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Review Article

Overview on Transferosomes: A Unique Novel Nanocarrier System

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ABSTRACT

Today, transdermal delivery technologies are becoming more and more significant. Although transdermal drug administration has significantly improved medical practice, it still hasn't reached its full potential as a substitute for oral medication delivery and hypodermic injections. A number of novel technologies have been developed to deliver some significant medications transdermally. The outermost layer of the skin, the lipophilic stratum corneum, is being studied by physical and chemical means. The majority of transdermal medicines that have proved effective do so by utilising smaller lipophilic compounds, which have molecular weights of a few hundred Daltons. Transferosomes have become an effective technique for transdermal distribution of a range of therapies, including hydrophilic actives, bigger molecules, peptides, proteins, and nucleic acids, in order to get around the medications' size and lipophilicity constraints. A wide variety of pharmacological compounds, including big molecules like peptides, hormones, and antibiotics, as well as medications with low penetration owing to undesirable physicochemical characteristics, can be delivered via transfersomes with significant potential. Creating the medication in a transfersome is one way to address these issues. Because of its extreme deformability and elasticity, a transfersome can fit through a pore that is several times smaller than its actual size. The characteristics of transferosomes, their preparation process, and various assessment metrics are covered in this article.

INTRODUCTION

Most of the time, an effective therapeutic therapy cannot be administered for a variety of reasons, including hepatic first-pass metabolism, unfavourable side effects, patient noncompliance, and rejection of invasive treatments [1]. To address these issues, a number of medication delivery strategies have been created and researched during the past few decades. Transdermal delivery systems are a viable strategy because they are non-invasive and have no first-pass effects [2]. This has a number of potential benefits over traditional methods, including the avoidance of first pass metabolism, a consistent and longer duration of action, a reduction in unwanted side effects, the use of drugs with short half-lives, an improvement in physiological and pharmacological response, the avoidance of intra- and inter-patient variations in drug levels, and, most importantly, convenience for the patient [3]. Medical research has used a number of techniques, including vesicular constructions, iontophoresis, sonophoresis, enhancers, and penetration enhancers, to improve the effectiveness of material transfer over intact skin. Singh et al. referred to liposomes, niosomes, virosomes, ethosomes, and transfersomes as "vesicular constructs"[4].

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Transferosomes

Gregor Cevc first coined the name and concept of transferosomes in 1991. The German business IDEA AG has registered the phrase "Translosomes" as a trademark. The Latin term transferee, which means "to carry across," and the Greek word soma, which means "a body," are the sources of the name, which means "carrying body." Complex vesicles known as transferosomes are more deformable due to their highly flexible and self-regulating membrane [5]. One particular kind of liposome is the transfersome. They squeeze themselves along the stratum corneum's intracellular sealing lipid to get around the skin penetration issue. It enters the stratum corneum either through a

transcellular or intracellular pathway, creating an osmotic gradient as a result of water evaporation. Therefore, transferosome vesicles have a tendency to cross the skin's barrier and migrate into the water-rich deep when applied to an open biological surface such as non-occluded skin [6, 7]. The transferosome membrane can be made flexible or elastic by properly combining surface active components, or edge activators, in the right proportions. When given topically, it takes advantage of a hydrophilic channel or network of pores that opens up sufficiently to allow the drug molecule and the entire vesicle to pass through the stratum corneum. Even if the microporous barriers are substantially smaller than the size of the vesicles, transferosomes can traverse them with efficiency. Transferosomes, then, are artificial vesicles that mimic cell vesicles and can be used for targeted and regulated drug delivery [5].

Structure and Composition of Transferosomes

A transferosome is an artificial vesicle that can be used for targeted and regulated medication administration since it mimics the properties of a cell vesicle or a cell undergoing exocytosis. Complex vesicles known as transferosomes feature a membrane that is incredibly flexible and self-regulating, allowing the vesicle to be deformed [8]. Phospholipids such as phosphatidyl choline, which self-assemble into a lipid bilayer in an aqueous environment to create vesicles, are the building blocks of transferosomes. Additionally, it has an edge activator made of a single chain surfactant that destabilises the lipid bilayer, increasing its elasticity and fluidity.

