EUROPEAN JOURNAL OF BIOMEDICAL AND PHARMACEUTICAL SCIENCES
http://www.ejbps.com

ISSN 2349-8870
Volume: 11
Issue: 6
366-372
Year: 2024

TRANSFEROSOMES: INNOVATIVE VESICLES FOR EFFICIENT TRANSDERMAL TRANSPORTATION

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Article Received on 24/04/2024 **Article Revised on 13/05/2024** **Article Accepted on 03/06/2024**

ABSTRACT
Transferosomes are novel vesicular drug delivery systems characterized by ultra-flexible lipid bilayers, enabling efficient penetration through biological barriers. Transferosomes are composed of phospholipid bilayers with added edge activators, such as surfactants or bile salts, which impart high deformability to the vesicles. This deformability allows transferosomes to squeeze through narrow pores and permeate deep into the skin, mucous membranes, and other tissues, overcoming the limitations of traditional liposomes. These vesicles can encapsulate a wide range of drugs, including hydrophilic and hydrophobic compounds, peptides, and nucleic acids, offering versatility in drug delivery. Transferosomes have shown promising potential in various therapeutic applications, including transdermal drug delivery, ocular drug delivery, and targeted drug delivery to tumors and inflammatory sites. Their ability to enhance drug absorption, improve bioavailability, and minimize systemic side effects makes them an attractive option for pharmaceutical formulations. This review provides an overview of transferosomes, focusing on their structure, advantages, disadvantages, and materials used for formulation, and evaluation techniques of transferosomes, as well as their potential applications in drug delivery.

KEYWORDS: Edge activators, Liposomes, Transferosomes, Vesicular drug delivery.

INTRODUCTION
In recent years, new and innovative methods for drug delivery have been developed to overcome the limitations of traditional methods. These advanced systems are highly favoured for their ability to improve the effectiveness and therapeutic potential of both existing and novel medications.[1,2,3] However, delivering drugs through the skin can prove to be challenging due to the protective barrier it provides. Achieving successful and effective treatment is often difficult due to several factors such as the body's metabolic processes, unwanted side effects, reluctance towards invasive procedures, and patient adherence issues.[4] The outermost layer of our skin, which is called the stratum corneum (SC), is made up of flattened, keratinized skin cells that are impermeable to water. These cells act as a resilient and flexible barrier to protect our body. However, this layer presents a challenge when trying to apply medications or other topical treatments. To overcome this challenge, scientists have developed a new type of lipid vesicle called transferosomes. Transferosomes are highly deformable and can easily pass through the intact skin when applied in a non-occlusive manner. They are engineered to traverse the intercellular lipid pathway within the subcutaneous tissue by exploiting their flexibility. Essentially, transferosomes are specialized vesicles that have an inner aqueous compartment surrounded by a lipid bilayer, along with an edge activator to facilitate their penetration.[5] In 1991, Gregor Cevc introduced the concept of transferosomes. It is a patented technology owned by the German company IDEA AG. The term "Transferosomes" is derived from Latin and Greek words, with "transfer" meaning to carry and "soma" meaning body, referring to a carrier body.[6,7] Transferosomes are highly flexible vesicles that can transport large molecules through intact mammalian skin. This innovative drug delivery system has recently been introduced. A transferosome, in its broadest definition, is a vehicle that can effortlessly penetrate the skin barrier and transport medications from the point of application to the desired site.[8,9,10]

Transferosomes are artificial vesicles that imitate the behavior of natural cell vesicles that play a role in exocytosis. They are designed to deliver drugs with precision and accuracy to targeted areas. Vesicles are particularly useful in transdermal drug delivery because they can effectively transport drug molecules across the

skin and improve penetration due to their unique composition. One of the significant benefits of transferosomes is their capability to navigate through narrow openings without losing their cargo. Transferosomes can traverse small pores with the same efficiency as water, even when the pores are 1500 times smaller. This makes transferosomes an ideal choice for delivering drugs in a controlled and targeted manner.[11,12]

