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Transferosomes: A Novel Approach for Nanoencapsulation of Drugs for Transdermal Delivery

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Aimen Fatima, Dr. M Suresh Babu

Deccan School of Pharmacy, Dar-us-salam, Aghapura, Hyderabad 500001 India.

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ABSTRACT

Transdermal administration of drugs is generally limited by the barrier function of the skin. Vesicular systems are one of the most controversial methods for transdermal delivery of active substances. To resolve these issues, a novel type of highly deformable lipid vesicle known as transferosome has been reported recently to go through intact skin, if applied non-occlusively. Transferosomes are vesicular carrier systems that are specially designed to have at least one inner aqueous compartment that is enclosed by a lipid bilayer, together with an edge activator. Transferosomes majorly involve the ingredients like amphipathic ingredients (a combination of hydrophilic and lipophilic molecules like soy phosphatidylcholine), surface activators (e.g., surfactants), alcohol, and water. The major driving factor for the movement of transferosomes into the deeper epidermal layers is the osmotic gradient. As a result, it easily enters skin pores much smaller than itself to achieve transdermal penetration, prolonging the drug's release and increasing its action. The present review aims to describe the concept of transferosomes, the mechanism of action, different methods of preparation and their recent applications in the transdermal administration of drugs.

INTRODUCTION

Transdermal administration of drugs is generally limited by the barrier function of the skin. An efficacious, successful therapeutic treatment cannot be achieved in most cases, often due to many reasons, such as the occurrence of hepatic first-pass metabolism, adverse side effects, the rejection of invasive treatments and poor patient compliance [1]. SC (Stratum Corneum) is a superficial layer of the skin that comprises keratinized, flattened residues of dividing epidermal cells, impermeable to water and behaves as a tough flexible membrane. To resolve these issues, a novel type of highly deformable lipid vesicle known as transferosome has been reported recently to go through intact skin, if applied non-occlusively. They are highly deformable, and this property assists in their quick penetration through the intercellular lipid pathway of the subcutaneous tissue.

Transferosomes are vesicular carrier systems that are specially designed to have at least one inner aqueous compartment that is enclosed by a lipid bilayer, together with an edge activator [2]. The newly presented novel drug carriers are highly deformable vesicles, i.e., transferosomes can carry large molecules across intact mammalian skin. A transferosome, in the widest sense of the word, is a tool that can pass instinctively through the skin and transfer drugs from the application to the target site [3,4,5]. In the year 1991, the concept of transferosomes was launched by Gregor Cevc. Transferosome is a registered trademark technology of the German company IDEA AG. The name implies a "bearing body" according to the Latin and Greek names "transferred" and "soma" respectively. Transfer literally means to carry while "soma" means a body [6,7].

Transferosomes majorly involve the ingredients like amphipathic ingredients (a combination of hydrophilic and lipophilic molecules like soy phosphatidylcholine), surface activators (e.g., surfactants), alcohol, and water (Jiang et al., 2018). Surfactants such as sodium cholate, sodium deoxycholate, span 80 and tween 80 have been used as edge activators. The ratio of individual surfactants and the total amount of surfactants control the flexibility of the vesicle [8]. These vesicles serve as a depot for the sustained release of active compounds in the case of topical formulations, as well as a rate-limiting membrane barrier for the modulation of systemic absorption in the case of transdermal formulations.

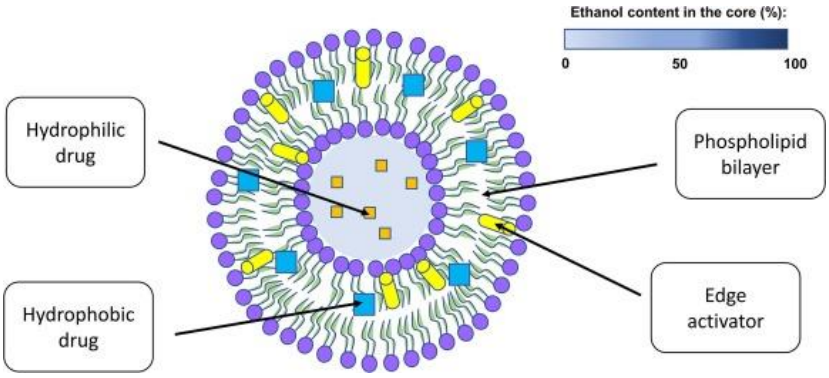

FIGURE 1: STRUCTURE OF TRANSFEROSOME

ADVANTAGES OF TRANSFEROSOMES

1. Due to self-optimized and ultra-flexible membrane properties, successively delivers drug either into or through the skin, with high efficiency.