Phospholipids

- Vesicles with phospholipids (e.g., soy phosphatidylcholine, egg phosphatidylcholine, dipalmitoyl phosphatidylcholine) as the primary ingredient; 10–25% surfactant to impart flexibility; and a variety of solvents, such as methanol, ethanol, and hydrating medium made of saline phosphate buffer (pH 6.5-7). dyes such as Nile red, Rhodamine 123, etc.

- Phosphatidylcholine is mostly an unsaturated fatty acid and can come from both plant and human sources. Up to 70% of the total fatty acids in these unsaturated fatty acids are primarily linoleic acid.

- Soy phosphatidylcholine, which has a very low phase-transition temperature of below 0°C in water-containing systems and can be measured by measuring the increase in trans epidermal water loss (TEWL) after application for a brief period of time, is the primary cause of phospholipids' ability to fluidize the lipid bilayer [9].

Edge Activators

- The edge activator, sometimes referred to as the "bilayer softening component," is introduced to increase the flexibility and permeability of the lipid bilayer. It could be an amphiphilic medication or a biocompatible surfactant.

- An edge activator primarily consists of a non-ionic single chain surfactant that destabilises the lipid bilayer. Consequently, by making it more elastic and flowing. It is possible to alter the transferosome membrane's flexibility by combining the right surfaceactive substances in the right amounts.

- In transferosome preparations, the most often used edge activators that are biocompatible, boost the bilayer flexibility of the vesicle, and enhance permeability are surfactants like sodium cholates, sodium deoxycholate, Tweens and Spans (Tween 20, Tween 60, Tween 80; Span 60, Span 65, and Span 80), and dipotassium glycyrrhizinate [10].

Advantages of Transferosomes as a Carrier of Drugs

- They possess versatility as they can encapsulate and distribute a broad spectrum of active moieties, regardless of their physicochemical features, such as molecular weight and size.

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

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

- Transferosomes have the ability to enhance transdermal flux.

- They enhance site specific delivery of bioactives.
- They have the potential to circumvent first-pass metabolism which in turn leads to enhanced bioavailability of drugs.
- They minimize degradations of therapeutic agents due to their ability to encapsulate the therapeutics within them.
- They exhibit high encapsulation of lipophilic drugs.
- Transferosomes enhance permeability of drugs due to their elastic and ultra-deformable properties.
- They can be used for both systemic as well as topical delivery of drugs.
- They have the potential to deliver both lipophilic and hydrophilic therapeutics.
- They have the potential to be easily scaled up due to their simple and short process of manufacturing [11, 12].

Limitations of Transferosomes as a Carrier of Drugs

- The tendency to undergo degradation by oxidation renders transferosomes chemically unstable.
- The purity of the natural phospholipids used in the formulation of transferosomes is also a challenge to be addressed by formulators.
- The excipients like phospholipids and equipments used in the formulation of transferosomes are expensive, thereby enhancing the overall cost of the formulated product [13].

Scope of Transfersomes

For the non-invasive delivery of therapeutic compounds across open biological barriers, transfersome technology is most suitable. Molecules that are too large to diffuse across the epidermal barrier, for example, can be transported across it by the Transfersome vesicles. Examples include the systemic administration of macromolecules like insulin or interferon in therapeutically significant levels through intact mammalian skin. Transporting tiny molecules that would otherwise be unable to diffuse across a barrier due to specific physicochemical features is one of the other uses. The capacity of the carrier to target subcutaneous and peripheral tissue is another appealing feature of Transfersome technology. This ability depends on minimising the carrier-associated drug clearance through the plexus of cutaneous blood vessels. The skin's non-fenestrated blood capillary walls and the tight connections between endothelial cells prevent vesicles from entering the bloodstream directly, maximising local drug retention and increasing the likelihood that the drugs will reach their target peripheral tissues [14].