Transferosome technology is a method used to target the peripheral subcutaneous tissue. The NSAID ketoprofen is formulated in transferosomes as Diractin, which received approval from the Swiss regulatory agency (Swiss Medic) in 2007. Using cationic transferosomes for topical immunization with DNA vaccines offers the benefits of DNA vaccines while addressing the limitations of traditional invasive vaccination methods. Liposomal and niosomal systems are not ideal for transdermal delivery due to issues such as poor skin permeability, vesicle breakage, drug leakage, aggregation, and fusion. To overcome these challenges, a new carrier system called "Transferosomes" has been developed. This system enables transdermal delivery of both low and high-molecular-weight drugs. Transferosomes are highly optimized, ultra-flexible lipid structures that can penetrate through mammalian skin without breaking apart. Each Transferosome is made up of a central aqueous compartment surrounded by a lipid bilayer that has been modified with specific properties by incorporating "edge activators" into the vesicular membrane. These edge activators, such as sodium cholate, sodium deoxycholate, span 80, and tween 80, play a crucial role in enhancing the structure of the lipid bilayer. Transferosomes are utilized in the form of a semi-dilute suspension, without causing any blockage.

The transferosomes are composed of phospholipids including soya phosphatidylcholine, egg phosphatidylcholine, and dipalmityl phosphatidylcholine. They also contain 10-25% surfactants, such as sodium cholate, Tween 80, and Span-80, which provide flexibility. In addition, 3-10% alcohol, such as ethanol and methanol, acts as a solvent, while a hydrating medium consisting of saline phosphate buffer (pH 6.5-7) maintains the stability of the transferosomes.[13-16]

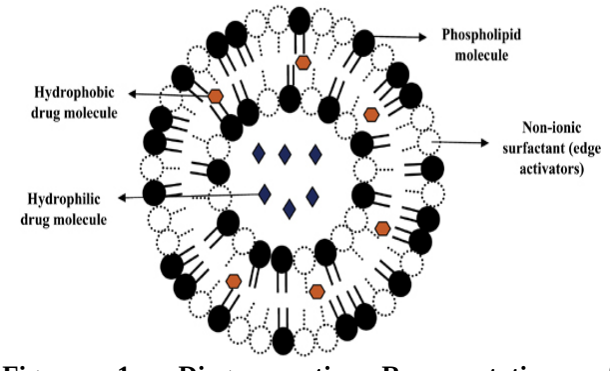

Figure 1: Diagrammatic Representation of transferosomes.

Advantages

The exceptional flexibility of this system allows for improved penetration of fully intact vesicles. These vesicles can function as a vehicle for a wide range of drugs, this includes both low and high-molecular-weight substances such as anesthetics, corticosteroids, painkillers, sex hormones, anticancer drugs, albumin, and insulin.[17,18]

- These materials are biocompatible and biodegradable since they are derived from natural phospholipids that closely resemble liposomes.
- They act as reservoirs, gradually releasing their contents over time, and can be used for drug delivery both internally and externally.
- Transferosomes have a structure made up of both hydrophobic and hydrophilic components, allowing them to effectively encapsulate drug molecules with varying solubility levels.
- A similar healing outcome can be reached with a reduced daily amount of the medication compared to what is typically required.
- They shield the enclosed medication from breakdown by metabolic processes such as proteins and peptides.
- Administer a continuous or consistent medication delivery for an extended duration to ensure the sufficient presence of powerful drugs in the bloodstream.
- By extending the period of effectiveness, these medications allow for less frequent dosing, ultimately improving patient adherence to the treatment regimen.

Disadvantage

- A significant limitation of these vesicles is the challenge of effectively incorporating hydrophobic drugs into them without negatively impacting their ability to change shape and maintain elasticity.[19,20]
- The formulations of transferosomes come at a high cost.
- Possible allergic reactions and skin irritations could potentially arise.
- The tendency to undergo degradation by oxidation renders transferosomes chemically unstable.
- Drug molecules which are used for transferosome delivery must be potent.

Composition of Transferosomes

Transferosomes are a unique and innovative lipid delivery system designed to be highly adaptable and optimized for efficient drug delivery. These lipid aggregates are primarily composed of phospholipids, such as phosphatidylcholine, that naturally form a bilayer structure when in contact with an aqueous environment, ultimately forming vesicles. To enhance the flexibility and permeability of the lipid bilayer, a bilayer softening component known as an edge activator is incorporated into the transferosomes. The edge activator typically consists of a single-chain surfactant destabilizing the lipid bilayer, increasing its fluidity and elasticity. This

crucial component allows the transferosomes to easily adjust their shape in response to external stress by modifying the local concentration of each bilayer component.[21-24] Materials commonly used for the preparation of transferosomes are summarized in Table 1.

Table 1: Transferosomes composition.

