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# TRANSFEROSOMES IN TRANSDERMAL DRUG DELIVERY SYSTEM: STRUCTURE, MECHANISM AND THERAPEUTICS

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## ABSTRACT

Transdermal drug delivery systems (TDDS) have gained significant attention as a non-invasive alternative to conventional oral and parenteral drug administration, as they bypass first-pass metabolism, reduce gastrointestinal degradation and improve patient compliance. Despite these advantages, the highly protective nature of the stratum corneum restricts efficient drug permeation through the skin. To address this limitation, transferosomes have been developed as ultra-deformable vesicular carriers capable of enhancing transdermal drug delivery. Transferosomes consist of phospholipids combined with edge activators that provide exceptional membrane elasticity, allowing the vesicles to deform and pass through narrow intercellular skin pores without disruption. Their movement across the skin is primarily driven by hydration and osmotic gradients rather than concentration-dependent diffusion. Various preparation methods such as rotary film evaporation, reverse phase evaporation, ethanol injection, vortex-sonication, and freeze–thaw techniques have been employed to produce stable and efficient transferosomal formulations. These carriers exhibit high entrapment efficiency and are capable of delivering both hydrophilic and lipophilic drugs. Transferosomes have demonstrated promising applications in the transdermal delivery of insulin, proteins, peptides, anticancer agents, corticosteroids and herbal drugs. Although challenges related to stability, scalability, and cost remain, transferosomes represent a versatile and advanced drug delivery system with significant future potential.

**KEYWORDS:** Transdermal drug delivery, Transferosomes, Ultra-deformable vesicles, Vesicular drug delivery systems, Skin permeation enhancement.

## INTRODUCTION

Most drugs are commonly administered orally, but this route often fails to achieve the desired therapeutic effectiveness. To overcome these limitations, transdermal drug delivery systems (TDDS) were developed, in which drugs are delivered through the skin to produce systemic effects. TDDS also enables drug penetration into the epidermal and dermal layers, providing both local and systemic therapeutic benefits.[1]

The skin is the largest organ and provides a potential route for drug delivery, although its protective nature—mainly due to the stratum corneum—restricts drug permeation. This approach has been widely applied in treating conditions such as cancer, diabetes, cardiovascular disorders, and central nervous system diseases.[2]

Although oral administration is widely used, it suffers from limitations such as first-pass metabolism, gastrointestinal degradation and variable bioavailability. To address these issues, TDDS was developed in the 1990s and has since become an important, though challenging, area of pharmaceutical research due to the skin's barrier properties.[3]

Transdermal drug delivery systems offer a non-invasive alternative by bypassing the gastrointestinal tract, enabling controlled and sustained drug release with improved therapeutic efficacy.[4]

Transdermal drug delivery systems (TDDS) are self-contained formulations applied to intact skin to deliver drugs into the systemic circulation at a controlled and reproducible rate over an extended period. The main goal of TDDS design is to enhance skin permeation while reducing drug retention and metabolism within skin layers.[5]

## TRANSFEROSOMES

Transferosomes are ultradeformable vesicular carriers designed for topical application, composed of a phospholipid bilayer modified with an edge activator and enclosing an aqueous phase.[6]

These vesicular carriers improve drug transport across biological barriers while shielding the drug from degradation.[7]

These vesicles exhibit enhanced skin penetration due to their highly elastic lipid bilayer, which is modified by surfactants known as edge activators, enabling them to deform and pass through the skin barrier efficiently.[8]

**STRUCTURE**

The term *transferosome* refers to a "carrying body," derived from the Latin word *transferre* meaning "to carry across" and the Greek word *soma* meaning "body." Transferosomes are nanoscale carrier systems developed as an advanced and innovative approach for efficient drug delivery.[9]

Transfersomes possess both hydrophilic and lipophilic components, (as shown in Fig: 1) allowing them to accommodate drugs with diverse solubility and enhance skin permeation. Vesicle size plays a crucial role in penetration, with smaller transfersomes (around 70–120 nm) showing superior deposition in viable epidermal and dermal layers compared to larger vesicles. Their exceptional deformability arises from phospholipids combined with edge activators such as bile salts or non-ionic surfactants, which impart greater flexibility than conventional liposomes and improve transdermal drug delivery efficiency.[10]

