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Review Article

EFFECTIVE TARGETED DRUG DELIVERY SYSTEM AN REVIEW OF TRANSFEROSOME

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Abstract:
Transdermal drug delivery is considered the safest and most effective method due to its constant and prolonged half-life and prevention of first-pass metabolism, and fewer side effects. Transfersomes, a type of malleable vesicle, are widely used for effective transdermal administration of bioactive materials. Researchers have added an edge activator to the lipid bilayer structure to alter their flexibility. Transferosomes can penetrate stratum-corneum lipid lamellar areas due to osmotic force or skin moisture. They can compress or collapse to fit through a tiny aperture and lose five to ten times their initial diameter before starting again. Research is ongoing on using transferosomes for targeted cancer treatment, as they can maintain an assembly of hydrophilic and hydrophobic components.

Keywords: *Transdermal, Extended, Bioactive, Transferosomes, Hydrophilic, Hydrophobic*

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INTRODUCTION

To obtain high therapeutic activity and higher patient compliance, the research focus has switched from traditional to new drug delivery systems (NDDS) in the current environment. Transdermal patches, microsomes, and other drug delivery methods with improved therapeutic action are now being developed and will soon be available on the market. Due to a number of benefits, including predictable and prolonged duration of action, avoiding first phase metabolism, less side effects, etc., the transdermal route is considered to be the safest and most effective in innovative drug delivery systems. [01-06]

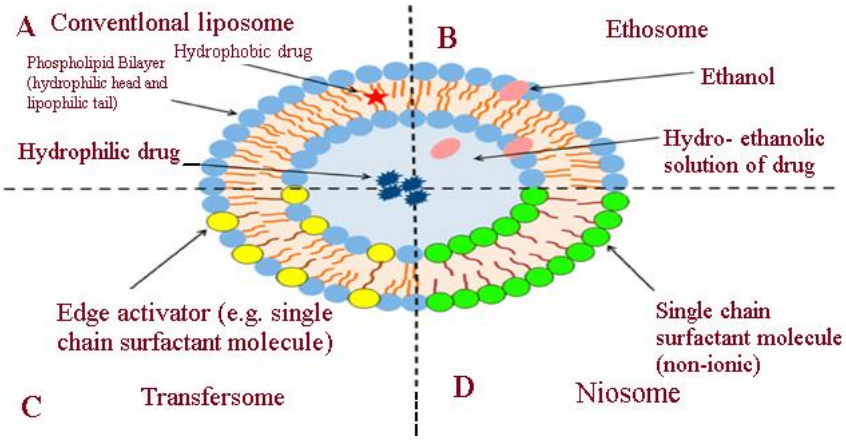

Figure 1 Transfersome

These aqueous-cored, ultra-deformable, lipid bilayer-topped vesicles may be capable of self-optimization and self-regulation. Transferosomes may, therefore, deform and squeeze themselves as intact vesicles through microscopic holes or skin constrictions that are substantially smaller than the vesicle size since they are elastic in nature Transfersomes, a modified liposomal vesicular system, are made up of phospholipids and a single-chain surfactant that acts as an edge activator. This is not the case with conventional liposomes, which consist of synthetic phospholipids such as dipalmitoyl phosphatidylcholine (DPPC), dimyristoyl phosphatidylcholine (DMPC), and dipalmitoyl phosphatidyl glycerol (DPPG), or natural phospholipids such as egg phosphatidylcholine (EPC) and

soybean phosphatidylcholine (SPC). In order to improve the deformability of vesicle membranes, edge activators (EAs) function very effectively as membrane-destabilizing agents. The transfersomes are rendered deformable and ultra-flexible, which boosts their ability for permeation when mixed in the optimum ratio with the proper lipid Transfersomes are able to pass through holes that are significantly smaller than their own diameters, which allows them to circumvent the main limitations of traditional liposomes.The fragmentation did not cause the transfersomes to lose their diameters even after they had passed through the smaller holes. Performance has improved over that of conventional liposomes thanks to the incorporation of EAs into the transfersomal formulation. The use of EAs in the transfersomal formulation has led to an improvement in performance above that of traditional liposomes. The EAs utilized in transfersomal formulations can also help hydrophobic medicines become soluble, improving the effectiveness of drug trapping. Transfersomes' structural makeup.[04,10,14,19]

An index of transferosomes[06,09,11]

