TRANSFEROSOMES - ULTRADEFORMABLE DELIVERY CARRIERS

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***Abstract*: Administration of drugs through skin had a major barrier of skin layers. This article emphasizes on the delivery of drugs through ultra-deformable vesicular drug delivery system known as Transferosomes. Complex lipid layers flexible to penetrate into skin which is enhanced compared to liposomes. Phospholipids (Soya phosphatidyl choline, egg phosphatidylcholine) and surfactants (Tween-80, Span-80, Tween 20) are used for to vesicle formation and providing flexibility to transferosome. Characters are defined to enable the drug to transfer into layers of skin by determining the vesicle size, entrapment efficiency, stability and surface charge.**

***Keywords*: Ultradeformable, phospholipids, surfactants**

INTRODUCTION

Skin is considered as the largest organ of the body making up 16% of the body weight and consists of three functional layers:epidermis, dermis, and subcutis. The skin acts as a barrier and prevents transcutaneous delivery of therapeutic agents.The major barrier in transdermal delivery of drug is the skin intrinsic barrier, the stratum corneum, the outermost layer of the skin is major hurdle for diffusion of hydrophilic ionizable bioactives.

TRANSFEROSOMES

Transferosomes are ultra-deformable vesicles containing an aqueous core surrounded by the complex lipid bilayer (similar to liposomes). The size and shape of these vesicles is self-coordinating and self-optimizing based on the composition. A transferosomes are artificial vesicular carriers which are engineered to be similar cell vesicle in exocytosis, and hence appropriate for controlled and potentially targeted drug delivery. Strong bilayer deformability is another valuable significance of transferosomes which include increased affinity of transferosomes to bind and retain water

FEATURES OF TRANSFEROSOMES

- These vesicular carriers are suitable for low as well as high molecular weight drugs e.g. analgesic, anesthetic, corticosteroids, hormone, anticancer etc.
- These are made of natural phospholipids similar to liposomes which are biocompatible and biodegradable.
- Lipophilic drugs nearly have 90% entrapment efficiency.
- Metabolic degradation is prevented for encapsulated drugs.
- They also act as depot preparation as they release the contents slowly and gradually.
- They can be employed for both systemic as well as topical delivery of drug.
- Preparations of these transferosomes are non complex and easy to scale up

ADVANTAGES

- First-pass metabolism of drugs is restraint.
- Fewer side effects can be observed.
- Lipophilic drugs have 90% entrapment efficiency.
- Transferosomes are delivery system which are compatible for a range of low and high molecular weight drugs such as analgesic, protein, anesthetic, corticosteroids, hormone, anticancer etc.
- Transferosomes are convenient for drug molecules with wide range of solubility.
- They also act as depot preparation as they release the contents slowly and gradually.
- They are biocompatible and bio- degradable.

- They are suitable for both systemic and topical drug delivery.
- Metabolic degradation of encapsulated drugs can be prevented.
- In case of toxicity, termination of drugs can be achieved easily.
- Decrease in dosing frequency and improvement in patient compliance can be achieved

LIMITATIONS

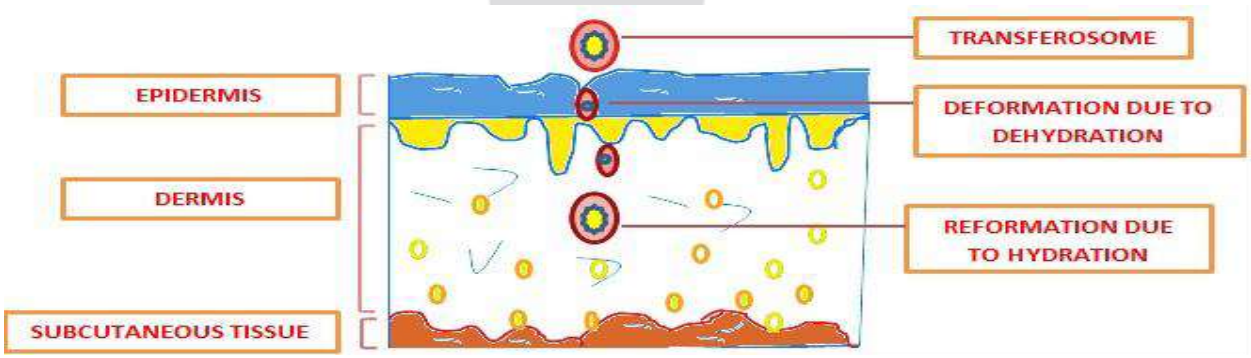
- Transfersomes are chemically unstable because these are prone to oxidative degradation.
- Purity of natural phospholipids is an important aspect and influences against adoption of transfersomes as drug delivery vehicles.
- Transfersomes formulations are expensive.

