Transferosomes: A Highly Effective Vesicular Carrier System for Improved Transdermal Drug Delivery

Bhagya Shree

e- mail – singhmanssi31@gmail.com

Hindu college of Pharmacy, Sonipat - 131001

ABSTRACT

A new vesicular derivative called transferosomes has been created to lessen improper transdermal absorption of both high and low molecular-weight drugs. Surfactants and transferosomes can be used together to enhance drug loading, stability, skin penetration, and controlled drug distribution. They can be used topically or systemically to provide medications, and scaling them up is made simple by their basic processes. Nanotechnology is advancing the development of vesicular drug delivery systems like transferosomes, niosomes, proniosomes, liposomes, ethosomes, and electrosomes.The "osmotic gradient" or transdermal gradient, where an amphiphilic bilayer forms, is the primary method for delivering active chemicals through the skin.The release of medication from transferosomes, which can pass through mucosal layers and aid in the distribution of drugs via transdermal and dermal routes, is governed by the diffusion mechanism.Through the use of a thin film hydration process, transfersomes are created by dissolving surfactant and phosphatelipids in a volatile organic solvent. The finished goods are homogenised by hand extrusions and then exposed to sonication. Transferosomes are useful in the transport of insulin, corticosteroids, proteins, and peptides. They can also be utilised to transport non-steroidal anti-inflammatory drugs, herbal treatments, anaesthetics, and anticancer drugs.

KEYWORDS: Transferosomes, Transdermal drug delivery system, Modified Transferosomes, drug carrier.

INTRODUCTION

One of the most significant advances in vesicle research has been the development of a novel vesicular derivative called "transferosomes," which has made it possible to reduce the faulty transdermal penetration of several low- and high-molecular-weight medications [1].The recently introduced unique drug carriers are transfersomes, highly malleable vesicles that can transport big molecules through intact mammalian skin. In its broadest definition, a transfersome is a device that naturally penetrates skin to transfer medications from the application to the intended location [2-4].Transferosomes are a unique kind of liposome that are made up of an edge activator and phosphatidylcholine. These are flexible, soft vesicles designed to improve the delivery of active drugs [5].The German business IDEA AG registered them, and it uses them to refer to its in-house developed medicine delivery technique.The Latin term "transfere," which means "to carry across," and the

Greek word "soma," which means "body," are the sources of the name, which means "carrying body."An artificial vesicle that mimics a real cell vesicle is called a transferosome carrier. It is hence appropriate for regulated and focused medication delivery. It can be functionally understood as a lipid droplet with enough deformability to easily pass through pores considerably smaller than the droplet itself. It is a complicated aggregate that is extremely flexible and sensitive to stress.Its ideal shape is a very malleable vesicle with a complex lipid bilayer encircling an aqueous centre.The vesicle is both self-regulating and self-optimizing due to the interdependency of the bilayer's structure and local composition .Because of this, transferosomes are able to effectively pass through a variety of transport barriers and function as drug carriers for targeted, non-invasive drug delivery and therapeutic agent release that is sustained.Using vesicle formulations as skin delivery systems is one of the most contentious approaches of drug delivery through the skin. Combining solid and liquid (oil) lipids with surfactants in an aqueous solution is a common technique to get around some of the difficulties associated with transdermal medication administration. Edge activators are employed in addition to PCs and liposome-derived cholesterol to cause vesicle deformability. Better drug loading, stability, skin penetration, and regulated drug distribution are the outcomes of this combination [6-9]. These characteristics can be modified further to create transferosomes, a novel class of ultra-flexible carriers that improve skin permeability [10]. Because transferosomes may deliver higher concentrations of active ingredients to the skin's deeper layers, they are a desirable drug delivery vehicle for transdermal therapy. Transferosomes enter the SC via the intracellular or transcellular pathway by forming a "osmotic gradient" [11]. Transferosomes exhibit demonstrable losslessness in the face of narrow constriction, ranging from five to ten times smaller than their own diameter. Higher deformability allows intact vesicles to penetrate more easily.Both low and large molecular weight medications, including as albumin, corticosteroids, sex hormone, insulin, gap junction protein, and analgesics, can be carried by them. They are similar to liposomes in that they are made of natural phospholipids, making them both biocompatible and biodegradable. When it comes to lipophilic drugs, their entrapment efficiency is close to 90%.They guard against the drug's metabolic breakdown while it is encapsulated. They serve as a depot, progressively discharging their contents. They can be applied topically or systemically to deliver drugs. Simple procedures that don't require long processes, needless use, or compounds that are unsuitable for use in pharmaceuticals make them easy to scale up [12].

