their permeation to the skin.

LITERATURE REVIEW

Transfersomes

Deformable liposomes, also known as transfersomes, are liposomes that contain edge activators including Tween 20, Tween 60, Tween 80, Span 60, Span 65, Span 80, dipotassium glycyrrhizinate, sodium cholate or sodium deoxycholate. These edge activators destabilize the lipid bilayer of liposomes and increase the flexibility of liposomes. Numerous reports have shown that the drug delivery across the skin from DLs was more effective than that of rigid liposomes such as CLs [7]. Nevertheless, several studies showed that the DLs were not able to penetrate the low layers of stratum corneum although they could improve the skin deposition of hydrophobic drugs such as 5-fluorouracil [8].

Transfersomes are one form of ultradeformable vesicle system that has an aqueous core surrounded by a complex double lipid layer. Transfersomes consist of water, surfactants, and phospholipid. Transfersomes are 2nd generation flexible liposomes with a combination of phospholipids and edge activators, typically single-chain surfactants that cause destabilization of lipid vesicle bilayers and increase vesicle elasticity or fluidity [9, 5]. The combination of corresponding lipids with membrane softening agents can allow the transfersome to penetrate pores that are five times smaller than their own diameter. In addition, the diameter is maintained even after the transfersom passes through small pores against fragmentation. Surfactants are suggested as examples of softening materials, such as sodium cholate (SDC), Span 80 and Tween 80, referred to as *Edge Activator* (EA) (Figure 1.). The EA serves as a membrane destabilizing factor to increase the deformability of the vesicle membrane so that when combined in the right ratio with the corresponding lipid, it provides an optimal mixture, allowing the transfersome to be deformable, as well as ultra-flexible, which results in a higher permeation ability.

Transfersomes are ultra-deformed or ultraflexible liposomes that easily cross the skin under the influence of a gradient of transepidermal water activity. Transferosomes vesicles easily access the stratum corneum of the skin in search of aqueous hydration [10]. Surfactants such as Tween 80, Span 20, sodium deoksikolat, have been used as *edge activators* (EAs). Due to its deformability, transfersomes are one of the good carriers for the non-invasive delivery of small, medium, and large-sized drugs. Skin permeation and penetration of these elastic vesicles result from a synergistic mechanism between the carrier properties and the ability to increase permeation. Transfersomes can cross the skin layer by different mechanisms depending on its composition, in which these vesicles retain their intact structure or coalesce and mix with skin lipids [11, 12].

Transfersomes, or can also be referred to as transferosomes, are ultra-flexible vesicles with a bilayer structure consisting of phospholipids, *edge activators* (surfactants), and water. In transfersomes, hydrophilic drugs are encapsulated inside the aqueous central cavity, while

hydrophobic drugs are more abundant in the phospholipid bilayer [13].. The characteristic of the transfersome is that it is able to penetrate the skin easily and pass through the barrier function by squeezing itself through the intracellular lipid stratum corneum. This can occur due to the high deformability of the vesicles so that it is possible to enter by self-adapting [13, 14, 15. Transfersom is a drug carrier that can penetrate the intact inner skin. It is based on two main factors, namely the high elasticity (ultraflexible or deformability) of the bilayer vesicles and the reality of the osmotic gradient around the skin. The transfersome penetration mechanism is the development of an osmotic gradient produced due to the evaporation of lipid suspensions on the surface of the skin as the water evaporates. Transfersomes have a high surface hydrophilicity, and respond to hydration gradients throughout the dermal tissue; it pushes vesicles through transcutaneous channels, allowing transfersom vesicles to act as carriers of noninvasive drugs [16, 17, 18].

When transfersome dispersion is applied to the skin nonoclusively, the excess water applied begins to evaporate immediately and osmotic gaps are built to facilitate the transfersome to cross the main barrier of the stratum corneum of the skin. The high deformability and hydration driving forces of the transfersome allow and encourage drug-filled vesicles to cross the skin barrier

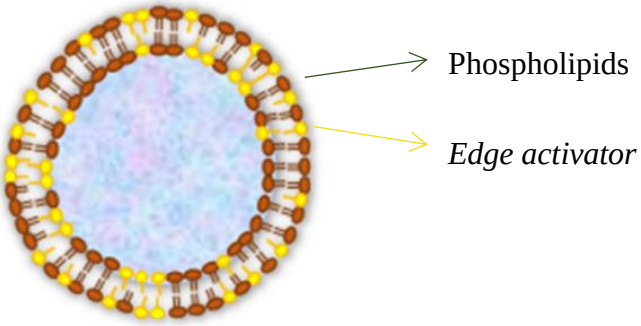

Figure 1. Transfersom Structure [17]

