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Case Report

Transferosomes-A Novel Carrier for Drug Delivery

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Abstract

Transferosomes are a type of lipid-based drug delivery system that is designed to enhance the delivery of drugs through the skin or other biological barriers. They are composed of phospholipids, surfactants, and sometimes cholesterol, which form a bilayer structure that encapsulates the drug. Additionally, transferosomes can be tailored to target specific tissues or cells, which can increase the efficacy of drugs while reducing the risk of side effects. For example, transferosomes can be designed to deliver drugs to cancer cells, allowing for targeted cancer therapy with fewer side effects than traditional chemotherapy. In this article detailed discussion was made on formulation and applications of transferosomes.

Keywords: gerhard Hansen; leprosy; philately; postage stamps; envelopes; numismatics; commemorative medals

Introduction

Transferosomes were first introduced in the 1990s as a novel drug delivery system, and they have since been studied extensively for their potential therapeutic applications. One of the key advantages of transferosomes is their ability to improve the bioavailability of drugs that have poor water solubility, which can limit their effectiveness when administered by traditional methods.

Overall, transferosomes are a promising drug delivery system with potential applications in a wide range of therapeutic areas. Ongoing research is focused on improving the stability, efficacy, and safety of transferosomes, as well as exploring new ways to use them in clinical practice.[3]

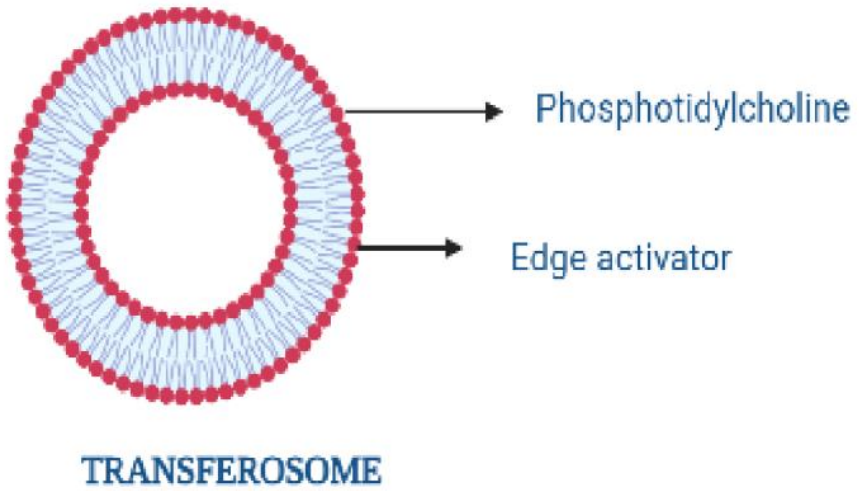

Figure 1.1 : Structure of transferosomes

Class	Example	Uses
Phospholipids	Soya phosphatidyl choline, Dipalmitoyl phosphatidyl choline, Distearoyl phoshatidyl choline	Vesicles forming component
Surfactant	Sod. Cholate, Sod.deoxycholate, tween-80, Span-80	For providing flexibility
Alcohol	Ethanol, methanol	As a solvent
Buffering agent	Saline phosphate buffer (pH 6.4)	As a hydrating medium
Drug	Fluconazole	A.P. I

Table 1: Composition of transferosomes

Advantages of Transferosomes:

Enhanced Penetration: Transferosomes possess high deformability and elasticity, allowing them to squeeze through narrow pores and penetrate deep into the skin or mucosal tissues. This property facilitates the efficient delivery of drugs to target sites that are otherwise difficult to reach, including deeper skin layers or systemic circulation.

Increased Drug Bioavailability: The deformability of transferosomes enhances the bioavailability of drugs by promoting their absorption through the skin or mucosal membranes. This is particularly beneficial for drugs with poor oral bioavailability or those that require localized delivery.

Improved Stability: Transferosomes provide improved stability to encapsulated drugs by shielding them from enzymatic degradation, pH variations, and other environmental factors. This helps maintain the integrity and activity of the drug during storage and transportation.

Targeted Drug Delivery: Similar to invasomes, transferosomes can be surface-modified with targeting ligands to achieve targeted drug delivery. These ligands can recognize specific receptors or molecules on the target cells, allowing for precise and localized drug delivery while minimizing off-target effects.

Versatile Formulation: Transferosomes can encapsulate a wide range of drugs, including both hydrophilic and hydrophobic compounds. This versatility makes them suitable for various types of drugs, allowing for flexibility in drug formulation and delivery.[4]

Disadvantages of Transferosomes:

Complex Manufacturing Process: The preparation of transferosomes requires specialized techniques and equipment, which can increase the complexity and cost of manufacturing. This can limit their widespread use and availability, especially for small-scale production or in resource-limited settings.