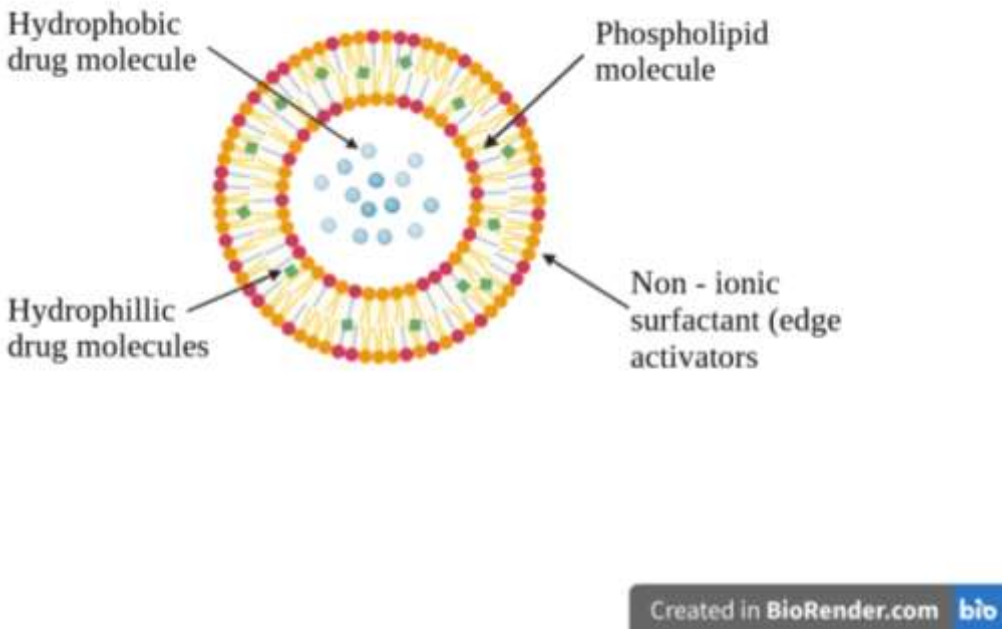

Figure1:- An illustration of a transferosome vesicle.

Transferosome composition and structure

Phospholipids such as phosphatidylcholine are included in transferosomes, which form lipid bilayers in aqueous environments to create vesicles. Bilayer elasticity and fluidity are increased by edge activators, which are typically single chain surfactants like sodium cholate or Tween 20 [13, 14]. Phospholipids and surfactants combine to form transferosomes, a kind of vesicular carrier that can encapsulate drugs that are both hydrophilic and hydrophobic [15,16]. Their structure combines hydrophilic and hydrophobic moieties, allowing them to store a variety of solubility-based medicinal compounds. In transfersome preparations, 10–25% surfactants or edge activators are frequently used. These consist of dipotassium glycyrrhizinate, sodium cholates, sodium deoxycholate, Tweens and Spans (Tween 20, Tween 60, Tween 80, Span 60, Span 65, and Span 80), and Tweens and Spans. These compounds are biocompatible and soften bilayers, increasing the permeability and bilayer flexibility of vesicles [17–20]. Transferosomes have the ability to bend and pass through microscopic constriction (between five and ten times smaller than their own diameter) without causing obvious loss, which allows for better penetration of intact vesicles. They can be made using a variety of techniques, such as ether injection, reverse-phase evaporation, and thinfilm hydration [21].A saline phosphate buffer (pH 6.5–7) or water make up the hydrating medium, while 3–10% alcohol (ethanol or methanol) serves as the solvent [22-23].Because they are composed of phospholipids and surfactants, they have the potential to encapsulate both hydrophilic and hydrophobic medicines. Transferosomes can adapt to environmental stress and change the makeup of their membrane locally and reversibly because of their high and self-optimizing deformability. They may pass through small constrictions thanks to this characteristic without noticeably losing distortion. Since intact vesicles are highly deformable and hence easier to penetrate, they are an excellent choice for transdermal medication delivery. The infrastructure of transferosomes, which consists of hydrophobic and hydrophilic

moieties, allows them to retain therapeutic compounds with varying degrees of solubility [20].As a result, the resulting transfersome vesicle with optimised permeability and flexibility can quickly and readily change its form by modifying the local concentration of each bilayer component in response to the bilayer's local stress. Thus, the "softer," more malleable, and more adaptable artificial membrane of the transfersome sets it apart from such more traditional vesicles Table 1

