

Transferosomes - An Ultra-Deformable Vesicular System for Enhanced Transdermal Drug Delivery

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ABSTRACT

Transferosomes are ultra-flexible lipid vesicular carriers designed to overcome the barrier properties of the skin and enhance transdermal drug delivery. Conventional transdermal drug delivery systems are limited by the impermeability of the stratum corneum, especially for hydrophilic and high molecular weight drugs. Transferosomes, composed of phospholipids and edge activators, possess unique deformability that allows them to penetrate through narrow skin pores and deliver drugs effectively into deeper tissues or systemic circulation. These vesicular systems can encapsulate both hydrophilic and lipophilic drugs and provide controlled and sustained drug release. Their ability to bypass first-pass metabolism, improve bioavailability, reduce dosing frequency and enhance patient compliance makes them a promising alternative to conventional drug delivery methods. Various preparation techniques such as rotary evaporation, reverse phase evaporation, ethanol injection and sonication methods are employed to formulate transferosomes. Additionally, transferosomes have been widely investigated for the treatment of skin disorders, cancer, ocular diseases, and other systemic conditions. Despite their advantages, challenges such as chemical instability, cost and skin irritation remain. Overall, transferosomes represent a novel and efficient carrier system with significant potential in modern drug delivery research.

KEYWORDS: Transferosomes, Transdermal drug delivery system, Vesicular Carriers, Edge Activators, Stratum Corneum.

I. INTRODUCTION

Transdermal drug delivery systems (TDDS) offer a number of potential advantages over conventional methods such as injectable and oral

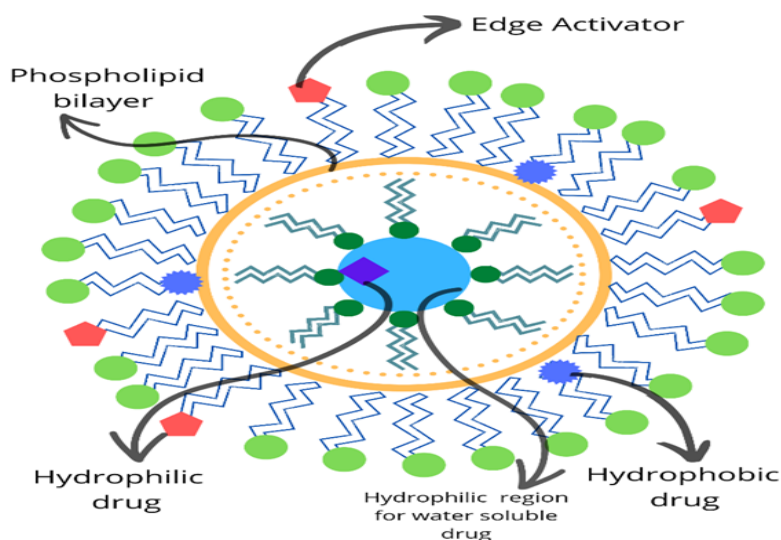
delivery. However, the major limitation of TDDS is the permeability of the skin, it is permeable to small molecules, lipophilic drugs and highly impermeable to macromolecules and hydrophilic drugs. The main barrier and rate-limiting step for diffusion of drugs across the skin is provided by the outermost layer of the skin, the stratum corneum (SC). Recent approaches in modulating vesicle compositions have been investigated to develop systems that are capable of carrying drugs and macromolecules to deeper tissues. These approaches have resulted in the design of two novel vesicular carriers, ethosomes and ultra flexible lipid-based elastic vesicles, transferosomes. Transferosomes are ultra deformable vesicles possessing an aqueous core surrounded by the complex lipid bilayer. Interdependency of local composition and shape of the bilayer makes the vesicle both self-regulating and self-optimizing.

