Review Article

Transferosomes - A Lipid Based Vesicular Carrier with Versatile Applications

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ABSTRACT

Transferosomes are elastic compounds capable of deforming their structure and squeezing themselves through narrow pores smaller than their size, making them a useful drug delivery system for poorly soluble drugs. They are ultra-deformable vesicles with an hydrophillic core in the center which is surrounded by a bilayer composed of lipid. To address the issues of conventional oral drug delivery, different formulations of transferosomes have been prepared using non-ionic surfactants like Span 80, Span 20, soya lecithin, Carbopol 940, and Tween 80 through rotary film evaporation and vortexing/sonication methods. This carrier system has gained the interest of pharmaceutical researchers as it improves patient acceptability and minimizes side effects associated with the conventional oral route by avoiding first-pass metabolism, thereby enhancing the physiological and pharmacological response through a consistent drug level. The present review provides an insight into its structure, advantages, disadvantages, materials used for their formulation, formulation techniques, evaluation techniques besides providing an overview of their applications and patents reported in literature.

Keywords: Transferosomes, elastic liposomes, permeation, Edge activators.

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INTRODUCTION

Novel drug delivery systems have been developed to overcome several issues associated with conventional drug delivery. This system is preferred as it increases the therapeutic activity and effectiveness of both already existing drugs and new pharmaceuticals[1,2,3]. Entrapment of therapeutics in vesicle based dosage forms is proposed to enhance drug amount circulating in the body besides decreasing toxicity. Vesicular carriers help to regulate and/ or assist drug release by traditional methods[4,5]. These systems confine drug action by controlled release systems near the disease site or organ, while sustained released medication releases a therapeutic agent at a rate which is predefined, in order to maintain a stable concentration of the active ingredient in the body over a predetermined time period[6,7,8]. Amphiphilic, lipophilic, or charged hydrophilic drugs can be incorporated in vesicular formulations to sustain release and act as a rate-limiting membrane for drug delivery. They can incorporate both hydrophilic & lipophilic drugs [9,10]. The advantages of vesicular drug delivery systems include reduced unwanted effects as well potential to enhance therapeutic efficacy of entrapped drugs for longer periods of time besides providing optimum bioavailability of drugs to target sites. The major key role of vesicular systems is to control drug degradation and provide prolonged drug release to the target sites. The drug entrapment in vesicle based systems is focused to provide a prolonged concentration of the therapeutic agent in blood circulation. Lipids have been mainly used for providing controlled release of drugs[11].

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[12,13].

Due to their high permeability, transferosomes have been widely utilised, for the delivery of both high as well as low molecular weight drugs[14]. 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'[15]. 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 (figure 1)[16]. 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 [17,18].

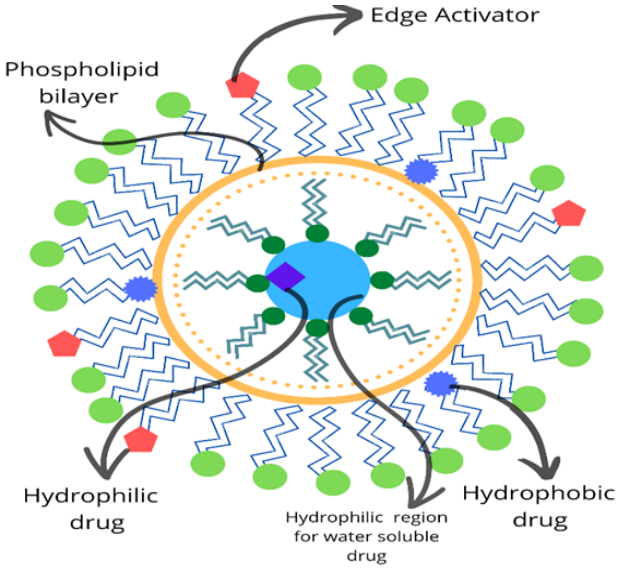

Figure 1: Structure of Transferosomes

In comparison of traditional liposomes, which comprise of phosphospholipids which are either of natural or synthetic origin[19], transferosomes are formulated using a combination of phospholipid and an edge activator[20]. Edge activators (EAs) impart deformability as well as flexibility to the transferosomes when they are combined with chosen phospholipid in optimum ratio, which in turn improves their penetration across biological membranes even through pores which are having lesser size than their own size. Therefore, based on the advantages of edge activators in formulation of transferosomes, it can be concluded that they serve as a major component responsible for improving the performance of transferosomes as compared to traditionally formulated liposomes[21,22].