Transfersomes are highly elastic lipid vesicles developed to cross the skin barrier without structural disruption, making them effective carriers for transdermal drug delivery. They consist of phospholipids, water and surfactants known as edge activators, which impart exceptional flexibility to the lipid bilayer. The vesicles contain an internal aqueous core surrounded by a modified bilayer that adapts easily to skin pores. Common edge activators include sodium cholate, deoxycholate, span 80 and Tween 80, which reduce membrane rigidity. Typically, transfersomal formulations contain 5–10% total lipids and may include small amounts of ethanol to further enhance deformability and drug delivery efficiency.[11]

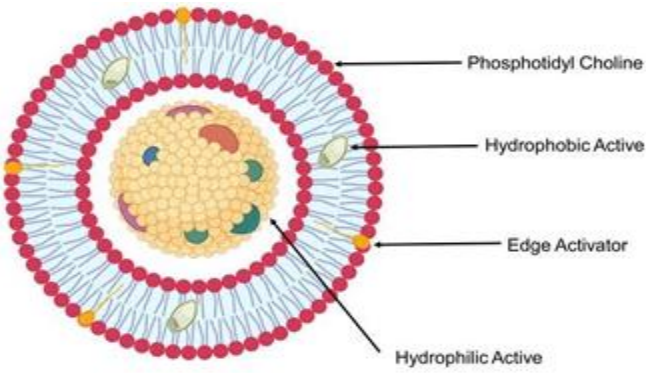


**Figure 1: Structure of Transfersomes.**

## TRANSFERSOMES V/S OTHER CARRIERS

1. **Relation to Liposomes**: Transfersomes are structurally similar to liposomes as they are lipid-based vesicles, but functionally, they are far more flexible and adaptable.
2. **High Membrane Flexibility**: Their membranes are extremely elastic, allowing them to pass through pores smaller than their own size. This flexibility results from the combination of phospholipids with a biosurfactant, as their differing packing characteristics enhance membrane adaptability.
3. **Spontaneous Skin Penetration**: The deformable nature of transfersomes, along with their hydrophilic surface, drives them to move toward areas of higher water activity, enabling spontaneous penetration into the skin.
4. **Superiority Over Micelles**: Unlike mixed micelles, which contain higher surfactant levels, transfersomes penetrate deeper because micelles remain mostly on the skin surface and are less responsive to water activity gradients.
5. **Water-Filled Core Advantage**: Transfersomes are larger than micelles and contain a water-filled core, allowing them to carry both water-soluble and fat-soluble drugs, whereas micelles only carry lipid-soluble substances.
6. **Demonstrated Penetration**: Studies using fluorescent labelling and Confocal Scanning Laser Microscopy (CSLM) show that transfersomes penetrate the stratum corneum effectively and reach the viable epidermis in significant amounts, unlike liposomes and micelles.[12]

## MECHANISM OF ACTION

The transport of transferosomes across the skin is driven by an osmotic gradient created by water evaporation following topical application. Their movement is governed by trans-epidermal hydration rather than concentration, allowing the highly elastic vesicles to deform and pass through pores smaller than their size Upon application.[13] As shown in Fig: 2.

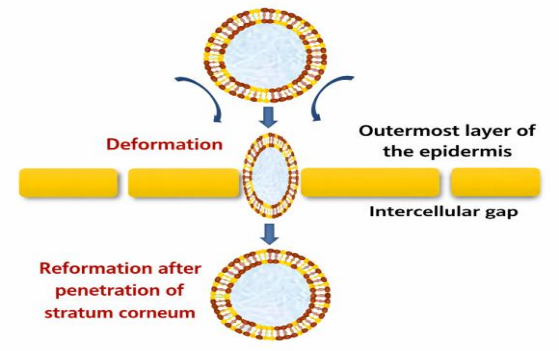


**Figure 2: Mechanism of Action.**

They may function either as in tact carriers that transport the drug into the skin or as penetration enhancers that transiently disturb the ordered lipid structure, thereby facilitating drug diffusion across the skin barrier.[15]

