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A Review on Transferosomes as Novel Topical Technique for Drug Delivery

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Abstract:

Transferosomes are ultra-deformable vesicles for transdermal applications. It majorly consists of a Lipid bilayer along with phospholipids and an edge activator and a core of ethanol or even aqueous. It also has advantages over other forms of the carrier. Transferosomes, as compared to liposomes, can deliver larger concentrations of active ingredients to deeper parts of the skin after topical treatment, making them an effective drug delivery carrier for transdermal applications. Formulation of transferosomes can bring out the best properties for topical delivery, also, the development on a large scale at the industrial level for the manufacturing process is simple. A wide range of medications, including phytocompounds like sinomenine or apigenin for treating leukaemia and rheumatoid arthritis, respectively, micro hydrophobic treatments, along with macromolecules like insulin, have been effectively encapsulated within transferosomes. The goal of this paper is to explain the idea of transferosomes, the mechanism of action, various synthesis and characterization techniques, and factors impacting the properties of transferosomes, as well as their latest applications in the transdermal delivery of pharmaceuticals.

Keywords **—Transferosomes, Vesicles, Novel Delivery of Drug, Topical or Transdermal application.**

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1. INTRODUCTION

Due to its advantages over traditional oral and parenteral administration systems, transdermal delivery systems have attracted a lot of attention in recent years. They are self-administered, non-invasive delivery devices that can increase patient compliance and offer a regulated release of medicinal ingredients. The barrier function of the top layer of skin is the biggest difficulty for transdermal delivery methods. Ionized substances and molecules with molecular weights larger than 500 Da typically cannot penetrate through the skin. As a result, this route can only be used to provide a small number of medications. One potential solution to this issue is to encapsulate the medications in transferosomes.

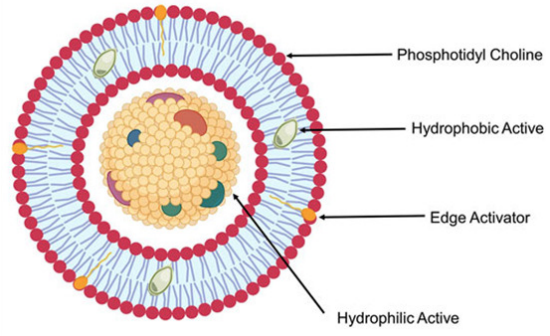

FIGURE NO: 1- STRUCTURE OF TRANSFEROSOME

As seen in the above image no: 1 transferosomes have a bilayered structure that facilitates the encapsulation of lipophilic and hydrophilic, as well as an amphiphilic, drugs with higher permeation efficiencies.

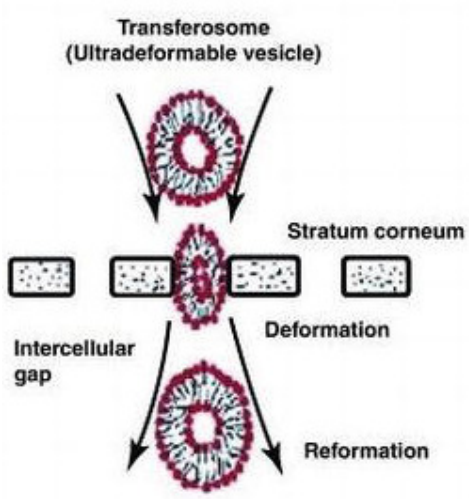

FIGURE NO: 2- MECHANISM OF TRANSFEROSOME PENETRATION

As seen the image no: 2 when transferosomes reach the skin pores, they are capable of changing their membrane flexibility and passing through the skin pores spontaneously. This is the so-called self-optimizing deformability. Furthermore, transferosomes are extremely deformable; therefore, they easily cross even very narrow pores.

There are many drugs loaded in transferosomes which are in clinical phases. A few examples are that has been found that when the drug contained within transfersomal carriers had higher therapeutic potency when compared to a placebo over a six-week treatment period for the relief of knee osteoarthritis pain, as well as relatively fewer adverse effects. In phase, I clinical research, the topical administration of insulin-loaded transferosomes (Transfersulin®) for hypoglycemic effects is being examined. Transfersulin® was able to lower blood glucose levels in alloxan-induced diabetic rabbits in a preclinical trial. A randomized controlled trial has already evaluated the topical triamcinolone acetonide in transferosomes versus commercially available triamcinolone acetonide-containing cream and ointment in terms of the risk-benefit ratio. The risk-benefit ratio of topical triamcinolone acetonide may be greatly improved by transferosomes, it has been determined. Because of this, transferosomes are known to be the most outstanding innovative transdermal drug carrier to this date.