Transfersomes can cross the skin layer by different mechanisms depending on their composition, in which these vesicles retain their intact structure or coalesce and mix with lipid. The transfersome can easily change its shape and cross the skin barrier due to the action of the EA in response to mechanical stress by relocating inside the vesicles to zones with a smaller curvature, thereby reducing the elastic energy of the membrane to a minimal level. Due to this mechanism, the transfersome can easily enter through a channel with one-tenth of the diameter of the vesicles, and across the SC driven by an osmotic transdermal gradient. These elastic vesicles can only penetrate the skin layer under nonoclusive conditions to allow evaporation of excess water from the formulation and maintain this hydration gradient. Therefore, they pass in a nondifusive way, which means that the penetration rate will not depend on the concentration gradient. Transfersomes also have the ability to protect the drug from rapid cleansing into the blood vessels of the skin and to increase the retention of the drug in the layers of the skin if needed [19].

Transethosome can be used transdermally, with the drug transethosomal system having a better permeation rate, being biodegradable and biocompatible providing very efficient absorption capabilities. Transethosomes can be applied to semisolid preparations so that they are easier to apply, increase patient adherence to drug use, and avoid cross-first metabolism. The raw materials contained in the formulation are not toxic in nature and are also more stable than other vesicle systems. Transfersomes have been studied as carriers for dermal or transdermal delivery to different drugs. However, one major drawback of these vesicles is the difficulty of introducing hydrophobic drugs into the vesicles without reducing their deformability and elasticity properties. In general, transfersomes have been shown to be

superior to conventional gel- and liquid vesicles as well as conventional liposomes in terms of increased drug permeation and interactions with human skin.

Mechanism of Action of Transfersom

The transfersome efficiently penetrates the intact skin if applied under nonoclusive conditions; this specific nonoclusive skin state is necessary especially to initiate a transepidermal osmotic gradient across the skin. The transfersom can compress itself through the pores on its surface, which are many times smaller than its size and exhibit enhanced skin penetrating properties. Hydrotaxis (xerophobia) is a transfersome permeation mechanism, which is further described as the moisture-seeking tendency of the transfersom to the deeper layers of the skin than the dry outside due to the state of evaporation of moisture from the transfersomal formulation after its application to the skin (nonoclusive condition). Transfersome vesicles have a tendency to avoid dry environments (xerorphobia). Thus, the transfersome is attracted by the layers of the skin with a higher water content, resulting in spontaneous migration of the drug-containing vesicles through the skin barrier [12]. The difference in transdermal water activity, which comes from the natural transdermal gradient, creates a very strong force that acts on the skin through the transfersome vesicles, which promote the dilation of the intercellular joints with the lowest resistance and produce transcutaneous channels at a width of 20-30 nm. This created channel allows ultra-deformable, slimy transfersomes to cross the skin in relation to the hydration gradient (Figure 2.). In addition, an osmotic gradient develops as a result of evaporation of the surface water of the skin due to body heat, which exerts its action as a driving force to facilitate flexible transportation across the skin to deliver the therapeutic agent from the place of application to the target area for local or systemic treatment in effective therapeutic concentrations and minimum [20].

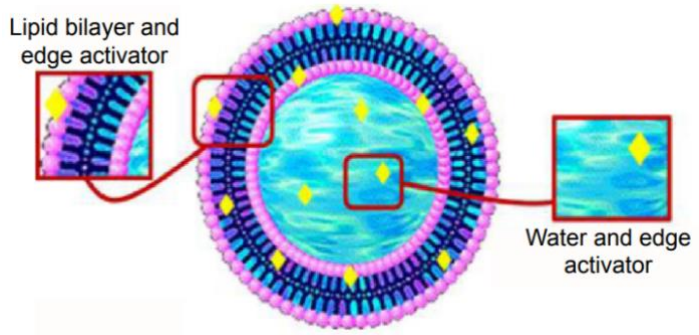

Figure 2. Ultra-deformable vesicles overview [19].

Transfersomes show higher permeation efficiency (through small skin channels) compared to conventional liposomes but have a similar bilayer structure that facilitates the encapsulation of lipophilic and hydrophilic drugs. Transfersomes vary from liposomes, mainly because artificial membranes are better adjustable and very deformable. The interdependence of the local composition, as well as the form of a double lipid layer, makes the vesicles self-optimize and self-regulate. This allows the transfersome vesicles to efficiently cross various transport barriers. Therefore, the transfersome is a supramolecular entity consisting of at least one type of amphipathic substance and, with the addition of at least one type of bilayer softening agent (*edge activator*), generates a greatly increased flexibility and permeability of the lipid bilayer [21]. Transfersomes are highly deformable (ultra-flexible) and self-optimizing new drug-carrying vesicles, where their passage across the skin is mainly related to the flexibility of the transfersom membrane, hydrophilicity and the ability to maintain vesicles integrity (Figure 3.) [20].