Transferosomes have recently been introduced, which are capable of transdermal delivery of low as well as high molecular weight drugs. Transferosomes are specially optimized, ultra flexible lipid supra molecular aggregates, which are able to penetrate the mammalian skin intact and then act as a drug carrier for non-invasive targeted drug delivery and sustained release of therapeutic agents. Each transferosome consists of at least one inner aqueous compartment, which is surrounded by a lipid bilayer with specially tailored properties, due to the incorporation of "edge activators" into the vesicular membrane. Surfactants such as sodium cholate, sodium deoxycholate, span 80 and Tween 80, have been used as edge activators. Due to their deformability, transferosomes are good candidates for the non-invasive delivery of small, medium, and large sized drugs. Delivery via the transdermal route is an interesting option in this respect because a transdermal route is convenient and safe. This offers

several potential advantages over conventional routes like avoidance of first pass metabolism, predictable and extended duration of activity, minimizing undesirable side effects, utility of short half-life drugs, improving physiological and pharmacological response, avoiding the fluctuation in drug levels, inter and inpatient variations, and most importantly, it provides patients convenience.

Transferosomes have been used for the treatment of many diseases like skin diseases, ocular disorders, brain diseases etc. For example, as per reports in literature, the chemotherapy given conventionally for treating infections within the cells is not as much effective to treat cancer because of its inability to permeate within the cells. Therefore, novel carriers such as transferosomes were formulated, which had ability to penetrate deep into cells.

Due to their high permeability, transferosomes have been widely utilised, for the delivery of both high as well as low molecular weight drugs. It is reviewed that transferosome is a hallmark which a German company named IDEA AG has registered. The word transferosomes refers to “carrying body”. It is a combination of Latin word 'transferre', which means 'to carry across' and 'soma' which is a Greek word which refers to 'a body'. With reference to the structure of transferosomes it is figured that they are vesicular carriers with self-regulatory and self-optimizing properties, which are composed of edge activator and a lipid bilayer which surrounds a hydrophilic core. Transferosomes, due to the elasticity imparted by the presence of edge activators, are elastic in nature, due to which they undergo easy deformation and can squeeze intact through tight junctions and pores even lesser in size than their own size.



Structure of Transferosomes

Advantages

- Transdermal medication delivers a steady infusion of a drug over an extended period of time.
- An equivalent therapeutic effect can be elicited via transdermal drug input with a lower daily dose of the drug than is necessary.
- Self-administration is possible with these systems.
- They are easily and rapidly identified in emergencies (e.g. unresponsive, unconscious or comatose patient) because of their physical presence, features and identifying markings.
- They can be used for drugs with narrow therapeutic window.
- Longer duration of action resulting in a reduction in dosing frequency.
- Increased convenience to administer drugs which would otherwise require frequent dosing.
- Improved bioavailability.
- More uniform plasma levels and maintain plasma concentration of potent drugs.
- Reduced side effects and improved therapy due to maintenance of plasma levels up to the end of the dosing interval.
- Flexibility of terminating the drug administration by simply removing patch from the skin.
- Improved patient compliance and comfort via non-invasive, painless and simple application.

- Avoid inter and intra patient variation and enhance therapeutic efficacy.

Disadvantages

- Many drugs especially drugs with hydrophilic structures permeate the skin too slowly to be of therapeutic benefit.
- The barrier function of the skin changes from one site to another on the same person, from person to person and also with age.
- Drug molecule must be potent because patch size limits amount that can be delivered.
- Not suitable for high drug doses.
- Adhesion may vary with patch type and environmental conditions.
- Skin irritation and hypersensitivity reactions may occur.
- Drugs that require high blood levels cannot be administered.
- Along with these limitations the high cost of the product is also a major drawback for the wide acceptance of this product.
- Transferosomes are chemically unstable because of oxidative degradation makes its predisposition.
- Purity of natural phospholipids is another criterion for achievement for adoption of transferosomes as drug delivery vehicles.

Why Only Transferosomes For Skin

Transferosomes are advantageous as phospholipid vesicles for transdermal drug delivery. Because of their self-optimized and ultra flexible membrane properties, they are able to deliver the drug reproducibly either into or through the skin, depending on the choice of administration or application, with high efficiency. The vesicular transferosomes are more elastic than the standard liposomes and thus well suited for the skin penetration. Transferosomes overcome the skin penetration difficulty by squeezing themselves along the intracellular sealing lipid of the stratum corneum. These are characteristic with transferosomes, because of the high vesicle deformability which permits the entry due to the mechanical stress of

surrounding, in a self-adapting manner. Flexibility of transferosomes membrane is governed by mixing suitable surface-active components in the proper ratios with phospholipids.