2. SKIN AS AN BARRIER FOR DRUG DELIVERY:

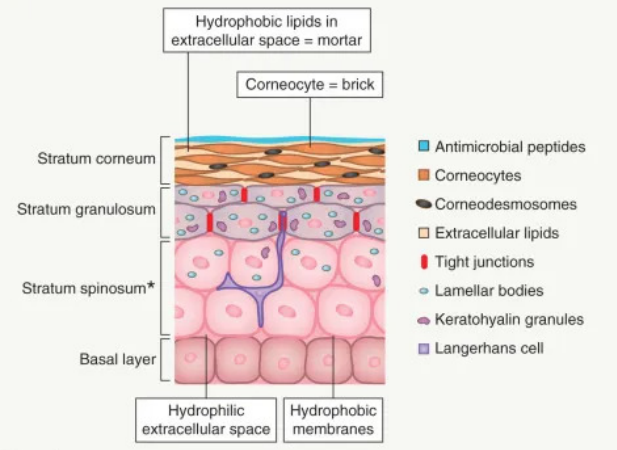

FIGURE NO: 3- STRUCTURE OF SKIN

As we know skin is composed of complex structures and layers. Delivery of drugs through the skin is a major task.

2.1. Stratum Corneum (SC):

The SC is the first environmental mechanical barrier. It is extremely important for the method through which the vast majority of drugs are absorbed through passive diffusion. It is made up of intercellular lipids, corneocytes connected by corneodesmosomes and TJ remnants, and other components. Keratinocytes with terminal differentiation are called corneocytes. Lack of cell nuclei and organelles, a buildup of cytokeratin filaments that are bundled, among other things, by filaggrin, and the presence of a hard cornified membrane are characteristics of these cells (CE). Envoplakin, periplakin, filaggrin, small proline-rich proteins (SPRs), involucrin, loricrin, and cysteine protease inhibitor A (cystatin A) are a few of the proteins that make up the CE. These proteins are cross-linked by transglutaminases. The extracellular area of the SC is filled with densely packed lipid layers, so-called lipid lamellae. They are made up of ceramides, free fatty acids, and cholesterol. The long periodicity phase (LPP), with a repetition distance of roughly 13 nm, and the short periodicity phase (SPP), with a repeat distance of roughly 6 nm, are the two crystalline lamellar phases that they generate. Additionally, the lateral packing is significant. While a small subpopulation of SC lipids adopts a less dense hexagonal packing, the majority of SC lipids in healthy skin are arranged in a dense orthorhombic packing. Additionally, there is a liquid-crystalline packing that gives the lipids the most freedom of movement. Also, various components of the SC such as filaggrin, CE-proteins and corneodesmosin have been shown to be involved in skin barrier function. Additionally, it was established that decreased epidermal barrier function is brought on by irregular lipid organization brought on by alterations in lipid composition. Changes in cholesterol and free fatty acids appear to have little effect on the barrier function. Skin pH also has an impact on a number of elements regulating the integrity of the epidermal barrier, including proteases crucial for desquamation and enzymes crucial for lipid synthesis [35,58]. Microenvironmental pH is crucial for appropriate molecular folding and therefore good interaction, for example in TJs, even in deeper layers. Therefore, changes in pH during drug administration may be used to affect the function of the epidermal barrier in addition to its direct physicochemical impact on the administered medication or drug carrier system itself, but they also carry the risk of adverse effects.

2.2. Tight Junctions (TJ):

In the epidermis stratum granulosum (SG), TJs create a continuous barrier. On molecules' journey from the outside to the inside of a paracellular cell, they serve as the second barrier. The smallest measured molecule was Biotin-SH, which has a mass of 556 Da, and TJs in the epidermis act as a barrier to other molecules of various sizes. TJs, and particularly claudins, can impede the passage of substances in a charge-selective manner depending on their chemical makeup. As a result, they lessen the movement of ions including calcium, sodium, and chloride across paracellular spaces.

2.3. Basement Membrane (Basal Lamina):

The dermo-epidermal junction is where the basement membrane (BM) is located, on the basal side of the stratum basal. It consists of a variety of matrix proteins and carbohydrates assembled together. Laminins, collagens, proteoglycans like perlecan, and hyaluronic acid are a few examples of major components. Together with numerous other molecules, they create a structure that resembles a cross-linked mat.