There are 2 main mechanisms for the delivery of skin via ultradeformable liposomes (transfersomes). The first mechanism states that intact vesicles enter the stratum corneum

which bindsa drug molecule into the skin. It is recommended that due to its deformable nature, these vesicles are able to penetrate the stratum corneum into the deeper layers of the skin intact, under the influence of naturally occurring transcutaneous hydration gradients. The surface of the skin is relatively dry compared to the living epidermis. When ultradeformable li posom is applied to the surface of partially dehydrated skin, the vesicles move towards the deeper layers of the skin (for example, the living epidermis and dermis) that are relatively hydrated. The pressure generated during movement to the deeper layers of the skin is reduced by the deformation properties of these vesicles. In in vitro skin permeation studies (thickness 200-300 mm), pretreatment of deformable empty liposomes on the surface of the skin was followed by the application of a solution of drug-saturated aqueous (pergolide or rotigotine) compared to deformation liposomes filled with drugs. It was observed that skin permeation is significantly higher in the case of deformable liposome encapsulated drugs compared to pre-treatment of deformable empty liposomes followed by the application of a solution of the drug. This study shows that ultradeformable liposomes can also act as a carrier system (rather than acting as a permeation enhancer for over-the-counter drugs) to deliver the drug to the deeper layers of the skin (up to 200-300 mm from the surface of the skin) [22, 1].

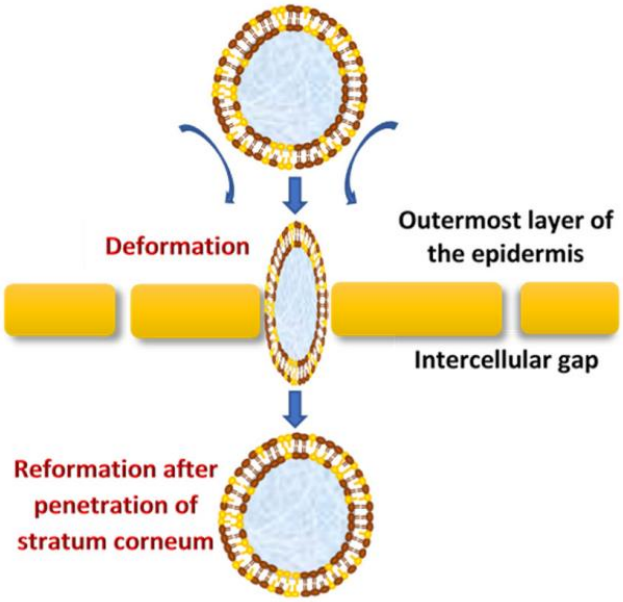

Figure 3. Mechanism of action of the transfersome [20]

The second mechanism is with vesicles acting as penetration enhancers, where vesicles enter the stratum corneum layer and then modify skin lipids between cells This will facilitate the penetration of over-the-counter drug molecules into and across the stratum corneum. In a recent study, it was observed that deformable vesicles actually reduce the transdermal absorption of calcein, most likely by controlling the release of the drug from the formulation on the surface of the skin. In an interesting study, skin permeation and skin deposition of deformable liposome fumarate-loaded ketotifene (phosphatidylcholine with ratio of Tween 80 84.5:15.5 b/b) and conventional liposomes (without Tween 80) were studied, respectively. It was observed that for deformable liposomes, skin deposition is 5 times higher than skin permeation. In addition, although the skin deposition for deformable liposomes is similar to conventional liposomes, the skin permeation of deformable liposomes is significantly higher (2 times) than for conventional liposomes. Based on these findings, it is suggested that deformable liposomes act as penetration enhancers of the drug by interacting with skin lipid. Despite the various scientific efforts summarized above, it is still controversial whether the deformable liposome acts as a drug carrier or permeation enhancer or both [1, 22].