Advantages of transferosomes as a carrier of drugs

Transferosomes offer a number of advantages over other drug delivery systems, a few of which are summarized as follows[23-26]:

a) They are versatile, with capability to encapsulate and deliver a wide range of active moieties irrespective of their physicochemical properties like molecular size, weight etc.

b) They confer biocompatibility as well as biodegradability as they are composed of phospholipids of natural origin in majority of the cases.

c) They have potential to provide sustained and predictable release as well as duration of action of the encapsulated drug.

d) Transferosomes have the ability to enhance transdermal flux.

e) They enhance site specific delivery of bioactives.

f) They have the potential to circumvent first-pass metabolism which in turn leads to enhanced bioavailability of drugs.

g) They minimize degradations of therapeutic agents due to their ability to encapsulate the therapeutics within them.

h) They exhibit high encapsulation of lipophilic drugs.

i) Transferosomes enhance permeability of drugs due to their elastic and ultra-deformable properties.

j) They can be used for both systemic as well as topical delivery of drugs.

k) They have the potential to deliver both lipophilic and hydrophilic therapeutics.

l) They have the potential to be easily scaled up due to their simple and short process of manufacturing.

Limitations of Transferosomes as a carrier of drugs

Transferosomes are also associated with a number of disadvantages[27-29], a few of which are listed below:

a) The tendency to undergo degradation by oxidation renders transferosomes chemically unstable.

b) The purity of the natural phospholipids used in the formulation of transferosomes is also a challenge to be addressed by formulators.

c) The excipients like phospholipids and equipments used in the formulation of transferosomes are expensive, thereby enhancing the overall cost of the formulated product.

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[30-33]. 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, rhodamone 123 etc.

The components used in the formulation of transferosomes are compiled in the table 1.

Table 1: 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, Dipalmitoyl phosphatidylcholine	To form self-assembled vesicles
Solvents	Chloroform, Methanol, Ethanol	Solvent system to dissolve different components
Hydrating Agent	Distilled Water or Saline phosphate buffer Distilled Water	To hydrate the lipid film formed after evaporation of the solvent
Active Pharmaceutical ingredient	Miconazole Nitrate, Itraconazole, Ketoprofen, Diclofenac Sodium	For providing pharmacological effect

Formulation techniques for Transferosomes

The techniques widely used for the formulation of transferosomes are given below[34]:

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[35, 36]. 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. Figure 2 illustrates the 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[37]. Hydrophillic 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 hydrophillic 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.

