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Transferosomes – A Versatile and Flexible Nano Vesicular Therapeutic Delivery System

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ABSTRACT

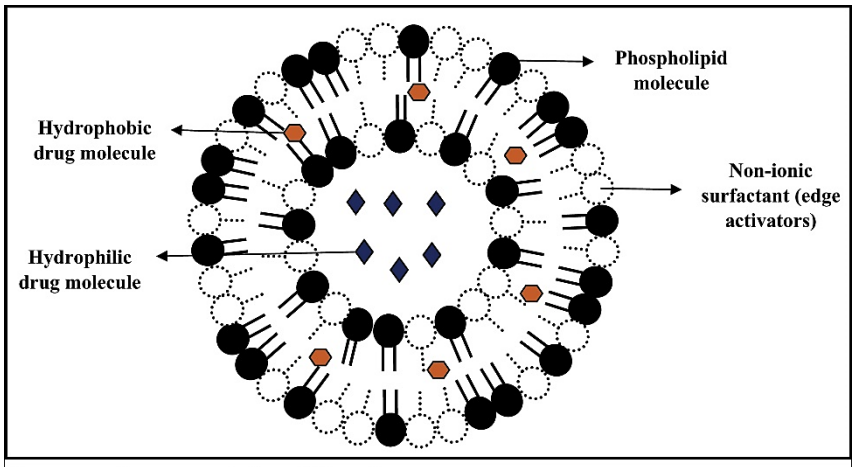
Vesicular carriers based on phospholipids have been extensively studied for improved drug delivery. Liposomes, which are traditional phospholipid vesicles, are limited to the upper stratum corneum and cannot enter the deeper layers of the skin. This prompted research on Transferosomes, a unique class of ultra-deformable vesicular carriers. High concentrations of different active drugs can be delivered via this deformable vesicular carrier, which can pass through other transmucosal membranes and the deep layers of skin. It is made up of at least one inner aqueous compartment that is encircled by a lipid bilayer that has unique characteristics because the vesicular membrane has "edge activators" included in it, which facilitate the passage through membrane barriers. This study explains the conventional method of transferosome preparation, the thin film hydration technique and other modified preparation methods. Characterization of transferosomes reveals entrapment efficiency, vesicular morphology, surface charge, and drug release by *In-vitro* and *In-vivo* studies along with factors affecting the properties of transferosomes. The review presents a large number of active molecules incorporated in these carriers and investigated *In vitro* and *Ex vivo* studies.

INTRODUCTION:

The oral route of drug delivery is the most convenient and widely used method. Although oral delivery is widely used, other delivery methods, such as trans-mucosal delivery, have been thoroughly studied for drugs that do not have an effective and successful therapeutic therapy because of a variety of factors, including poor patient acceptance, hepatic first-pass metabolism, unwanted side effects, and refusal of invasive treatments.[8] Several drug delivery systems have been developed and researched over the past few decades to overcome these problems. These challenges have resulted in the creation of unique vesicle transferosomes, which primarily provide safe and convenient transdermal delivery of drugs. However, the attention to study the effect of transferosomes elasticity in other delivery systems has not been yet done. Hence the present study aims to investigate and review features, composition, mechanism of action, preparation methods, factors affecting, characterization and applications of novel ultra-deformable vesicular carrier transferosomes in transdermal and other delivery systems.

The term "Transferosomes," which was initially used by Cevc, refers to the first generation of ultra-deformable vesicles and has been the focus of numerous patents and literature articles since the 1990s (Transferosomes is a trademark of IDEA AG, Munich, Germany). The Latin term "transferre," which means "to carry across," and the Greek word "soma," which means "a body," are the sources of the name, which means "carrying body."[1]

A Transferosome **novel ultra-deformable vesicular carrier** designed to exhibit the characteristics of a cell vesicle or a cell engaged in exocytosis, and thus suitable for controlled and potentially, targeted drug delivery. Transferosomes are complex vesicles that have extremely flexible and self-regulating membranes, which make the vesicle very deformable. Transferosome vesicles can cross microporous barriers efficiently, even if the porous are much smaller than the vesicles size. This elasticity is generated by the incorporation of an edge activator in the lipid bilayer structure. Each transferosome consists of at least one inner aqueous compartment, which is surrounded by a lipid bilayer with specially tailored properties, due to the incorporation of "edge activators" into the vesicular membrane. Surfactants such as sodium cholate, sodium deoxy-cholate, Span 80, and Tween 80, have been used as edge activators. [2,3]



Diagrammatic representation of Transfersomes.

SALIENT FEATURES OF TRANSFEROSOMES [4-7]

✓ Transferosomes possess an infrastructure consisting of hydrophobic and hydrophilic moieties together and as a result, can shows drug molecules with wide range of solubility.

✓ Transferosomes exhibit a high degree of deformability, allowing whole vesicles to pass through tiny constrictions with no discernible loss.

✓ Both low and high molecular weight medications, including as analgesics, antifungals, anesthetics, corticosteroids, sex hormones, anticancer, insulin, gap junction protein, and albumin, can be carried by transferosomes.