S.No.	Example	Class	Uses
01	• Egg Phosphatidyl CholineSoya Phosphatidyl choline, • Dipalamitoylphosphatidyl choline	Phospholipids	Vesicles forming component
02	• Ethanol, • Methanol, • Isopropyl Alcohol, • Chloroform	Solvents	As a solvent
03	• Sod. Cholate, • Sod. Deoxycholate, • Tween-80, • Span 80, • Tween 20	Surfactants	Vesicles forming component (Edge Activators)
04	• Saline phosphate buffer (pH 6.4), • Phosphatebuffer pH 7.4	Buffering agent a hydrating	As medium
05	• Rhodamine-123 Rhodamine –DHPE • Fluorescein –DHPE Nile-red	Dye	For CSLM study

Features of Transfersomes[01,02,0320 to 24]

- Since the architecture of transfersomes is composed of lipophilic and hydrophilic moieties, these molecules can have a variety of solubilities and yet be accepted.
- As transfersomes are ultrafoldable vesicles, they may deform and pass through a thin constriction that is five to ten times smaller than their own diameter without exhibiting any noticeable loss. The exceptional deformability of these vesicles makes their penetration more effective.
- They can act as a delivery system for drugs with both high and low molecular weights. A few examples are analgesics, anesthetics, corticosteroids, sex hormones, cancer-fighting medications, insulin, gap junction protein, and albumin.
- They are biocompatible and biodegradable due to the use of natural phospholipids during manufacturing that are equivalent to liposomes.
- When it comes to lipophilic medicines, transfersomes have a high entrapment efficiency that is close to 90%.
- They stop the drug that is encapsulated from being broken down metabolically.
- They release their contents gradually, serving as a depot or reservoir.
- They can be used to administer medications topically or systemically.

Mechanism of Action[16,17,19,28,29,30]

Transferosomes circumvent the obstacle of getting into the skin by pressing across the outer layer of corneum's internal sealing lipids. The process for improving the transport of active ingredients into and through the skin is currently not well understood. Two hypothesized modes of operation have been developed.

- Transferosomes serve as medication delivery systems and stay whole after penetrating the skin.
- Transferosomes have the effect of enhancing the penetration of drug molecules into and across the outermost layer of cells by dislodging the stratum corneum's highly structured intercellular lipids.

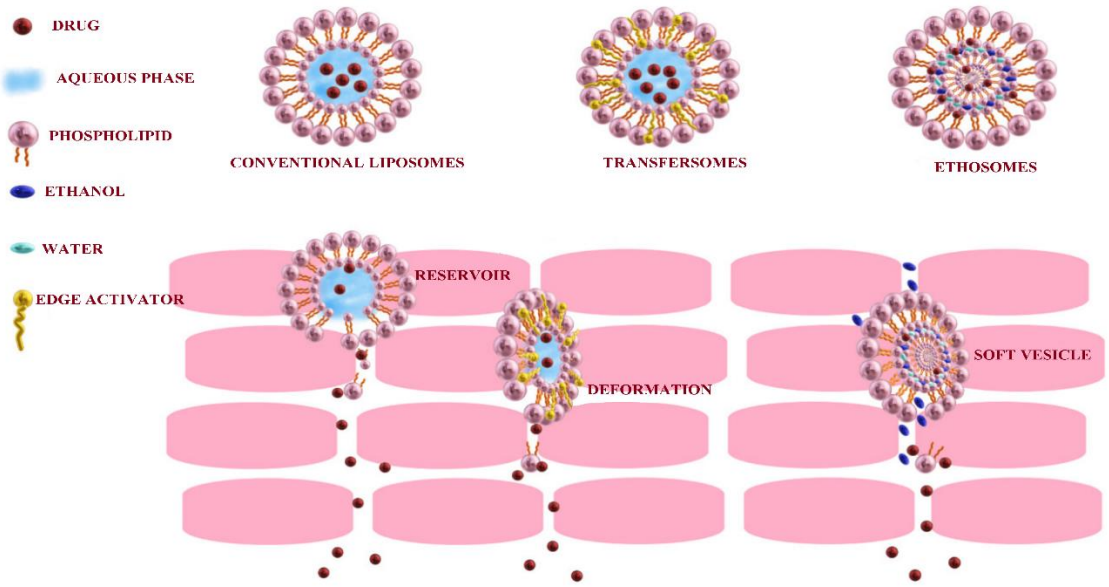

Figure 2 Mechanism of Action

The use of transfersomes vesicles in drug administration therefore depends on the carrier's capacity to enlarge and circumvent the hydrophilic nature of pores in the skin. Transport of drugs into cells may entail vesicle lipid bilayer diffusion with the cell membrane, similar to normal endocytosis. Thus, the process is complicated and makes use of cutting-edge mechanics, material transportation, and hydration/osmotic pressure. Possible methods that apenetrant might get through the skin wall.