Materials	Examples	Uses
Phospholipids	Egg Phosphatidylcholine Soya phosphatidylcholine,	Vesicles forming component
Surfactants	Span-80,Tween-80,	For providing flexibility
Alcohols	Ethanol, Methanol	As a solvent
Buffering agent	Saline Phosphate buffer	As a hydrating medium

Mechanism of Action of Transferosomes

The main component of a biomembrane is phosphatidylcholine, which has a hydrophilic polar head group containing a phosphate group and two hydrophobic fatty acid chains. The edge activator, which is both hydrophilic and hydrophobic, is typically a single-chain surfactant with a significant curvature. It disrupts the lipid bilayer of vesicles, improving their flexibility by reducing interfacial tension. The osmotic gradient drives transferosomes into deeper epidermal layers, slightly affecting their physical properties. This enables transferosomes to easily penetrate skin pores smaller than themselves, facilitating transdermal drug delivery, extending drug release, and enhancing effectiveness.[25-27]

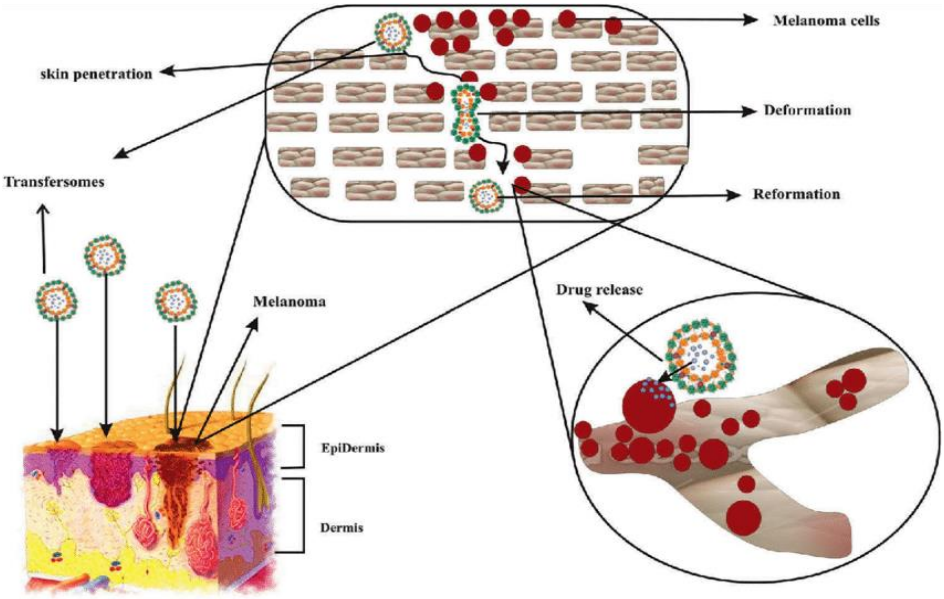

Figure 2: Transferosome mechanism of action.

Transferosomes preparation methods

1. Rotary Flask Evaporation-Sonication Method
2. Modified Handshaking Process
3. Vortexing - Sonication Method
4. Suspension Homogenization Method
5. Centrifugation Process
6. Reverse-Phase Evaporation Method
7. Ethanol Injection Method

1. Rotary Flask Evaporation-Sonication Method

The process involves dissolving phospholipids and an edge activator in a round-bottom flask using a chloroform and methanol mixture. This solution forms a thin film by evaporating the solvent above the lipid transition temperature with a rotary evaporator. The film is then hydrated with a phosphate buffer at pH 6.5 while rotating at 60 rpm for 1 hour. The resulting vesicles swell at either room temperature or 50°C for 30 minutes before being sonicated and homogenized by extrusion through 200 nm and 100 nm polycarbonate membranes.[28]

2. Modified Handshaking Process

The lipid film hydration technique dissolves drugs, phosphatidylcholine, and edge activators in an equal parts ethanol and methanol mixture. The solution is then shaken above the lipid transition temperature of 43°C, causing the organic solvent to evaporate and form a thin film along the container walls due to continuous rotation. The mixture is left to evaporate overnight to ensure complete solvent evaporation. The resulting film is then hydrated with a phosphate buffer of pH 6.4 by gently shaking for 15 minutes. The suspension of transferosomes is further hydrated at a temperature range of 2-8°C for approximately 1 hour.[29,30]