✓ As transferosomes are derived from natural phospholipids, just like liposomes, they are both biocompatible and biodegradable.

✓ Transferosomes exhibit a high entrapment efficiency, reaching over 90% when enclosed with lipophilic drugs.

✓ The drug that is encapsulated is shielded from the metabolic breakdown by transferosomes.

✓ They function as a depot, releasing their contents gradually.

✓ They can be used for topical and systemic drug administration.

✓ Easy to scale up, as the procedure is simple, do not involve lengthy procedures and unnecessary use or pharmaceutically unacceptable additives.

LIMITATION OF TRANSFEROSOMES [4,6,7]

✓ Transferosomes are considered as chemically unstable due to their tendency to oxidative degradation. The oxidation of transferosomes can be significantly decreased when the aqueous media is degassed and purged with inert gases, such as nitrogen and argon. Storage at a low temperature and protection from light will also reduce the chance of oxidation. Post-preparation processing, such as freeze-drying and spray-drying, can improve the storage stability of transferosomes.

✓ Another obstacle of utilizing transferosomes as a drug delivery system is the difficulty of achieving the purity of natural phospholipids. Therefore, synthetic phospholipids could be used as alternatives.

✓ The expensiveness of transferosomal formulations is associated with the raw materials used in lipid excipients, as well as the expensive equipment needed to increase manufacturing. Hence, the widely used lipid component is phosphatidylcholine, because it is relatively low in cost and ethanol injection method which is more suitable and cost-effective in large scale manufacturing can be used.

COMPONENTS OF TRANSFEROSOMES

Transferosomes are generally composed of

✓ Initially, the primary component, is an amphipathic substance, which may consist of a blend of lipids—the vesicle-forming elements responsible for building the lipid bilayer. [10,9]

✓ Secondly, biocompatible bilayer-softening chemicals, such as edge activators or surfactants, which range from 10% to 25%, improve the permeability and bilayer flexibility of vesicles. [9,11–14]

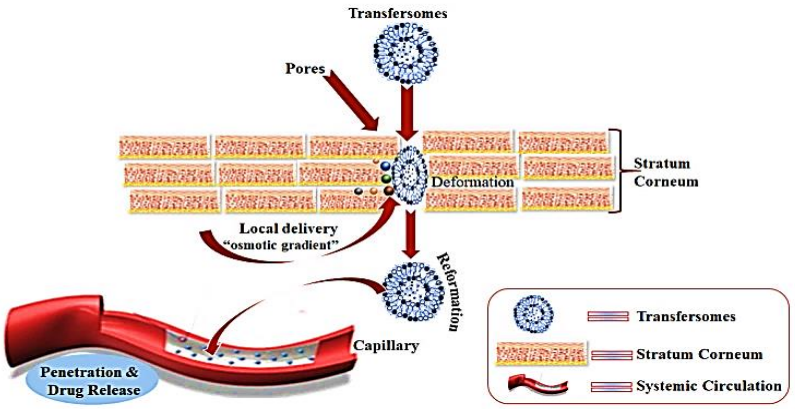
✓ Alcohol content: 3–10%, acting as the solvent.

✓ Lastly, hydrating media are made up of either buffering agent or water. [15,16]

INGREDIENTS	USES	EXAMPLE
Phospholipids	Vesicle forming Component	Soya Phosphatidylcholine Egg Phosphatidylcholine Disteryl Phosphatidylcholine
Edge activator/ Surfactants	For Flexibility	Tween 80 Span 80 Sodium Cholate Sodium deoxy Cholate
Alcohol	Solvent	Ethanol Methanol isopropyl alcohol Chloroform
Dye	For Confocal Scanning Laser Microscopy (CSLM) Study	Rhodamine-123 Rhodamine-DHPE Fluorescein-DHPE Nil red 6 Carboxy fluorescein
Buffering Agent	As a hydrating medium	Saline phosphate buffer (pH 6.5-7.5) 7% v/v ethanol Tris buffer (pH 6.5)

MECHANISM OF ACTION [3,17]

Two main elements are thought to be responsible for the unhindered transit of these carriers: the vesicle bilayers' great elasticity (deformability) and the existence of an osmotic gradient across the skin. The natural transdermal gradient, which causes the transdermal water activity difference, acts as a force on the skin through transferosome vesicles, forcing the widening of intercellular junctions with the lowest resistance and creating transcutaneous channels that are 20–30 nm wide. These channels facilitate the transfer of ultra-deformable, slimed transferosomes across the skin about the hydration gradient.



Additionally, the development of the osmotic gradient is caused by the body's heat-induced evaporation of skin surface water. This driving force helps to deliver therapeutic agents in

effective therapeutic concentrations with minimal systemic toxicity from the site of application to the target area via flexible transport across the skin. A transferosome's self-optimizing deformability allows it to alter its membrane function reversibly once it reaches a pore. The transferosome mechanism responsible for its deformability begins to accumulate at the site of tension to travel throughout the pore. In contrast, the less elastic mechanism undergoes dilution, which drastically lowers the active rate of membrane deformation and permits the highly elastic particles to travel throughout the pores. Their capacity to penetrate is contingent upon the transferosomal membrane's deformability, which is a result of the makeup of the vesicles.