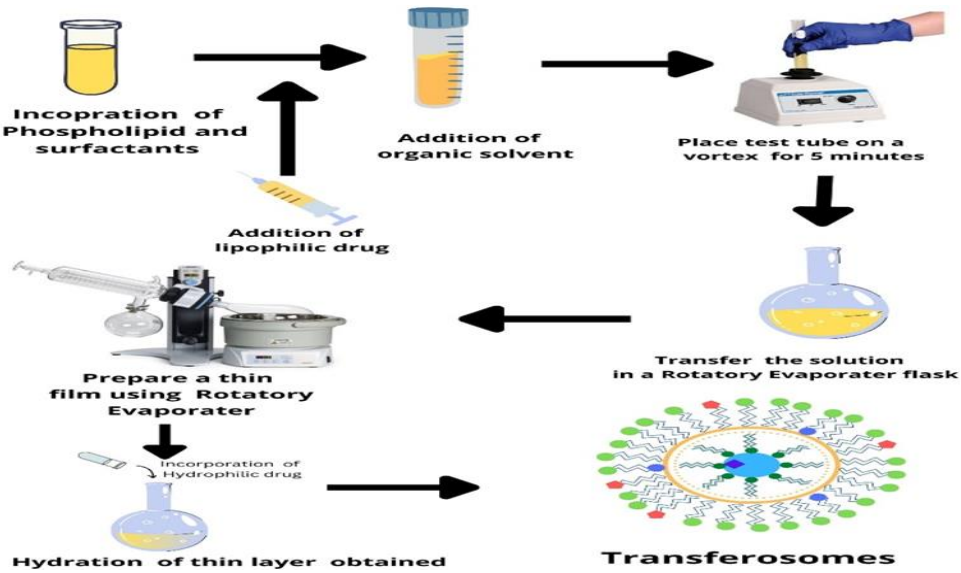

Figure 2: Rotary Film Evaporation Method

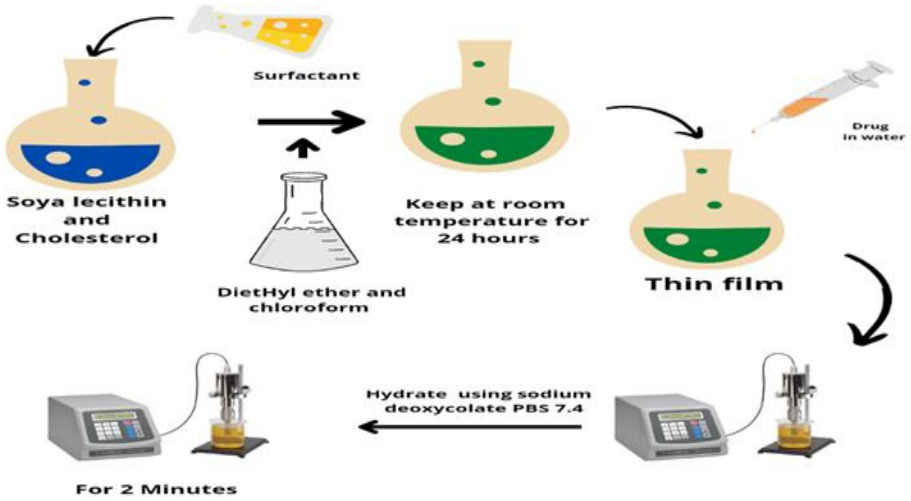

Figure 3: Reverse Phase Evaporation Method

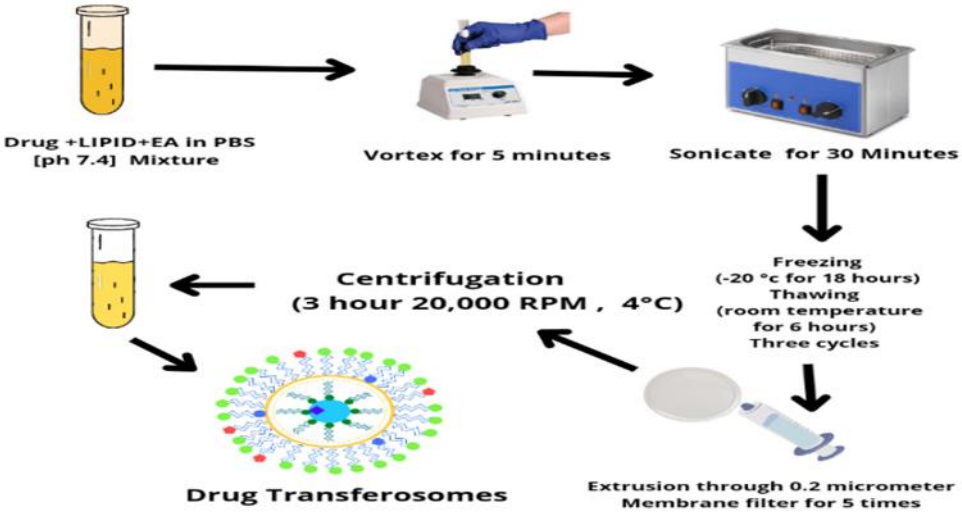

Figure 4: Ethanol Injection Method

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[38]. The process is illustrated in Figure 4.