The effectiveness of transferosomes in drug delivery depends on their capacity to deform and traverse hydrophilic pores within the skin barrier. Drug transport may occur through fusion of the vesicular lipid bilayer with cellular membranes, similar to endocytic processes, driven by a combination of mechanical flexibility and hydration-induced osmotic forces. Penetration can take place across the stratum corneum or through appendageal routes such as hair follicles and sweat glands.[16]

**ADVANTAGES**

1. Transferosomes are biocompatible and biodegradable since they are composed of natural phospholipids similar to conventional liposomes.
2. They protect encapsulated drugs from enzymatic and metabolic degradation as well as from environmental factors.
3. These vesicles exhibit enhanced skin permeation due to their high elasticity and deformability.
4. Transferosomes can effectively encapsulate both low and high-molecular-weight drugs, including hydrophilic and lipophilic compounds.
5. They show high entrapment efficiency, which can reach nearly 90% for lipophilic drugs.
6. Their exceptional deformability allows intact vesicle penetration through the skin barrier.
7. Transferosomes are suitable carriers for a wide range of therapeutic agents such as analgesics, anaesthetics, corticosteroids, hormones, anticancer drugs, insulin, proteins, and albumin.
8. The presence of both hydrophilic and hydrophobic domains enables them to accommodate drugs with diverse solubility profiles.
9. They can function as a drug reservoir, providing sustained and controlled drug release.
10. Transferosomes are applicable for both topical and systemic drug delivery.[17]

**DISADVANTAGE**

1. High production costs and the use of expensive phospholipids and equipment limit large-scale application.
2. Drug loading capacity is restricted and drugs requiring high systemic levels may not be suitable.

3. Stability is affected by temperature, pH changes and purity of natural phospholipids can be difficult to maintain.
4. Skin barrier variability (due to age, individual differences, or site of application) can influence drug delivery efficiency.[18]

## METHOD OF PREPARATION

1. Rotary Film Evaporation Method
2. Reverse Phase Evaporation Method
3. Vortex/Sonication Method
4. Ethanol Injection Method
5. Freeze Thaw Method

### 1. Rotary Film Evaporation Method

This technique, also referred to as the modified hand-shaking method, involves dissolving lecithin, edge activator and the drug in a chloroform–ethanol mixture (1:1). As shown in Fig:3. The organic solvents are removed by evaporation at a temperature above the lipid transition point with continuous manual agitation, and the thin lipid film is kept overnight to ensure complete solvent removal. The dried film is then hydrated with pH 6.5 buffer while rotating at 60 rpm for 1hour, followed by swelling at room temperature. Finally, the vesicles are sonicated to obtain smaller and uniform-sized vesicles.[7]