3. Vortexing - Sonication Method

The vortexing sonication technique involves mixing different types of lipids (such as phosphatidylcholine, EA, and the active ingredient) in a phosphate buffer and then vortexing the mixture until a milky suspension is achieved. This suspension is then subjected to sonication and extrusion through polycarbonate membranes. Cationic transferosomes can also be created using this method by mixing cationic lipids like DOTMA with PBS to reach a concentration of 10 mg/ml, then adding sodium deoxycholate (SDC). The mixture is vortexed, sonicated, and extruded through a 100 nm polycarbonate filter.[31]

4. Suspension Homogenization Method

To create transferosomes, an ethanolic solution of phospholipids is blended with a suitable amount of edge activator. The resulting mixture is then combined with buffer to achieve the desired concentration of lipid. This formulation is then subjected to sonication and undergoes two to three cycles of freezing and thawing.[32]

5. Centrifugation Process

Phospholipids, edge activators, and lipophilic drugs are mixed and dissolved in an organic solvent. The solvent is then evaporated using a rotary evaporator under reduced pressure and at the required temperature. Any remaining solvent traces are removed under vacuum. The remaining lipid film is hydrated with a suitable buffer solution by centrifugation at room temperature. At this point, the hydrophilic drug can be added. The resulting vesicles are allowed to swell at room temperature. The obtained multilamellar lipid vesicles are further sonicated at room temperature for optimal dispersion.[33]

6. Reverse phase evaporation method

During this stage, the process will transform into a thick gel before the vesicles are formed. Any surplus material and solvents that are not enclosed can be separated using dialysis or centrifugation. The technique involves dissolving lipids in organic solvents in a flask, followed by adding aqueous media containing EAs while purging nitrogen. Depending on its solubility, the drug can either be mixed with the lipids or the aqueous solution. The resulting mixture is then sonicated until it becomes a uniform dispersion that stays stable for at least 30 minutes after sonication. Finally, the organic solvent is evaporated under reduced pressure.[34]

7. Ethanol injection method

In this process, we warm up a liquid solution containing a drug while stirring it continuously at a consistent temperature. Then, we add a solution made of phospholipids and EAs (dissolved in ethanol) slowly to the liquid solution. As the solution interacts with the liquid medium, the lipid molecules get separated and create double-layered structures. This method offers several advantages over other techniques, such as being simple, consistent, and scalable.[35-36]

Characterization of Transferosomes

1. Entrapment Efficiency

The trapped medication in the transferosomes solution is separated from the untrapped medication through centrifugation using one milliliter of the solution. The sediment that remains after centrifugation is treated with methanol and the resulting solution is analyzed using a UV spectrophotometer. A specific equation can calculate the percentage of entrapped medication in the prepared transferosome solution.[37-38]

Entrapment Efficiency = (Amount of entrapped drug / Total amount of drug) x 100%

2. Vesicle Size, Zeta Potential and Morphology

The vesicle size, distribution, and zeta potential were measured using Dynamic Light Scattering (DLS) with a Malvern Zetasizer. The vesicles of transferosomes were visualized using Transmission Electron Microscopy (TEM). Samples were prepared with distilled water and filtered through a 0.2 µm membrane. Filtered saline was used to dilute samples as needed.

3. Turbidity Measurements

The sample was sonicated for five minutes and then diluted with distilled water to a lipid concentration of 0.312 m before measuring turbidity at 274 nm using a UV-visible spectrophotometer.[39]

4. Number of Vesicle per Cubic mm

Optimizing transferosome formulations requires careful consideration of composition and process variables. The formulations can be diluted up to 5 times with a 0.9% sodium chloride solution and examined using optical microscopy.[40]

5. Drug Content

An effective way to analyse the drug content is by using advanced instrumental techniques, such as the modified high-performance liquid chromatography (HPLC) method. This method involves the utilization of a UV detector, column oven, auto-sampler, pump, and computerized analysis software.[41-42]

6. Occlusion Effect

Topical medications are believed to be more effective when applied to covered skin. Similarly, elastic vesicles also face difficulty in penetrating the skin. The movement of water molecules is crucial for pushing cysts from the dry surface into the moisture-rich deeper layers of the skin. Skin occlusion is responsible for preventing water evaporation and, as a result, impacts hydration levels.[43]

7. *In Vitro* Drug Release

Drug release from a controlled release system can be measured using a Franz diffusion cell. The donor chamber is securely attached to the receptor chamber, with the receptor fluid continuously stirred by a magnetic bar. At specific intervals, 1 ml samples are taken from the receptor chamber and replaced with fresh phosphate

buffer to maintain sink conditions. These samples are then analyzed by UV or HPLC to measure drug release.[44]