2. An equivalent therapeutic effect can be achieved with a lower daily dose of the drug than necessary.

3. Suitable for skin penetration and permits entry due to the mechanical stress of surrounding, in a self-assembling manner.

4. The extremely high flexibility of their membrane permits transferosomes to squeeze themselves even through pores much smaller than their own diameter.

5. They are biocompatible and biodegradable as they are made from natural phospholipids similar to liposomes.

6. They have high entrapment efficiency, in the case of lipophilic drugs near to 90%.

7. They protect the encapsulated drug from metabolic degradation e.g.: protein and peptides.

8. Provide a constant or steady infusion of drugs over a long period of time and hence maintain adequate plasma concentration of potent drugs.

9. As they provide a longer duration of the action hence permit a consequent reduction of the dosing frequency, thereby increasing the patient compliance.

DISADVANTAGES OF TRANSFEROSOMES

1. One main drawback of these vesicles corresponds to the difficulty of loading hydrophobic drugs into the vesicles without compromising their deformability and elastic properties [9].

2. Transferosomes, by virtue of their enhanced elasticity in contrast to standard liposomes, are more amenable to the transport of therapeutic agents across the human skin [9].

3. Hypersensitivity directions and skin irritation may occur [10].

4. Transferosomes are expensive.

COMPOSITION OF TRANSFEROSOMES

Transferosomes consist of phospholipids like phosphatidylcholine which is an amphipathic component and a lipid bilayer constituent known as edge activator which leads to the arrangement of the vesicle.

TABLE: 1

Class	Examples	Uses
Phospholipids	Soya phosphatidylcholine, Egg Phosphatidyl Choline	Vesicles forming component
Surfactants	Tween-80, Span-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 bio membrane's primary component is phosphatidylcholine, which is made up of a hydrophilic polar head group comprising a phosphate group and two hydrophobic fatty acid chains. Edge activator is a structure that is both hydrophilic and hydrophobic, and it is usually a single chain surfactant with a significant curvature that destabilizes the lipid bilayer of the vesicles and enhances its ultra-deformability by reducing its interfacial tension. The major driving factor for the movement of transferosomes into the deeper epidermal layers is the osmotic gradient. It also has a small impact on the transferosome's physical characteristics. As a result, it easily enters skin pores much smaller than itself to

achieve transdermal penetration, prolonging the drug's release and increasing its action [11,12,13].

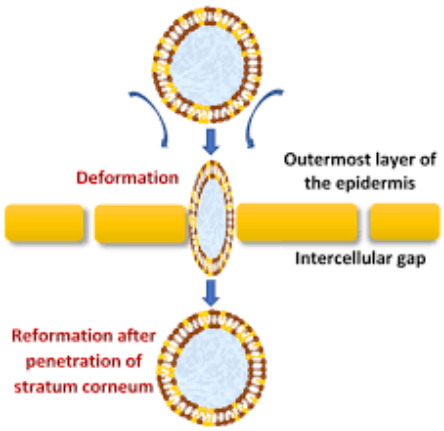

FIGURE 2: MECHANISM OF ACTION OF TRANSFEROSOMES

PREPARATION OF TRANSFEROSOMES

1. Rotary film evaporation method

Rotary film evaporation method is also known as hand shaking method which was first invented by Bagham. The amount needed of phospholipids and surfactants is essential to form a thin film and arrangement of phospholipids and surfactants are arranged in solvents of chloroform and methanol. This method is often employed in multilamellar vesicles. The produced solution is then transferred to the round bottomed flask and rotated at a constant temperature (above glass transition temperature) and reduced pressure Further a layer of lipids and edge activators are found on the walls of the round bottomed flask. The formed film containing the drug is then hydrated with an aqueous media. This leads to swelling of lipids and the form bilayer vesicles. Further desired vesicle size can be obtained by sonication or extrusion [14,15].