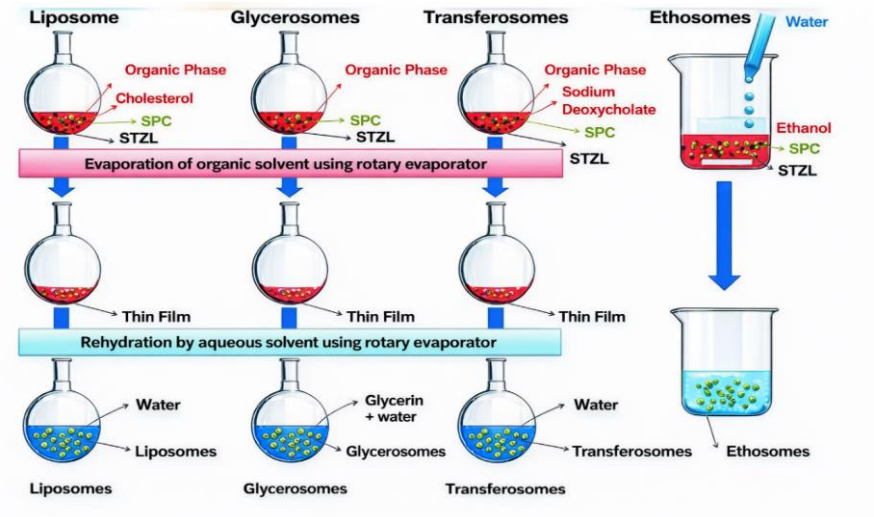


**Figure 3: Rotary Film Evaporation Method.**

### 2. Reverse Phase Evaporation Method

In the reverse phase evaporation method, lipids are first dissolved in organic solvents and

placed in a round-bottom flask. As shown in Fig: 4. An aqueous phase containing edge activators is slowly added under nitrogen atmosphere and the drug is incorporated into either phase depending on its solubility. The mixture is sonicated until a stable and uniform dispersion is obtained, followed by removal of the organic solvent under reduced pressure.[19]

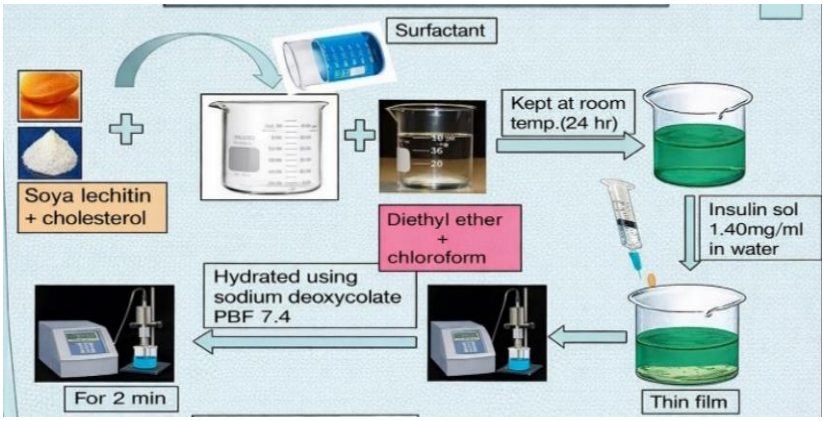


**Figure 4: Reverse Phase Evaporation Method.**

### 3. Vortex/Sonication Method

In this method, the drug, phospholipids, and edge activator are dispersed in phosphate buffer and mixed thoroughly to form a milky transferosomal dispersion. The suspension is then subjected to sonication at room temperature using a bath sonicator to reduce vesicle size. As shown in Fig: 5. Subsequently, the formulation is passed through polycarbonate membranes of defined pore sizes (such as 450 and 220 nm) to o obtain uniform and size-controlled transferosomes.[20]

