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A COMPREHENSIVE REVIEW ABOUT THE DEVELOPMENT, CHARACTERIZATION AND SKIN DELIVERY STUDIES OF ULTRADEFORMABLE VESICLES: TRANSFERSOMES

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ABSTRACT

Transdermal delivery systems have attracted significant interest in recent years due to their advantages over traditional oral and parenteral delivery systems. These are self-administered, non-invasive delivery systems that improve patient compliance and enable controlled release of therapeutic agents. The biggest challenge with transdermal delivery systems is the barrier function of the outermost layer of the skin. Molecules with a molecular weight greater than 500 Da and ionized compounds generally do not pass through the skin. Therefore, the drugs that can be used in this way are limited. A possible solution to this problem is to encapsulate drugs in transfersomes. They feature a bilayer structure that facilitates the encapsulation of lipophilic and hydrophilic drugs as well as amphipathic drugs with higher permeation efficiency than traditional liposomes. The transfer thumb is elastic in nature and can deform and contract like an intact vesicle through a narrow opening significantly smaller than its size. This review aims to explain the concept of transfersomes, their mechanism of action, various methods of preparation and characterization, factors that influence the properties of transfersomes, and their current applications and role in drug delivery through the skin.

KEYWORDS: Transfersomes, Nanoencapsulation, Transdermal drug delivery, Non-invasive.

INTRODUCTION

The transdermal route of administration is considered patient friendly as many of the gastrointestinal side effects of oral drugs can be avoided by choosing this route of administration. This route of administration has the potential to maintain therapeutically effective drug concentrations in the body for long periods of time to avoid first-pass effects. Normal skin has a 30 μm thick stratum corneum that acts as the main barrier for transdermal drug delivery, and its penetration is often considered the rate-limiting step in this route of administration. Over the years, these drugs have been found to have no significant effects on drug resistance, inability to reach the target site, short residence time, low bioavailability, lack of penetration ability, etc. To overcome these challenges, new delivery systems need to be investigated to achieve effective results with these drugs. Vesicular nanocarrier delivery system "VNCDS" is one such method. These include liposomes, niosomes, ethosomes, transferosomes, transethosomes, etc. Topical treatments are the most common and are used to combat fungal diseases of the mucous membranes and skin. It has advantages such as delivering medicine to the infected area and reducing the side effects of medicine.

Criteria For Selection Of Transdermal Candidate

Despite the growing interest in advanced drug delivery systems, there are few pharmaceutical products that meet the requirements. List of requirements for transdermal absorption agent candidates in table 1.

Table 1: Ideal Properties For Drug Candidate For Transdermal Drug Delivery System.

Conditions	Properties
Skin Reaction	Non- Irritant
ph of aqueous solution	5-9
Lipophilicity	10<ko/w<100
Molecular Wt.	<500
Dose amount	<20mg/day
Shelf life	Up to 2 years

STRUCTURE OF THE SKIN

In terms of surface area, the skin is the largest organ in the body, covering an area of 2 square meters in adults. The pH value of the skin is between 4 and 5.6. This is a common route of administration for dermatological drugs that are expected to have local pharmacological effects. Drug molecules diffuse into the skin to perform their function before entering the blood for excretion.

PHYSIOLOGY

The skin is one of the largest organs in the human body and provides an important surface area for drug application. The skin receives about one-third of the blood circulating in the body.

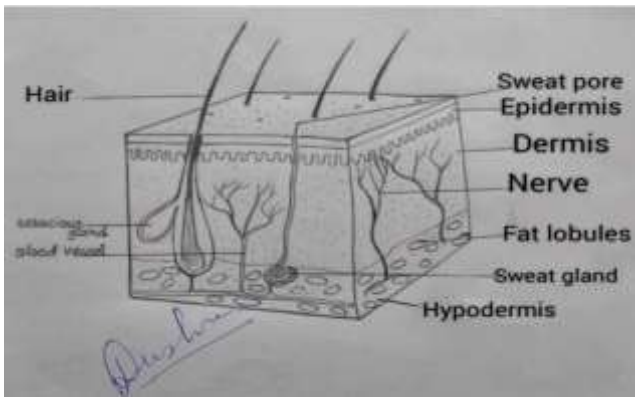

Figure 1: Physiology of Skin.