FACTORS AFFECTING PROPERTIES OF TRANSFERSOMES

A multitude of process variables may impact the properties of the transferosomes throughout the process of optimizing their formulation. The following are these variables:

- **Effect of phospholipids: Edge Activator Ratio:** Higher surfactant concentrations have generally been found to have the potential to alleviate entrapment efficacy. The reason for this could be attributed to the permeability of the vesicle membrane becoming more enhanced, potentially creating pores within the membrane that increase fluidity and cause the drug that is trapped to leak out. Low surfactant concentrations may cause the vesicle size to expand, while a further increase in the edge activator content may cause pore formation in the bilayer and a decrease in the vesicles' ability to permeate. [6,18-21]

- **Effect of various solvents:** There are several solvents utilized, including methanol and ethanol. The solubility and compatibility of all formulation constituents in the solvent will determine which solvent is best. The formulation's solvents may also serve as penetration enhancers, increasing the drug's flow across the membrane. For example, ethanol increases the permeation through different mechanisms. [22,23]

- **Effect of various edge activators:** The type of edge activators used in their formulations influences the deformability and entrapment efficiency of transferosome vesicles. Generally speaking, the vesicle size decreases with an increase in surfactant concentration, the hydrophilicity of the surfactant head group, carbon chain length, and the hydrophilic-lipophilic balance (HLB). The transferosomes were prepared using three different surfactants: tween 80, span 80, and sodium deoxycholate. The use of higher surfactant concentrations resulted in a reduction of vesicle size because these concentrations (above 15%) induce micelle formation rather than vesicle formation. The increased surfactant concentration was

associated with a smaller polydispersity index (PDI). A homogenous formulation and a constant size distribution are attributed to a minimal PDI, which is also considered a significant contributor to the lowering of interfacial tension. Moreover, a rise in surfactant concentration may increase vesicle charge, which lowers vesicle aggregation and improves system stability. [18]

➢ **Effect of the hydration medium:** One of the two possible hydrating media is saline phosphate buffer (pH 6.5–7) or water. The formulation's pH level needs to be appropriate to strike a balance between its biological applications and formulation attributes. Using the appropriate pH of the hydration medium is crucial since it maintains the drug's unionization, increasing the drug's entrapment and penetration. [24]

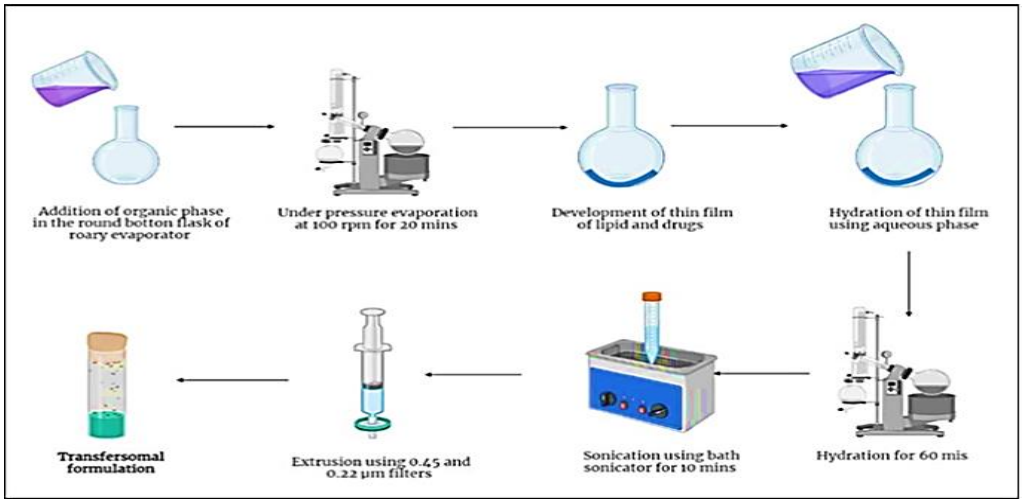
PREPARATION METHODS

A universal preparation methodology or a particular formula for transferosome preparation does not exist, despite the existence of several patented processes. To obtain the most appropriate carriers with the best deformability, drug-carrying capacity, and stability, the optimal preparation conditions and vesicle compositions must be identified, designed, and optimized by conducting individually designed experimental procedures for each therapeutic agent. Thin film hydration, sometimes referred to as the rotary evaporation-sonication process, is the traditional method for transferosome preparation. Vortexing-sonication, the modified handshaking procedure, centrifugation, suspension homogenization, reverse-phase evaporation, high-pressure homogenization, and ethanol injection are further modified preparation techniques. The following is a general description of each method:

1. Thin Film Hydration Technique/Rotary Evaporation-Sonication Method [4,25]:

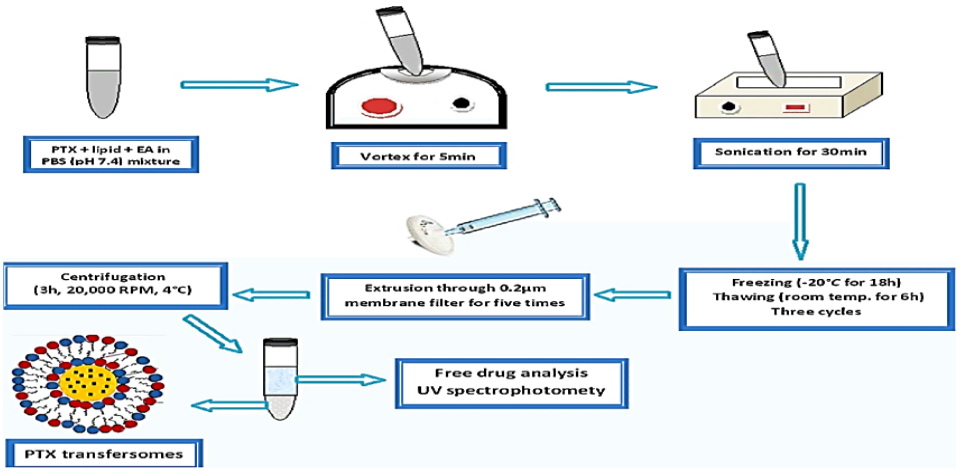
In a round-bottom flask, the phospholipids and edge activator (the components that form vesicles) are dissolved using a mixture of volatile organic solvents (for instance, methanol and chloroform in an appropriate (v/v) ratio). This stage can include the incorporation of the lipophilic drug. A rotary vacuum evaporator is used to evaporate the organic solvent above the lipid transition temperature under reduced pressure to generate a thin layer. Sustain it under a vacuum to get rid of any remaining solvent residue. After the thin film has been formed, it is hydrated by rotating it for the necessary amount of time at the appropriate temperature using a buffer solution with a suitable pH (for instance, pH 7.4). At this point, the hydrophilic drug inclusion can be completed. The resultant vesicles are sonicated in a bath or probe sonicator to produce tiny vesicles after being swelled at ambient temperature. The

process of homogenizing the sonicated vesicles involves extrusion through a sandwich of polycarbonate membranes ranging in size from 200 nm to 100 nm.



2. Vortex-Sonication Method [22,26]:

In a phosphate buffer, the drug, the edge activator, and phospholipids are combined. After that, the mixture is vortexed to produce a milky transferosomal suspension. After being sonicated for the appropriate amount of time at room temperature using a bath sonicator, it is extruded through polycarbonate membranes (450 and 220 nm, for example).



3. Modified Handshaking Process [25]:

The rotary evaporation sonication method and the modified handshaking method have the same fundamental idea. The organic solvent, lipophilic drug, phospholipids, and edge activator are added to a round-bottom flask during the modified handshaking procedure. The solvent should entirely dissolve each excipient, yielding a transparent, clear solution. Then, rather than employing a rotating vacuum evaporator, the organic solvent is eliminated by

evaporation while shaking hands. Meanwhile, the round-bottom flask is partially submerged in a water bath that is kept at a high temperature (40–60 ◦C, for example). Within the flask wall, a thin lipid coating subsequently forms. The solvent is allowed to completely evaporate in the flask overnight. After that, the produced film is gently shaken and hydrated with the suitable buffer solution at a temperature higher than its phase transition temperature. At this point, the hydrophilic drug inclusion can be done.

4. Suspension Homogenization Method [27,28]:

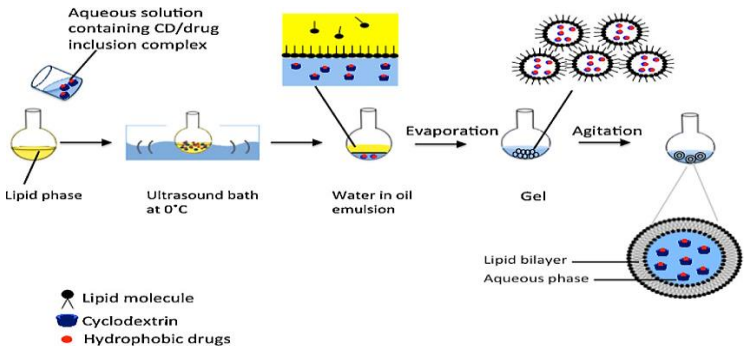
To make transferosomes, combine a suitable quantity of edge activator with an ethanolic phospholipid solution. After the suspension is created, it is combined with buffer to obtain the total lipid concentration. The resulting formulation is then sonicated, frozen, and thawed respectively two to three times.