Formulation of Transfersomes

Unlike conventional liposomes, transfersomes consist of phospholipids, an aqueous medium, and *an edge activator*. A biocompatible membrane softener, also known as an *edge activator* (EA), is a single-chain surfactant that joins into the transfersom structure and facilitates the destabilization of the double layer of lipid vesicles and increases their fluidity and elasticity. The surfactant part directly affects the physicochemical characteristics of the resulting vesicles because it is considered the main component of its structure. In an aqueous environment, phospholipids assemble themselves into flexible and close lipid bilayers to form vesicles. According to the results of studies that have been carried out by, transfersomes with Tween 80 surfactants (HLB 15) have a much smaller particle size and higher deformability. The total number of surfactants and the exact ratio of each surfactant to phospholipids are responsible for controlling the flexibility of the vesicle membrane and minimizing the risk of vesicle rupture in the skin. These results encourage transfersomes to follow a natural osmotic gradient across the epidermis after application under a nonoclusive way

The combination of surfactant molecules with phospholipids as well as high elasticity and deformation structure makes the transfersom vesicles adsorbed or fused with the stratum corneum and reach deeper dermal tissue and even systemic circulation. In addition, the drug can quickly move to the deeper layers of the stratum corneum when it is strongly associated with vesicles. Therefore, these elastic vesicles have superior characteristics and higher skin permeation compared to conventional vesicles. In addition, the effect of increasing the penetration of these vesicles depends on the concentration and type of surfactant, the type of lipid, the shape of the size and elasticity of the vesicles.

A. Phospholipids

Phospholipids are the complexity of glycerides with hydroxyl modifications including with polar head groups forming phospholipids. Phospholipids derived in name from the phosphate group are bound to one of the final terminal hydroxyls of glycerol. The charged phosphate group is also used as a bridge between the glycerol skeleton and the subsequent head cluster (Figure 4.). Due to its amphiphatic properties, phospholipids are used as emulsifying and dispersing agents. Phospholipids are able to assemble themselves into a lipid bilayer, when placed in an aqueous environment, it closes itself to form vesicles [23].

Lecithin is commonly widely used in cosmetics, food products and is also used in pharmaceutical products. Although the highest concentration of phospholipids is found in animal-derived products such as meat, fish, eggs and milk. The main commercial source is found in soybeans containing 0.3-0.6% phospholipids. Soybean lecithin is a by-product of soybean oil processing. The purification process in producing lecithin can remove oil and will affect the composition of phospholipids in lecithin. The main phospholipids in soy lecithin are phosphatidylcholine, phosphatidylletanol amin, and phosphatidlinositol. Soy lecithin contains 21% phosphatidylcholine, 22% phosphatidyl ethanolamine, and phosphatidyllinositol 19%, along with other components. soy lecithin contains 21% phosphatidylcholine, 22% phosphatidylletanolamine, and phosphatidyllinositol 19%, along with other components

Lecithin application is usually used as:

- Acts as a wetter, stabilizer, carrier of choline enrichment.
- Good dispersing agent.
- Helps in emulsification and encapsulation.
- Acts as a catalyst, a color-enhancing agent. Good stabilizing and suspending agent. Removes foam on water-based paints.

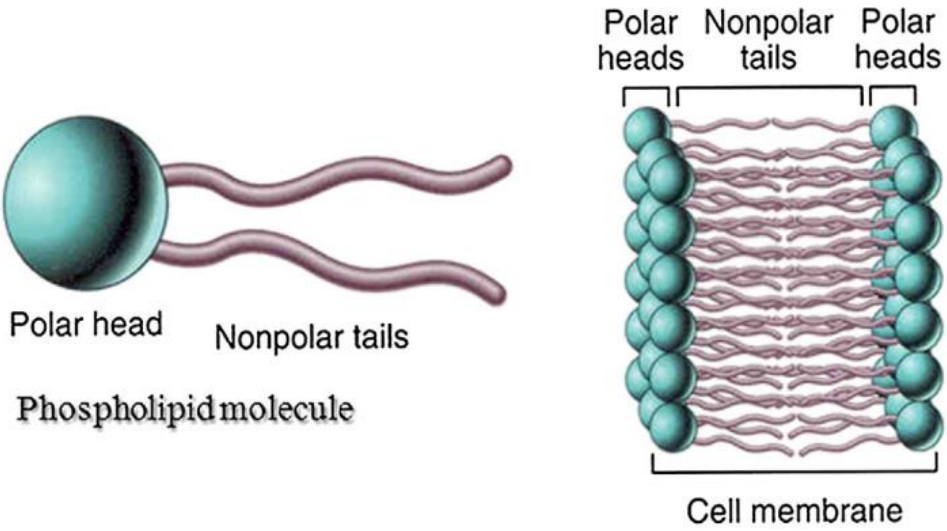

Figure 4. Chemical Structure of Phospholipid Molecules

B. *Edge Activator*

The edge activator is responsible for weakening the double lipid layer of the vesicles, increasing its flexibility and deformability, and allowing it to be wedged through the pores of the stratum corneum directly into the systemic circulation. *The edge activator* is able to increase the deformability of the bilayer by influencing the interface voltage of these vesicles. Transmission electron microscopy has conclusively shown deformation of vesicles into oval and irregular structures at the addition of *edge activator* [24]. Many attempts have been made to investigate the effects of surfactants on improved encapsulation efficiency (EE), but there is still no definitive evidence that certain surfactant properties can lead to certain pitfalls. Such may require many surfactant properties, such as type and concentration, which can have an effect on the EE of certain drugs in a particular lipid composition.