1. Throughout the layer of horns,
2. 2. Through the sebaceous glands connected to the ends of hair follicles, or
3. By way of the sweat glands

Applications

- These are safe approaches for administering medications deep into the skin to treat cutaneous cancer.
- Large molecular weight medications can pass through mucosal membranes.
- Making use of lipid vesicles to deliver medicines with physiological activity and DNA.
- Ultra-deformable vesicles can be used to combat drugs with documented GI adverse effects, such NSAIDs.
- These are used to distribute corticosteroids.
- Interferons can be distributed as carriers by using transfersomes.
- Proteins and peptides may be transported by transferosomes extremely well.
- Transcutaneous hepatitis B immunizations produced better results.

Advantages

- The self-optimized and very flexible membrane's features allow for highly effective medication delivery through or into the skin over time.
- The drug dose required each day can be reduced to have a similar therapeutic effect.
- Suitable for penetration through the skin and enables entrance owing to mechanical stress in the immediate vicinity in a self-assembling way.
- When transfersomes are utilized in non-occlusive settings, their capacity to follow the natural water gradient across the epidermis lessens the chance of vesicle rupture in the skin.
- By altering the vesicles composition or surface characteristic of the transfersome the membrane, the rate of drug release and the deposition to the target location may be controlled.
- Provide a continuous or steady infusion of medications over an extended period with time, maintaining a sufficient plasma concentration of the powerful medications.
- Since they last longer after administration, this enables a reduction in dosage frequency, which improves patient compliance.
- Transfersomes can be used to administer medications more conveniently and with improved bioavailability.

- Lessened adverse effects and enhanced treatment as a result of maintaining plasma levels across the dosing interval.

Disadvantages

- The costly nature of the good prevents these transfersomes from being widely used.
- Many medications, particularly hydrophilic ones, penetrate through skin too slowly to be considered therapeutically useful.
- The function of the skin barrier varies from site to site on an identical individual, from person to person, and with age, which affects how consistently drugs are released.
- Skin discomfort and hypersensitivity responses might happen.
- It is impossible to provide medications that need high blood levels.
- Highly vulnerable to the unstable oxidative destruction of transfersomes.
- Another requirement that creates difficulties when employing transfersomes as drug delivery systems is their purity of natural phospholipids.

Material for Transferosomes[30 to 36]

In a solution of water, amphipathic substances or phospholipids like phosphotidylcholine self-assemble into a lipid bilayer that then seals to create a vehicle. By softening the lipid bilayer, bilayer softening agents including Tween 80, Span 85, Span 80, sodium cholate, sodium deoxycholate, and other surfactants serve to give the tiny particles their distinctive malleable and flexible quality.

Various Ingredients Are Added When Making Transfersomes

Ingredient	Examples	Functions
Phospholipids	• Soya Phosphatidylcholine Egg Phosphatidylcholine Disteryl Phosphatidylcholine	Vesicle formingComponent
Surfactant	• Sodium Cholate Sodium deoxy Cholate • Tween 80 • Span 80	Vesicle formingComponent
Alcohol	• Ethanol • Methanol	As a Solvent
Dye	• Rhodamine-123 Rhodamine-DHPE Flurescein-DHPE Nil red • 6 Corboxy fluorescence	For Confocal ScaningLaseer Microscopy (CSLM) Study
Buffering Agent	• Saline phosphate buffer(PH 6.5) • 7% v/v ethanol • Tris buffer (PH 6.5)	As a hydratingmedium

Methods of preparation

1. Rotary film evaporation
2. Reverse Phase evaporation
3. Vortexing sonication
4. Ethanol injection
5. Freeze thaw

- **Evaporation from a rotary film:** This approach is often referred to as the modified hand-shaking approach. Lecithin, the edge activator (surfactant), and medicine are mixed in a 1:1 combination of ethanol and chloroform. By hand shaking at a temperature above the lipid transition temperature, the mixture is exposed

to evaporation to remove the organic solvent. To guarantee that the organic solvent is completely removed, the thin lipid film is left on all night. The aforementioned thin film is hydrated by spinning at 60 RPM for an hour at the proper temperature and utilizing a pH 6.5 buffer. For two hours, the resulting vesicles inflated at room temperature. Tiny vesicles were produced by sonicating the resulting vesicles at ambient temperature.

