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TRANSFEROSOMES AND ITS APPLICATION: A REVIEW

Prashant Singh*[1], Navneet Kumar Verma[1], Sushil Kumar Tiwari[1], Dilip Kumar Mishra[2], Uma Srivastava[3]

[1*]Buddha Institute of Pharmacy, GIDA, Gorakhpur, Uttar Pradesh, India.
[2]Faculty of Pharmaceutical Sciences, Mahayogi Gorakhnath University, Gorakhpur, Uttar Pradesh, India.
[3]Deen Dayal Upadhyaya Gorakhpur University, Gorakhpur, Uttar Pradesh, India.

ABSTRACT

Transferosomes serve as carriers for a targeted transdermal drug delivery system, constituting a specialized class of liposomes characterized by the presence of phosphatidylcholine and an edge activator. This innovative system capitalizes on phospholipid vesicles as carriers for transdermal drug delivery, effectively permeating the stratum corneum through either the intracellular or transcellular route, facilitated by the creation of an "osmotic gradient". Notable advantages of Transferosomes include a broad spectrum of solubilities, enhanced penetration capabilities, biocompatibility and biodegradability. However, it is essential to acknowledge certain drawbacks such as susceptibility to oxidative degradation and higher production costs. The formulation of transferosomes involves employing the conventional rotary evaporation sonication method, incorporating phospholipids, surfactants and the desired drug. Evaluation parameters encompass vesicle size distribution, zeta potential, vesicle morphology, number of vesicles per cubic millimeter, entrapment efficiency, drug content, turbidity measurement, degree of deformability or permeability, penetration ability, occlusion effect, surface charge and charge density, in-vitro drug release, *in-vitro* skin permeation studies and physical stability. Transferosomes exhibit versatile applications, including controlled release, transport of high molecular weight compounds, targeted delivery to peripheral subcutaneous tissues and transdermal immunization.

KEYWORDS

Transferosomes, Transdermal drug delivery, Liposomes, Phosphatidylcholine, Osmotic gradient and Controlled release.

Author for Correspondence:
Prashant Singh,
Buddha Institute of Pharmacy,
GIDA, Gorakhpur, Uttar Pradesh, India.

Email: prashantsingh30785@gmail.com

INTRODUCTION

In recent years, vesicular systems have gained prominence as a method for achieving sustained or controlled drug release. The term "transferosome" and its underlying concept were first introduced in 1991 by Gregor Cevc. The name "Transferors" is a combination of the Latin word meaning "to carry

across" and the Greek word "soma," which refers to a body[1]. A transferosome is a complex and resilient aggregate that exhibits high adaptability to stress. Its preferred structure is an ultra-deformable vesicle with an aqueous core enveloped by a sophisticated lipid bilayer. These vesicles are colloidal particles filled with water. The capsules' walls are composed of amphiphilic molecules, such as lipids and surfactants, arranged in a bilayer conformation[2]. In the context of topical formulations, these vesicles act as reservoirs for the prolonged release of active compounds. Additionally, for transdermal formulations, they function as a membrane barrier that regulates the rate of systemic absorption[3].

Transferosomes are composed of a phospholipid component combined with a surfactant mixture. The flexibility of the vesicle is determined by the ratio of individual surfactants and the total amount of surfactants. What sets this drug carrier system apart is its ability to accommodate hydrophilic, lipophilic, and amphiphilic drugs[4]. Transferosomes are applied to the skin in a non-occluded manner and have demonstrated the ability to permeate through the lipid lamellar regions of the stratum corneum, facilitated by skin hydration or osmotic force. Remarkably, these vesicles can deform and traverse narrow constrictions, with minimal loss, at a size 5 to 10 times smaller than their own diameter. Furthermore, transferosomes exhibit efficient passage through tiny pores (100mm), nearly as effectively as water, which is 1500 times smaller.

They serve as carriers for both low and high molecular weight drugs, including analgesics, anesthetics, corticosteroids, sex hormones, anticancer agents, insulin, gap junction proteins, and albumin. Transferosomes provide protection to encapsulated drugs against metabolic degradation. Functioning as depots, they release their contents slowly and gradually. Notably versatile, transferosomes can be employed for both systemic and topical drug delivery. Their scalability is facilitated by a straightforward procedure that avoids unnecessary complexities and the use of pharmaceutically unacceptable additives[5].