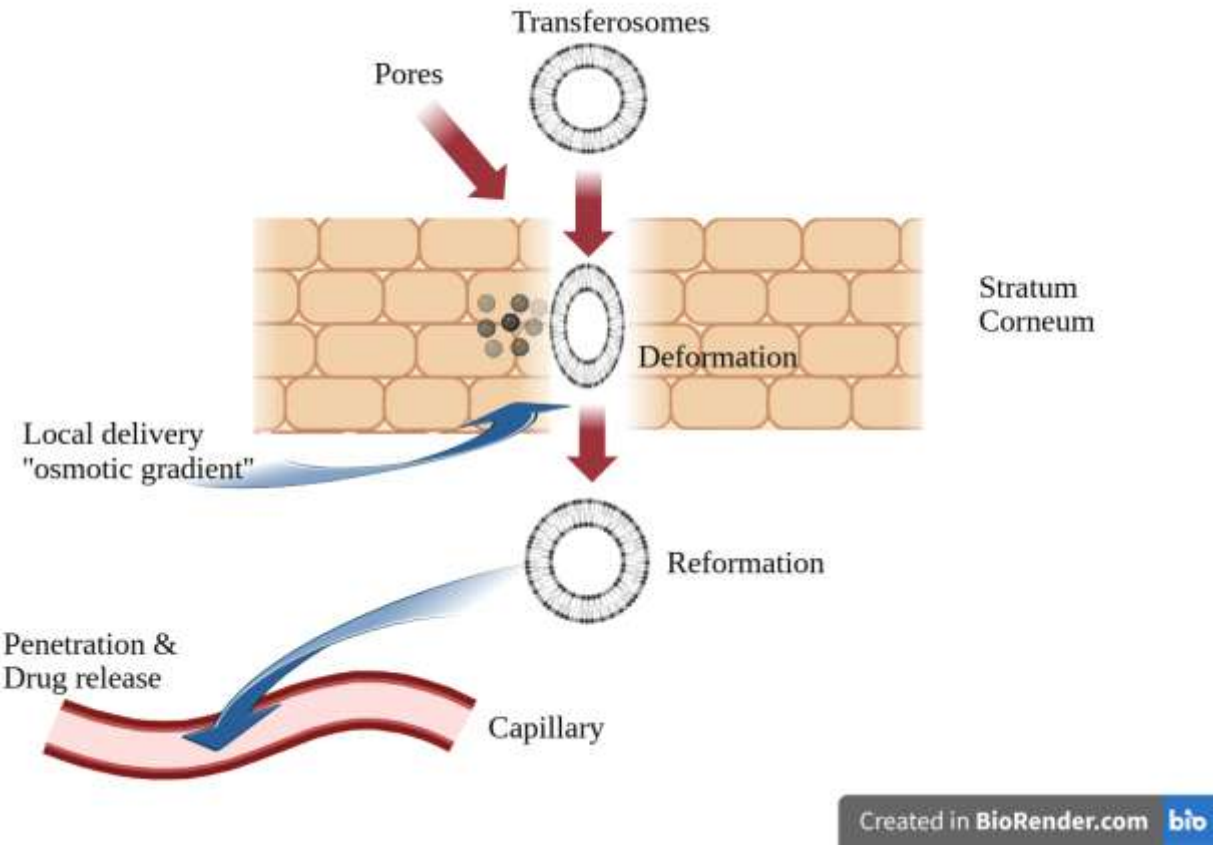

Figure 2:- Transferosome penetration mechanism through the skin.

Ingredient	Examples	Functions
Phospholipids	Soya Phosphatidycholine Egg Phosphatidycholine Disteryl Phosphatidycholine	Vesicle forming Component
Surfactant	Sodium Cholate Sodium Deoxy Cholate Tween 80 Span 80	For providing Flexibility
Alcohol	Ethanol	Solvent

	Methanol	
Dye	Rhodamine-123 Rhodamine –DHPE Flurescein –DHPE Nil red 6 Carboxy fluorescence	Scanning Laseer Microscopy (CSLM) Study
Buffering Agent	Saline phosphate buffer (Ph-6.5) 7% v/v ethanol Tris buffer (Ph-6.5)	Hydrating medium

