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Review Article

Transferosomes: A promising vesicular-based skin-oriented drug delivery system

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ABSTRACT

Using vesicular carriers to reduce the obstructive effects of the stratum corneum has recently become a feasible option. The use of transferosomes, also known as ultradeformable lipids or elastic liposomes, for cutaneous administration has generated a lot of interest. They are mainly used to treat a range of chronic skin diseases, but they may also be used to guarantee patient compliance by allowing for concentrated and controlled distribution. The pore size of the stratum corneum may be adjusted by these self-assembled nanocarriers. In transferosomes, you may find edge activators (particular surfactants), phospholipids, buffering agents, and other things. Constructed vesicles have the required flexibility due to the effect of edge activators and their concentration. Elastic liposomes may improve drug solubility, drug loading efficiency, and therapeutic molecule permeability. Transferosomes have a high reflectivity as nanocarriers and offer a flexible basis for transdermal applications. These one-of-a-kind nanocarriers are also very supple and penetrate deeply. These systems are considered to be safe, with efficient delivery methods for chemical moieties that are pharmaceutically or aesthetically active. Recent research has revealed that ultradeformable liposomes are necessary for constant and efficient medication penetration.

Keywords: Transdermal delivery, Transferosomes, Self-assembled, Bioavailability, Ultradeformable vesicles, Skin permeation

INTRODUCTION

'Transferosome' is derived from the Latin word 'transferre,' which means 'to carry over,' and the Greek term 'soma,' which means 'body.' A transferosome (Figure 1) is a synthetic vesicle that resembles the characteristics of a cell vesicle or a cell in exocytosis, making it suitable for controlled and potentially targeted drug delivery. In 1991, Gregor Cevc proposed the transferosome as a

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fundamental concept. [1] A transferosome is a multi-component aggregation that is highly adaptive and stress-resistant. It's a vesicle with an aqueous core surrounded by a complicated lipid bilayer that's highly malleable. The vesicle is self-regulating and self-optimizing because the local composition and shape of the bilayer is interdependent. This enables the transferosome to effectively navigate through various transportation barriers. [2] The transferosomal drug delivery method acts as a drug carrier for non-invasive targeted drug administration and therapeutic agent sustained release, making medicine delivery simple and safe. The transferosomal drug delivery system has several potential advantages over traditional drug delivery systems, including avoiding first-pass metabolism, predictable and extended activity duration, the utility of short-half-life drugs, improved physiological and pharmacological response, minimizing undesirable side effects, avoiding drug level fluctuations, inter-patient and intra-patient variations, and mosiac delivery. In medical research, penetration enhancers, enhancers, iontophoresis, sonophoresis, and vesicular structures have all been utilized to increase the efficiency of material transfer across intact skin. [3]