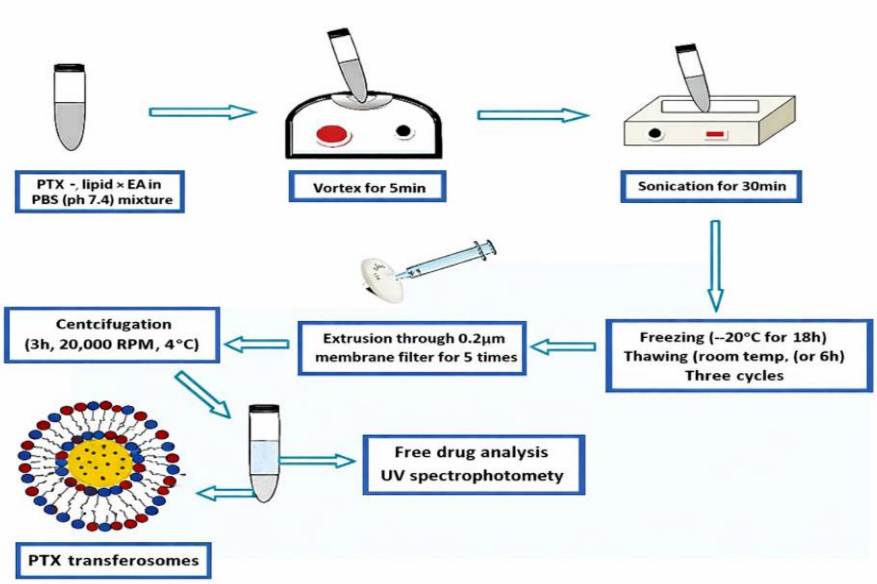


**Figure 5: Vortex/Sonication Method.**

### 4. Ethanol Injection Method

This technique is considered advantageous compared to other methods due to its simplicity and efficiency. In this process, the drug and aqueous phase are maintained at a uniform temperature under continuous stirring. Phospholipids and edge activators are dissolved in ethanol and gradually introduced into the aqueous medium, where they interact and form vesicles. Controlled heating and agitation facilitate uniform mixing and efficient formation of transferosomes.[6] The Ethanol Injection Method has been shown in Fig: 6.

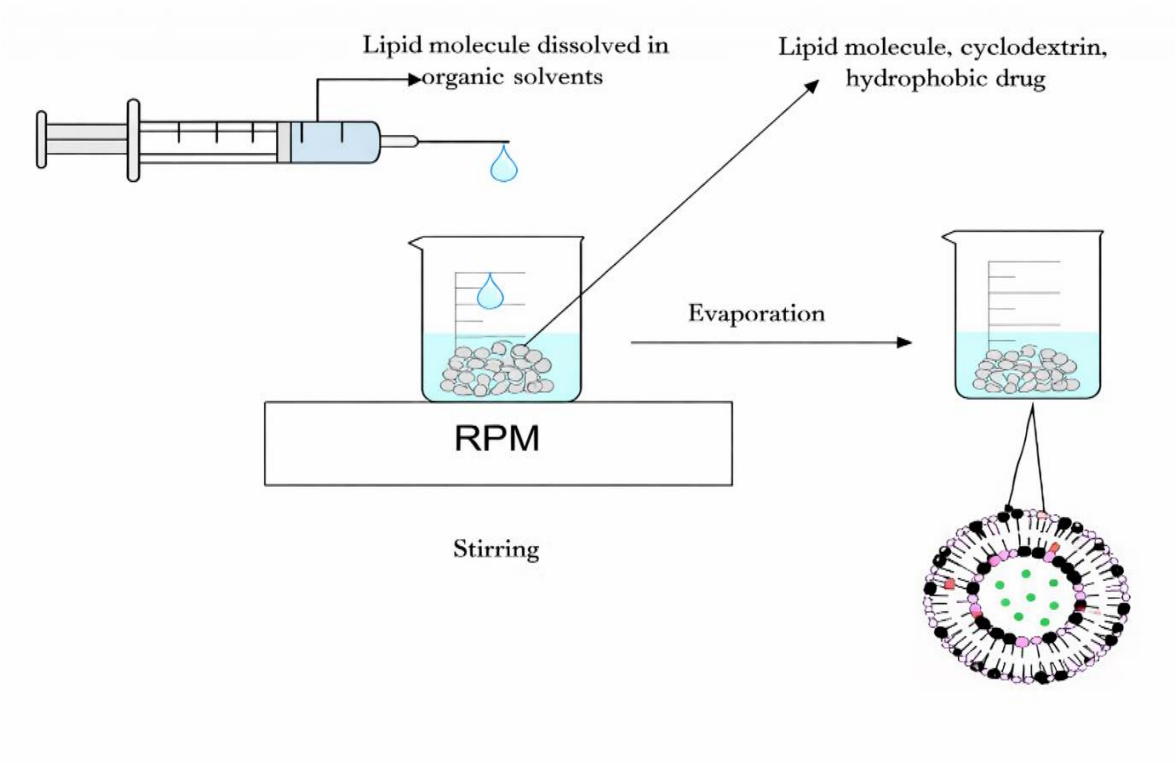


**Figure 6: Ethanol Injection Method.**

### 5. Freeze Thaw Method

In this approach, transferosomes are prepared using repeated freeze–thaw cycles. Multilamellar vesicles are first subjected to rapid freezing by immersing them in a nitrogen bath at −30 °C for about 30 seconds, followed by heating in a water bath. These alternating low- and high-temperature cycles are repeated multiple times, resulting in the formation of uniform and stable transferosomal vesicles.[20] The Freeze Thaw Method has been shown in Fig: 7.