Transdermal drug delivery systems refer to medicaments administered topically, typically in the form of patches or semisolids. These formulations are applied to the intact skin to deliver the drug at a controlled rate to the systemic circulation. In recent times, several advanced Transdermal Drug Delivery Systems (TDDS) have emerged, showing promise in the rate-controlled delivery of various drugs. These systems are specifically designed to ensure a controlled and continuous release of drugs through the skin into the systemic circulation. The transdermal delivery approach holds the potential to enhance both the therapeutic efficacy and safety of drugs by achieving more precise administration. However, optimal results require careful consideration of spatial and temporal placement within the body, ultimately reducing the size and number of doses needed for effective systemic medication through topical application on the intact skin surface[6].

Over the past two decades, the development of controlled transdermal drug delivery systems has been pursued to circumvent the hepatic first-pass effect, enhance drug bioavailability, and mitigate side effects linked to the oral route. The transdermal approach has emerged as a highly successful and innovative area of research in drug delivery. Approximately 40% of drug candidates undergoing clinical evaluation are associated with transdermal or dermal systems. The inaugural approval of a transdermal patch by the FDA occurred in 1981[7].

ADVANTAGES OF TRANSFEROSOMES[8,9]

Versatile composition

Transferosomes possess a dual infrastructure comprising hydrophobic and hydrophilic moieties, allowing accommodation of drug molecules with a wide range of solubilities.

Deformability and penetration

High deformability enables transferosomes to deform and navigate through narrow constrictions, even 5 to 10 times smaller than their own diameter, with minimal loss.

This exceptional deformability enhances penetration, facilitating intact vesicles to pass through tight junctions effectively.

Drug compatibility and carrier function

Acting as carriers, transferosomes accommodate both low and high molecular weight drugs, including analgesics, anesthetics, corticosteroids, sex hormones, anticancer agents, insulin, gap junction proteins and albumin.

They exhibit biocompatibility and biodegradability due to their natural phospholipid composition, similar to liposomes.

Entrapment efficiency

Transferosomes demonstrate high entrapment efficiency, particularly with lipophilic drugs, reaching close to 90%.

Metabolic protection

They provide protection against metabolic degradation for encapsulated drugs, such as proteins and peptides.

Depot and gradual release

Functioning as depots, transferosomes release their contents slowly and gradually.

Suitable for both systemic and topical drug delivery, they offer flexibility in usage.

Scalability and simplicity

Transferosomes are easy to scale up, owing to a simple procedure that avoids unnecessary complexity and the use of pharmaceutically unacceptable additives.

Distinct from liposomes

While transferosomes may seem remotely related to liposomes at first glance, functionally they differ significantly.

Transferosomes exhibit much higher flexibility and adaptability compared to commonly used liposomes.

Membrane Flexibility

The extremely high flexibility of transferosome membranes allows them to squeeze through pores significantly smaller than their own diameter.

Overall Advantages

Biocompatible, biodegradable, and with exceptional deformability, transferosomes offer a promising avenue for drug delivery, catering to a diverse range of drugs with varying solubilities.

Versatile Application[10]

Applicable for both systemic and topical drug delivery, offering flexibility in therapeutic use.

Metabolic Protection[11]

Shields the encapsulated drug from metabolic degradation, ensuring sustained efficacy.

Biodegradability and Safety[12]

Demonstrates biodegradability with a notable absence of toxicity, promoting safety in pharmaceutical applications.

DISADVANTAGES[8,9]

Chemical Instability

Transferosomes exhibit chemical instability, primarily due to their vulnerability to oxidative degradation.

Purity Concerns

The purity of natural phospholipids poses a challenge, discouraging the widespread adoption of transferosomes as drug delivery vehicles.

Cost Considerations[13]

Transferosomes formulations are characterized by their high cost, contributing to economic considerations in their application.

METHODS FOR PREPARATION OF TRANSFERSOME

Vertexing-sonication method

Preparation

Blend mixed lipids (phosphatidyl choline, EA, and therapeutic agent) in a phosphate buffer.

Vortex the mixture to achieve a milky suspension.

Sonication and extrusion

Subject the suspension to sonication.

Extrude the sonicated suspension through poly-carbonate membranes.

Suspension homogenization process

Lipid mixture

Mix an ethanolic soybean phosphatidyl choline solution with an appropriate edge-active molecule (e.g., sodium cholate).

Buffer addition

Combine the prepared suspension with Triethanolamine-HCl buffer to achieve a total lipid concentration.

Modified handshaking process

Lipid film formation

Dissolve drug, lecithin (PC), and edge activator in an ethanol: chloroform (1:1) mixture.