The resulting flexibility of transferosome membrane minimizes the risk of complete vesicle rupture in the skin and allows transferosomes to follow the natural water gradient across the epidermis, when applied under non-occlusive condition. Transferosomes can penetrate the intact stratum corneum spontaneously along two routes in the intracellular lipid that differ in their bilayer properties. Bangham discovered liposomes in 1963 and since then vesicular systems have attracted increasing attention. But recently it has become evident that classic liposomes are of minor values in terms of penetration. Confocal microscopic studies have shown that intact liposomes are not able to penetrate into granular layer of epidermis but, they rather remain on the upper layer of stratum corneum. The modification of the vesicular compositions or surface properties can adjust the drug release rate and the deposition to the target site.

Composition Of Transferosomes

Transferosome, a lipidic vesicular carrier is composed of phospholipids which can either be of natural origin or can be synthetic in nature and edge activators. The lipids after coming in contact with the aqueous environment, self-assemble to form a bilayer and in the process enclose a hydrophilic core in the centre. The edge activators or softening agents as they are also referred to as, added during the formulation steps, enhance the flexibility and deformability of the lipidic vesicle, by causing the lipid bilayer to destabilize. Their flexibility imparts them the ability to squeeze even through skin and membrane pores smaller than their own size without any rupture. Since transferosomes are made of lipids, both hydrophilic as well as lipophilic drugs can be delivered by them. For imaging purposes, transferosomes can also be incorporated with dyes for example Nile red, rhodamine 123 etc.

Components used in the formulation of transferosomes

Components	Examples	Purpose
Edge activator	Span 80, tween 80, sodium deoxy cholate, sodium cholate	To impart flexibility to formed vesicles
Phospholipid	Phosphatidylcholine, soya Phosphatidylcholine	To form self-assembled vesicles
Solvents	Chloroform, Methanol, Ethanol	Solvent system to dissolve different components
Hydrating agent	Distilled water or saline	To hydrate the lipid film formed after

	phosphate buffer distilled water	evaporation of the solvent
Active pharmaceutical ingredient	Miconazole nitrate, itraconazole, ketoprofen, diclofenac sodium	For providing pharmaceutical effect

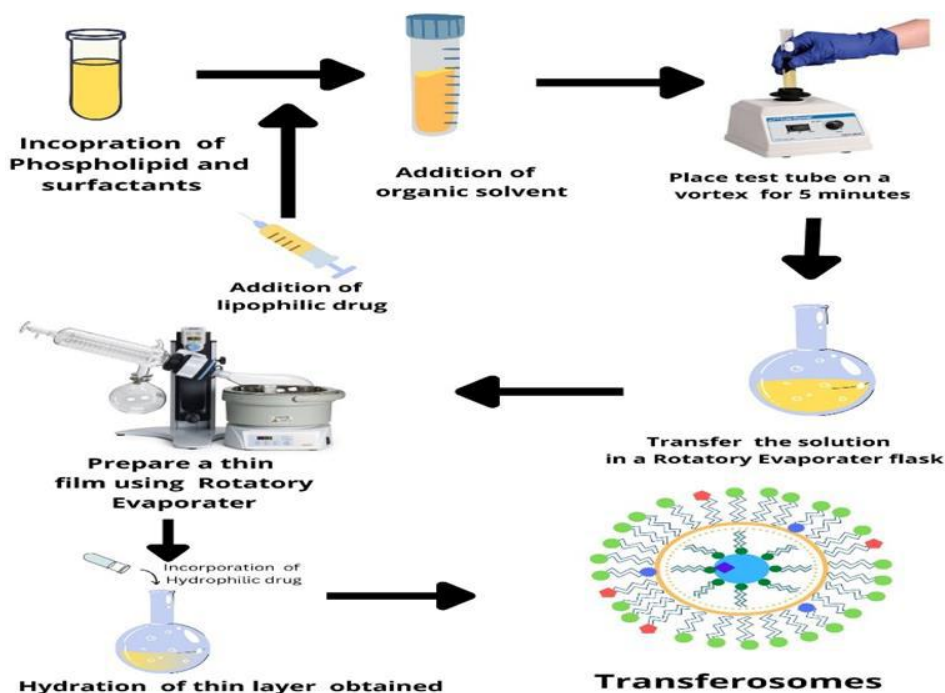
II. FORMULATION TECHNIQUES FOR TRANSFEROSOMES