2. Modified handshaking process

This process is also known as the lipid film hydration technique. In this process drug, phosphatidylcholine and edge activators are dissolved in ethanol and methanol in a 1:1 ratio. While handshaking above lipid transition temperature (43°C) organic solvent is removed by evaporation. A thin film is formed inside the walls of the flask as a result of continuous rotation. The preparation is kept overnight to allow for the complete evaporation of solvent. After which the film is hydrated with a phosphate buffer of pH-6.4

with gentle shaking for 15 minutes. The obtained transferosomes suspension is further hydrated for about 1 hour at 2-8°C [15,16].

3. Thin film hydration technique /Rotary evaporation-sonication method

The phospholipids and edge activator are dissolved in a round-bottom flask using organic solvent mixture of chloroform and methanol in a suitable (v/v) ratio to form a thin film. The solvent is evaporated beyond lipid transition temperature using a rotary evaporator and the obtained film is hydrated with a phosphate buffer o pH-6.5 by rotation of 60 rpm for 1 hour. The obtained vesicles are swollen at room temperature or 50°C for 30 min. By manually extruding a sandwich of 200 and 100nm polycarbonate membrane, the sonicated vesicles are homogenized [15,17].

4. Ethanol injection method

The organic phase is formed by dissolving phospholipids, EA and active substances with magnetic stirring for a certain period, until a clear solution is formed. Meanwhile, water soluble substances are dissolved in a phosphate buffer to prepare an aqueous phase. Both the solutions are heated up to 45°C-50°C. After which the phospholipids solution is drop-wise injected into an aqueous solution with continuous stirring for some time. Ethanol removal is done by shifting the dispersion into a vacuum evaporator and then sonicating it for vesicle size reduction [15,17].

Reverse phase evaporation method

Firstly, Lipids are dissolved in organic solvents placed in a round bottom flask. An aqueous medium containing edge activators is introduced under nitrogen purging. The drug is added into a lipid or aqueous media based on its solubility characteristics. After which, the created system is sonicated until it becomes a homogenous dispersion, which should not be separated for at least 30 minutes. Under decreased pressure, the organic solvent is then extracted. The system will then transform into a thick gel, followed by the formation of vesicles. Centrifugation or dialysis method may be used to remove non-encapsulated material and residual solvents [15].

CHARACTERIZATION OF TRANSFEROSOMES

1. Entrapment Efficiency

The entrapped medication is separated from the un-entrapped drug by centrifuging one milliliter of Transferosomes solution. The sediment is lysed with methanol after the supernatant is removed, and then spectrophotometrically examined with a UV spectrophotometer [18,19]. Using the following equation, the % Entrapment efficiency in the prepared Transferosomes is calculated:

% Entrapment Efficiency = Amount of entrapped drug/ Total amount of drug X 100

2. Vesicle size, morphology and zeta potential

The Dynamic Light Scattering (DLS) method can be used to determine the vesicle diameter. In this, vesicle suspension is mixed with an appropriate medium, and the vesicular size measurements can be obtained in triplicate or the sample can be prepared in distilled water and filtered through a 0.2mm membrane filter. In order to estimate the size of the vesicles by DLS, the filtered sample is diluted with saline and for the determination of the vesicle size and size distribution, Malvern Zeta Sizer is used, whereas the structural changes and visualization are observed by transmission electron microscopy (TEM) [17].

3. Turbidity Measurements:

The turbidity measurements were diluted with distilled water to give a total lipid concentration of 0.312m. sonicate for 5 min. Measure turbidity at 274 nm with a UV-visible spectrophotometer [20].

4. NUMBER OF VESICLE PER CUBIC mm

It is an important parameter for optimizing the composition and other process variables. Transferosome formulations can be diluted for 5 times with 0.9% sodium chloride solution and studied with optical microscopy [21].

5. Drug content

The drug content can be determined using one of the instrumental analytical methods such as modified high performance liquid chromatography method (HPLC) using a UV detector, column oven, auto sample, pump, and computerized analysis program [22,23].

6. Occlusion effect

For topical medicines, occlusion of the skin is thought to aid drug penetration. Elastic vesicles, on the other hand, suffer from the same problem. The hydro taxis of water are the primary driving force behind vesicle penetration through the skin from its relatively dry surface to its water-rich deeper layers. Occlusion has an effect on hydration forces because it stops water from evaporating from the skin [15].