Solvent Removal

Evaporate the organic solvent by hand shaking above the lipid transition temperature (43°C).

Allow a thin lipid film to form inside the flask wall with rotation.

Aqueous lipid suspension process

Vehicle Composition

Fix the Drug-to-lipid ratio between 1/4 and 1/9 in the vehicles, depending on the formulation type.

Flexibility Assurance

Choose compositions ensuring high flexibility of the vesicle membrane compared to standard phosphatidyl choline vesicles in the fluid phase.

Vesicle Preparation

Prepare vesicles with sizes ranging from 100-200 nm, utilizing soy phosphatidyl choline, with a standard deviation of size distribution (around 30%).

Centrifugation Process[14-16]

Lipid Dissolution

Dissolve phospholipids, surfactants, and the drug in alcohol.

Solvent Removal

Remove the solvent by rotary evaporation under reduced pressure at 40°C.

Eliminate final traces of solvent under vacuum.

Lipid Film Hydration

Hydrate the deposited lipid film with the appropriate buffer through centrifugation at 60 rpm for 1 hour at room temperature.

Vesicle Formation

Swell the resulting vesicles for 2 hours at room temperature.

Sonicate the multi-lamellar lipid vesicles obtained at room temperature.

CHARACTERIZATION OF TRANSFEROSOMES[17-19]

Entrapment efficiency

Determine entrapment efficiency using the centrifugation method, calculating the amount entrapped by disrupting vesicles with phosphate buffer and quantifying the drug spectrophotometrically.

Entrapment Efficiency = (Amount Entrapped / Total Amount Added) × 100

Vesicle shape and type

Visualize transferosomes vesicles using Transmission Electron Microscopy (TEM) with an accelerating voltage of 100 kV.

Phase contrast microscopy can be employed without sonication, utilizing an optical microscope.

Number of Vesicles per Cubic mm

An essential parameter for optimizing formulation composition and process variables.

Dilute transferosomes formulations (without sonication) with 0.9% sodium chloride solution and study using optical microscopy with hemocytometers.

Penetration Ability

Use fluorescence microscopy to evaluate the penetration ability of transferosomes.

Surface charge and charge density

Employ the Zetasizer to determine surface charge and charge density of transferosomes.

Confocal Scanning Laser Microscopy (CSLM)

Overcome challenges in conventional light and electron microscopy by minimizing fixation, sectioning, and staining issues.

Utilize CSLM with different fluorescence markers such as Fluorescein-DHPE and Rhodamine-DHPE.

Degree of Deformability or Permeability Measurement

Evaluate permeability as a crucial and unique parameter for characterizing transferosomes.

Assess deformability against pure water as a standard by passing transferosomes through microporous filters of known size, noting size and distribution changes through dynamic light scattering (DLS) measurements.

***In vitro* drug release study**

Perform in vitro drug release studies to determine permeation rates.

Incubate transferosomes suspension at 32°C, collect samples at different times, and separate free drug using the centrifugation method. Calculate released drug indirectly from the initial amount.

Vesicle Size Distribution and Zeta Potential

Utilize Dynamic Light Scattering (DLS) with a computerized inspection system by Malvern Zetasizer to determine vesicle size, size distribution, and zeta potential.

Vesicle Morphology

Determine vesicle diameter using Photon Correlation Spectroscopy or DLS method.

Visualize transferosomes vesicles using Transmission Electron Microscopy (TEM) and phase contrast microscopy.

Assess vesicle stability over time by evaluating size and structure changes through DLS and TEM measurements.

APPLICATIONS OF TRANSFEROSOMES

Insulin Delivery[20]

Transferosomes offer a successful method for delivering large molecular weight drugs like insulin to the skin.

Transfersulin, encapsulated in transferosomes, overcomes inconveniences associated with conventional subcutaneous insulin delivery.

Therapeutic effects are observed 90-180 minutes post-application on intact skin, dependent on the carrier composition.

Corticosteroids Delivery

Transferosomes address issues with corticosteroids delivery by incorporating them.

Achieve site specificity and enhanced safety in corticosteroid delivery into the skin through optimized percutaneously administered drug doses using transferosome encapsulation.

Transferosome technology reduces the dose required for the biological activity of corticosteroids.

Proteins and Peptides Delivery[21]

Transferosomes serve as a carrier for safely transporting proteins and peptides.

Overcome challenges associated with oral administration of large biogenic molecules, preventing GI tract degradation.