5. Centrifugation Process [27]:

The organic solvent dissolves the lipophilic medication, edge activator, and phospholipids. After that, the solvent is removed at the appropriate temperature using a rotating evaporator operating under low pressure. Under vacuum, the last remnants of solvent are eliminated. The deposited lipid film is hydrated with the appropriate buffer solution by centrifuging at room temperature. The hydrophilic drug incorporation can be done in this stage. The resulting vesicles are swollen at room temperature. At ambient temperature, the resulting multilamellar lipid vesicles undergo further sonication.

6. Reverse-Phase Evaporation Method [29,30]:

In a round-bottom flask, the phospholipids and edge activator are combined with an organic solvent mixture (diethyl ether and chloroform, for example) and dissolved. This stage can include the incorporation of the lipophilic medication. The lipid films are then obtained by utilizing a rotary evaporator to evaporate the solvent. The lipid films are redissolved in the organic phase mostly composed of isopropyl ether and/or diethyl ether. The organic phase is then combined with the aqueous phase to create a two-phase system. At this point, the hydrophilic drug inclusion can be done. After that, this system is sonicated with a bath sonicator until a uniform w/o (water in oil) emulsion forms. The organic solvent is slowly evaporated using a rotary evaporator to form a viscous gel, which then becomes a vesicular suspension.

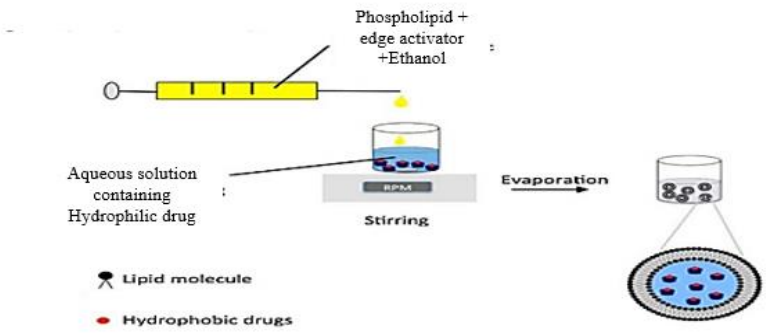


7. High-Pressure Homogenization Technique [31,32]:

The phospholipids, edge activator, and the drug are uniformly dispersed in PBS or distilled water containing alcohol and followed by ultrasonic shaking and stirred simultaneously. After that, the mixture is shaken intermittently with ultrasonic technology. A high-pressure homogenizer is then used to homogenize the resultant mixture. The transferosomes are then placed in suitable storage.

8. Ethanol Injection Method [33,34]:

The phospholipid, edge activator, and lipophilic drug are dissolved in ethanol with magnetic stirring for the appropriate amount of time to yield a transparent solution, which creates the organic phase. The water-soluble materials are dissolved in the phosphate buffer to create the aqueous phase. At this point, the hydrophilic drug inclusion can be completed. The temperatures of both solutions are raised to 45–50 °C. Subsequently, the aqueous solution is continuously stirred for the designated amount of time while the ethanolic phospholipid solution is added dropwise. The process of removing ethanol involves placing the resulting dispersion into a vacuum evaporator and sonicating it to reduce the particle size.



Characterization of Transferosomal formulations

➢ Vesicle size and polydispersity index [35,37]

The Zeta sizer (Malvern Zeta sizer, UK) can be used in the dynamic light scattering (DLS) method to determine the vesicle size and polydispersity index (PDI) of transferosomes. The principle of DLS is based on constant random thermal motion of particles which is known as Brownian motion and it diffuses the particles at a speed related to their size. Compared to bigger particles, smaller particles disperse more quickly. The laser creates a speckle pattern that is used to determine the diffusion speed. The avalanche photodiode detector detects changes in the intensity of scattering at a given angle over time. Zeta Sizer uses a laser, temperature control, optical design, and detector to get the best possible outcome. To a certain degree, the drug can be delivered to the deeper layer of skin via vesicles 300 nm in diameter or less. Vesicles of size range 10–210 nm may penetrate the trans follicular route. Stable and efficient transferosomes require homogeneous particles of a certain size. One measure that is utilized to ascertain the size range of nanocarriers is the PDI. This word refers to the uniform distribution of vesicle sizes. A sample with an extremely broad particle size distribution has a PDI value greater than 0.7. A PDI value of 0.5 is considered acceptable, whereas a value of less than 0.3 suggests a homogenous distribution of vesicles.