Mechanism of Action of Transfersomes

Transfersomes enter the deeper skin layer after passing through the outermost layers. Normally, they are then flushed out into the bloodstream. If applied properly, it should be able to reach every tissue in the body.

The process of putting transfersomes to the skin surface causes water to evaporate, which creates a "osmotic gradient" that is part of the penetration mechanism. Thus, concentration has no effect on the elastic vesicles' transit. The skin penetration barrier, which keeps water from escaping the skin and preserves a water activity differential in the viable portion of the epidermis, is what creates this osmotic gradient. Because of their elastic nature, vesicles are able to pass through the stratum corneum's pores, despite the fact that these pores are only a tenth of the vesicles' width. By forging their own pathway, transfersomes cause moisture, which widens the skin's hydrophobic pores and allows the medicine to gradually escape, binding to the intended organ.Transfersomes act as penetration enhancers that disrupt the intercellular lipids from stratum which ultimately widens the pores of skin and facilitate the molecular interaction and penetration of system across skin[15].

Challenges of Transferosomes

Although transferosomes are useful for delivering a variety of medication classes to their intended locations, there are still certain obstacles that researchers must overcome in order to develop transferosomes further.

1. Delivery of hydrophilic drugs and high molecular weight complexes is becoming a big challenge because the outer most layer of skin is of hydrophobic nature which

creates a problem of delivering drug to the inner starta of skin.
2. Stability of transferosomes during their storage [16].

Method of Preparation

1. Rotary Evaporation-Sonication Method

Drug, Phospholipid along with surfactants was placed in a round-bottomed flask. The solvent system is then added to the mixture and the ingredients were dissolved in the solvent (Chloroform: methanol) by handshaking. The flask was attached to a rotary evaporator and immersed in a water bath maintained at 60°C, rotated with 100rpm for 45min. The formation of the thin film at the bottom was observed. The thin film is hydrated using 6.8 pH buffer. The resultant solution was sonicated in probe sonicator for 30mins [17].

2. Vortexing - 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 pore [18].

3. Modified Handshaking Process

This modified thin film involves the same basic principle as that of rotary film evaporation technique, but here instead of using rotary evaporator, hand shaking will be done for evaporation of solvent. this method involves the addition of mixture of phospholipids, edge activator (surfactant-non ionics/biosurfactants) and lipophillic drug to round bottomed flask containing organic solvents. After the formation of clear solution, by hand shaking evaporation of organic solvent takes place concurrently the place the round bottomed flask on water bath maintained at a temperature of range 40-60°C. After allowing for complete evaporation of organic solvent for overnight formation of thin film takes place. Incorporation of hydrophilic drug can be done at this step. Above transition temperature, buffer solution is then added with gentle shaking [19].

4. Reverse-Phase Evaporation Method

In a glass beaker, the components such as cholesterol and phospholipids are added. The surfactant is then added to same beaker and dissolved in a separate solvent solution. The beaker is left at room temperature for 24 hours to produce a thin layer. The drug solution is poured over the thin film and sonicated for 2 minutes at a frequency of 20 KHz using a probe sonicator. After that, the film is hydrated in phosphate buffer saline (pH 7.4) with edge activator before being sonicated for 2 minutes to get transferosomal suspension. After that, different transferosomal suspensions should be filtered using Whatman filter paper (No. 40) [20].

5. 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[21].

Characterization of Transfersomes [22-27]

1. Vesicle Size Distribution and Zeta Potential

Dynamic light scattering method (DLS) using a computerized inspection system by Malvern Zeta sizer used for determination of vesicle size, size distribution, and zeta potential.