Transferosomes offer an alternative to injectables, showing promising bioavailability and inducing a strong immune response with repeated percutaneous applications.

Interferon (INF) Delivery[22]

INF is successfully delivered using transferosomes as carriers.

Leukocyte-derived INF-α, a naturally occurring protein with antiviral and immunomodulatory effects, is effectively delivered through transferosome formulations.

Transferosomes offer controlled release and increased stability for labile drugs.

Anticancer Drugs Delivery[23]

Transferosome technology presents a novel approach to cancer treatment, particularly for skin cancer.

Favorable results are observed when methotrexate is delivered transdermally using transferosome technology.

Anesthetics Delivery[24]

Application of transferosomes containing anesthetics induces topical anesthesia within 10 minutes, comparable to subcutaneous injection.

Transdermal anesthetics preparations exhibit long-lasting effects under suitable conditions.

Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) Delivery[25]

Overcome GI side effects associated with most NSAIDs by using transdermal delivery with transferosomes.

Successful studies have been conducted on diclofenac and ketoprofen, with ketoprofen in a transferosome formulation gaining marketing approval in 2007.

Herbal Drugs Delivery[26]

Transferosomes facilitate the delivery of herbal drugs, as demonstrated by the improved topical absorption of capsaicin compared to pure capsaicin.

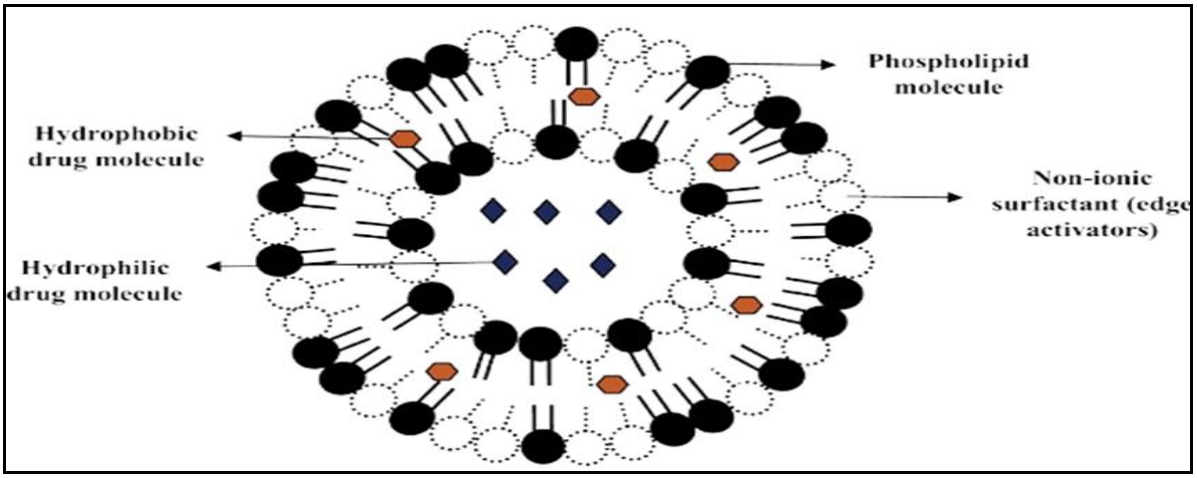

Figure No.1: Representation of a single transferosome structure

CONCLUSION

Transferosomes represent optimized vesicles capable of rapid and energetically economical shape transformations in response to external stress. These highly deformable particles serve as efficient carriers for transporting drugs across biological permeability barriers, such as the skin. In artificial systems, transferosomes have demonstrated remarkable efficiency, comparable to water, even when passing through tiny pores (100mm), which are 1500 times smaller. Drug-laden transferosomes exhibit an unprecedented drug-carrying capacity across the skin (up to 100mg cm2h-1).

While transdermal drug delivery systems offer numerous advantages, the penetration of drugs through the stratum corneum remains a rate-limiting step, particularly for larger molecules. Vesicular systems like transferosomes have been developed to address these limitations. The elastic nature of transferosomes allows them to deform and penetrate the skin through pores efficiently. This approach is not only more effective but also safer in composition compared to other methods.

In this delivery system, drug release can be controlled according to specific requirements, offering a solution to challenges encountered in conventional techniques. Overall, transferosomes present a promising strategy to overcome the limitations of traditional drug delivery methods and enhance the efficiency, safety, and controlled release of drugs through transdermal applications.

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CONFLICT OF INTEREST

We declare that we have no conflict of interest.

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