DIFFERENT ADDITIVES USED IN TRANSFEROSOMES

S.no.	CLASS	EXAMPLE	USE
1.	Phospholipids	Soya phosphatidyl choline, egg phosphatidylcholine, di-palmitoylphosphatidyl choline	Vesicles forming Component
2.	Surfactant	Sod.cholate, Sod.deoxycholate, Tween-80, Span-80, Tween 20	Providing flexibility
3.	Solvents	Ethanol, methanol, isopropyl alcohol	As a solvent
4.	Buffering agent	Saline phosphate buffer (pH 6.4), phosphate buffer pH 7.4	As a hydrating medium
5.	Dye	Rhodamine-123 Rhodamine-DHPE Fluorescein-DHPE Nile-red	Used for confocal laser Scanning microscopy study

MECHANISM OF PENETRATION

Transferosomes when applied to skin are able to transfer about 0.1mg to 0.5mg of lipid per hour across the skin. This value is considerably high when compare to the values of transdermal concentration gradients. Skin penetration barrier leads to the enhancement of osmotic gradient which restrict water loss from the skin and manage a water activity difference in the viable part of epidermis (75% water content) and close to the skin surface, around a dry stratum corneum (15% water content) and this gradient is very stable. There is an attraction of hydrophilic lipids towards water due to active interaction between hydrophilic lipid residues and their adjacent water. Thus induced dehydration is resisted by most of the lipid bilayers. Henceforth all hydrophilic lipid vesicles move from dry location sites to the sites which have considerably high water content. When transferosomes are applied on the skin, they will get dehydrated to some extent due to water loss by evaporation and when lipid vesicles sense this osmotic gradient they try to avoid completely drying by migrating along the gradient. They can escape complete drying only if they are considerably deformable to pass through the narrow pores in the skin. As transferosomes are sufficiently flexible and have suitable rheologic and hydration properties and they can easily pass through the narrow pores in the skin. Conventional liposomes which are less flexible compare to transferosomes get confined to skin surface, where they get completely dehydrated and fused together and because of these conventional liposomes have less penetration power than transferosomes



PREPARATION OF TRANSFEROSOMES

The first step includes dissolving phospholipids (vesicle forming component) and surfactant (provide flexibility) in volatile organic solvent mixture (chloroform: methanol). Lipophilic drug is incorporated at this stage in above mixture. A thin film is prepared by evaporating organic solvent (room temperature for pure phospholipid vesicles and 50C for dipalmitoyl phosphatidyl choline). It can be done by using rotary evaporator. Keep under vacuum for 12hr. The accumulated lipid films were hydrated using phosphate buffer (pH 6.5) by rotating at 60 rpm for 1 hr. The formed vesicles were kept at room temperature for swelling for 2 hr. At this stage hydrophilic drug can be incorporated. For preparing small vesicles, the resulted large multi vesicles are sonicated using bath or probe sonicator for 30 minutes at 40C. Homogenization of sonicated vesicles is carried out by manual extrusion by using a sandwich of 200 and 100nm polycarbonate membrane.

CHARACTERIZATION OF TRANSFEROSOMES

The following are characterization parameters of transferosomes:

i. **Vesicle size distribution of transferosomes and zeta potential**
Dynamic Light Scattering method by Malvern Zetasizer can be used to determine the vesicle size, size distribution and zeta potential.

ii. **Vesicle diameter**
Photon correlation spectroscopy or dynamic light scattering (DLS) method is used to determine the vesicle diameter. Distilled water is use to prepare samples and filtration is done using a 0.2 mm membrane filter and then diluted with filtered saline and photon correlation spectroscopy or dynamic light scattering (DLS) method is use to measure the diameter of vesicles.

iii. **Entrapment efficiency**
Percentage of the drug entrapped in vesicles can be determined by initially separating the un-entrapped drug by using mini column centrifugation method. Then 0.1% Triton X-100 or 50% n-propanol was used to disarray the vesicles. The entrapment efficiency can be calculated by using following formula:
Entrapment efficiency = (Amount entrapped / Total amount added) ×100

iv. **Drug content**
Determination of drug content can be done by using one of the analytical method high performance liquid chromatography (HPLC) method using a UV detector.

v. **Surface charge and charge density**
Zetasizer is used to study Surface charge and charge density of Transferosomes.

vi. ***In vitro* Skin permeation Studies**
Modified Franz diffusion cell contain receiver compartment, donor compartment having volume of 50ml capacity and effective diffusion area of 2.50 cm^2 which is used for In vitro study. For skin permeation study, treated skin was kept horizontally on the receptor compartment to the stratum corneum side facing upwards towards the donor compartment of modified Franz diffusion cell. 2.50cm^2 effective permeation area of donor compartment was exposed to receptor compartment. The receptor compartment contained 50ml of phosphate buffer saline was maintained at 37 ± 0.5˚C and stirred by a magnetic bar at 100rpm. At regular time intervals 1 ml sample from the receptor medium were withdrawn and replaced by an equal volume of fresh phosphate buffers to maintain sink conditions. The samples were examined by any analytical technique.

vii. **Physical stability**
The ampoules containing transferosomal formulation were kept at 4 ± 2 C (refrigerated temperature), 25 ± 2 C (room temperature), and 37 ± 2 C (body temperature) for about 3 months. Samples from each ampoule were evaluated after 30 days to determine drug leakage. Percentage of drug lost was calculated by considering the initial entrapment of drug as 100%**.**

APPLICATIONS

i. Transferosomes as a carrier for protein
ii. Transferosomes as a carrier for insulin
iii. Transferosomes as a carrier for interferon
iv. Transferosomes as means of transdermal immunization
v. Transferosomes as a carrier for corticosteroids
vi. Transferosomes as carrier for topical analgesics and anaesthetic agent
vii. Transferosomes as a carrier for anticancer agents
viii. Transferosomes as a carrier for non- steroidal anti-inflammatory agents

CONCLUSION

Transferosomes are designed specifically to respond external stress by squeezing themselves into skin skin pores that are narrow enhancing the delivery of drugs. Transferosomes are capable of transferring both high and low molecular weight therapeutic agents. The transferosomes are good carrier option for deliverying the drug into skin layers hence are used for the treatment of cancer.

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