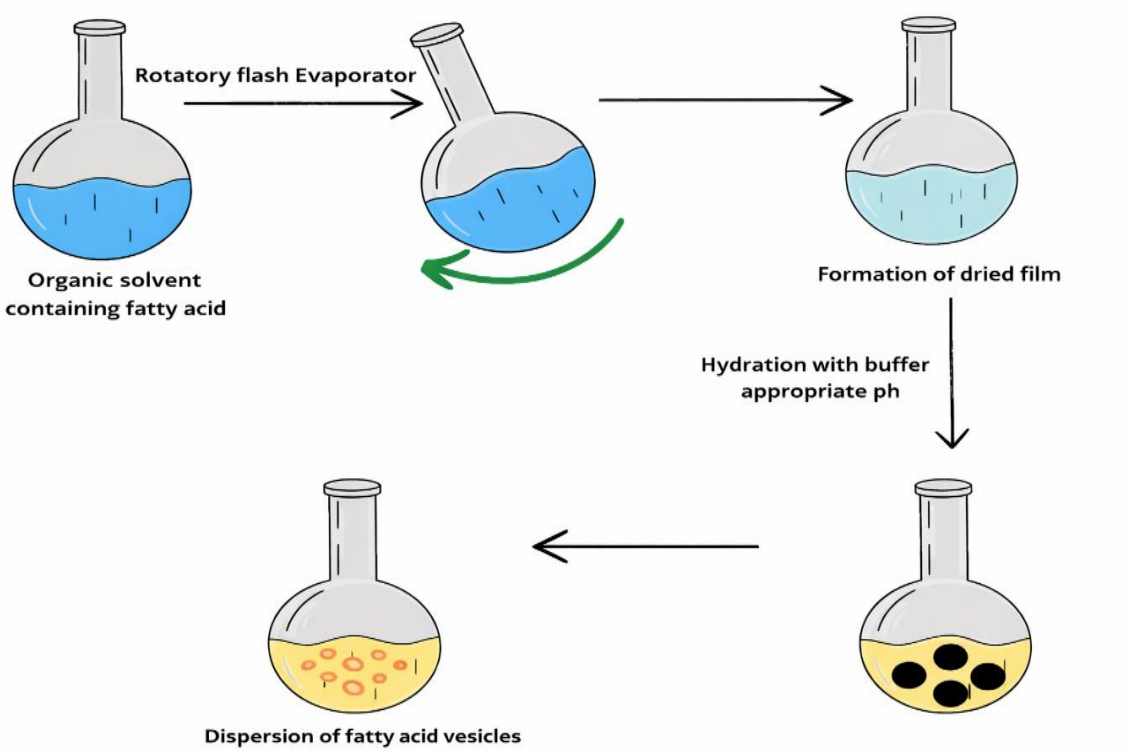


**Figure 7: Freeze Thaw Method.**

## EVALUATION OF TRANSFERSOMES

### 1. Entrapment efficiency (%EE)

The entrapment efficiency refers to the proportion of drug successfully incorporated within the vesicular system. It is evaluated by separating free drug from vesicles using techniques such as mini-column or ultracentrifugation, followed by direct or indirect analysis. In the direct method, vesicles are disrupted using agents like Triton X-100 or n-propanol after removing the supernatant. The solution is then diluted, filtered through a 0.22–0.45 µm membrane, and the drug content is quantified using HPLC or spectrophotometric methods. The %EE is calculated as

$$\%\text{Entrapment efficiency} = \frac{Amount\ of\ drug\ entrapped}{Total\ amount\ of\ drug\ added} \times 100$$