The type and concentration of *the edge activator* can significantly affect the physicochemical properties of the transfersom vesicles. *Edge activators* are commonly used for transfersom preparations including sodium kolate, sodium deoxycolate, Span 60, Span 65, Span 80, Tween 20, Tween 60, Tween 80, and dipotassium glycyrrhizinate. The concentration of *the edge activator* plays an important role as well. For ultradeformable liposomes containing diclofenac (consisting of phosphatylcholine and Span 80), an increase in the concentration of Span 80 (*edge activator*) from 2% to 5% (w/w) resulted in an increase in absorption efficiency from 50.73% to 55.19% respectively. However, with a further increase in the concentration of *edge activator* to 15% then 25% (w/w), the absorption efficiency decreased from 44.93% to 42.80% respectively. A decrease in absorption efficiency at higher concentrations of edge activators is associated with the formation of micellar aggregates. Some researchers have also reported the influence of surfactant concentrations on EE vesicles that higher concentrations of surfactants reduce EE. This effect is due to the possibility of micelle formation when the concentration of surfactants in the bilayer exceeds the temperature of the critical lamellar/micellar transition

The permeability of vesicle membranes may increase due to the arrangement of surfactant molecules in the lipid structure of the bilayer, which can insert pores inside the membrane and increase its fluidity. Overall, this will lead to a trapped drug leak. In addition, it is estimated that the optimum amount of surfactant depends on the density of the phospholipids used and the surfactant-phospholipid interaction. When the concentration of surfactants increases and has a high tendency to interact with lipids, this leads to a decrease in the entrapment as it competes on loading inside the double layer.

The type of surfactant also affects because of the carbon chain that each surfactant has. Based on the results of research on nanoparticles formulated with different types of

spans, it was observed that all span surfactants have the same head group and differ only in their hydrophobic. Nanoparticles, in this study were niosomes, which were prepared with a span of 60 showing the highest absorption because they had the longest carbon chain. In contrast, span 80 produces the lowest absorption efficiency, which is thought to be associated with unsaturated double bonds in its alkyl carbon chain. The presence of a double bond in the carbon chain can make it bend and make the niosome bilayer more permeable because the packaging of adjacent molecules may not be tight.

Ethosomes

Ethosomes represent the 3rd generation of elastic lipid carriers, developed by Touitou [6]. Ethosomes are liposomes with modified ethanol that act as reservoir systems and offer the continuous delivery of drugs to the desired site (Figure 5). Ethosomes are a vesicle system of bilayer lipid nanoparticles formed from phospholipids and a relatively high ethanol concentration [25]. The vesicle system structurally consists of a system of phospholipid bilayers and an aqueous nucleus with the inside containing the drug [26].

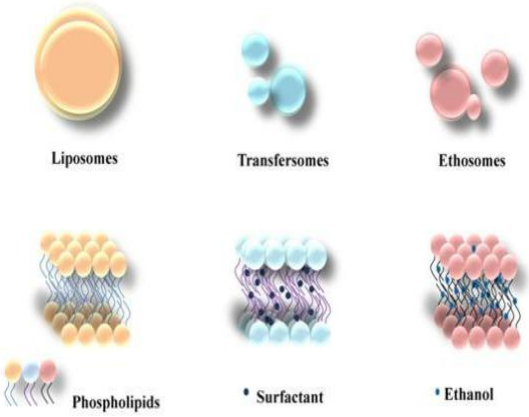

Figure 5. Schematic diagrams of Liposomes, Transfersomes, Ethosomes [7]

In general, the structural form of the ethosome system is compared to the structure of the bilayer lipid vesicles shown in **Figure 6.**

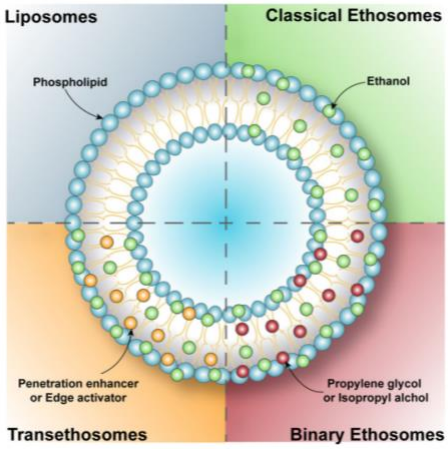

Figure 6. Ethosome structure and lipid system bilayer [27]