- **Phase-reversal evaporation:** In this approach, lipids that have been dissolved in organic solvents are added to a flask with a flat bottom. Edge activators are introduced into aqueous media during nitrogen purging. Depending on the characteristics of the drug's solubility, it may be introduced to a lipid or aqueous media. After the system is produced, it is sonicated until a homogenous dispersion is obtained, which should not separate for at least half an hour. After that, the organic solvent is removed while the pressure is lowered. The system will now change into a thick gel, and vesicles will start to develop. Using centrifugation or dialysis, the non-encapsulated material and leftover solvents can be eliminated.
- **Sonication with a vortex:** Phospholipids and edge activators are mixed well in this process and then suspended in phosphate buffer. The resultant creamy liquid is extruded through polycarbonate membranes after being sonicated with a bath sonicator or vortex.
- **Alcohol infusion:** In this procedure, Drug coupled with aqueous solution is heated with continuous stirring at steady temperature. Drop by drop, phospholipid- and edge-activating-containing ethanolic solution is added to an aqueous solution. Lipid molecules precipitate out of the solution and create bilayered structures when it comes into touch with watery medium. Compared to other ways, this one is better.
- **Freeze thaw:** With this technique, multi-lamellar vesicles are suspended and subjected to alternating cycles of freezing at very low temperatures and then being heated to extremely high temperatures. The prepared suspension is put in a tube and submerged for 30 seconds in a nitrogen bath (-30° C). It is heated to a high temperature in a water bath after it has frozen. This is done eight to nine times.

Transferosome Characterization [38, 40 to 45]

- **Vesicle size distribution and zeta potential**
  Malvern zeta seizer used the dynamic (DLS) light method to measure vesicle size, size distribution, and zeta potential. When preparing the sample, distilled water is utilized. After the sample has been passed by a membrane filter with a 0.2 mm opening, the sample is thinned out or diluted with filter saline.
- **Entrapment efficiency**
  The amount of drug entrapped in a percentage of the added substance or the percentage of drug entrapment are the typical ways that entrapment efficiency is expressed. By using a mini-column centrifugation technique, the unentrapped medication is extracted in this process. Following centrifugation, 0.1% Triton X-100 or 50% n-propanol were used to break up the vesicles. This formula is used to calculate the entrapment efficiency.

$$\text{Entrapment Efficiency} = \frac{(\text{Amount Of Drug Entrapped})}{(\text{Total Amount Added})} \times 100$$

- **Vesicle morphology**
  Vesicle shapes can be determined using the dynamic light technique (DLS) or photon correlation spectroscopy. Following their creation in distilled water, these samples were diluted with filtered saline and passed through a 0.2 mm barrier filter. Next, the sizes of the samples were ascertained by means of dynamic light scattering (DLS) experiments or photon correlation spectroscopy. Using TEM (Transmission Electron Microscopy), transferosome vesicles may be seen, and their stability can be ascertained by monitoring changes in their size and shape over time. The DLS and TEM are used to obtain or monitor changes in structure and mean size as determined by DLS.
- **Drug content**
  A high-pressure liquid chromatography method (HPLC) that uses a UV detector (ultraviolet), the column oven, pump, autosample, and computerized analysis program can be used to determine or express the drug content, depending on the pharmacopoeial analysis technique.
- **Turbidity measurement**
  Turbidity in aqueous solutions is typically measured using the nephelometer technique.
- **Number of vesicles per cubic mm**
  The crucial parameter for the optimization of composition and other process factors is the number of vesicles per cubic millimeter. Unsonicated transferosomes are multiplied by five in a 0.9% sodium chloride solution. Hemocytometers and the best microscope are employed for the upcoming experiments.
- **In vitro drug release[50, 51]**
  This inquiry aims to determine the penetration rate for in vitro drug release. Before more expensive in vivo tests are conducted, the formulation is optimized based on results from in vitro research, the time required to

attain steady state permeation, and the permeation flux at steady state. The transferosome solution is incubated at 32°C to determine drug release. After that, samples are collected, and micro column centrifugation is used to isolate the free drug. Multiply the original quantity (i.e., 100% entrapped and 0% liberated) by the amount of drug that was initially entrapped in order to get the amount of drug released.

- **In vitro skin permeation studies**
  Tran's diffusion apparatuses that have been modified are utilized for in vitro skin permeation tests in this study. The effective diffusion area for this study was 2.50 cm^2. An in vitro experiment with phosphate buffer solution (pH 7.4) was conducted using goat skin. For the permeation test, fresh goat belly skin was procured from the butchery. After the skin of the abdomen was cleared of hairs, a regular saline solution was used to hydrate it. The layer of adipose tissue on the sin was removed with a cotton swab. The skin was immersed in an isopropyl alcohol solution to maintain a temperature of 40°C. An instrumental analytical method was used to assess the components.

Conclusion: The benefits of employing transferosomes for transdermal drug delivery, including their improved deformability and skin penetrating capacity, have been covered in this work. They are hydrophilic in nature. They successfully capture both big and tiny molecules using skin. The most important component of an ideal formulation is the appropriate ratio of edge activators to phospholipids, which controls the formulation's flexibility, integrity of the vesicle layers, efficacy of entrapment, and stability. We look at the macro- and micromolecular makeup of transferosomes.

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