In the indirect method, the supernatant obtained after vesicle separation is appropriately diluted with a suitable solvent and filtered to eliminate impurities. The concentration of drug present in this supernatant represents the unentrapped or free drug. This amount is quantified using an appropriate analytical technique, allowing indirect calculation of the entrapment efficiency. it is calculated as

% Entrapment Efficiency = [(Total amount of drug added − Amount of free drug) / Total amount of drug added] × 100.[21]

**2. Number of Vesicles per Cubic MM**

Vesicle count is an important parameter for optimizing formulation composition and processing conditions. Unsonicated transferosomal dispersions are diluted fivefold using 0.9% sodium chloride solution before analysis. The diluted sample is examined under an optical microscope using a hemocytometer, where vesicles present in 80 small grids are counted. The total number of transferosomes is then calculated using the appropriate mathematical expression.[22]

Total number of transferosomes per $mm^3$ = (Number of transferosomes counted × Dilution factor × 4000) / Total number of squares counted

**3. Degree of Deformability**

In this analysis, pure water serves as the reference medium. The sample is filtered through a series of microporous membranes with defined pore sizes ranging from 50 to 400 nm to ensure uniformity. Particle size and size distribution of the vesicles are then determined using dynamic light scattering (DLS) techniques.

$$D = J(rv/rp)$$

where D is the degree of deformability, J is the amount of suspension extruded over the course of five minutes, rv is the vesicle's size and rp is the barrier's pore size.[23]

**4. Charge density and surface charge**

A Zetasizer is commonly used to evaluate the surface charge and zeta potential of transferosomal vesicles. This measurement provides information on charge density and colloidal stability when the drug is completely entrapped within the vesicles. The results also help in understanding the interaction between the vesicle surface and the encapsulated drug.[24]

**5. Vesicle size distribution and zeta potential**

Vesicle size, particle size distribution, and zeta potential were evaluated using the Dynamic light scattering (DLS) technique. These measurements were carried out with a computerized particle analysis system equipped with a Malvern Zetasizer. The method provides precise information on vesicle uniformity and surface charge, which are critical indicators of formulation stability.[25]

**6. Shape of the vesicles**

The morphology and shape of the vesicles are examined using scanning electron microscopy (SEM).[26]

**7. Drug content**

Drug content is quantified using suitable instrumental analytical techniques, most commonly a modified high-performance liquid chromatography (HPLC) method. The analysis is carried out using an ultraviolet detector, column oven, autosampler and pump connected to a computerized data analysis system. The specific analytical conditions are selected according to the pharmacopeial requirements of the drug.[27]

**8. Penetration ability**

The skin penetration ability of transferosomes can be assessed using fluorescence microscopy techniques.[28]

**9. Physical stability**

For stability evaluation, the samples are stored under different temperature conditions, including refrigerated (4 ± 2 °C), room temperature (25 ± 2 °C), and body temperature (37 ± 2 °C), for at least three months. At predetermined intervals, samples are withdrawn and examined for changes in physical appearance. Parameters such as drug content, particle size, and zeta potential are also analysed to assess formulation stability.[20]

**10. *In vitro* drug release**

Studies are conducted to evaluate the permeation behaviour of transferosomes. The beaker method is commonly employed, where the transferosomal suspension is maintained at 32 °C using a cellophane membrane as the diffusion barrier. Samples are withdrawn at predetermined time intervals and analysed using techniques such as UV spectroscopy, HPLC or HPTLC. Free drug is separated by minicolumn centrifugation, and the cumulative drug release is subsequently calculated.[29]

**11. *In vitro* Skin Permeation Studies**

Skin permeation studies were carried out using Franz diffusion cells to assess the transdermal transport efficiency of the formulations. Selected membranes, including porcine skin or synthetic Strat-M membranes, were mounted between the donor and receptor compartments with the stratum corneum facing the donor side. The receptor compartment was filled with

phosphate buffer saline and maintained at 37±0.5°C under continuous stirring. The formulation was applied to the donor compartment under non-occluded conditions. At predetermined intervals, samples were withdrawn from the receptor medium and replaced with fresh buffer to maintain sink conditions. Drug content was analysed using HPLC or spectroscopic methods.[30]