Stability Challenges: Transferosomes may face stability issues during storage, such as aggregation, leakage of encapsulated drugs, or changes in their physical properties. These challenges need to be addressed to ensure consistent and reliable performance of transferosomes.

Variable Performance: The performance of transferosomes can be influenced by various factors, including the physicochemical properties of the drug, formulation parameters, and the site of application. Achieving consistent and predictable performance across different drug molecules and conditions may require optimization and customization for each specific application.

Regulatory Considerations: Like other novel drug delivery systems, transferosomes may require specific regulatory considerations for approval and commercialization. Compliance with regulatory standards, safety assessments, and demonstrating the efficacy of transferosomes may add complexity and time to the development process.

Limited Drug Loading Capacity: Transferosomes may have a limited drug-loading capacity due to their vesicular structure. This can be a drawback when delivering drugs with high dosage requirements or large molecular sizes, potentially requiring higher doses or more frequent administration.[5]

Mechanism of transport:

The mechanism of transport involves the generation of an "osmotic gradient" resulting from water evaporation when a lipid suspension, known as transferosomes, is applied to the skin surface. The transport of these elastic vesicles is not dependent on concentration. The process relies on trans-epidermal hydration as the driving force for vesicle transport. Due to their elasticity, the vesicles can pass through the pores in the corneum, although these pores are smaller in diameter compared to the vesicles. When transferosomes are applied to an open biological surface, such as non-occluded skin, they tend to penetrate the barrier and migrate into the water-rich deeper layers to maintain sufficient hydration [6,7].

During penetration through the corneum, reversible deformation of the bilayer occurs. However, it is crucial to ensure that vesicle integrity, gradient, and barrier properties for underlying hydration affinity are not compromised during this deformation.

Since transferosomes are too large to diffuse through the skin, they need to identify and establish their own pathway through the organ. The effectiveness of transferosomes in drug delivery relies on their ability to expand and overcome hydrophilic pores within the skin. Intracellular drug transportation may involve diffusion of the vesicle lipid bilayer with the skin, similar to normal endocytosis involving the diffusion of vesicles through cytomembrane. The mechanism is intricate and incorporates advanced principles of elasto-mechanics, combined with material transport and hydration/osmotic forces [7,8].

Methods to prepare transferosomes:

1. Ethanol Injection Method
2. Thin Film Hydration Method
3. Reverse Phase Evaporation
4. Ether Injection
5. Solvent Injection Method. [6]

There are several methods used to prepare transferosomes. Here are some commonly employed techniques:

Thin Film Hydration Method: this technique has 3 steps:

- The process begins by dissolving phospholipids and surfactants in an organic solvent (chloroform-methanol) to create a thin film of vesicles. This mixture is then heated above the lipid's transition temperature using a rotary evaporator to remove the organic solvents. Any remaining traces of the solvent are eliminated by placing the film in a vacuum overnight.
- Next, the formed film is hydrated by adding an appropriate buffer and agitating it at a speed of sixty revolutions per minute for 60 hours. The vesicles formed are left at room temperature to swell.

- To create smaller vesicles, the prepared vesicles are subjected to sonication using a bathtub sonicator for 60 minutes at either room temperature or 50°C. In the case of a probe sonicator, the vesicles are sonicated by manually extruding them 200 times through a sandwich layer of two 100 nm polycarbonate membranes. [9,10]

Modified hand shaking method:

- Lecithin together with the edge activator (surfactant) and drug are dissolved in a mixture of chloroform and ethyl alcohol in the magnitude relation 1:1. The mixture is subjected to evaporation to get rid of the organic solvent using temperature higherthan the transiktion temperature of lipid by hand shaking. The thin lipid film is left long to make sure complete removal of organic solvent [11,12].
- The film that is formed is then hydrated with buffer of choices in conjuction with gentle shaking for quarter- hour. The suspension formed is further hydrated at 43oC for 1-2 hr
- Variables that have an effect on the method of preparation are:
- Lecithin: Surface -active agent
- Solvent used
- Surfactant used Hydration medium.

The selection of the drug's effectiveness is prioritized to enhance the specified parameters. While maintaining consistency with other factors during the preparation of a particular system, the selection and utilization of edge activators become pivotal, influencing the surface charge and thereby contributing to the advancement of highly flexible vesicles, enhancing the drug delivery system.

Reverse Phase Evaporation Method: In this method, a water-in-oil (W/O) emulsion is formed by dissolving lipids and the drug in an organic solvent and then adding an aqueous phase. The resulting W/O emulsion is subjected to high-speed homogenization, leading to the formation of a water-rich vesicle system, which is subsequently converted into transferosomes.