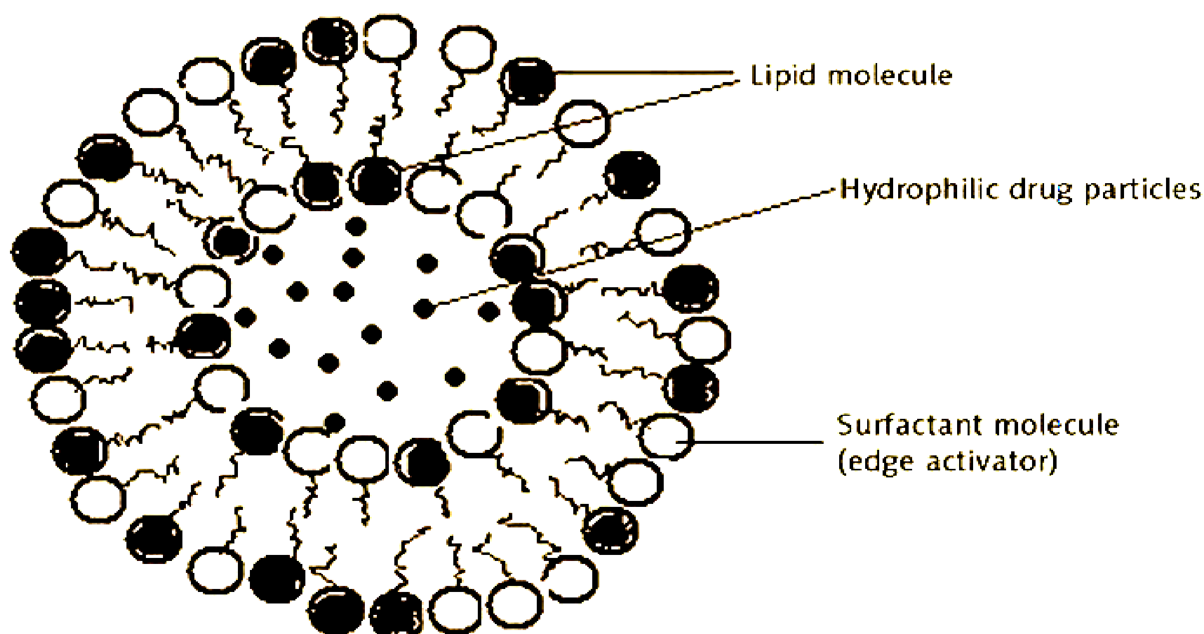

Figure 1. Structural representation of one transferosome unit.

Transferosomes were developed in order to utilise phospholipid vesicles as a transdermal drug carrier. Depending on the administration or application technique, these self-optimized aggregates with ultra-flexible membranes may reliably and effectively transport the medication into or through the skin. By squeezing themselves along the stratum corneum's internal sealing lipid, transferosomes overcome the barrier to skin penetration. [4] Due to the high vesicle deformability, which allows for self-adapting entry in response to mechanical force from the environment, this is feasible. The resulting flexibility of the transferosome membrane lowers the risk of complete vesicle rupture in the skin and allows transferosomes to follow the natural water gradient across the epidermis when applied under non-occlusive circumstances. Transferosomes may penetrate the intact stratum corneum through two intracellular lipid routes with distinct bilayer properties. [5] The self-optimizing deformability of traditional composite transferosomes membrane reacts to ambient stress when pushed against or lured into a small hole, enabling ultra-deformable transferosomes to change their membrane composition locally and reversibly. The transferosome components that can tolerate substantial membrane deformation concentrate in high-stress environments, whereas the molecules that are less adaptable are diluted. This lowers the energy cost of membrane deformation, enabling the ultra-flexible particles that arise to enter and flow through holes rapidly and efficiently. [6]

HUMAN SKIN - ANATOMY AND PHYSIOLOGY

The skin is a crucial organ that covers the whole external surface of the human body and serves as a barrier between the internal organs and the environment. The skin is a living organ that changes continuously during one's life as outer layers are shed and inner layers are replaced. The thickness of a person's skin varies depending on his or her anatomical position, gender, and age. [7] The skin is continuous and mucous membranes line the body's surface. The skin of an average adult covers

around 2 square metre and absorbs about a third of the blood that circulates through the body, as well as acting as a permeability barrier against the transdermal absorption of a variety of chemical and biological substances. The skin serves as a barrier between the inner workings of the circulatory system and the outside environment. [8] It guards against dangers such as physical, chemical, and microbiological. It acts as a thermostat to keep the body at a constant temperature. It helps to regulate blood pressure and protects the human body from UV radiation. The skin plays a significant role in medication permeation and absorption via the dermis. [9]

The structure of the skin is indicated by three distinct layers:

- The epidermis is the skin's outermost layer, which serves as a waterproof barrier and determines the color of our skin.
- The dermis, which lies under the epidermis and includes tough connective tissue, hair follicles, and sweat glands, is located beneath the epidermis.
- The hypodermis (deeper subcutaneous tissue) is made up of fat and connective tissue.