➢ Microscopy and morphology

A transmission electron microscope (TEM) may be used to assess the morphological characteristics of vesicles, such as their form and surface. [35] One drop of transferosome suspension can be added to a copper grid-coated collodion to conduct this test. Give the transferosomal suspension two minutes to dry and adhere to the collodion. The grid should receive one drop of uranyl acetate solution before drying. After that, a TEM is used to evaluate the substance. [36]

➢ Surface charge

A crucial factor that shortens development times, enhances formulation stability and inhibits aggregation is a surface charge. Malvern Zeta Sizer is used to quantify surface charge in terms of Zeta Potential. By displaying the degree of repulsion between neighboring vesicles, zeta potential assesses the surface charge of vesicles. It is calculated by measuring the particle's velocity as it passes through electrophoresis. Zeta potential, which is the charge that a vesicle gains in a solution or suspension, is contingent upon the kinds of ions that are in the

solution. A high zeta potential number means that there is a lot of positive or negative charge between the particles, which causes them to repel or move apart and prevent flocculation or aggregation. Conversely, a low zeta potential value indicates aggregation as a result of vesicles becoming closer to one another. Zeta potential values between +30 mV and -30 mV show a tendency to flocculate, but values more than +30 mV and less than -30 mV are thought to represent a stable formulation [36]. The zeta potential value is increased and formulation stability is increased by the addition of an edge activator to the formulation. [21,38]

- **Entrapment efficiency**

The centrifugation process determines the amount of drug entrapped within the transferosome. The proportion of drug entrapped inside the vesicle is used to represent entrapment efficiency. By removing the free drug from the vesicles, it is determined [16]. This approach involves diluting transferosomal dispersion with an appropriate vehicle, centrifuging it at maximum speed for a certain amount of time, and then/ separating the supernatant solution to find the amount of free drug that is available. Following vesicle breakage with an appropriate solvent, the total quantity of drug contained is determined from the residual sediment suspension. HPLC, UV, or any other appropriate equipment is used to evaluate the quantity of drug contained in the sediment and supernatant. The entrapment efficiency is expressed by the following Eq. (1) or (2): [37,38,40]

$$\text{Entrapment efficiency (\%)} = \frac{\text{Amount of drug entrapped}}{\text{Total amount of drug loaded}} \times 100 \quad (1)$$

$$\text{Entrapment efficiency (\%)} = \frac{\text{Total amount of drug loaded} - \text{Free drug}}{\text{Total amount of drug loaded}} \times 100 \quad (2)$$

- **Elasticity** [41,42]

The extrusion method describes the flexibility of transferosomal vesicles. By passing the vesicles through a polycarbonate membrane filter with a known pore diameter at a constant pressure, elastic properties are determined. The amount of transferosomal suspension extruded during 5 min will be measured by DLS for vesicle size and by TEM for vesicle shape. The vesicle size before and after extrusion is monitored by DLS using Zetasizer to compare the differences. The elasticity of the vesicle membrane is calculated by the following Eq. (3):

$$\text{Elasticity} = J\, x(rv/rp)^2 \quad (3)$$

where J = amount of transferosomal suspension extruded during 5min, rv = vesicle size after passing through the extruder and rp = pore size of the barrier.

- **Drug content** [43]

Using UV, HPLC, or any other equipment, the drug content of transferosomes and transferosomal gel is ascertained. Transferosomal gel formulation will be developed by the required label claim of the molecule, taking into account the drug content of the transferosome. Throughout its shelf life, the final gel formulation product's drug content should remain between 90% and 110%.

- **In-vivo percutaneous permeation study by CLSM**

Confocal laser scanning microscopy (CLSM) is a useful tool to study drug penetration through the use of fluorescence probes. It is possible to know the behavior of drug penetration when applied to the skin, like (1) Depth of drug penetration, (2) Route of penetration into the skin, (3) Effect of therapies for different types of diseases, and (4) Quantification of drug that penetrates the skin. [44] The final tested formulation that is applied to an animal's dorsal skin depends on the chemical and the research design for a certain amount of time. Following a 24-hour administration of the formulation, the animal is slaughtered, and any remaining formulation is removed by excising the dorsal skin and washing it with water. Subcutaneous tissue or fat is then removed, and a portion of the skin sample is cut and examined under CLSM microscopy. [43,45,46]

- **In-vitro drug diffusion study** [47-50]

The Franz diffusion cell is used to conduct an in-vitro drug release study. The donor compartment and the receptor compartment are the two chambers that make up the cell. The donor compartment of the Franz diffusion cell and the receptor compartment would be separated by a dialysis membrane or skin. Vesicular transferosomal gel in a weighted quantity will be added to the donor compartment. Phosphate buffer solution or any other appropriate dissolving medium is put into a receptor compartment, and a magnetic stirrer is added. Throughout the experiment, the temperature of the receptor compartment should be kept at 32 or 37 ± 0.5°C depending on where the drug molecule is applied, and the fluid is continuously stirred at the ideal rpm. At predetermined intervals, solution samples from the receptor compartment would be collected. UV or HPLC analysis will be used to modify and evaluate these samples to determine the percentage of drug content at various periods. It is possible to

interpret this study as an attempt to pinpoint the precise dosage of medication that will permeate the skin and then bind to a receptor. The transdermal administration of vesicular gel through the skin is perfectly correlated with these outcomes.

➢ **In-vivo studies** [49,51]

In-vivo studies conducted in a suitable animal model depend on the drug molecule. The institutional animal ethics committee must provide its clearance before any animal experiments may begin. For better understanding, comparison research between the optimized transferosomal formulation and the commercially available placebo and standard formulations might be planned. Treatment will be performed for a certain period based on the type of drug and the plan of treatment. Animals will be slaughtered twenty-four hours after the last dose of drug has been administered. fragments of skin will be excised and further processed for evaluation by electron microscopy. Several other characteristics will be examined in order to understand the drug's activity.