Although skin is composed of many histological and anatomical layers, it is often defined in terms of three major tissue layers: epidermis, dermis, and hypodermis.

- ❖ Epidermis
- ❖ Dermis
- ❖ Hypodermis

TRANSFERSOMES

A new type of transport system, namely the transfersome, was reported by Cevc et al. Introducd. 1990s. Transfersomes are composed of phospholipids and edge activators (EAs), which are membrane plasticizers (such as Tween 80, Span 80, and sodium cholate) that promote hyperdeformation of transfersomes. When a substance enters the skin's pores, the flexibility of the membrane changes and it automatically penetrates into the skin's pores. This is called self-optimizing deformability. Additionally, transgenes are highly malleable. Therefore, it easily passes through very narrow pores. A new vesicle derivative, the 'transferosome', paves the way to minimizing the skin permeation defects of several low and high molecular weight drugs and proves to be one of the greatest advances in vesicle research it was done.The name means "to carry" and is derived from the Latin "transfer", meaning "to carry", and the Greek "soma", meaning "body". The basic structure of transfersomes is similar to conventional liposomes, but there are some differences in their softness.

Fig 2: Structure of transferosome

An important property of transferosomes is their ability to bind water to the skin and retain moisture. Transferosomes contain many hydrophilic molecules to prevent dehydration. Transferosomes are defined as specially designed vesicular particles consisting of at least one internal water compartment surrounded by lipid vesicles. Although in the form of liposomes, functionally transferosomes have adequate deformability to pass through pores much smaller than their own size. Typically, in 1992, second generation vesicle carriers Ceve and Blume, known as hyper deformable liposomes or transferosomes, have (usually) lighter vesicle sizes.

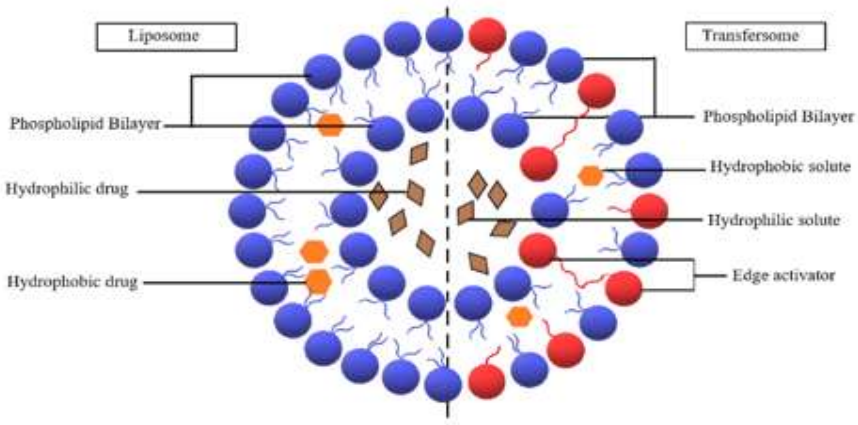

Fig 4: Detailed Description Of The Composition Of Liposomes And Transferosomes.

MECHANISM OF ACTION

Transferosomes, when applied under appropriate conditions, can transfer 0.1 mg of lipid per hour per square centimetre to intact skin. This value is significantly higher than that typically determined by transdermal concentration gradients. The reason for this high flow rate is due to the natural "skin permeation gradient", that is, there is another, much larger permeation gradient across the skin. This osmotic gradient develops because the skin's permeability barrier prevents trans epidermal water loss and maintains a difference in water activity in the