The epidermis is primarily made up of surface ectoderm, but it also contains melanocytes produced from the neural crest, antigen-processing Langerhans cells derived from bone marrow, and pressure-sensing Merkel cells derived from the neural crest. The dermis, which is mainly made up of the mesoderm, is made up of collagen, elastic fibres, blood vessels, sensory structures, and fibroblasts (**Figure 2**). [10]

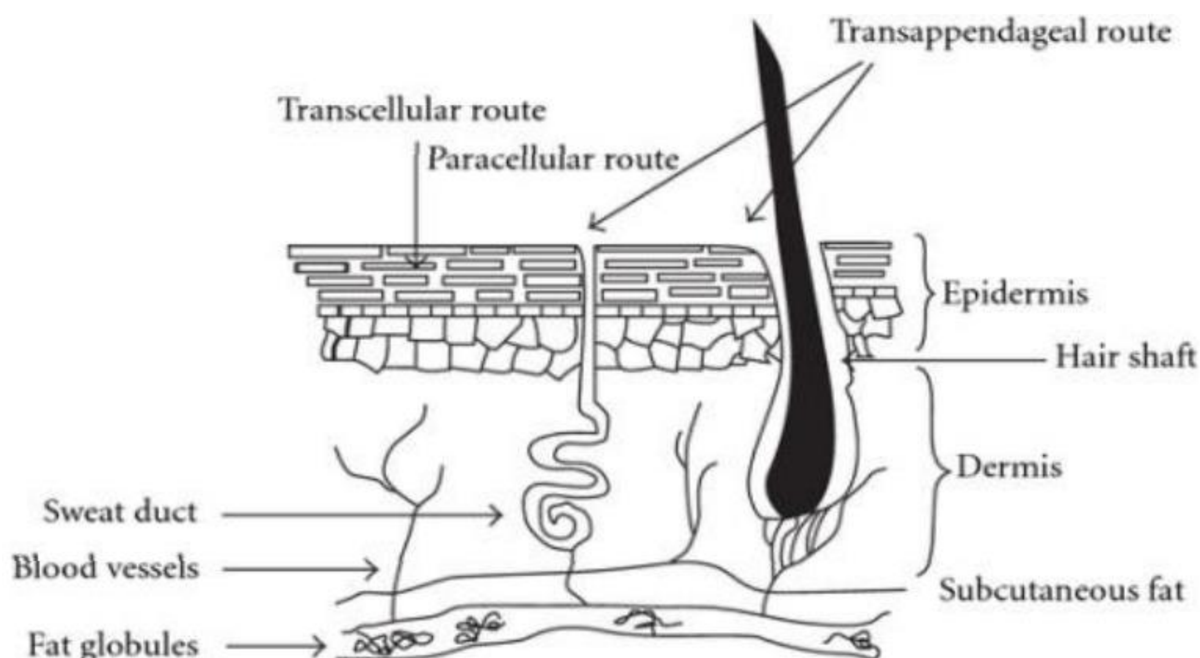

Figure 2. Schematic presentation of human skin.

Subcutaneous fat layer

The hypodermis, often known as the subcutaneous fat layer, links the dermis to the underlying body components. This layer is several centimetres thick in most regions of the body. This layer of adipose tissue's main job is to insulate the body and provide mechanical protection against physical damage. The major blood arteries and nerves supply oxygen and nutrients to the skin through the subcutaneous adipose layer, which may also provide a fast source of high-energy molecules. [11]

Dermis

The dermis contains blood and lymphatic vessels, nerve endings, pilosebaceous units such as hair follicles and sebaceous glands, and sweat glands such as eccrine and apocrine. It provides physiological support to the epidermis. It makes up the majority of human skin and is usually 3–5 mm thick. It's made up of a network of connective tissue that's submerged in a mucopolysaccharide gel, containing collagen fibrils for support and elastic tissue for flexibility. In terms of transdermal drug delivery, this layer is often regarded as merely gelled water, and therefore provides a minimal barrier to most polar medications, whereas the dermal barrier should be addressed when administering highly lipophilic substances. [12]

Epidermis
10 to 20 layers of cells make up the epidermis. This pluristratified epithelium also contains melanocytes, which play a role in skin coloration, and Langerhans' cells, which play a function in antigen presentation and immunological responses. The epidermis, like any epithelium, receives nutrition from the dermal vascular network. The epidermis is split into many layers. The stratum germinativum is the epidermis's most fundamental layer. The layers above the base layer are the stratum spinosum, stratum granulosum, stratum lucidum, and stratum corneum. [13]