2. Vesicle Morphology

Vesicle diameter can be determined using photon correlation spectroscopy or dynamic light scattering (DLS) method. Samples were prepared in distilled water, filtered through a 0.2 mm membrane filter, and diluted with filtered saline, and then size measurement is done by using photon correlation spectroscopy or dynamic light scattering (DLS) measurements. Transfersomes vesicles can be visualized by TEM, phase contrast microscopy, etc. The stability of the vesicle can be determined by assessing the size and structure of vesicles over time. Mean size is measured by DLS and structural changes are observed by TEM.

3. No. of Vesicles Per Cubic mm

This is an important parameter for optimizing the composition and other process variables. Non-sonicated transfersome formulations are diluted five times with 0.9% sodium chloride

solution. Haemocytometer and the optical microscope can then be used for further study. The Transfersomes in 80 small squares are counted and calculated using the following formula:

Total number of Transfersomes per cubic mm = Total number of Transfersomes counted × dilution factor × 4000

4. Entrapment Efficiency

Entrapment efficiency was determined by first separation of the unentrapped drug by use of minicolumn centrifugation method. After centrifugation, the vesicles were disrupted using 0.1% Triton X-100 or 50% n-propanol.

Entrapment efficiency= (amount entrapped/ total amount added)*100.

5. Drug Content

The drug content is determined using one of the instrumental analytical methods such as a modified highperformance liquid chromatography method using an ultraviolet detector, column oven, auto sample, pump, and computerized analysis program depending on the analytical method of the pharmacopoeial drug.

6. Turbidity Measurement

One tool that is frequently used to assess turbidity in aqueous solutions is the nephelometer.

7. Degree of Deformability or Permeability Measurement

Permeability study is one of the important and unique parameters for characterization in case of transfersomes. The deformability study is done by taking pure water as standard. Transfersomes preparation is passed through a number of pores of known size (through a sandwich of different microporous filters, with pore diameter between 50 and 400 nm, depending on the starting transfersomes suspension). Particle size and size distributions are noted after each pass by DLS measurements.

8. Penetration Ability

Fluorescence microscopy can generally use for evaluation of penetration ability of transfersomes.

9. *In-vitro* Drug Release

In vitro drug release study is performed for determining the permeation rate. Time needed to attain steady state permeation and the permeation flux at steady state and the information from *in vitro* studies are used to optimize the formulation before more expensive in vivo studies are performed. For determining drug release, transfersomes suspension is incubated at 32°C and samples are taken at different times and the free drug is separated by minicolumn centrifugation. 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).

Table 1: Applications of Transferosomes [28]

Sr. No.	Drug	Category	Result
1	Repaglinide	Anti- hypoglycaemia drug	Improved site specificity and prolonged the release of the drug
2	Lidocaine	Local anaesthetic	Improved skin permeation
3	Itraconazole	Antifungal drug	Prolonged release of the drug
4	Carvedilol	β- Blocker	Transferosomal vesicles were substantially more effective at delivering carvedilol through the nose with a bioavailability of 63.4%
5	Insulin	Anti-diabetic	prolonged hypoglycaemic effect in diabetic rats over 24 h after transdermal administration
6	Mefenamic acid	NSAID	Better outcomes were obtained using the thin-film hydration technique, which had the maximum drug content, spread ability, and sustained drug release profile for 12 hours
7	Sildenafil citrate	Phospho Diesterase (PDE) Inhibitors	Improved transdermal permeation and bioavailability with reduced dose administration frequency
8	Tacrolimus	Immunosuppressants	Better antipsoriatic activities compared to liposomes due to better skin permeations

CONCLUSION

Continuous efforts are being made to develop new transdermal medication delivery techniques that will provide an effective therapeutic response. In the modern era of research, the utilisation of vesicles in the development of transferosomes is essential. They facilitate improved medication penetration through the skin. Drug release in this kind of delivery can also be regulated in accordance with the needs. As a result, this method can solve the issues that traditional approaches cannot.

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