TRANSFEROSOMES V/S OTHER CARRIER SYSTEM

The vesicular drug delivery systems known as transferosomes, niosomes, proniosomes, liposomes, ethosomes, and electrosomes have garnered interest in the field of nanotechnology [24–27]. from these, transferosomes hold great promise for transdermal drug delivery because of their capacity to enter the skin through the pores, encapsulate molecules that are both hydrophilic and lipophilic, extend the duration of the drug in the systemic circulation, reach the intended organs and tissues, and decrease toxicity while boosting bioavailability [25–26]. Because of the great aggregate deformability that results, transfersomes can spontaneously pierce the skin. The high transfersome surface hydrophilicity, which compels people to look for areas with strong water activity, supports this propensity. Given that the micellar suspension has a far higher surfactant content than transfersomes (PC/sodium cholate, 65/35 w/w%, respectively), it is quite likely that the surfactant's fluidisation of the stratum corneum is not the only factor contributing to the transfersomes' high penetration capacity. Therefore, if the improved penetrating capability of the transfersomes was produced by the solubilisation of the skin lipids, one would expect even better penetration performance from the micelles. The fact that the higher surfactant content in the mixed micelles has no influence on the efficiency of material transport into the skin disproves this theory. Conversely, even when administered non-occlusively, mixed micelles remain restricted to the uppermost layer of the stratum corneum [28]. Conversely, prosniosomes are aqueous formulations of nonionic surfactant-coated carrier systems that dissolve in water and instantly transform into niosomes when hydrated. They may also improve the solubility, bioavailability, and absorption of specific drugs in addition to resolving the instability problems with liposomes and niosomes [24]. Niosomes are tiny lamellar structures that are created when cholesterol and a non-ionic surfactant from the alkyl or dialkyl polyglycerol ether family are mixed together and then hydrated in water. These structures can be used as drug carriers for both lipophilic and amphiphilic substances [27].

Advantages of Transferosomes

- They exhibit a high entrapment efficiency, close to 90% in the case of lipophilic drugs.
- Transferosomes are a valuable drug delivery mechanism for poorly soluble medicines because they are ultra-deformable vesicles that can fit through tiny pores that are smaller than their size [29].
- The architecture of transferosomes, which consists of both hydrophobic and hydrophilic moieties, allows them to store therapeutic compounds with a wide range of solubility. Transferosomes are able to bend and flow through constriction that is 5–10 times smaller than their own diameter with little loss.
- They are composed of biocompatible and biodegradable lipids and surfactants, transferosomes are a good choice for drug delivery applications [30].
- act as a transporter for drugs with and without high molecular weights, entering the stratum corneum by naturally generating an osmotic gradient [31, 32].
- Minoxidil cutaneous administration and possible ocular delivery of cyclosporine A have both been studied with transferosomes. Additionally, they are intended to deliver active pharmaceutical ingredients (APIs) to respiratory tract inflammation-affected cells selectively [31, 32].
- Transferosomes have the potential to enhance patient acceptability by facilitating painless drug delivery, lowering administration frequency.
- Various lipids, surfactants, and edge activators can be used into transferosome formulations to achieve enhanced penetration and a broad spectrum of solubilities [29].
- Transferosomes have the ability to circumvent first-pass metabolism, a prevalent problem with traditional oral drug delivery methods, which can result in more patient compliance and decreased adverse effects.
- These systems allow for self-administration [31, 32].

Disadvantages of Transferosomes

- Formulations for transfersomes are costly.
- The tendency of transfersomes to undergo oxidative destruction makes them chemically unstable [33].
- Another factor working against the use of transfersomes as drug delivery vehicles is the purity of natural phospholipids [34].
- It is possible that transferosomes have a restricted ability to load medications and that they are not appropriate for all drug kinds [35].
- It provides hydrophilic skin structures with progressive therapeutic advantages [36].
- Their stability and drug release qualities can be impacted by variations in pH and temperature, as they are susceptible to these changes [29].

