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TRANSFEROSOMES- A REVIEW

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Abstract
Novel drug delivery system aims to deliver the drug at a rate directed by need of body during the period of treatment and channel the active entity to the site of action. Transferosome is one of the novel vesicular drug delivery system which consists of phospholipids, surfactant and water for enhanced transdermal delivery. Transferosomes are able to reach intact deeper regions of the skin after topical drug administration while delivering higher concentrations of active substances making them a successful carrier for transdermal applications. These vesicular systems can deliver low as well as high molecular weight compounds. Targeted and controlled release formulations can also be prepared by transferosomes as it can accommodate drug molecules with wide range of solubility.
Transferosomes is an ultra-deformable vesicle and elastic in nature, they can squeeze itself as an intact vesicle through narrow pores that are significantly smaller in size. They can encapsulate both lipophilic, hydrophilic as well as amphiphilic drugs.

Keywords: Novel Drug Delivery System,Transferosomes, Transdermal Delivery,Vesicular System.

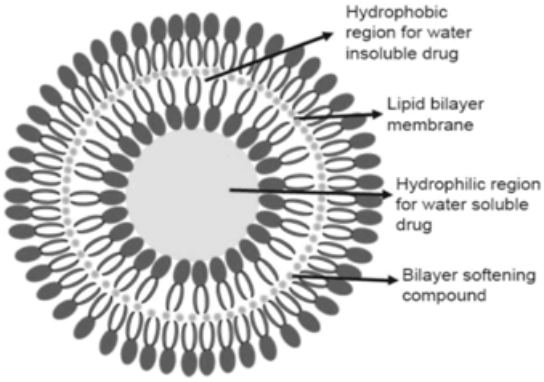
Introduction [1,2]

Currently, transdermal route of administration is one of the promising methods for application of drug. It has many advantages over other conventional route of administration. It improves bioavailability by reducing pre-systemic metabolism. Transferosomes were first developed by Gregor cevc in the year 1992. Transferosome is registered by a trademark by the german company IDEA,AG and it is derived from latin word, 'transferre' meaning carrying and 'soma' meaning body i.e 'carrying body'.

Transferosomes are recent novel drug delivery system and are special types of liposomes consisting of phosphatidylcholine and an edge activator.

Structure and Composition of Transferosomes [3,4]

Transferosome is an artificial vesicle designed to exhibit the characteristics of a cell vesicle or a cell engaged in exocytosis and thus suitable for controlled and potentially targeted drug delivery. Transferosomes are complex vesicles that have extremely flexible and self-regulating membrane, which make the vesicle deformable.



Structure of Transferosome

Composition of transferosomes

Transferosomes are composed phospholipids like phosphatidyl choline which self assembles into lipid bilayer in aqueous environment and forms a vesicle. It also contains an edge activator which consists of single chain surfactant which causes destabilization of lipid bilayer there by increasing its fluidity and elasticity.

The most commonly used surfactants in transferosomes are sodium cholates, sodium deoxycholate, tweens and spans {tween 20, tween 60, tween 80, span 60, span 65, span 80} dipotassium glycyrrhizinate. The nature and ratio of different edge activators affect the physicochemical properties of vesicles including their entrapment efficiency[EE], zetapotential and vesicle size.

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CLASS	EXAMPLE	USES
Phospholipids	Soya phosphatidyl choline, egg phosphatidyl choline, dipalmitoyl phosphatidyl choline	Vesicles forming complexes
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
Dye	Rhodamine 123, Nile red	for confocal scanning Laser microscopy (CSLM)

Mechanism of Action of Transferosomes [5,6]: Two mechanism have been proposed as mentioned below:

1) Transferosomes act as drug vectors, remaining intact after entering the skin.

When a transferosome vesicle applied on biological surface, nonoccluded skin, penetrate its barrier and migrates into deeper layers of stratum corneum to secure its adequate hydration. Transferosomes need to enforce its own route through organ. Its usage on its delivery relies on carrier's ability to widen the hydrophilic pores in the skin. During transportation to intracellular site involves the carrier's lipid bilayer fuses with the cell membranes, or else the vesicles are taken up by the endocytosis process.

Preparation of Transferosomes [7]

Thin film hydration technique

A thin film is formed by addition of phospholipid and surfactant by dissolving in organic solvent. Organic solvent is then evaporated above the lipid transition temperature using rotary evaporator a prepared thin film is then hydrated with buffer {ph 6.5} by rotation at 60rpm for 1hr at corresponding temperature. The resulting vesicles were sonicated at room temperature. The sonicated vesicles were homogenized by manual extrusion 10times through a sandwich of 200 and 100nm polycarbonate membrane.