The high concentration of ethanol content in the manufacture of ethosome systems makes this system different from other vesicle systems, because the ethanol content will interfere with the double layer of skin lipids and thus increase the ability of vesicles to penetrate into the stratum corneum. Another advantage of ethosomes is that they provide a softer vesicle system structure and increase the distribution ability of drugs in stratum korn lipids The advantages of ethosomes compared to other carrier vesicles are that ethosomes can increase drug penetration through the skin for both the dermal and transdermal routes. Ethosomes can deliver drug molecules with diverse physicochemical properties, ranging from

compounds that are hydrophilic lipophilic, as well as other macromolecules. The components of making ethosomes are proven to be safe and FDA approved for use in pharmaceutical and cosmetic preparations, generally ethosomes are formulated in the dosage form of patches and semisolids (gels or creams). So that it can improve patient compliance. Ethosomes are able to increase the delivery of drugs on the skin both in occlusive and non-occlusive conditions, the size of ethosomes is relatively smaller than conventional medicinal vesicles, ethosomes can increase drug permeation because it can carry drugs through the stratum corneum to the deeper layers of the skin, ethosomes can be formulated easily and do not require advanced equipment or specially designed equipment

Components of the Ethosome

The ethosome exhibits a double layer of liposome-like lipids; however they differ from liposomes in composition (high ethanol content). Ethosomes are composed of hydrocoholsteries or hydro/glycolicphospholipids whose alcohol concentrations are relatively high. Ethosomes may contain phospholipids with various chemical structures such as phosphatidylcholine, phosphatidic acid, phosphatidyl ethanolamine, phosphatidyl glycerol, phosphatidyl inositol, alcohol (ethanol or isopropyl alcohol), water and propylene glycol(or other glycol). Some phospholipids are preferred such as the structure of the skin**.** Phospholipion 90 (PL-90). is usually used in the range of 0.5-10% w/w. Cholesterol at concentrations ranging from 0.1-1% can also be added to the preparation. Ethosomes can contain phospholipids with various chemical structures (such as phosphatidylcholine and phosphatic acid), ethanol or isopropyl alcohol, water and propylene glycol (or other glycols). In addition, non-ionic surfactants (PEG-alkyl ether) and cationic lipids can be combined with phospholipids in the preparation. The concentration of the non-aqueous phase (alcohol and a combination of glycol) can range from 22 to 70% .

a. ethanol

Ethanol in ethosomes serves as a substance that makes vesicle membranes smooth and also as a penetration enhancer. As a penetration enhancer, ethanol will wet the lipid double layer of ethosome vesicles and stratum corneum simultaneously, so that very soft ethosome vesiclesn will penetrate the structure of the stratum corneum (28). Ethanol is used as a substance capable of increasing the penetration of drugs into the skin.

b. phospholipids

The study of the structure of phospholipids is important due to its relevance in the health sciences, the development of drug delivery. Phospholipids preserve the integrity of cells or organelles by forming a semipermeable barrier that separates them from their external environment. Cell membranes with phospholipids are generally composed of saturated fatty acids [29]. These fatty acids have a different structure and less fluidity that allows them to integrate with essential fatty acids. Phospholipids contain one saturated fatty acid and one unsaturated fatty acid connected to the glycerol head. The head of the phospholipid is hydrophilic, while the tail is hydrophobic. In the bilayer membrane, the hydrophobic part of the molecule is wedged in the middle, while the hydrophilic part forms the surface of the bilayer. Phospholipids in ethosomes serve as vesicular-forming components. Phospholipids are also reported to act synergistically with ethanol to improve drug permeation in ethosome formulations [28]. Some examples of phospholipids commonly used in the manufacture of ethosomes include phosphoric acid.

c. polyglycol

Polyglycol ordinary is added in the manufacture of ethosomes, but very rarely. If added to the ethosome, polyglycol serves as a penetrating agent on the skin. Examples of polygicol are propylene glycol and diethylene glycol monoethyl ether [28,29]

Ethosomal bilayer lipid vesicles systems are widely applied in the pharmaceutical field as shown in **Table 1.**