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[39,40]. The process is illustrated in Figure 5.

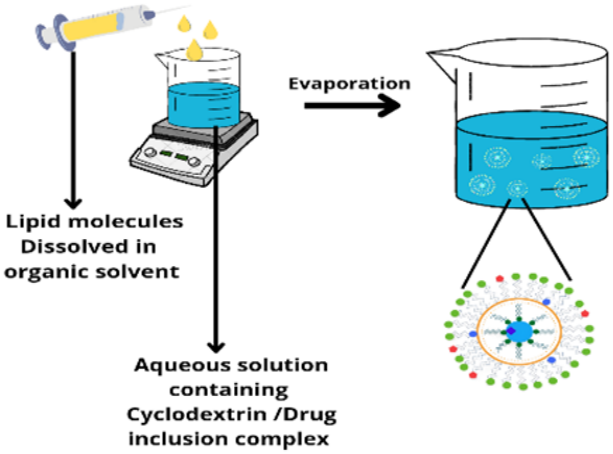

Figure 5: Ethanol Injection Method

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 transferosomes[41].

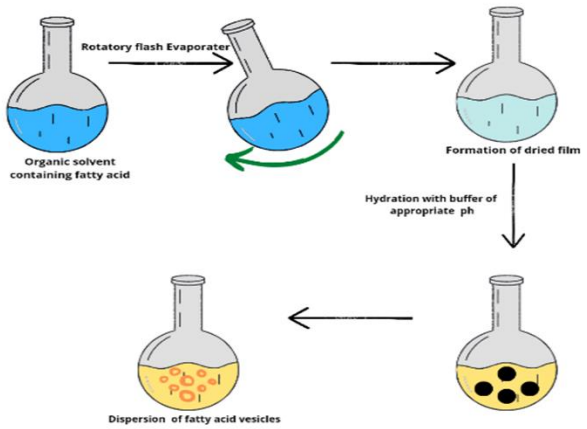

Figure 6: Freeze Thaw Method

Mechanism of permeation of transferosomes

The mechanism by which the active pharmaceutical ingredients are delivered by transferosomes is not very well known. It is however postulated that transferosomes disrupt the lipids present intercellularly within the stratum corneum and then permeate across the skin. As per reports in literature, besides the flexible as well as elastic nature of transferosomes which plays a pivotal role in their permeation, the hydration gradient among the topmost and deeper layers of the skin also has an important role in their enhanced permeation. It is reported that while undergoing squeezing through the tight junctions, they deform, which leads to their dehydration. Further, when these deformed transferosomes go deeper into the skin layers they get reformed by rehydration[42,43,44]. This helps them to retain their original size.

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[45].

b) Vesicle morphology

For the determination of vesicular morphology Scanning Electron Microscopy (SEM) and Transmission Electron Microscopy (TEM) are used[46].

c) Total number of vesicles present per cubic mm

The total number of vesicles present per cubic mm is determined using a Hemocytometer 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[47]:

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[48].

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[49]. 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 transferosomesis measured after each pass using DLS[50].

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[51].

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 ± 0.5°C. Sample aliquots are withdrawn and used for determination of percentage drug permeated by suitable methods of analysis[52,53].

i) Physical stability

For the study samples are stored at different temperatures [4 ± 2°C (refrigerated), 37 ± 2°C (body temperature) and 25 ± 2°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, zeta potential etc.[54]

CONCLUSION

Transferosomes are specialized vesicles or particles that have been optimized to undergo rapid shape transformations in response to external stress. These highly deformable particles are capable of overcoming biological permeability barriers, such as the skin, and are developed to surpass the limitations of conventional drug delivery systems. The flexible vesicles can penetrate the skin pores by undergoing deformation, thereby making them a safer and effective drug delivery option. Additionally, drug release can be controlled to meet specific requirements. Due to their inherent advantages, they are versatile carriers which can be used for delivery of a large variety of drugs.

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