The techniques widely used for the formulation of transferosomes are given below

a) Rotary Film Evaporation Method/ Modified Hand Shaking Method

This transferosome preparation method is widely accepted due to its efficiency and effectiveness in delivering therapeutic agents to the target site. In this method, initially, a specific quantity of ego activators as well as phospholipids are added in a volatile organic solvent. If the drug is lipophilic, it is mixed with the solvent and other components. The mixture is then sonicated till a clear and homogeneous mixture is obtained. Subsequently, the treated solution is transferred to a flask for rotary

evaporation, where it is rotated at a constant temperature under vacuum to obtain a thin lipidic film composed of active ingredient and EAs flask walls. The aqueous medium is then used to hydrate the film formed, which swells and forms vesicles which are bilayer after hydration. If the drug is hydrophilic it can also be added to the aqueous medium. Sonication or extrusion techniques can be used for reducing the size of the formed vesicles. This method is particularly useful in delivering drugs to specific target sites due to the ability of the vesicles to permeate the skin's stratum corneum and enter the systemic circulation. Overall, this transferosome preparation method is a promising approach in drug delivery research.

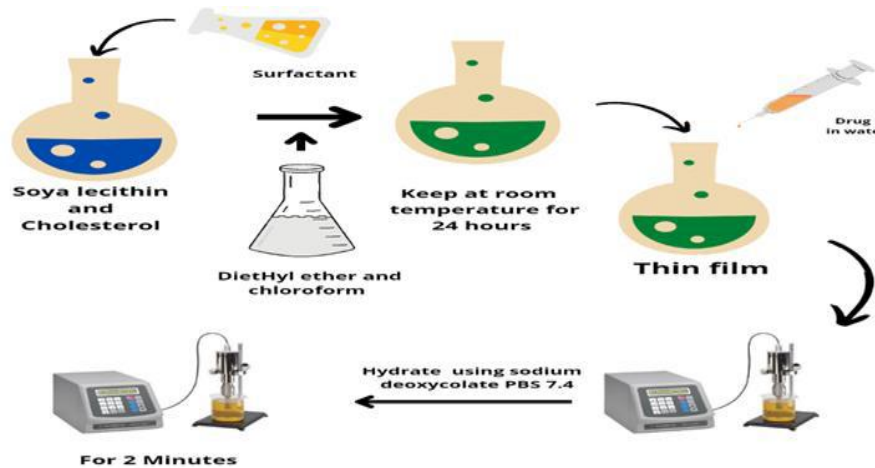


Rotary Film Evaporation Method / Modified Hand Shaking Method for the formulation of transferosomes.

b) Reverse Phase Evaporation Method:

In this technique phospholipids are dissolved in an organic solvent, such as chloroform, methanol, or ethanol, and placing the solution in a flask. Hydrophilic media consisting of a surfactant, such as EA, is added to the flask while purging with nitrogen gas. Depending on the solubility characteristics, the drug is incorporated either in the

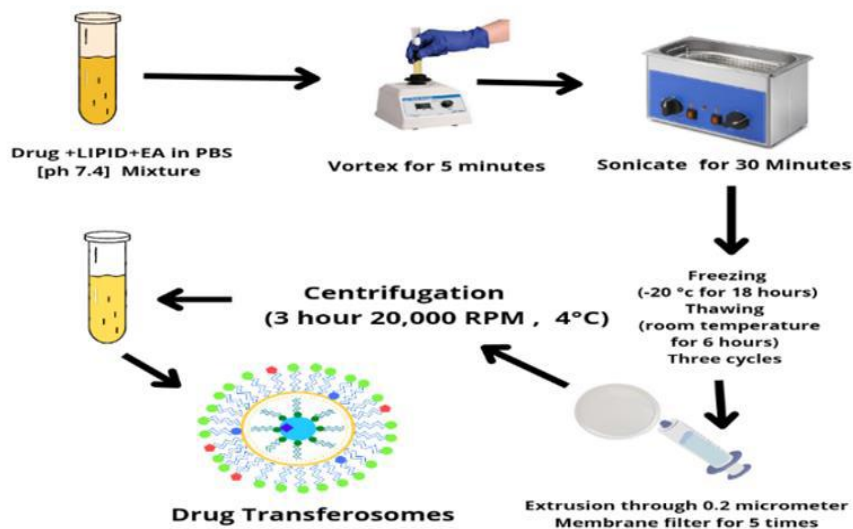
hydrophilic or the lipophilic media. The resulting mixture is subjected to sonication till it becomes a clear dispersion which is homogeneous in nature, and is observed minimum for thirty minutes after sonication to ensure that no separation occurs. Finally, the sonicated mixture is treated under reduced pressure to remove the organic solvent from the preparation.