Table 1. Application of vesicles ethosom systems in the pharmaceutical field

Drugs / Active Compounds	Disease/Activity	Information	Ref.
Tocotrienol	Melanoma	In vitro cytotoxicity studies on HaCat cells showed increased skin permeation and high cell viability.	30
Cholecalciferol (Vitamin D3)	Sarcopenia	The ability of the VD3 ethosome system to maintain its structural integrity for a long time in the intracellular environment makes it particularly suitable for the continuous release of VD3.	31
Mangiferin	Antioxidant and anti-inflammatory	Rt-PCR results and immunofluorescence show that the ethosome system can deliver Mangiferin to target cells, improving the antioxidant defense status of keratinocytes, while protecting against induced inflammatory damage.	32
Curcumin-loaded Glycyrrhetinic acid-D-α-tocopherol acid polyethylene glycol succinate (GA-TPGS)	Psoriasis	Cur@GA-TPGS-ES shows a strong treatment of inflammatory infiltration inhibition.	33
Curcumin	Anti tumor	curcumin ethosomal composite phospholipids as carriers of vesicular lipids can improve transdermal drug penetration and improve vesicle stability.	
Karanjin	Acne vulgaris	delivery of topical karanjin in the treatment of acne using ethosomal gel is a promising carrier system.	34
AgNPs, Sericin, Chitosan	Non melanoma skin carcinoma (NMSC)	Ethosomal formulations can go into the deeper layers of the skin and have better delivery with higher efficiency in NMSC therapy	35
Fenretinide	Breast cancer	Phenretinide esom can improve skin penetration without compromising cytotoxicity and selectivity in vitro against cancer cells.	36
Quercetin	Melanoma	Quercetin ethosomes can be used as an adjuvant in the treatment of melanoma, or possibly in other skin iperproliferative conditions, including psoriasis.	37
Metformin	Anti-proliferative and Melonoma	Metformin ethosome is a promising drug delivery system and a therapeutic approach that can be taken for the treatment of melanoma and wound healing.	38

Vesicular system had been use in wide range of either pharmaceuticals or cosmetical purposes [39]. In recent years there have been many studies using the application of transfersomes [4, 40]. Transfersomes for transdermal delivery had been developed with various drugs or active substances shown in Table 2.

Table 2. Transfersomes in medical applications

No.	Active Substances	*Edge Activator*	Reference
1.	Green Leaf Extract (*Camellia sinensis* L. Kuntze)	Lipoid P30 then Team 80	41
2.	Clindamycin Phosphate	Span 80	42
3.	Monoxidyl and Caffeine	Tween 80 dan Tween 20	43
4.	Mikonazole Nitrate (MIC)	Tween 80 dan Span 80	44
5.	Ivabradin HCl	Tween 80, SLS, dan *Cetrimide*	45
6.	Lornoksikam	Tween 80 dan *Sodium deoxycholate*	46
7.	*Ascorbic Palmitate*	*Sodium dodecyl sulfate* (SDS)	47
8.	*Phenylethyl Resorcinol*	Tween 80, Tween 20, Span 80, Span 20, *Sodium deoxycholate* (SDC)	48

Transethosom

Transethosomes are ethanol-based lipid vesicular systems resulting from modifications of ethosome and transfersome systems that can increase penetration in the skin. Transethosome is a new generation of the ethosome system. Transetosomes were first developed by Song et al in 2012, by increasing the flexibility of vesicles by redistributing edge activators and lipids on the skin. Ethosomes work with skin fluidization and lipid vesicles. So that the mechanism of action of transethosomes is a combination of advantages of both transferosome systems and ethosomes [12, 24]. Transethosomes consist of phospholipids, ethanol and edge activators or permeation enhancers [49]. This ethosome system contains the basic component of the classic ethosome and the auxiliary compound with an edge activator or penetration enhancer (Figure 7). With the combination of the two kind of vesicles, a better characteristic was developed. Transethosome can trap drugs with a molecular weight of 130,077 Da to 200 - 325 kDa [28].

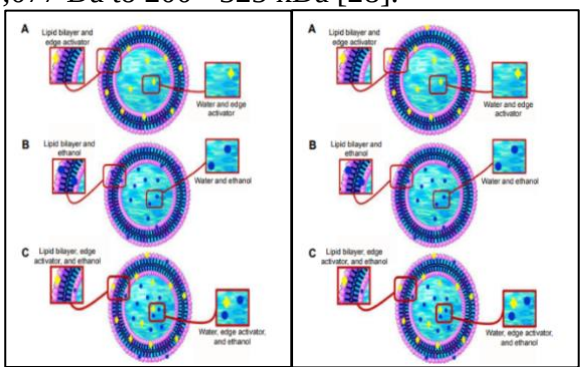

Figure 7 Schematic Overview of ultradeformable vesicles (A) Transfersom, (B) Ethosome, (C) Transethosome [19].