Stratum Corneum
Corneocytes are flat, polyhedral-shaped, 2–3 µm thick, non-nucleated cells that make up the stratum corneum, which is 10–20 µm thick. Corneocytes are mostly composed of insoluble bundled keratins enclosed in a cell envelope kept together by cross-linked proteins and covalently bonded lipids. Corneodesmosomes are membrane junctions that assist the stratum corneum remain together by connecting corneocytes. [14] Exocytosis of lamellar structures during keratinocyte terminal differentiation supplies the majority of the lipids that make up the intercellular space between corneocytes. To maintain a healthy skin barrier, these lipids are required. The stratum corneum protects the skin against penetration and permeability. A penetrating molecule passes through both the lipophilic stratum corneum and the watery environment of the underlying living epidermis and upper dermis to reach the dermal vasculature for fast systemic distribution. [15]

MATERIALS EMPLOYED
In the formulation of transferosomes, phospholipids, surfactants, alcohol, colour, buffering agent, and other ingredients are often used. Soya phosphatidylcholine, egg phosphatidylcholine, dipalmitoylphosphatidylcholine, and other phospholipids are employed as vesicles-forming agents. To enhance flexibility, sodium cholate, sodium deoxycholate, Tween-80, Span-80, and other surfactants are used. Solvents such as ethanol or methanol may be used. A saline phosphate buffer is used as the hydration medium (pH 6.4). [16]

FEATURES OF TRANSFEROSOMES
Transferosomes feature a structure that contains both hydrophobic and hydrophilic moieties, enabling them to accept a wide range of solubility in pharmaceutical compounds. Transferosomes may bend and pass through constrictions 5 times to 10 times smaller than their own diameter without losing any function. This high deformability makes it easier for intact vesicles to enter. They may carry medicines with low and large molecular weights, including as analgesics, anesthetics, corticosteroids, sex hormone, anticancer, insulin, gap junction protein, and albumin. [17] They are biocompatible and biodegradable, similar to liposomes, since they are made of natural phospholipids. They have a high entrapment efficiency, which in the case of lipophilic medicines may reach 90%. They keep the medication enclosed from being broken down by the body's metabolism. They act as a storage facility, slowly releasing their contents. They may be used to administer both systemic and topical medications. Because the method is simple and does not need the use of pharmaceutically undesirable substances, it is easy to scale up. [18]

ADVANTAGES OF TRANSFEROSOMES
Transferosomes can deform and pass through narrow constriction without measurable loss.

- They have high entrapment efficiency, reaching up to 90% for lipophilic medicines.
- Because of its high deformability, intact vesicles may be pierced more efficiently.
- They can carry analgesics, anesthetics, corticosteroids, sex hormones, anticancer drugs, insulin, gap junction protein, and albumin, among other pharmaceuticals with low and high molecular weights.
- Transferosomes feature a structure that blends hydrophobic and hydrophilic moieties, enabling them to receive a wide range of solubility therapeutic compounds. They act as a storage facility, slowly releasing their contents.
- They are biocompatible and biodegradable, similar to liposomes, since they are made of natural phospholipids.
- They keep the medication enclosed from being broken down by the body's metabolism.
- Scalability is simple since the method is simple and does not need the use of pharmaceutically unwanted substances. [19]

LIMITATIONS OF TRANSFEROSOMES
- Transferosomes are chemically unstable due to their propensity for oxidative degradation.
- The purity of natural phospholipids is another issue that works against the utilization of transferosomes as drug delivery vehicles.
- The cost of transferosome formulations is prohibitively expensive. [20]

PREPARATION OF TRANSFEROSOMES
There are a variety of patented and published techniques for making transferosomes. Phosphatidylcholine is usually combined with

sodium cholate or another suitable surfactant in ethanol. The following are some of the most common approaches:

Suspension Homogenization Process

In this method, ethanolic soybean phosphatidylcholine is mixed with a sufficient amount of edge activators, such as sodium cholate. This suspension is mixed with a Triethanolamine-HCl buffer solution to get a total lipid concentration, then sonicated, frozen, and thawed for 2 to 3 times before being brought to the desired size, which is measured by photon correlation spectroscopy. The water is sterilised by passing it through a 0.2 mm micro porosity filter. A dynamic light scattering method is used to validate the final vesicle size. [21]

Reverse Phase Evaporation Method

In this method, lipids dissolved in organic solvents are put in a round bottom flask. An aqueous solution containing edge activators is injected during nitrogen purging. The medicine may be delivered to a lipid or aqueous medium depending on its solubility properties. The system is then sonicated until it forms a homogeneous dispersion that does not separate for at least 30 mins. The organic solvent is subsequently extracted at reduced pressure. Following that, the solution will change into a thick gel, which will be followed by the formation of vesicles. Non-encapsulated material and leftover solvents may be removed using dialysis or centrifugation. [22]

Rotary Film Evaporation Method

Bangham was the first to develop the revolving film evaporator method, which is also known as handshaking. In order to organize a thin layer, phospholipids and surfactants are needed. A phospholipid and ethanol solution, that is structured in a combination of crude solvents such as chloroform and methanol. In the study of multilamellar vesicles, this technique is often used. The solution is poured into a flask with a circular bottom and rotated at a constant temperature and pressure (higher than the glass transition temperature of lipids). The flask's walls develop a coating of lipids and edge activators. The lipids expand and form bilayer vesicles when the twisted film is moistened with an aqueous solution containing medicine. To make the right size vesicles, the superior vesicles may be sonicated or extruded. [23]

Modified Handshaking Process

This method is also known as the lipid film hydration technique. In a 1:1 ratio, ethanol and chloroform are mixed. This pharmacological combination dissolves lipids and edge activators. Evaporation is used to get rid of the solvent. At temperatures above the liquid transition point (43°C), handshakes are feasible. As a consequence of the constant rotation, a thin lipid coating develops on the flask wall. To enable the solvent to fully evaporate, the preparation is left overnight. The film is hydrated for 15 minutes with phosphate buffer and gently shaken at the proper temperature. [24]

Thin Film Hydration Technique

This method is classified into three steps:

1. An organic solvent is used to dissolve a thin covering of vesicle phospholipids and surfactants (such as chloroform or methanol). Heating occurs at a temperature higher than the lipid's transition temperature. To release the organic solvent combination, the process is carried out in a rotary evaporator. Any solvent remains are removed overnight by vacuuming.

2. Using a suitable buffer, the produced film is hydrated for one hour at 60 RPM. At room temperature, the vesicles are allowed to grow for 2 hrs.

3. Prepare small vesicles by sonicating prepared vesicles for 30 mins at 50°C or at room temperature in a bath sonicator. Sonication is done for 30 mins at 40°C while utilising a probe sonicator. A sandwich layer of 200 nm – 100 nm is produced by manually extruding the sonicated vesicles 10 times through a polycarbonate membrane. [25]

Ethanol Injection Method

The medication-containing aqueous solution is kept at a constant temperature by constant stirring. Drops of edge activators are introduced into the aqueous solution, along with an ethanolic phospholipid solution. The lipid molecules precipitate and form bilayered structures when the aqueous media comes into contact with the solution. When compared to other methods, the methodology is easy to scale up, simple to use, and highly repeatable, which offers a number of benefits. [26]

Freeze-Thaw Method

This technique involves exposure to both low and high temperatures. The multilamellar vesicles are first frozen at very low temperatures, then heated to extremely high temperatures. After 30 sec at 30°C, the prepared suspension is transferred to a tube and submerged in a nitrogen bath. They are then exposed to high temperatures in a water bath after they have been frozen. This procedure is repeated 8-times to 9-times. [27]

Vortexing / Sonication Method

Phosphate buffer is used to integrate the mixed lipids (edge activators, phosphatidylcholine, and medicinal medicines). After that, it's vortexed to make a milky suspension. The suspension

undergoes sonication before being extruded via polycarbonate membranes. [28]

OPTIMIZATION OF FORMULATION CONTAINING TRANSFEROSOMES

A variety of procedural variables may influence the transferosomes' preparation and quality. As a consequence, the method for preparing the food was enhanced and verified. The manufacturing method for the formulation determines the process variables. [29] The following are critical process variables in the formation of transferosomes:

1. The lecithin-to-surfactant ratio
2. The effect of various solvents
3. The effect of various surfactants
4. A hydration medium

The medication's entrapment efficiency was selected for optimization. Through the creation of a particular system, the other factors were kept constant.