## APPLICATION OF TRANSFERSOMES

### 1. Delivery of insulin

Transferosomes offer an efficient non-invasive approach for delivering high-molecular-weight drugs through the skin. Insulin, which is traditionally administered by painful subcutaneous injections, can be successfully incorporated into transferosomes to improve patient comfort. Topical application of insulin-loaded transferosomes (transfersulin) results in a systemic hypoglycemic effect, with initial responses observed approximately 90–180 minutes after application. This demonstrates the potential of transferosomes for transdermal delivery of macromolecular therapeutics.[31]

### 2. Delivery of proteins and peptides

Transferosomes are widely employed for the delivery of proteins and peptides, as these high-molecular-weight biomolecules are unstable and poorly absorbed when administered orally due to gastrointestinal degradation. Consequently, they are conventionally given by injection. Transdermal delivery using transferosomes has been shown to provide bioavailability comparable to that obtained from subcutaneous administration of the same protein formulations.[9]

### 3. Delivery of Anticancer Drugs

In 2018, Jiang and co-workers reported a study on topical melanoma therapy using paclitaxel-loaded transferosomes incorporated into an oligopeptide hydrogel. The transferosomes were prepared by the thin-film dispersion technique. The formulation, containing phosphatidylcholine, Tween 80, and sodium deoxycholate, demonstrated efficient penetration into melanoma tumor tissues, highlighting its potential for topical chemotherapy.[30]

### 4. Delivery of Corticosteroids

Cevc and Blume investigated triamcinolone acetonide–loaded transferosomes prepared by the thin-film hydration method during 2003–2004. Their studies demonstrated that encapsulation in transferosomes significantly enhanced the biological activity of the corticosteroid.

Additionally, the formulation prolonged the therapeutic effect while allowing a reduction in the required drug dose.[11]

**5. Herbal transferosomes**

Transferosomes are widely explored as vesicular carriers for the transdermal delivery of herbal medicines. Along with other nano-vesicular systems such as phytosomes, niosomes, ethosomes and cubosomes, they have been shown to enhance skin permeation of phytoconstituents, leading to improved bioavailability and therapeutic effectiveness. Phospholipid-based nanocarriers offer advantages including targeted delivery, controlled drug release, improved patient compliance and avoidance of first-pass metabolism. This strategy helps overcome the limitations of oral herbal formulations, such as poor lipid solubility and large molecular size.[32]

## FUTURE SCOPE

Transferosomes represent a versatile and advanced platform for drug delivery with significant potential in various therapeutic applications. Their ability to effectively penetrate the skin enhances transdermal delivery of diverse agents, including proteins, vaccines, anticancer drugs, and corticosteroids, while improving drug bioavailability. Transferosomes can encapsulate both hydrophilic and lipophilic drugs and be engineered for targeted delivery, thereby reducing systemic side effects and improving therapeutic outcomes. Their non-invasive nature supports better patient compliance and allows convenient self-administration. Furthermore, transferosomes have demonstrated promising results in ocular, dermal and transdermal applications by improving drug stability, permeability and safety. Overall, these ultra-deformable vesicles offer a promising future for the development of efficient and safer drug delivery systems.[23]

## CONCLUSION

Transferosomes have emerged as an advanced and promising vesicular drug delivery system, particularly for transdermal applications by effectively overcoming the barrier properties of the stratum corneum. Their unique ultra-deformable structure, achieved through the incorporation of edge activators into phospholipid bilayers, enables efficient penetration through narrow skin pores without compromising vesicle integrity. This allows delivery of a wide range of therapeutic agents, including hydrophilic, lipophilic, and macromolecular drugs, with improved bioavailability and reduced systemic side effects. Transferosomes offer advantages such as enhanced skin permeation, high entrapment efficiency, controlled drug

release, and improved patient compliance due to their non-invasive nature. Despite challenges related to stability, cost, and large-scale production, continuous research and technological advancements are expected to address these limitations, making transferosomes a valuable and versatile platform for future drug delivery systems.

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