living part of the epidermis (75% water content) and in the stratum corneum. The horn is almost completely dry near the skin surface (15% water). This gradient is very stable because the surrounding air is a perfect absorber for water molecules even when the amount of water lost through the skin is not physiologically high. All polar lipids attract some water. This is due to the energetically favourable interactions between hydrophilic lipid residues and their nearest water. Therefore, most lipid bilayers are naturally resistant to induced dehydration. Therefore, all lipid vesicles formed from polar lipid vesicles move from a dry place to a place with a sufficiently high-water concentration. Therefore, when lipid suspensions (transferosomes) are deposited on the surface of partially dehydrated skin due to evaporative water loss, lipid vesicles sense this "osmotic gradient" and attempt to escape the dryness entirely by moving along this slope. They can only achieve this if they have sufficient deformability to pass through the narrow pores of the skin because the transfer bodies include surfactants with rheological and hydration properties more suitable than those of the skin their greater deformability: Less deformable vesicles, including standard liposomes, are confined to the skin surface, where they completely dehydrate and fuse, so they have less penetrating ability than transferosomes. Transferosomes are optimized in this regard and thus achieve maximum flexibility, so that they can take full advantage of the trans epidermal osmotic gradient (water concentration gradient). Transferosomes overcome the difficulty of penetrating the skin by squeezing along the intracellular sealing lipid layer of the stratum corneum. The carrier assembly includes at least one amphiphilic (such as phosphatidylcholine) that, in an aqueous solvent, self-assembles into a lipid bilayer that closes into a simple lipid vesicle. By adding at least one layer of softener component (such as a biocompatible surfactant or an amphiphile drug) lipid bilayer flexibility and permeability are greatly increased.

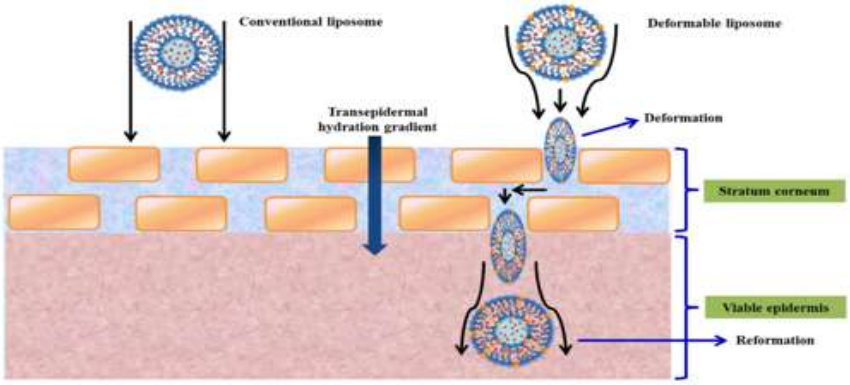

Fig 5: Mechanism Of Deformable Liposomes Permeation Through The Skin.

ADVANTAGES

- The carrier is composed of hydrophilic and hydrophobic parts, making it a unique drug delivery system that can deliver therapeutic agents over a wide range of solubility.
- Transfersomes can penetrate very narrow constrictions in the skin barrier, such as 5 to 10 times the diameter of the vesicle.
- Since they are composed of natural phospholipids and EA, they are expected to be biocompatible and biodegradable.
- Achieves optimal bioavailability of the drug, avoiding first-pass metabolism in the liver, which is a major drawback of oral drug administration.

COMPOSITION OF TRANSFERSOMES

- First, the main amphoteric components (soy phosphatidylcholine, egg phosphatidylcholine, etc.) are lipid mixtures and may be vesicle-forming components that form lipid bilayers.
- Second, 10-25% surfactant/edge activator. The most used edge activators in transferable formulations are surfactants such as sodium cholate. Sodium deoxycholate; Tween and Span (Tween 20, Tween 60, Tween 80, Span 60, Span 65, and Span 80) increase the flexibility of the vesicular bilayer and improve permeability of biocompatible skin It is a softened double layer compound.
- Approximately 3-10% alcohol (ethanol or methanol). It is used as a solvent and ultimately as a humectant. Contains water or phosphate buffered saline (pH 6.5-7).