Ethanol Injection Method

In this method, drug along with aqueous solution is heated with continuous stirring at constant temperature... Ethanolic solution containing phospholipids and edge activators are injected into an aqueous solution drop wise. When the solution comes in contact with aqueous media the lipid molecules get precipitated and form bilayered structures.

Reverse Phase Evaporation Method

In this method, in a round bottom flask lipids are dissolved in organic solvent. Aqueous media containing edge activators{surfactant] is added under nitrogen purging. The drug can be added to the aqueous medium or lipid based on its solubility characters. The formed system is then sonicated until it become a homogeneous dispersion and should not separate for at least 30 minutes after sonication. The organic solvent is then removed under reduced pressure. At this condition, the system will convert to a viscous gel followed by the formation of vesicles. The non-encapsulated material and residual solvents can be removed using dialysis or centrifugation process.

Charecterization of transferosomes [8,9]

The charectrization of transferosomes are similar to that of other vesicles like liposomes,niosomes etc.
It includes:

- **vesicle Size, size distribution and zeta potential:**These parameters can be determined by Dynamic Light scattering system by Malvern zeta sizer
- **Number of Vesicle per cubic mm:**Non sonicated Transfersome formulations are been diluted five times with 0.9% sodium chloride {nacl}solution. Haemocytometer and optical microscope can then be used for further study. The Transfersomes in 80 small squares are counted and is calculated by given formula:

Total number of transfersomes per cubic mm = (Total number of transfersomes counted × dilution factor × 4000) / Total number of squares counted.

- **Entrapment Efficiency:**Entrapment efficiency was determined by first separation of the un-entrapped drug by use of

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mini-column centrifugation method. The entrapment efficiency can be given by following equation
Entrapment efficiency =[Total amount of the drug added − Amount of the free drug] /{Total amount of the drug added} × 100

- **Drug Content**: The drug content can be determined using a UV spectroscopy and is given by following equation
  Drug content= practical drug content /theoritical drug content ×100
- **Turbidity Measurement:** Turbidity of the drug can be measured by using nephelometer.
- **Surface Charge and Charge Density:**Surface charge and charge density of Transfersomes can be determined usinga zeta sizer.
- **Penetration Ability:** Penetration ability of Transfersomes can be evaluated by using fluorescence microscopy.
- **Occlusion Effect**: Occlusion of the skin is considered to be helpful parameter for the permeation of drug in case of topical preparations.
- **In-vitro Drug Release:** It is performed for determining the permeation rate.For determining the drug release, transfersomes suspension is incubated at 320C and samples are taken at different times and the free drug is separated by mini column centrifugation method.The amount of drug released is then calculated indirectly from the amount of drug entrapped at zero times as the initial amount (100% entrapped and 0% released).
- **In-vitro Skin Permeation Studies:** Franz diffusion cell is used for the determination of the drug release studies. It contains a donor and a receptor compartment. . In the receptor compartment volume of 50 ml and effective diffusion area of 2.5cm used. Abdominal skin hair is removed and hydrated with saline solution. The adipose tissue layer removed by rubbing with a cotton swab. Then, treated skin was mounted horizontally on receptor compartment with the stratum corneum facing upwards towards the donar compartment of franz diffusion cell. The area of donar compartment is 250 cm and capacity of receptor compartment 50 ml of phosphate buffer of [7.4] at 37± 5° c stirreat a magnetic bar for 100 rpm. 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 to maintain sink conditions. The obtained samples can be analyzed by HPLC method or spectroscopic method.

Methods for the characterization of Transferosomes [8,9]

PARAMETER	METHOD/ EQUIPMENT
Vesicle size, size distribution	Dynamic light scattering (DLS) method
Zeta potential	Electrophoretic mobility technique
Vesicle morphology	DLS method, Photon correlation spectroscopy, Transmission electron microscopy
Number of vesicles for cubic mm	Hemocytometer and optical microscope
Entrapment efficiency	%Entrapment efficieny = Amount of the drug entrapped/ Total amount of the drug added × 100
Drug content	
Degree of deformability	Microporous filter with DLS, Transmission electron microscopy
In-vitro drug release	Franz diffusion cell with cellulose membrane, Extrusion method
In-vitro skin permeation studies	Franz diffusion cell

Figure 1: Transferosomes in microscopic view **2:** Double beam uv visible spectrophotometer