MECHANISM OF ACTION OF TRANSFEROSOMES

A single amphipathic polymer, such as phosphatidylcholine, forms the carrier aggregate, which self-assembles into a lipid bilayer in aqueous solvents and closes into a simple lipid vesicle. A bilayer softening component, such as a biocompatible surfactant or an amphiphile medicine, improves lipid bilayer flexibility and permeability. The resulting transferosome vesicle may easily and rapidly adapt its shape to the environment by matching the local concentration of each bilayer component to the local tension experienced by the bilayer. [30] The artificial membrane of the transferosome distinguishes it from other vesicles because it is softer, more flexible, and more variable. High bilayer deformability in transferosomes has a positive effect on their ability to bind and retain water. A highly deformable and hydrophilic vesicle will attempt to avoid dehydration at all costs; this may involve a transport mechanism comparable to but not identical to forward osmosis. [31] A transferosome vesicle put on an open biological surface, such as non-occluded skin, crosses the barrier and migrates into the water-rich deeper layers to ensure appropriate hydration. Barrier penetration requires reversible bilayer deformation, yet the integrity of the vesicle or barrier properties must not be compromised in order for the underlying hydration affinity and gradient to remain in place. Because the transferosome is too large to distribute through the skin, it must find and force its own route into the organ. The transferosome vesicles assist the carrier's ability to expand and overcome the hydrophilic pores in the epidermis or another barrier (e.g. the plant cuticle). Because the agent is gradually released from the drug carrier, the drug molecules may spread and bind to their target. Drug delivery to an intracellular action site may also involve the carrier's lipid bilayer fusion with the cell membrane unless the vesicle is actively picked up by the cell in a process known as endocytosis. [32]

CHARACTERIZATION OF TRANSFEROSOMES

Liposomes, niosomes, and micelles are all used to describe transferosomes. The following characterisation criteria for transferosomes must be evaluated.

1. Vesicle size distribution and zeta potential

The Dynamic Light Scattering device from Malvern Zetasizer was used to assess vesicle size, size distribution, and zeta potential.

2. Vesicle morphology

To determine vesicle diameter, photon correlation spectroscopy (PCS) or the dynamic light scattering (DLS) method may be employed. Samples were made in distilled water, filtered via a 0.2 mm membrane filter, and diluted with filtered saline for PCS or DLS investigations. Transferosome vesicles may be seen via TEM, phase contrast microscopy, and other methods. Vesicle stability may be estimated by tracking the size and form of vesicles over time. DLS searches for structural changes, while TEM looks for mean size.

3. Number of vesicles per cubic mm

This is a critical component for enhancing the composition of the process and other variables. In a 0.9 percent sodium chloride solution, non-sonicated transferosome formulations are diluted five times. A hemocytometer and an optical microscope may be used to further investigate the situation. The following formula is used to count and compute the transferosomes in 80 tiny squares:

Total number of Transferosomes per cubic mm = (Total number of Transferosomes counted × dilution factor × 4000) / Total number of squares counted

4. Entrapment efficiency

Entrapment efficiency is calculated using the percentage entrapment of the medicine added. The unentrapped medicine was separated using a mini-column centrifugation method to determine the entrapment efficiency. After centrifugation, the vesicles were burst with 0.1% Triton X-100 or 50% *N*-propanol. The entrapment efficiency is calculated as follows:

Entrapment efficiency = (Amount entrapped / Total amount added) × 100

5. Drug content

The drug content may be assessed using one of the instrumental analytical techniques, such as

modified high-performance liquid chromatography method (HPLC) with a UV detector, column oven, auto sample, pump, and computerized analysis software, depending on the pharmacopoeia drug's analytical method.