Table 2: Various Ingredients And Their Role For Synthesis Of Transfersome.

S. No.	Additive	Examples	Function
1.	Phospholipids	Soya phosphatidyl choline, Dipalmitoyl phosphatidyl choline, Distearoyl phoshatidyl choline	Vesicles forming component
2.	Surfactant	Sodium Cholate, Sodium deoxycholate, tween-80, Span80	provide flexibility
3.	Alcohol	Ethanol, methanol	As a solvent
4.	Buffering agent	Saline phosphate buffer (pH 6.4)	As a hydrating medium
5.	Dye	Rhodamine-123, Rhodamine-DHPE, Fluorescein-DHPE Nile red	For CSLM Study

METHOD OF PREPARATION

❖ Rotary Film Evaporation Method

This method is also known as the handshake method and was originally invented by Bangham. This process requires the necessary amounts of phospholipids and surfactants (such as EA) to form a thin film. Often used to study multilamellar vesicles.

Phospholipid and EA solutions are prepared in crude solvents such as a mixture of chloroform and methanol. The prepared solution was transferred to a rotating flask at constant temperature (above the glass transition temperature of the lipid) and vacuum. A film of lipids and EA forms on the walls of the bottle. The twisted membrane is then hydrated with an aqueous medium containing the active ingredient. This causes the lipids to expand and form a double layer foam. Vesicles of desired size can be obtained by extrusion or sonication of the vesicles described above.

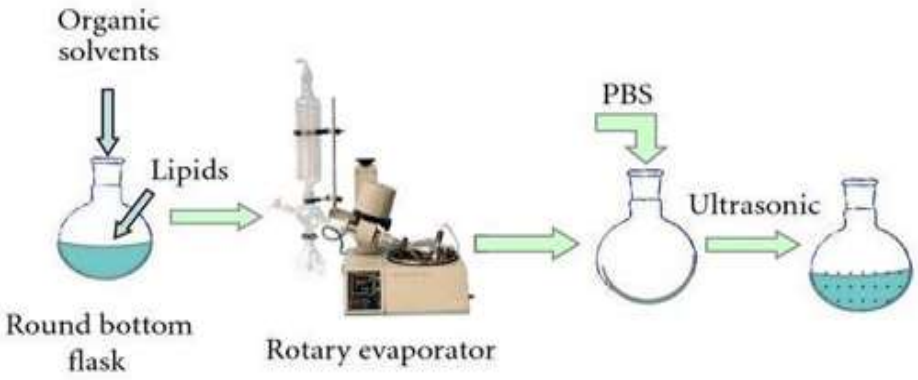

Figure 7: -Method Of Preparation Of Transfersomes By Thin Film Method.

❖ Reverse-Phase Evaporation Method

At this point, the pattern turns into a viscous gel, followed by an array of vesicles. Unencapsulated material and residual solvent can be separated by dialysis or centrifugation. In this method, lipids dissolved in an organic solvent are collected in a round-bottom flask. Aqueous medium containing EA was added during the nitrogen purge process. Depending on its solubility properties, drugs can be added to lipid or aqueous media. The formed system is then sonicated and allowed to transform into a normalized dispersion, which is not separated for at least 30 min after sonication. The organic solvent is then removed under reduced pressure.

❖ **Vortexing Sonication Method**

In the vortex ultrasound method, mixed lipids (phosphatidylcholine, EA, therapeutic agents) are mixed in phosphate buffer and vortexed to obtain a milky white suspension.

Sonicate the suspension and extrude it through a polycarbonate membrane. Cationic transfersome method. Cationic lipids such as DOTMA are mixed with PBS to reach a concentration of 10 mg/ml, and then sodium deoxycholate (SDC) is counted. The mixture was vortexed, sonicated, and then extruded through a polycarbonate filter (100 nm).