MECHANISM OF TRANSFEROSOMES

Transferosomes were developed in order to use the advantages of phospholipid vesicles as a transdermal drug delivery system. Depending on the application or administration technique used, these self-optimised aggregates can distribute medication through or into the skin with high efficiency and repeatability thanks to their ultra-flexible membrane. The process that improves the transport of active chemicals through and into the skin is currently poorly understood. Two different action mechanisms have been suggested.The "osmotic gradient or transdermal gradient" has been identified as the main mechanism by which transferosomes penetrate the skin [38]. where an amphiphilic bilayer is formed by the colloidal particles that comprise the vesicles. While the hydrophobic pharmaceuticals are confined in the lipid bilayer, the hydrophilic drugs are often transported by the vesicular drug delivery mechanisms within the internal aqueous compartment [39]. On the other hand, therapeutic agent carrier vesicles enable passage across skin, making transferosomes ultra-flexible and self-optimizing, due to their increased deformability and ability to associate with the tissue layer versatility and integrity of the transferosome [40].

The diffusion mechanism, which is impacted by the drug's concentration, the characteristics of the lipid matrix, and the external environment, controls the release of the medication from the transferosomes [41]. The capacity of transferosomes to deeply penetrate mucosal layers improves the bioavailability of medications. The transferosomes' elastic and pliable membrane is thought to be the cause of this penetration [42]. Drug distribution by transdermal and dermal means is possible using transferosomes. The contact between the lipids in the transferosomes and the lipid layer of the skin is the mechanism of skin permeation, and it can help the drug pass through the skin [43].

Method of Preparation of Transferosomes:

1. Thin film hydration technique is employed for the preparation of Transfersomes which comprised of three steps: [44,45,46]

- The components of vesicles, phospholipids and surfactant, are dissolved in a volatile organic solvent (chloroform-methanol) to create a thin layer. The organic solvent is then removed using a rotary evaporator above the lipid transition temperature, which is 50°C for dipalmitoylphosphatidylcholine and ambient temperature for pure PC vesicles. The final traces of the solvent were removed overnight under Hoover.
- The resulting thin film is hydrated with buffer (pH 6.5) by rotating it at 60 rpm for an hour at the proper temperature. The resulting vesicles inflated for two hours at room temperature.
- The finished products were sonicated for 30 minutes at ambient temperature or 50°C using a bath sonicator or a probe sonicated for 30 minutes at 4°C to produce small vesicles. The sonicated vesicles were homogenised by ten hand extrusions across a sandwich of 200 and 100 nm polycarbonate membranes.

2. The following procedures were included in the modified hand shaking, lipid film hydration technique that was developed for the creation of Transfersomes: [47-50]

- A 1:1 solution of ethanol and chloroform was used to dissolve the medication, lecithin (PC), and edge activator. While handshaking over the lipid transition temperature (43°C), the organic solvent was evaporated. A thin lipid coating formed inside the flask wall as it rotated. To allow the solvent to fully evaporate, the thin coating was left overnight.
- The film was then hydrated with phosphate buffer (pH 7.4) and gently shaken for 15 minutes at the proper temperature. The transfersome suspension was kept hydrating for an hour at 2–8°C.

EVALUATION OF TRANSFEROSOMES

Transferosomes are evaluated similarly to liposomes, niosomes, and micelles in general [51]. For transferosomes, the characterisation parameters listed below must be examined.

1. Vesicle size distribution and zeta potential - Malvern Zetasizer's Dynamic Light Scattering device was used to measure the vesicle's size, size distribution, and zeta potential [52, 53].

2. Vesicle morphology - Vesicle diameter can be determined using photon correlation spectroscopy or the dynamic light scattering (DLS) approach. Filtered saline was used to dilute the samples after they were produced in deionised water and run through a 0.2 mm membrane filter. The samples were sized using photon correlation spectroscopy or dynamic light scattering (DLS) measurements. Transferosome vesicles can be observed through the use of methods such as TEM and phase contrast microscopy. Vesicles' stability over time can be ascertained by their size and shape. DLS measures mean size, while TEM looks for structural alterations [52, 53].

3. Number of vesicles per cubic mm - In order to optimise the composition and other process factors, this parameter is crucial. The formulations of non-sonicated transferosomes are diluted five times using a 0.9% sodium chloride solution. For additional research, an optical microscope and hemocytometer can be employed [54].The Transferosomes in80 small squares are counted and calculated using the following formula: Total number of Transferosomes per cubic mm= (Total number of Transferosomes counted × dilution factor × 4000) / Total number of square counted.

4. Entrapment efficiency - The percentage of the additional medicine that is entrapped indicates the entrapment efficiency. The mini-column centrifugation method was used to separate the unentrapped medication in order to measure the entrapment efficiency. After centrifugation, the vesicles were disrupted using 0.1% Triton X-100 or 50% npropanol [53]. The entrapment efficiency is expressed as: Entrapment efficiency = (Amount entrapped / Total amount added) ×100.