6. Turbidity measurement
The turbidity of medicine in an aqueous solution may be determined using a nephelometer.

7. Degree of deformability or permeability measurement
One of the most important and distinctive criteria for the characterization of transferosomes is permeability study. Pure water is used as a control in the deformability test. Transferosomes are prepared by filtering them through a large number of pores of varying sizes. After each pass, DLS measurements are utilized to record particle size and size distributions.

8. Penetration ability
The ability of Transferosomes to penetrate may be assessed using fluorescence microscopy.

9. Occlusion effect
Occlusion of the skin is believed to enhance medication penetration in traditional topical treatments. Elastic vesicles, on the other hand, have a similar issue. The hydrotaxis of water is the primary driving force for vesicle penetration through the skin, from its relatively dry surface to its water-rich deeper layers. Because it prevents water from evaporating from the skin, occlusion has an impact on hydration forces.

10. Surface charge and charge density
Transferosomes' surface charge and charge density may be determined using Zetasizer.

11. *In vitro* drug release
In vitro medication release study is used to calculate the penetration rate. The time needed to establish steady-state permeation and the permeation flux at a steady-state, as well as information from in vitro testing, are used to enhance the formulation before more expensive in vivo studies. For evaluating drug release, transferosome suspension is incubated at 37°C for many hours, and samples are taken at different times, with the free drug separated by microcolumn centrifugation. The amount of drug released is then calculated indirectly, beginning with the initial amount of drug entrapped.

12. *In vitro* Skin permeation Studies
A modified Franz diffusion cell with a receiver compartment capacity of 50 ml and a diffusion area of 2.5 cm^2 was used in this study. *In vitro* drug study was carried out using goat-skin in a phosphate buffer solution (pH 7.4). The penetration experiments were performed using fresh goat abdomen skin acquired from the slaughterhouse. After removing the hairs from the abdomen, the skin was moistened in a normal saline solution. The adipose tissue layer was removed by rubbing it with a cotton swab on the skin's surface. The skin was kept at a temperature of 0-40°C and kept in an isopropyl alcohol solution. To perform the skin permeation study, the treated skin was put horizontally on the receptor compartment of the Franz diffusion cell, with the stratum corneum side pointing upwards towards the donor compartment. The effective permeation area exposed to the receptor compartment from the donor compartment was 2.5 cm^2, and the receptor compartment was 50 ml in capacity. A magnetic bar was used to swirl 50 ml of phosphate-buffered saline (pH 7.4) through the receptor compartment at 100 RPM. The formulation was applied to the skin (equivalent to 10 mg of medicine), and the top of the diffusion cell was covered. At regular intervals, 1 ml aliquots of the receptor media were withdrawn and replaced with an equal quantity of fresh phosphate buffers to maintain sink conditions (pH 7.4). Each aliquot's correction factors were used to determine the release profile. The materials were examined using any instrumented analytical technique.

13. Physical stability
The original percentage of medication entrapped in the formulation was determined, and it was preserved in sealed glass ampoules. The ampoules were maintained at 4 ± 2°C, 25 ± 2°C, and 37 ± 2°C for at least three months. Samples from each ampoule were examined after 30 days to determine whether there was any drug leaking. By keeping the original drug entrapment at 100%, the percent drug loss was calculated. [33-35]

APPLICATIONS OF TRANSFEROSOMES

1. Delivery of insulin
Transferosomes have shown to be a feasible technique for non-invasively delivering large molecular weight medicines to the skin. Insulin is often administered through a painful subcutaneous injection. All of these problems are addressed by encapsulating insulin in transferosomes (transfersulin). Depending on the carrier composition, the first sign of systemic hypoglare occurs 90 mins to 180 mins after Transfersulin injection on healthy skin.

2. Delivery of corticosteroids
Transferosomes have been used to administer corticosteroids in the past. Transferosomes improve site-specificity and overall drug safety of corticosteroid injection into the skin by changing the amount of medicine given epicutaneously. Transferosome-based corticosteroids are

physiologically active at far lower dosages than those currently utilised to treat skin conditions.