7. *In vitro* drug release

In vitro drug release is determined by the Franz diffusion cell. The donor chamber is fitted to the receptor chamber by means of adhesive tape. The fluid in the receptor chamber is continuously mixed by a magnetic bar. At the proper intervals (such as 0, 0.5, 1, 2, 3, 4, and 6 h), aliquots of 1 ml of the receptor media are removed, and at the same time, the withdrawn medium is replaced with a comparable volume of new phosphate buffer to maintain the sink conditions. The collected samples may be examined using UV or HPLC analysis [17].

8. *In vitro* skin permeation studies

Invitro drug study was performed by using goat skin in phosphate buffer (7.4). Modified Franz diffusion cell with a receiver compartment volume of 50 ml and an effective diffusion area of 2.5cm used for this study. Abdominal skin hair is removed and hydrated with saline solution. The adipose tissue layer was removed by rubbing with a cotton swab. To perform study, treated skin was mounted horizontally on the receptor compartment with the stratum corneum facing upwards towards the donor compartment of Franz diffusion cell. The area of donor compartment is 250 cm and capacity of receptor compartment 50 ml of phosphate buffer of 7.4) at 37± 5° c and stirred at a magnetic bar for 100 rpm. A formulation equivalent to 10 mg was placed on the skin and top was covered. At appropriate intervals, 1ml aliquots were withdrawn and immediately replaced by fresh volumes. Analyzed by any instrumental technique [24].

9. Physical Stability

The initial percentages of drug entrapped in the formulation determined were stored in sealed glass ampoules. The ampoules were placed at 4±20°C (refrigerator), 25±20°C (room temperature), and 37±20°C (body temperature) for at least 3 months. Samples were analyzed

for 30 days to determine drug leakage. Percent drug loss was calculated by keeping initial entrapment of drug as 100% [25,26].

APPLICATIONS [27-31]

●Transferosomes offer the potential to provide regulated medication release while also enhancing the stability of labile drugs.

●Insulin encapsulation in transferosomes (transfersulin) solves the difficulties of inconvenient administration, greater size (making it inappropriate for transdermal distribution using traditional methods), and a 50% response rate as compared to subcutaneous injection.

●Interferons, such as INF-, have been carried by transferosomes. INF-is a naturally occurring protein with antiviral, anti-proliferative, and immunomodulatory properties. As a drug delivery method, transferosomes offer the potential to provide regulated drug release and increase the stability of labile substances.

●Transferosomes containing soluble proteins such as integral membrane protein, human albumin, and gap junction protein are used in transdermal vaccination. By adjusting the percutaneously given medication dosage, transferosomes enhance the site specificity and overall drug safety of corticosteroid administration into skin.

●The adjuvant immunogenic bovine albumin in transferosomes, for example, induces a robust immune response after repeated percutaneous application and is immunologically as active as the equivalent injectable proteo-transferosome preparations after multiple skin challenges.

●Anticancer Drug Administration: Using transferosome technology, anticancer medicines like methotrexate were attempted for transdermal delivery. The outcomes were positive. This provides a novel therapeutic option, particularly for skin cancer.

●Delivery of NSAIDs: NSAIDs are connected with a variety of gastrointestinal adverse effects. Transdermal delivery of ultra-deformable vesicles can solve these issues. Diclofenac and Ketoprofen have both been the subject of research. In 2007, the Swiss regulatory body (Swiss Medic) approved ketoprofen in a Transferosome formulation for marketing.

CONCLUSION

Transferosomes ultra-deformable carriers that allow for more effective distribution of a wide range of drug compounds through the skin barrier than traditional vesicular systems. The vesicles are flexible and deformable and thus easily passes through the skin pores for the effective delivery of drugs. Despite being 1,500 times smaller than water, transferosomes can almost as easily pass through pores as narrow as 100 mm. They are not as stiff as typical vesicles and are capable of carrying even big molecules. Because of this, transferosomes have a significant chance of solving existing issues that are faced by the conventional techniques. Transferosomes serve as a depot for the sustained release of active compounds in the case of topical formulations, as well as a rate-limiting membrane barrier for the modulation of systemic absorption in the case of transdermal formulations.

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