2.4. Glands

Skin glands generally act as barriers. These pathways are not ideal for drug delivery due to the dermal glands' inside-out flow direction, although absorption into the glands can be achieved using certain methods, such as iontophoresis.

Because TJs are found in glands, it may be possible to increase transepidermal drug delivery by, for instance, using TJ barrier-modifying enhancers to attenuate the barriers in glands. As a result, this could have adverse effects including altered

sebaceous gland release of lipids or altered sweat flow.

3. TRANSFEROSOMES:

As an above topical barrier, transferosomes can act as promising topical drug delivery.
Phospholipids and an edge activator are components of a novel drug delivery mechanism termed transferosomes. The lipid bilayer of the vesicles is destabilized by an edge activator, which is a single chain of surfactants employed to increase the deformability of the bilayer by lowering its interfacial tension. In terms of functionality, its deformability allows for penetration via pores that are smaller than the size of a droplet.

Mechanism of Action:
After exposing the transferosomes to the skin's surface, water evaporates, which causes the osmotic gradient process, which is how the mechanism of action functions (Refer to image no-2). These vesicles can move without regard to concentration. The vesicle's ability to move is powered by trans-epidermal hydration. The vesicles' elastic qualities allow them to fit through the stratum corneum pores. Transferosomes tend to penetrate their barrier and move into the water-rich stratum when applied to an open biological surface, such as non-occluded skin, in order to ensure that the surface is adequately hydrated. The bilayer experiences reversible deformation as it penetrates the stratum corneum.

4. ADVANTAGES OF TRANSFEROSOMES:

1. Transferosomes are a special type of drug delivery system that may transport medicinal drugs with a wide range of solubilities since they are made up of hydrophilic and hydrophobic moieties.
2. Because of their extreme deformability and elasticity, transferosomes can force their way past skin barrier obstructions that are many times smaller than the vesicle width.
3. High vesicle deformability is useful for both topical and systemic treatments because it enables medication delivery across the skin without any discernible loss of intact vesicles.
4. Regardless of their size, structure, molecular weight, or polarity, a wide range of agents can be accommodated by transferosomes carriers with great efficiency.
5. They are composed of natural phospholipids and EAs, making them biocompatible and degradable in a promising manner.
6. Proteins and peptides, insulin, corticosteroids, interferons, anaesthetics, NSAIDs, anticancer medications, and herbal medicines are just a few of the active substances that can be delivered by transferosomes.
7. Transferosomes are a clear choice for achieving predictable and prolonged activity as well as a sustained medication release.
8. They have the ability to improve the site specificity of bioactive substances and increase transdermal flow.
9. By avoiding the first-pass metabolism, which is a significant disadvantage of oral medication administration, the drug's bioavailability is maximized.
10. reduce the negative effects of the medication, safeguard it from metabolic breakdown, and increase the usefulness of medications with brief half-lives.
11. They have the benefit of being produced using conventional techniques and chemicals that are appropriate for use in pharmaceutical products, but they still require case-by-case design and optimization.
12. It is simple to scale up manufacturing because the process is short and easy.

5. DISADVANTAGES OF TRANSFEROSOMES:

1. Due to their tendency for oxidative destruction, transferosomes are regarded as chemically unstable.
2. Formulations for transferosomes are costly.

6. COMPOSITION OF TRANSFEROSOMES:

TABLE NO: 1- COMPOSITION OF TRANSFEROSOMES

Sr. no	Ingredients	Examples	Role
1.	Amphipathic agent	Soy phosphatidylcholine, Phosphatidylcholine	Vesicle-forming components
2.	Surfactants/ Edge activators	Sodium cholates; sodium deoxycholate; Tweens and Spans	To improve flexibility and permeability
3.	Alcohol	Methanol or Ethanol	Hydrating medium

7. PREPARATION TRANSFEROSOMES:

7.1. Reverse Phase Evaporation Technique

Reverse phase evaporation entails evaporating the solvent from the emulsion. A two-phase mixture is bath-sonicated to create a water-in-oil emulsion, which is subsequently dried to a semisolid gel under reduced pressure in a rotary evaporator. The next stage is to use a vortex mixture and a forceful mechanical shake to cause a fraction of the water droplets to collapse. In these conditions, the lipid monolayer that covers the collapsing vehicles let neighbouring vesicles join together to form a bilayer, which led to the development of transferosomes.

7.2. Ethanol Injection Technique:

In this procedure, the drug-containing aqueous solution is heated while being stirred at a steady temperature. Aqueous solution is dropwise injected with an ethanolic solution of phospholipids and EAs. Lipid molecules precipitate when the ethanolic solution interacts with the aqueous medium, creating a bilayered structure. This method's benefits include scalability, reproducibility, and simplicity.