❖ **Ethanol Injection Method**

The aqueous solution containing the active ingredient is heated to a constant temperature by continuous stirring. An ethanol solution consisting of phospholipids and EA was injected dropwise into the aqueous solution. When the solution encounters an aqueous environment, the lipid molecules precipitate and form a bilayer structure. This method has several advantages over other methods, including simplicity, reproducibility, and scale-up.

EVALUATION OF TRANSFEROSOMES

Characterization Of Transfersomes Entrapment Efficiency (EE %)

The EE% of transfersomes was measured after separating the unentrapped drug. The entrapment efficiency of transfersome preparations can be achieved by freezing, thawing, and centrifugation methods. A 1 mL sample of the transfersome dispersion was frozen in an Eppendorf tube at −20°C for 24 h. Frozen samples were removed from the freezer, thawed at room temperature, and centrifuged at 14,000 rpm for 50 min at 4°C. The transfersome pellet was resuspended in PBS (pH 6.4) and centrifuged again. This washing step was repeated twice to ensure that no uncaptured drug was present. The supernatant was separated from the transfersome pellet each time and prepared for measurement of free drug. Drug content was measured spectrophotometrically at 306 nm using PBS (pH 6.4) as a blank. Each result was the mean (±SD) of three measurements. Capture efficiency was defined as the percentage ratio of captured drug concentration to total drug concentration and was calculated according to the following formula. **EE%** = Total drug concentration – Free drug concentration X 100 Total drug concentration **PS, PDI and ZP analysis** The PS, PDI and ZP, TFS were measured zeta sizer, Samples were diluted 5 folds with deionized water before analysis.[39]

Differential Scanning Calorimetry (DSC)

DSC thermograms were recorded using a Schimadzu-DSC 50 differential scanning calorimeter. DSC was performed on NYS powder as well as plain transfersomes and transfersomes loaded at a ratio of 90: 10% (w/w) (PL: EA). Analyzes were performed on 40 µL or 1 mg samples sealed in standard aluminium dishes. Thermograms were acquired under a nitrogen atmosphere over a temperature range of 0–300 °C and at a scan rate of 10 °C/min use phosphate buffer (pH 7.4)

Transmission Electron Microscopy (TEM)

The surface appearance and shape of the loaded transferosomes were analysed by taking TEM pictures using a transmission electron microscope (100 CX, Jeol, Tokyo, Japan). Transfersomes were dispersed in water, and a drop of the diluted dispersion was placed on a carbon-coated grid. The dispersion was allowed to stand for 2 minutes to be absorbed by the carbon membrane, and the excess liquid was sucked off with a filter paper. A drop of 2% ammonium molybdate was then placed on the grid. The excess was removed with distilled water, and the samples were examined using TEM.

In Vitro Drug Release From Transferosomes

In vitro release of supported transferosomes through an artificial cellophane membrane was measured by a simple dialysis method. The receptor medium consisted of 100 ml of PBS (pH 6.4) maintained at 37±0.2°C and constantly stirred at 100 rpm in a thermostatically controlled water bath shaker. A quantity of transferosome pellet corresponding to 2.5 mg of drug was added to the donor chamber. Four ml samples were removed from the receptor compartment at 0.5, 1, 2, 4, 6, 8, and 24 h intervals and immediately replaced with an equal volume of fresh receptor solution. Three experiments were performed for each study, and subsidence conditions were maintained throughout the experiment. All samples were analysed for their content spectrophotometrically at one wavelength against PBS (pH 6.4) as a blank value.

CONCLUSION

Transferosomes have several advantages over transdermal drug delivery systems. Transfersomes can effectively capture and transport large and small molecules through the skin. Their highly deformable properties allow them to overcome difficulties in penetrating the skin as they contract to overcome the skin barrier. However, the most important factor for an optimized formulation is the correct ratio of edge activators and phospholipids, which determines the flexibility and integrity of the vesicle layer, as well as the entrapment

efficiency and stability of the formulation. Further scientific research on gene transfer may lead to promising new treatments for various diseases.

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