3. Delivery of proteins and peptides

Proteins and peptides have been transported by transferosomes for a long time. Proteins and peptides are large biogenic molecules that are difficult to absorb and completely degraded in the gastrointestinal tract when consumed orally. These are the reasons why these peptides and proteins must be injected into the body in the first place. A number of solutions have been devised to alleviate these conditions. Transferosomes have a bioavailability that is similar to that of a subcutaneous injection of the same protein solution. A strong immunological response was elicited after several epicutaneous injections of transferosomal preparations of this protein.

4. Delivery of interferons

Transferosomes have been shown to carry interferons such as leukocytic produced interferon-α (INF-α). INF-α is an antiviral, antiproliferative, and immunomodulatory protein that occurs naturally. When employed as drug delivery vehicles, transferosomes have the potential to provide controlled drug release and improve the stability of labile medicines. For potential transdermal usage, researchers looked into the composition of transferosmes including interleukin-2 and interferon-α. Transferosome-trapped IL-2 and INF-α were shown to be supplied in sufficient quantities for immunotherapy.

5. Delivery of Anticancer

Transdermal delivery of anti-cancer medicines like methotrexate was tried utilising transferosome technology. The results were favourable. This offers a new treatment approach, especially for skin cancer.

6. Delivery of anesthetics

Under the proper conditions, the application of anesthetics in the suspension of highly deformable vesicles, transferosomes, produces topical anesthesia in less than 10 mins. The maximal level of pain insensitivity is comparable to that of a subcutaneous bolus injection (80%), although transferosomal anaesthetics have a longer duration of effect.

7. Delivery of Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)

The use of nonsteroidal anti-inflammatory drugs (NSAIDs) has been associated to a number of gastrointestinal side effects. These problems may be solved by delivering ultra-deformable vesicles through transdermal distribution. Both Diclofenac and Ketoprofen have been studied in the past. The commercialization of ketoprofen in a Transferosome formulation was authorised by Swiss regulatory authorities in 2007, and the medicine will be marketed under the brand name Diractin.

8. Delivery of Herbal Drugs

Transferosomes may penetrate the stratum corneum and provide nutrients to the skin, enabling it to continue to function. Capsaicin Transferosomes, which have better topical absorption than pure capsaicin, have been created in this respect.

9. Applications in cosmetics

Cosmetics demand is constantly rising across the world as people seek to improve their appearance and avoid skin damage. Cosmeceutical products enhance one's look while also offering medicinal benefits. [36-38]

CONCLUSION

The transdermal route has long been the favoured mode of drug administration due to its distinct and diverse characteristics. The stratum corneum's impermeability, on the other hand, poses a significant problem for transdermal medication delivery since it acts as a complete barrier to drug penetration. As a consequence, the effective delivery of hydrophilic and hydrophobic medications, as well as amphiphilic compounds, is emphasised by the transferosomal system. Transferosomes are an appropriate and exceptional method because of their decreased dose frequency, better efficacy, greater loading capacity, and larger topical applications, as well as greater stability properties. Transferosomes have a bright future as a site-specific delivery system for active medicines, as well as in a range of cosmetic applications. In terms of oxidative degradation, purity, and retention quality, there are still a few problems to iron out. As a consequence, future process enhancements will need special considerations and technological advancements. In order to promote the future possibilities of these endowed nanocarriers, advancements in the synergistic potential of components and active chemicals must be studied worldwide. It's also worth mentioning that, prior to industrial scale-up, substantial study based on compelling preclinical and clinical studies is required to get the data needed to establish the safety of complex medicines. Novel transferosomes will most likely focus on improved treatment regimens using more complex, promising, and well-organized new methods, which will need improvements in scientific perspectives. In order to mitigate the current drawbacks of transferosomes, it is also necessary to investigate new medicinal excipients with additional characteristics. In the future, industrial pharmaceutical companies may investigate new prospects for significant

developmental characteristics of properly tailored transferosomes.

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CONFLICT OF INTEREST
The authors declare no Conflict of Interest regarding the publication of the article.

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