7.3. Thin Film Hydration Technique:

Phospholipids with a surfactant can be dissolved in a volatile organic solvent to create a thin layer. Then, using a rotary evaporator, it is evaporated above the lipid transition temperature. The prepared film is rotated at 60 revolutions per minute for 15 minutes at the appropriate temperature to hydrate it with buffer. At room temperature, the resultant vesicles will swell for 30 minutes. Then, using a bath sonicator for five minutes, the vesicles are sonicated, and the resulting transferosomes are obtained.

7.4. Modified Handshaking Method

The modified handshaking method and the rotary evaporation-sonication method have the same fundamental ideas. The lipophilic drug, the phospholipids, the edge activator, and the organic solvent are all introduced to a round-bottom flask for the modified handshaking procedure. The solvent should thoroughly liquefy all of the excipients, producing a clear, transparent solution. The organic solvent is then eliminated using handshaking evaporation rather than rotational vacuum evaporation. The round-bottom flask is partially submerged in a water bath that is kept at a high temperature (for instance, 40–60 °C). The flask wall then starts to generate a thin lipid coating. The flask is left overnight to allow the solvent to completely evaporate. After that, the produced film is gently shaken and hydrated with the proper buffer solution at a temperature above its phase transition point. At this point, the hydrophilic drug incorporation is possible.

7.5. Method involving Suspension Homogenization

A suitable quantity of edge activator is added to an ethanolic phospholipid solution to create transferosomes. After that, the produced suspension and buffer are combined to produce a total lipid concentration. The resulting mixture is then twice to three times sonicated, frozen, then thawed.

8. FACTORS AFFECTING PROPERTIES OF TRANSFEROSOMES:

TABLE NO: 2- FACTORS AFFECTING PROPERTIES OF TRANSFEROSOMES

Sr. No.	Factors	Properties that affect
1.	Phospholipids: Edge Activator Ratio	Entrapment efficiency, vesicle size and permeation ability
2.	Effect of Various Solvents	Solubility of all the formulation ingredients in the solvent and their compatibility with the solvent and also clearity of the formulation
3.	Effect of Various Edge Activators (Surfactants)	Deformability, entrapment efficiency
4.	Effect of the Hydration Medium	pH of the medium

9. CHARACTERIZATION OF TRANSFEROSOMES:

TABLE NO: 3- CHARACTERIZATION OF TRANSFEROSOMES

Sr. No.	Characterization	Apparatus/Method/Equipment
1.	Vesicle Size, Zeta Potential and Morphology	**1.** Dynamic light scattering (DLS) method or photon correlation spectroscopy (PCS) can be used to determine the vesicle diameter **2.** Structural changes are observed by transmission electron microscopy (TEM) **3.** The zeta potential is measured by the electrophoretic mobility technique using Malvern Zetasizer. **4.** The visualization of transfersome vesicles can be done by using the phase contrast microscopy or TEM
2.	Number of Vesicles Per Cubic mm	Hemocytometer and Optical microscope
3.	Entrapment Efficiency (%EE)	Centrifugation (separating untrapped drug)
4.	Degree of Deformability	Preparation is passed through many microporous filters of known pore sizes between 50 to 400 nm
5.	In Vitro Drug Release	Franz diffusion cell
6.	Stability of Transfersomes	As per ICH guidelines
7.	Drug Content	HPLC using UV detector
8.	Penetration ability	Fluorescence Microscopy

10. APPLICATIONS:

The use of transfersomes in the field of transdermal drug delivery has been thoroughly investigated during the past few decades. The section below provides descriptions of a few of these uses.

1. Insulin Delivery
2. Proteins and Peptides Delivery
3. Topical/Transdermal Immunization
4. Administration of NSAIDs
5. Delivering anaesthetics
6. Drug delivery for cancer treatment
7. Delivery of Anti-oxidants
8. Delivery of Corticosteroids
9. Delivery of Anti-inflammatory drugs

11. CONCLUSION:

In comparison to traditional vesicular systems, transfersomes are ultra-deformable carriers that enable the administration of a wide variety of drug compounds over the skin barrier. The primary factor for the transfer of transfersomes into the deeper epidermal layers is the osmotic gradient. Transferosomes are specifically created vesicular systems that must be optimised for each instance of a drug of interest in order to produce the most potent formulations and conclusive pharmacological effects. Additional research on transfersomes may result in innovative, potential therapeutic strategies against a variety of ailments.

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