Transethosome which is included in the category of *Ultra Deformable Vesicles* (UDV) has advantages in terms of its non-toxic properties and a thermodynamically stable formula [19]. and can be used both for dermal and transdermal delivery, and has been successfully developed for both pharmaceutic and cosmetic uses. In addition, the production process is relatively simpler and easier to scale up [4].

Transethosomes can be used transdermally, with advantage of having a better permeation rate, being biodegradable and biocompatible providing a very efficient absorption ability. Transetosomes can be applied to semisolid preparations so that they are easier to apply, increase patient adherence to drug use, and avoid first cross-metabolism. The raw materials contained in the formulation are non-toxic in nature and are also more stable than other vesicle systems [50].

Formula of Tranethosome

Transethosomes were developed by combining the advantages of classical ethosomes and deformable liposomes (transferosomes). The general formulas on ethosome, transfersome and transethosome vesicle systems can be seen in Table 3. Transethosm consists of three main components namely phospholipids (phospholipids including phosphatidylhanolamine, phosphatidylinositol, phosphatidyl choline, and fosfatidylkolin hydrogenated) as the primary lipid structure; stabilize lipid bilayer and increase flexibility. Surfactants are divided into two groups, namely anionic surfactants such as sodium kolat, sodium deoxycolates, deoxycolic acids and nonionicular surfactants such as Span 60, Span 65, Span 80, Tween 20, Tween 60, Tween 80 and Span 85 and ethanol with high concentrations as penetration enhancers [19].

Table 3. General Formula of Ethosome, Transfersome and Transethosome Vesicle Systems [24, 28]

Formula	Ethosom	Transfersome	Transethosom
Phospholipids	in	in	in
Ethanol	in	-	in
Edge activator	-	in	in
water	in	in	in

The content of phospholipids and ethanol can help facilitate drug penetration by helping to pave the way through the stratum corneum layer so that the drug can penetrate properly into the skin and achieve systemic circulation [31]. The content of Phospholipids serves to form a system of transetosome vesicles, which have an integral role in the formation of bilayers; consists of a hydrophilic head and a hydrophobic tail. Commonly used phospholipids in the manufacture of vesicular systems are phosphatidylcholine, soybean phosphatidylcholine (Phospholipon 90), soya lecitin, soy phospholipids and phosphatidylanolateamines [24, 51].

The ethanol content serves to soften membrane vesicles, stabilize the condition of the vesicle system, increase the solubility of drugs of a lipophilic nature [24]. Ethanol concentrations suggest that it can affect physical properties such as improving the stability of the vesicle system, increasing the flexibility of the system to be softer, and affecting the surface charge of the vesicle system

The content of *edge activator* or surfactant serves to increase the penetration or permeation of medicinal preparations applied to the skin, modifying the deformability of vesicles. Surfactants that can be used include span 60, span 25, span 80, tween 20, tween 60, tween 80, *sodium deoxycholate*, and *sodium cholate* [24, 31, 51, 52]. The concentration of surfactants used in the formulation can affect the particle size. In addition, the HLB value of the surfactant used in the formula can affect the particle size produced by the system. The systematic structure of the transethosome system can be described as in Figure 8.

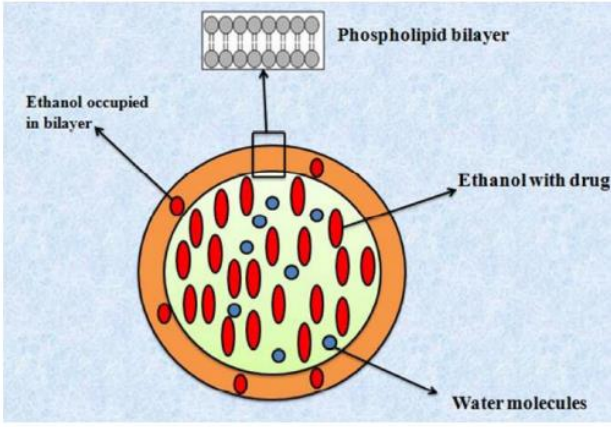

Figure 8. General Structure of Transethosome Systems [51].

The transethosome system can be manufactured by various methods, namely the cold method, the hot method, the thin layer hydration method, and also the ethanol sonication-injection method.

CONCLUSION

Transethosomes are ethanol-based lipid vesicular systems resulting from modifications of ethosome and transfersome systems that can increase penetration in the skin. It is a new generation of the ethosome system which developed by increasing the flexibility of vesicles by redistributing edge activators and lipids on the skin. The mechanism of action

of transethosomes is a combination of advantages of both transferosome systems and ethosomes.

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