8. *In Vitro* Skin Permeation Studies

Goat skin was used in an in vitro drug study conducted in a phosphate buffer at pH 7.4. The study employed a Modified Franz diffusion cell with an effective diffusion area of 2.5cm and a receiver compartment volume of 50 ml. Before the study, abdominal skin hair was removed, and the skin was hydrated with a saline solution. The adipose tissue layer was gently removed with a cotton swab. During the study, the treated skin was placed horizontally on the receptor compartment of the Franz diffusion cell, with the stratum corneum facing the donor compartment. The donor compartment covered an area of 250 cm^2, while the receptor compartment held 50 ml of phosphate buffer (pH 7.4) at 37±5°C, stirred at 100 rpm. A 10 mg equivalent formulation was applied to the skin and covered. At specific intervals, 1 ml samples were taken and replaced with fresh buffer. The samples were then analyzed using instrumental techniques.[45]

9. Physical Stability

The initial drug percentages trapped in the formulation were measured and sealed in glass ampoules. These ampoules were stored for at least 3 months at 4±2°C (refrigerator), 25±2°C (room temperature), and 37±2°C (body temperature). Samples were regularly tested over 30 days to monitor drug leakage. Drug loss was calculated assuming initial entrapment was 100%.[46-47]

Therapeutic applications[48-50]

Ultra-deformable vesicles are effective carriers for delivering various drugs with better skin permeation and promising pharmacokinetic profiles. They have therapeutic applications in drug delivery.

Proteins and peptides' drug delivery: Self-regulating transferosomes have been studied to deliver proteins and peptides.

- **NSAIDs**: Transferosomes are potentially employed to deliver anti-inflammatory and antipyretic drugs successfully, e.g., corticosteroids, ketoprofen, diclofenac sodium, etc.
- **Anti-hypertensive drugs**: Hypertension is a disease condition that can be treated by incorporating drugs in transferosomes preparations, e.g., propranolol hydrochloride, valsartan, and nifedipine, with better therapeutic effects.
- **Anti-fungal drugs**: Growth of microbes can be retarded by transferosomes applications, e.g., metronidazole, itraconazole, miconazole nitrate, amphotericin B, and terbinafine.
- **Local anaesthetics**: Local anaesthetic nanocarriers are explored to improve the action of drugs, e.g., butamben and benzocaine.
- **Anti-androgenic alopecia**: Finasteride transferosomes vesicles have been investigated for the management of androgenetic alopecia.
- **Anti-gout agents**: The elastic liposomal formulation of colchicine revealed great potential in the treatment of acute gout.
- **Anti-obesity agents**: Transferosomes of nano emodin have been investigated for anti-obesity.
- **Anti-cancer drugs**: Transferosomes and nano vesicular systems have shown the capability to deliver anticancerous drugs effectively, e.g., celecoxib, cisplatin, and vincristine.
- **Anti-migraine drugs**: Neurological disorder has been examined by the sustained delivery of anti-migraine drug rizatriptan.

Applications in cosmetics[51,52]

The demand for cosmetics rises worldwide progressively to intensify the appearance and avoidance of skin damage. Cosmeceutical products enhance beauty aspects and also confer various therapeutic benefits.

- **Anti-wrinkle agents:** Anti-wrinkle effects have been investigated by incorporating Curcuma longa and rosemary extracts into transferosomes vesicles.
- **UV protectant**: Formulation of transferosomes gel has been investigated for UV radiation skin damage, e.g., C. longa and quercetin.
- **Anti-acne agents:** Topical delivery of transferosomes has the potential to reduce acne, e.g., clindamycin and Vitamin C.

CONCLUSION

Transferosomes offer a promising platform for advanced drug delivery systems due to their unique properties, including ultra-flexible lipid bilayers and high deformability. These vesicles have demonstrated significant potential in overcoming biological barriers and enhancing drug delivery efficiency. With the ability to encapsulate a wide range of drugs and target specific tissues. Transferosomes hold the ability to improve therapeutic outcomes while minimizing systemic side effects. However, further research and development in this field are warranted to optimize their formulation, stability, and scalability for widespread clinical applications.

ACKNOWLEDGMENT

The authors would like to gratefully acknowledge the Dean Dr.A. RATHINAVEL, M. S, M. Ch, Ph.D. Madurai Medical College, Madurai, for providing the necessary facilities for this research work.

Conflicts of interest

There are no conflicts of interest regarding the publication of this article to disclose.

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