APPLICATIONS OF TRANSFEROSOMES IN DRUG DELIVERY

1. AS TRANSDERMAL DELIVERY SYSTEM

• **Delivery of Anticancer Drugs:** Jiang et al. in 2018 research was associated with the topical chemotherapy of melanoma by transferosome-embedded oligopeptide hydrogels containing paclitaxel prepared by the thin-film dispersion method. Transferosomes composed of phosphatidylcholine, tween80 and sodium deoxycholate were shown to effectively targeted into tumor tissues. [9]

Mohammed Ashif Khan et al investigated transferosomal gel containing 5-Fluorouracil for the treatment of skin cancer. Different formulation of transferosomes was prepared using Tween-80 and Span-80 as edge activators. The in vivo results concluded that vesiculation of 5-FU not only improves the topical delivery, but also enhances the cytotoxic effect of 5-FU and it provided efficient results against the treatment for AK and non-melanoma skin carcinoma, which showed up to a twofold increase of transdermal release in contrast to other marketed formulations. [52,53]

• **Delivery of Corticosteroids:** [54-56] Transferosomes are used for delivery of corticosteroids due to site specificity and overall drug safety when applied to the skin at doses much lesser than the doses required in other conventional formulation techniques. Halogenated corticosteroid triamcinolone-acetonide-loaded transferosomes prepared and tested for

biological activity and characteristics by the conventional thin-film hydration technique were studied by Cevc and Blume in 2003 and 2004. The results showed that transferosomes had increased the biological potency and prolonged effect, as well as the reduced therapeutic dosage.

• **Delivery of Proteins and Peptides:** V. Padma Prashanthini et al developed a Transferosomal gel for transdermal delivery of insulin. The transferosomes were produced by the hand-shaking method using soy lecithin phospholipid and sodium deoxycholate as the objective of the surfactant. The ex-vivo skin permeation study indicated good permeability across the biological membrane. [57]

Transferosomes have also been used as a carrier for interferons, for example INF-α is a naturally occurring protein having antiviral, anti-proliferative and some immunomodulatory effects. Transferosomes as drug delivery systems have the potential to provide controlled release of the administered drug and increase the stability of labile drugs. [58]

• **Delivery of NSAIDs:** The typical problems associated with NSAIDs like GI irritation can be overcome by transdermal delivery using transferosomes. Some drugs like diclofenac and ketoprofen are already studied for their efficacy using transferosomes and the ketoprofen formulation is already approved by a Swiss regulatory agency. [22]

• **Delivery of Anti-Inflammatory Drugs:** [59] Diclofenac sodium, celecoxib, mefenamic acid and curcumin-loaded transferosomes were developed and studied for topical administration by several research groups. Research findings suggested that transferosomes could improve the stability and efficacy of the anti-inflammatory drugs.

S.No.	DRUG	STUDY	INFERENCE	REFERENCE
1.	Tetanus toxoid	Tetanus toxoid-loaded transferosomes for topical immunization.	An in-vivo study revealed that topically administered tetanus toxoid-loaded transferosomes, after secondary immunization, elicited an immune response (anti-TT-IgG) comparable with that produced by intramuscular alum adsorbed tetanus toxoid.	61
2.	Stavudine	Transferosomes- a Novel Vesicular Carrier for Enhanced Transdermal Delivery of Stavudine: Development, Characterization and Performance Evaluation.	Improved the in vitro skin delivery of Stavudine for antiretroviral activity.	62
3	Indinavir	Enhanced transdermal delivery of indinavir sulfate via transferosomes.	Transferosomes significantly improve the in vitro skin delivery of indinavir sulfate compared to a saturated aqueous solution (maximum thermodynamic activity) when applied non-occlusive	63

2. AS INTRANASAL DELIVERY SYSTEM

Drugs with local effects in the nose or therapeutic compounds with systemic or central nervous system effects can be delivered through the nasal route, which shows great potential. This is explained by the nasal epithelium's high vascularization and permeability, which guarantee the drug's quick absorption. The addition of transferosomes may help to overcome the short nasal residence duration of the formulations and the low bioavailability of hydrophilic medications. When transferosomes are used as a carrier, a high concentration of active substances is delivered by the nose; this process is controlled by the physical properties of the system and its composition. Numerous recent research examined the flexibility of transferosomes during nasal transport to the brain.