Reverse Phase Evaporation Method

c) Vortex/Sonication Method:

The vortexing method involves mixing phospholipids, drug, and edge activator in a phosphate buffer saline (PBS) solution followed by vortexing of the mixture until a suspension milky white in colour is obtained. The product is then subjected to sonication for a few minutes, followed by extrusion through a membrane filter made of polycarbonate with 100nm as the size of the pores.

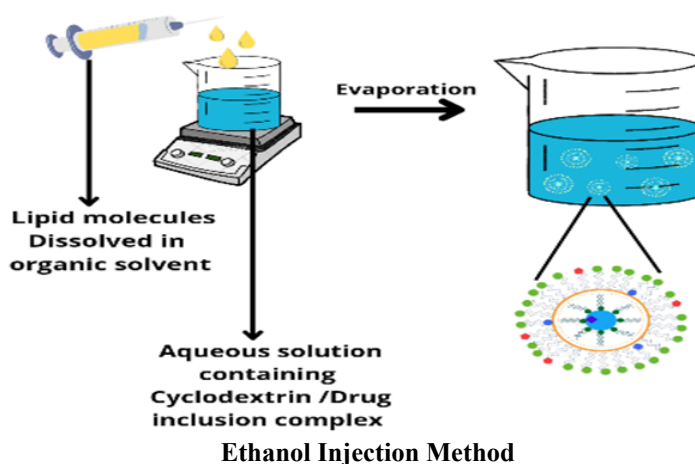


Vortex / Sonication Method

d) Ethanol Injection Method:

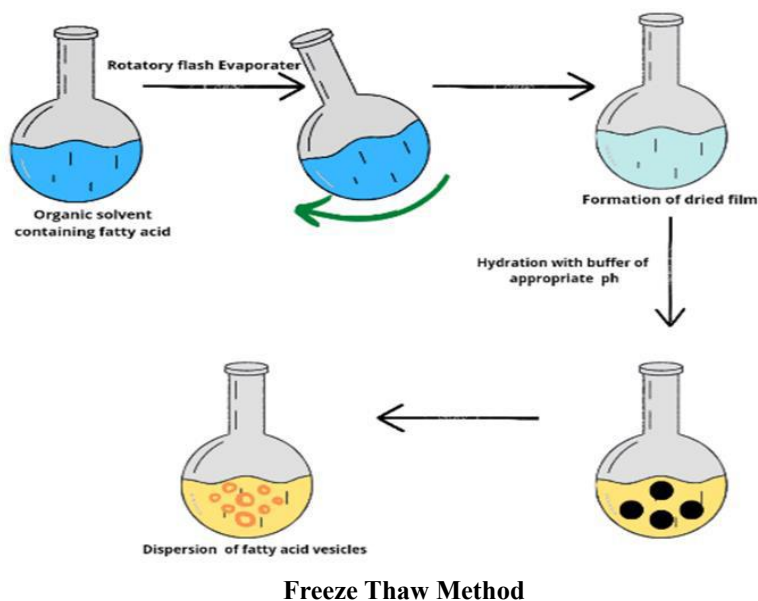
The technique is a popular technique used for the formulation of elastic liposomes. To begin the process, the drug is dissolved in an aqueous medium which is followed by heating the contents at a fixed temperature with constant stirring. Next, the solution of ethanol containing edge activator as well

as phospholipids is injected dropwise into the aqueous medium. When the ethanolic solution of phospholipids and EA is mixed with the aqueous solution, it results in the precipitation of the lipid molecules which in turn leads to the formation of bilayer structures.



e) Freeze Thaw Method:

To obtain the transfersomal formulation, a method involving alternate cycles of freezing and heating is employed. The multilamellar vesicles (MLV) are exposed to very low temperatures, by dipping for 30 s at -30°C (nitrogen bath), followed by high temperature exposure in a water bath. The steps are repeated several times to produce the desired transfersome.