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3: Projection microscope

Figure 4: Differential scanning calorimetry

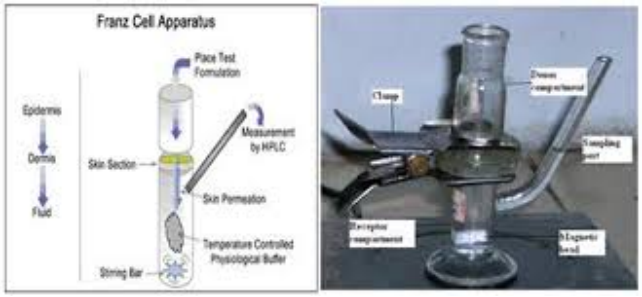

Figure 5: Franz diffusion cell apparatus

Advantages of Transferosomes [10]

1. High entrapment efficiency can be achieved
2. Transferosomes are Biocompatible and biodegradable.
3. It Protects the drug product from metabolic degradation.
4. Transferosomes act as depot the release will be slow and gradual.
5. Transferosomes consists of both hydrophilic and hydrophobic substances possess a higher solubility range.

Disadvantages of Transferosomes [10]

1.Transferosomes are chemically unstable due to their predisposition to oxidative degradation.
2.Purity of natural phospholipids is another criterion which resist against adoption of transferosomes as drug delivery vehicles.
3.Transferosomes are expensive

Applications of Transferosomes [10]:

Over the past few years,applications of the transfersomes in the field of transdermal drug administration have been extensively studied. Some of these applications are given below

- **Delivery of Anticancer Drugs:** A research conducted by Jiang et al. in 2018 was associated with the topical chemotherapy of melanoma by transfersome-embedded oligopeptide hydrogels containing paclitaxel prepared by the thin-film dispersion method. Transfersomes composed of phosphatidylcholine, tween80 and sodium deoxycholate were shown to effectively penetrate into tumor tissues.
- **Controlled release and sability enhancement:** transferosomes have the ability for providing controlled release of the administered drug and increasing its stability of the drugs.
- **Deliveryof Anti-Inflammatory Drugs**: Diclofenac sodium, celecoxib, mefenamic acid and curcumin-loaded transfersomes were developed and studied for the purpose of topical administration by several research groups. It can be concluded that Tansferosomes could improve the stability and efficacy of the anti-inflammatory drugs.
- **Peripeheral drug targeting/ minimal carrier associated drug clearance**: Transferosomes helps in drug targeting to peripheral blood vessels in the subcutaneous tissue.

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- **Delivery of Herbal drugs**: Herbal drugs can also be incorporated into transferosomes as they can penetrate stratum corneum supply nutrients locally to maintain its functioning. Curcumin, Capsaicin showed topical administration through transferosomal formulations.
- **Delivery of NSAIDS**: NSAIDS are associated with number of GI side effects. These can be overcome by transdermal delivery using ultra deformable vesicle.

Different Additives Used in the Formulation of Transferosomes [5]

Class	Example	Uses
Phospholipids	Soyaphosphatidyl choline Dipalmitoyl phosphatidyl choline, disteroyl phosphatidyl choline	Vesicles forming component
Surfactants	Sodium cholate, sodium deoxy cholate, tween 80, span 80	Flexibility
Alcohol	Ethanol, methanol	Solvent
Buffering agent	phosphate buffer ph(6.5-7)	Hydrating medium
Dye	Rhodamine-123, rhodamine DHPE, flourescein DHPE, nile red	CSLM study (Confocal scanning laser microscopy)

Some Examples of applications of transfersomes as a transdermal delivery system [9]

DRUG	INDICATION	RESULT
Curcumin	NSAID	Improved bioavailability and permeability
Meloxicam	NSAID	Improved skin permeation
Methotrexate	Anticancer drug	Improved skin permeation
Insulin	Hypoglycemic	High encapsulation efficiceny
Oestradiol	Estrogen	Improved transdermal flux
Corticosteriod	Virtiligo	Improved site specificity and drug safety
Repaglinide	Anti-hyperglycemic agent	Improved topical delivery and site specificity
Ibuprofen	NSAID	Improved stability
Lidocaine	Local anesthetic	Enhanced skin permeation with increased local anesthetic efficacy
5-fluorouracil	Antineoplastic agent	Exhibited better skin penetration, as well as skin deposition, of the drug
Sertraline	Anti-depressant agent	Increased permability

Conclusion

Transferosomes are the most promising transdermal drug carrier is the recently developed and patented.They are specially optimized particles or vesicles, which can respond to an external stress by rapid and energetically inexpensive, shape transformations. Transferosomes can pass through even tiny pores (100 mm) nearly as efficiently as water, which is 1500 times smaller. Transferosome carriers can create a highly concentrated drug depot in the systemic circulation. Transferosomes are stable at low temperatures compared to high temperatures. Transferosomes are emerging vesicular systems due to their abilities of site specificity, sustained release and has higher penetration power across skin, high deformability, and has higher stability and has the ability of encapsulation of high molecular weight compounds when compared to other vesicular systems.

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