S.NO.	DRUG	STUDY	INFERENCE	REFERENCE
1.	Rasagiline Mesylate	Investigating the Targeting Power to Brain Tissues of Intranasal Rasagiline Mesylate-Loaded Transferosomal *In-situ* Gel for Efficient Treatment of Parkinson's Disease.	The transferosomal gel shows safety and biocompatibility on rats' nasal mucosa with enhanced brain bioavailability by nose-to-brain drug delivery.	64
2.	Curcumin	Formulation and Evaluation of Curcumin Loaded Transferosomal Nasal In-Situ Gel for Alzheimer's Disease.	Transferosomal gel prolongs the drug contact time and releases the drug in a controlled manner, which results in improved bioavailability, reduced dose requirements, and improved patient safety and acceptability.	65
3.	Carvedilol	Nanotransferosomes of carvedilol for intranasal delivery: formulation, characterization and in vivo evaluation.	Intranasal route delivery of nanotransferosomes of carvedilol remarkably enhanced the bioavailability as compared to oral route.	66
4.	Insulin	Design and development of chitosan- insulin - transferosomes (Transfersulin) as effective intranasal nanovesicles for the treatment of Alzheimer's disease: In vitro, in vivo, and ex vivo evaluations.	These nanoformulations exhibited greater neuroprotective effects on rats via increased intracellular drug uptake and sustained retention, and it appears to be a promising and effective intranasal drug delivery system (IDDS) for treating Alzheimer's disease (AD).	67

3. IN COSMECEUTICALS INVESTIGATIONS

Due to its flexibility, transferosomes are used in many cosmeceutical investigations. They are used for both topical and transdermal drug delivery as it facilitates the permeation of drug through the skin to reach the systemic circulation whereas in topical drug delivery it provide local action.

S.No.	DRUG	STUDY	INFERENCE	REFERENCE
1.	Minoxidil and Caffeine	Formulation and optimization of transferosome containing minoxidil and caffeine.	Improved drug delivery to hair follicles which enhanced the hair length and weight in vivo.	68
2.	N-acetylcysteine	Effect of transferosome formulation on the stability and antioxidant activity of N-acetylcysteine in anti-aging cream.	The transferosome formulations in creams were able to increase the cumulative amount and flux of penetrated N-acetylcysteine in anti-aging cream preparations relative to those non-transferosomal cream.	69
3.	Tazarotene	Formulation development and evaluation of Transferosomal drug delivery for effective treatment of acne.	The Tazarotene transferosomes were found to increase the skin residence time leading to a faster healing of external lesions and to a reduction of side effects and duration of therapy.	70
4.	Adapalene	Ethosomal and transferosomal gel of adapalene for the treatment of acne: a comparative study.	The study concludes that the transferosomal gel was found to be better for topical application as compared to that of ethosomal gel for acne treatment.	71

4. OTHER APPLICATIONS

S.No.	DRUG	STUDY	INFERENCE	REFERENCE
1.	Rasagiline Mesylate	Investigating the Targeting Power to Brain Tissues of Intranasal Rasagiline Mesylate-Loaded Transferosomal *In-situ* Gel for Efficient Treatment of Parkinson's Disease.	The transferosomal gel shows safety and biocompatibility on rats' nasal mucosa with enhanced brain bioavailability by nose-to-brain drug delivery.	72
2.	Curcumin	Formulation and Evaluation of Curcumin Loaded Transferosomal Nasal In-Situ Gel for Alzheimer's Disease.	Transferosomal gel prolongs the drug contact time and releases the drug in a controlled manner, which results in improved bioavailability, reduced dose requirements, and improved patient safety and acceptability.	73
3.	Carvedilol	Nanotransferosomes of carvedilol for intranasal delivery: formulation, characterization and in vivo evaluation.	Intranasal route delivery of nanotransferosomes of carvedilol remarkably enhanced the bioavailability as compared to oral route.	74
4.	Insulin	Design and development of chitosan- insulin - transferosomes (Transfersulin) as effective intranasal nanovesicles for the treatment of Alzheimer's disease: In vitro, in vivo, and ex vivo evaluations.	These nanoformulations exhibited greater neuroprotective effects on rats via increased intracellular drug uptake and sustained retention, and it appears to be a promising and effective intranasal drug delivery system (IDDS) for treating Alzheimer's disease (AD).	75
5.	Triamcinolone acetonide	In vitro and ex vivo evaluation of triamcinolone acetonide-loaded transferosome gel-based novel carrier for the treatment of osteoarthritis.	Remarkable permeability was observed in goat skin, as confirmed by ex vivo permeability experiments, as compared to suspension and pure drug.	76

CONCLUSION:

Transferosomes are novel ultra-deformable carriers that facilitate the delivery of a diverse array of drug molecules across the skin and mucosal barrier with superior efficacy compared to the conventional vesicular systems due to its flexibility and self-regulating membranes, which make the vesicle extremely malleable. Drug release can be controlled by specifications in this mode of delivery, hence overcoming the constraints encountered in traditional drug delivery. Beyond being utilized for transdermal drug permeability, it has a versatile application in therapeutic delivery. Crucially, transferosomes are specially engineered vesicular systems that must be fine-tuned to the unique circumstances of each drug of interest to provide the best formulations and ultimate pharmacological responses. Further investigations on transferosomes may result in innovative, potential treatment strategies for distinct kinds of ailments. It is likely that several transferosome products for pharmaceutical applications will be developed in the future.

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