5. Drug content - Depending on the analytical method of the pharmacopoeial drug, the drug content can be found using one of the instrumental analytical methods, such as modified high performance liquid

chromatography method (HPLC method) using a UV detector, column oven, auto sample, pump, and computerised analysis program [55].

6. Turbidity measurement - The nephelometer can be used to measure the turbidity of a medication in an aqueous solution [52].

7. Degree of deformability or permeability measurement - Permeability analysis is one of the crucial and distinctive parameters for characterising transferosomes.The pure water standard is used in the deformability investigation. The manufacture of transferosomes is run through a large number of known-sized pores (via a sandwich of several microporous filters, whose pore diameters range from 50 nm to 400 nm, contingent upon the transferosome suspension used initially). Dynamic light scattering (DLS) measurements are used to record particle sizes and size distributions following each pass [52, 56].

8. Penetration ability - Fluorescence microscopy can be used to assess the penetration capacity of transferosomes [53, 56].

9. Occlusion effect - When using traditional topical medicines, occlusion of the skin is thought to aid in drug penetration. However, this turns out to be harmful for elastic vesicles. The primary mechanism for vesicles to permeate through the skin from its comparatively dry surface to its deeper, water-rich parts is hydrotaxis, or movement in the direction of water. Because it stops water from evaporating off skin, occlusion has an impact on hydration forces [52].

10. Surface charge and charge density - Zetasizer can be used to measure the surface charge and charge density of transferosomes [53, 54].

11. In-vitro drug release - A drug release study conducted in vitro is used to calculate the penetration rate. Prior to more costly in vivo tests, the formulation is optimised using data from invitro research, the time required to reach steady state permeation, and the permeation flow at steady state. Transferosome suspension is incubated at 320C, samples are taken at various periods, and the free drug is separated using micro column centrifugation in order to determine drug release. Next, using the amount of drug entrapped at zero times as the beginning amount (100% entrapped and 0% released), the amount of drug released is computed indirectly [53,54].

12. In-vitro Skin Permeation Studies: A modified Franz diffusion cell used in this study had a receiver compartment volume of 50 ml and an effective diffusion area of 2.50 cm^2. An in vitro drug study using goat skin in phosphate buffer solution (pH 7.4) was conducted. Fresh goat belly skin was used in the permeation testing after being procured from an abattoir. The skin on the abdomen was moisturised with a standard saline solution after the hair was shaved off. The fat layer was removed by rubbing the skin with a cotton swab. Between 0 and 40°C, skin was maintained in an isopropyl alcohol solution. To investigate skin permeation, the stratum corneum side of the treated skin was placed horizontally on the receptor compartment, pointing upward

towards the donor compartment of the Franz diffusion cell. Receptor compartment volume was 50 ml, and effective permeation area between donor and receptor compartments was 2.50 cm^2. The receptor compartment was maintained at 37 ± 0.5°C, and 50 ml of phosphate buffer (pH 7.4) saline was stirred with a magnetic bar at 100 RPM. The formulation (equivalent to 10 mg of medication) was applied to the skin, and the top of the diffusion cell was then covered. At appropriate intervals, 1 ml aliquots of the receptor media were removed, and they were promptly replaced with an equivalent volume of fresh phosphate buffers (pH 7.4) to maintain sink conditions. Correction factors for each aliquot were included while calculating the release profile. Samples were examined using any instrumental analytical method [49, 50].

13. Physical stability: The first proportion of the medication trapped in the formulation was noted when glass ampoules were sealed. The ampoules were stored at 4 degrees Celsius (refrigerated), 25 degrees Celsius (room temperature), and 37 degrees Celsius (body temperature) for at least three months. Samples from every ampoule were analysed after 30 days to see whether any medication had been spilt. The percentage of drug loss was calculated by keeping the initial drug entrapment at 100% [55, 56].

APPLICATION OF TRANSFERSOMES

1. Delivery of Insulin:Transferosomes are a successful method for applying such high molecular weight medications topically in a non-invasive manner. Insulin is usually injected subcutaneously, which is a cumbersome method. Encapsulating insulin into transferosomes, also known as transfersulin, solves all of these issues.Depending on the particular carrier composition, the first signs of systemic hypoglycemia can appear 90 to 180 minutes after transfersulin is applied to intact skin [57,58].