Ether Injection Method: Lipids and the drug are dissolved in an organic solvent mixture containing ether. The organic phase is then rapidly injected into an aqueous medium under high-speed homogenization or sonication, resulting in the formation of transferosomes.

Ethanol Injection Method: Similar to the ether injection method, lipids and the drug are dissolved in an organic solvent mixture containing ethanol. The organic phase is rapidly injected into an aqueous medium under high-speed homogenization or sonication, leading to transferosome formation.

Dehydration-Rehydration Vesicle Method: This method involves the dehydration of preformed liposomes or multilamellar vesicles (MLVs) followed by rehydration with an aqueous medium containing the drug. The dehydration process can be achieved using freeze-drying, spray-drying, or other techniques, and the resulting dehydrated vesicles are subsequently rehydrated to form transferosomes [13,14].

Lipid Film and Remote Loading Method: This method combines the lipid film hydration technique with remote loading of the drug. Lipids are dissolved in an organic solvent to form a lipid film, which is then hydrated with an aqueous medium containing a pH gradient or an ion gradient. The pH or ion gradient drives the active ingredient into the vesicles during hydration, resulting in remote loading of the drug. [15,16]

Characterization of Transferosomes:

i. Entrapment Efficiency: The entrapment efficiency of transferosomes is determined by separating the unentrapped drug from the vesicles. After centrifugation to separate the untrapped drug, the vesicles are ruptured, and an appropriate analytical technique is employed to quantify the amount of entrapped drug.

ii. Vesicular Diameter: The size of vesicles is determined by employing techniques such as photon correlation spectroscopy or dynamic light scattering (DLS). These techniques provide information about the vesicular diameter and size distribution.

iii. In vitro Drug Release: In vitro drug release studies are conducted by incubating the transferosomes suspension at a specific temperature. Samples are withdrawn at different time intervals, and the amount of released drug is detected using techniques such as UV spectrophotometry, high-performance liquid chromatography (HPLC), or high-performance thin-layer chromatography (HPTLC). The quantity of free drug is separated and measured to calculate the drug release profile.

iv. Vesicular Shape and Type: The shape and type of transferosomes vesicles can be visualized using techniques like transmission electron microscopy (TEM) or phase contrast microscopy. The stability of the vesicles can be assessed by monitoring the size and structure of the vesicles over time. Mean size measurements can be obtained using DLS, while TEM allows observation of structural changes.

v. Surface Charge and Charge Density: The surface charge and charge density of transferosomes are determined using a zetasizer instrument. This technique provides information about the electrostatic properties of the vesicles.

vi. Drug Content:The drug content in transferosomes is quantified using a modified HPLC method, which involves utilizing specific equipment and analytical parameters. This method involves employing a UV detector, column oven, autosampler, pump, and a computerized analysis program to quantify the amount of drug present in the vesicles. [17,18]

Application of transfersomes:

1) The use of transfersomes for delivering insulin offers a successful method of administering large molecular weight medications through the skin. Traditional subcutaneous administration of insulin can be inconvenient for patients. By encapsulating insulin in transfersomes (referred to as transfersulin), all the challenges associated with conventional insulin delivery can be overcome. Therapeutic effects can be observed within 90-180 minutes after the application of transfersulin on intact skin, depending on the composition of the carrier.
2) Transfersomes also provide a solution for the delivery of corticosteroids. By incorporating corticosteroids into transferosomes, the issues associated with their delivery can be addressed. Transfersome encapsulation enables site-specific and safe delivery of corticosteroids into the skin through epicutaneous administration. The use of transfersomes technology also reduces the required dosage for achieving the biological activity of corticosteroids.
3) Transfersomes have been widely employed as carriers for the transportation of proteins and peptides, allowing for their safe administration through transfersome technology. Proteins and peptides face challenges in transferring into the body due to their large molecular size and susceptibility to degradation in the gastrointestinal tract when administered orally. Therefore, injectables have been the preferred method of administration. Various approaches have been developed to overcome this limitation. Transfersomes demonstrate bioavailability comparable to subcutaneous injection when used for protein suspension. Additionally, repeated epicutaneous application of transfersome preparations of proteins can elicit a strong immune response, demonstrating their potential in immunotherapy.