III. EVALUATION OF TRANSFEROSOMES

The different parameters used for the evaluation of transferosomes are:

a) Zeta potential and Distribution of Vesicle size

For determination of zeta potential and distribution of vesicle size and diameter, dynamic light scattering (DLS) technique is used. Before determination, samples are diluted and then filtered through a 0.2 mm membrane filter.

b) Vesicle morphology

For the determination of vesicular morphology Scanning Electron Microscopy (SEM) and Transmission Electron Microscopy (TEM) are used.

c) Total number of vesicles present per cubic mm

The total number of vesicles present per cubic mm is determined using a Haemocytometer and an optical microscope. 0.9% sodium chloride solution is used to dilute the non-sonicated Transferosome formulations five times and then the total number of vesicles present per cubic mm is determined using the following formula:

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

d) Drug content

To determine the drug content, an instrumental analytical method such as the UV detectors or a computerized analysis program or chromatographic techniques can be used. The method chosen for analysis may vary depending on the analytical method specified for the pharmacopeial drug.

e) Entrapment efficiency

The percentage entrapment of the added drug is used to express the entrapment efficiency. Initially, the un-entrapped drug is separated through a mini-column centrifugation method. Following centrifugation, the vesicles are disrupted using 0.1% Triton X-100 or 50% n-propanol. The entrapment efficiency is then calculated using the following formula:

(Amount entrapped / Total amount added) × 100.

f) Degree of deformability or permeability measurement

Permeability study is a crucial and distinct parameter for characterizing transferosomes. To conduct this study, transferosomes preparation is passed through a sandwich of different micro-porous filters with pore diameters ranging from 50 nm to 400 nm. The size of particles as well as the distribution of sizes of transferosomes measured after each pass using DLS.

g) *In vitro* drug release

To conduct the study, formulation is placed on a treated dialysis membrane mounted between the different compartments of the Franz diffusion cell (FDC). The receptor compartment is filled with a suitable release media. At regular time intervals, a sample is taken from the receptor and replaced with an equivalent amount of release media. The withdrawn sample is analyzed using a suitable analytical method to determine the percentage of drug release.

h) *In vitro* skin permeation studies

To conduct the *in vitro* drug study, a Franz diffusion cell is utilized. For the permeation experiments, biological membranes such as goat skin or rat skin are used. To carry out the study, the skin is first treated to remove hairs and adipose, after which it is horizontally mounted between the compartments of the Franz diffusion cell. The receptor compartment is filled with saline buffer (phosphate buffer pH 7.4), which is maintained under stirring at $37 \pm 0.5^\circ\text{C}$. Sample aliquots are withdrawn and used for determination of percentage drug permeated by suitable methods of Analysis.

i) Physical stability

For the study samples are stored at different temperatures [$4 \pm 2^\circ\text{C}$ (refrigerated), $37 \pm 2^\circ\text{C}$ (body temperature) and $25 \pm 2^\circ\text{C}$ (room temperature)] for a minimum of three months. Samples are taken at suitable time intervals and observed for physical properties, drug content, particle size and zeta potential etc

IV. CONCLUSION

Transferosomes have emerged as a highly promising vesicular drug delivery system capable of overcoming the limitations of conventional transdermal therapies. Their ultra-deformable nature, due to the presence of edge activators, enables efficient penetration through the stratum corneum, facilitating the delivery of both small and large molecular weight drugs.

The system offers multiple advantages including improved bioavailability, sustained drug release, reduced side effects, avoidance of first-pass metabolism, and enhanced patient compliance. Moreover, their versatility allows application in various therapeutic areas such as dermatology, oncology, and neurological disorders.

However, certain limitations such as formulation instability, high production cost, and potential skin irritation need to be addressed for wider clinical application. Future research should focus on improving stability, scalability and

exploring novel drug combinations including herbal and dual drug-loaded transferosomes.

In conclusion, transferosomes represent a significant advancement in transdermal drug delivery systems and hold great potential for future pharmaceutical innovations.

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