2. Delivery of Interferon: Drugs can be released under controlled conditions and their stability can be increased by transferosomes. They serve as transporters for interferone (INF-α), a leukocyte product with immunomodulatory and antiviral properties. In addition to providing immune treatment and regulated release of the active ingredient to stabilise labile medicines, transferosomes also capture INF [59, 60].

3. Delivery of Proteins and Peptides:Proteins and peptides have been transported using transferosomes as a carrier. Large biogenic molecules like proteins and peptides are extremely difficult for the body to absorb; when taken orally, they are entirely broken down in the gastrointestinal tract.Since peptides are broken down by the body, they are not designed for injection. Numerous strategies have been devised to ameliorate these circumstances. Transferosome-derived bioavailability is comparable to that of subcutaneous injection of the identical protein solution.Transferosomal preparations of this protein have also been shown to elicit a robust immune response upon repeated application to the skin. For instance, adjuvant immunogenic serum albumin in transferosomes has been shown to be immunologically active following multiple dermal challenges, in line with transferosome preparations [61–63].

4. Delivery of Anticancer Drugs:Transfersome technology has been used to try transdermal delivery of anti-cancer medications like methotrexate. The outcomes were positive. This offered a fresh method of treating cancer, particularly skin cancer [60,64,65].

5. Delivery of Corticosteroids: Corticosteroids have also been delivered using transferosomes. By optimising the dosage of medication applied topically, transferosomes enhance both the site specificity and overall drug safety of corticosteroid delivery into the skin. For the treatment of skin conditions, transferosome-based corticosteroids are biologically active at doses several times lower than those seen in the formulations currently on the market [66- 70] .

6. Transdermal Immunization: Transdermal immunisation employing transferosomes loaded with soluble proteins such as gap junction protein, integral membrane protein, and human serum albumin is one of the most significant uses of transferosomes.These methods have at least two benefits: they can be used without injection, and they produce a relatively high titer and perhaps even relatively high IgA levels. Corticosteroids have also been delivered using transferosomes. By optimising the dosage of medication applied topically, transferosomes enhance both the site specificity and overall drug safety of corticosteroid delivery into the skin.

7. Delivery of NSAID: Anaesthetics can be administered as solutions using transferosomes, which are incredibly malleable vesicles. In comparison to subcutaneous delivery, they demonstrated good results in less than 10 meters. Anaesthesia administered by transferosomal suspensions has a longer-lasting impact [71,73].

8. Delivery of Herbal Drugs:Another method of delivery for herbal drugs is transfersome. Xiao-Ying et al., who demonstrate that capsaicin transferosomes had superior topical absorption as compared to pure capsaicin [74–76].

9. Delivery of Anesthetic: Under the right circumstances, the application of a transferosome-containing anaesthetic causes topical anaesthesia in less than ten minutes. Effect in cases of pain sensitivity is almost as powerful (80%) as that of a similar subcutaneous bolus injection; however, the duration of the effect is longer with transfersomal anaesthetic formulation [77,78].

Conclusion

With specific advantages over conventional carriers, including liposomes, niosomes, and ethosomes, transferosomes represent an exciting advancement in the realm of transdermal and skin-based drug delivery systems. They can effectively penetrate the stratum corneum and deliver both hydrophilic and lipophilic medications thanks to their highly deformable and elastic bilayer structure, which is made up of phospholipids and edge activators. This characteristic lowers systemic toxicity, retains therapeutic benefits, and improves absorption. Transferosomes' clinical relevance has been expanded by their shown capacity to deliver a range of therapeutic substances, including proteins, peptides, corticosteroids, anticancer medications, and even herbal

formulations.

Notwithstanding these benefits, there are still some drawbacks, such as their oxidative degradation-induced chemical instability, formulation costs, and variations in drug loading effectiveness. Their performance and stability can also be impacted by environmental variables, including pH and temperature changes. However, their biocompatibility, biodegradability, and ability to bypass first-pass metabolism provide significant therapeutic advantages. Additionally, transferosomes make non-invasive, painless administration easier, which increases patient acceptability and compliance. Taking everything into account, transferosomes have emerged as a unique and versatile vesicular carrier system that holds significant potential for modern medication delivery. Future studies should concentrate on resolving their stability issues, refining large-scale manufacturing processes, and carrying out more thorough clinical assessments. These developments have the potential to make transferosomes a dependable platform for targeted, safe, and efficient drug administration in a variety of therapeutic applications.

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