4) Transfersomes can be utilized as carriers for delivering antiviral drugs such as INF (interferon). For example, leukocyte-derived INF-a, a naturally occurring protein with antiviral, antiproliferative, and immunomodulatory effects, can be delivered using transfersomes as drug delivery systems. Transfersomes enable controlled release of the administered drug and enhance the stability of labile drugs. Studies have shown promising delivery of IL-2 (interleukin-2) and INF-a through transfersomes for potential transcutaneous applications.
5) Transfersomes offer a new approach for the transcutaneous delivery of anti-cancer drugs, particularly for skin cancer treatment. Methotrexate, when delivered using transfersomes technology, has shown favorable results.
6) Transfersome applications extend to the delivery of anesthetics. The use of transfersomes containing anesthetics can induce topical anesthesia within approximately 10 minutes under appropriate conditions. The impact of transfersomal anesthetics is comparable to a subcutaneous bolus injection, with nearly 80% effectiveness, but the transfersome preparation provides a longer-lasting effect.
7) Transfersomes can also be employed for the transdermal delivery of non-steroidal anti-inflammatory drugs (NSAIDs) to overcome the gastrointestinal adverse effects associated with most NSAIDs. Studies have been conducted on diclofenac and ketoprofen. In 2007, the Swiss regulatory agency (Swissmedic) granted regulatory approval to a transfersome formulation containing ketoprofen. This formulation is anticipated to be marketed under the brand name "Diractin." Furthermore, IDEA AG has ongoing clinical development plans for additional therapeutic products utilizing transfersome technology.
8) Transfersome technology can also be utilized for the delivery of herbal drugs. Xiao-Ying et al. demonstrated higher topical absorption of transfersomes containing capsaicin compared to pure capsaicin. [18,19]

1.2.8 Silent Features of Transfersomes

a) Transfersomes possess several distinctive features that make them a promising option for drug delivery. These features include:
b) Transfersomes exhibit high deformability, enabling them to effectively penetrate narrow constrictions and maintain the integrity of the vesicles.
c) Wide Range of Drug Solubility: The infrastructure of transfersomes consists of hydrophobic and hydrophilic moieties, enabling them to accommodate drug molecules with varying solubilities. They can effectively carry both hydrophilic and lipophilic drugs.
d) Transfersomes are a versatile drug carrier capable of delivering drugs with varying molecular weights. They have been successfully employed to transport a diverse range of substances such as analgesics, anesthetics, corticosteroids, sex hormones, anticancer agents, insulin, gap junction proteins, and albumin. This broad applicability highlights the potential of transfersomes as an effective delivery system for various therapeutic compounds.
e) Biocompatibility and Biodegradability: Transfersomes are composed of natural phospholipids, similar to liposomes, making them biocompatible and biodegradable. This enhances their safety profile and minimizes potential adverse effects.
f) High Entrapment Efficiency: Transfersomes exhibit high entrapment efficiency, particularly for lipophilic drugs, with rates reaching close to 90%. This ensures that a significant amount of the encapsulated drug is retained within the vesicles.
g) Protection from Metabolic Degradation: Encapsulating drugs within transfersomes provides protection against metabolic degradation. The vesicles shield the drug molecules from enzymatic degradation, thereby maintaining their stability and potency
h) Controlled Release: Transfersomes can act as depots, releasing their contents in a slow and gradual manner. This controlled release mechanism allows for sustained drug delivery, prolonging the therapeutic effect and reducing the frequency of dosing.
i) Easy Scalability: The manufacturing process of transfersomes is relatively simple, without the need for lengthy procedures or the addition of pharmaceutically unacceptable additives. This makes it easier to scale up production for commercial purposes.
j) Systemic and Topical Delivery: Transfersomes can be utilized for both systemic and topical delivery of drugs. They have the potential to transport drugs across the skin barrier for transdermal delivery or to target specific tissues and organs for systemic effects. [20,21]

Limitations of Transfersomes

1) Stability: Transfersomes may have stability issues, particularly during long-term storage. Factors such as vesicle leakage, aggregation, and fusion can impact their stability and potentially affect the efficacy of the encapsulated drugs.

2) Complexity of Formulation: Formulating transfersomes requires careful optimization of various components, including lipids, surfactants, and edge activators. Achieving the desired vesicle characteristics and drug-loading capacity can be challenging and time-consuming.

3) Scalability: While transfersome preparation methods are relatively straightforward, scaling up the production process for commercial purposes may pose challenges. Ensuring consistent quality, batch-to-batch reproducibility, and large-scale manufacturing feasibility need to be addressed.

4) Skin Irritation: Transfersomes, when used for transdermal drug delivery, can cause skin irritation or sensitization in some individuals. The components of transfersomes or the drugs themselves may trigger adverse reactions on the skin.

5) Limited Penetration Depth: Despite their deformability, transfersomes have a certain limit to their penetration depth through the skin. They may not be able to reach deeper layers or specific target sites, which could limit their effectiveness for certain applications.

6) Cost: The production of transfersomes can be relatively expensive due to the cost of high-quality phospholipids and other components involved. This cost factor may influence their practicality and accessibility for widespread use.

7) Regulatory Considerations: Transfersomes are still a relatively new technology, and their regulatory approval for specific drug formulations may require additional studies and evidence of safety and efficacy.

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