



## TRANSDERMAL DELIVERY OF DRUGS USING TRANSFEROSOMES: A COMPREHENSIVE REVIEW

Sanjana Muthangi\*, Praneetha Pallerla, Srinivas Nimmagadda

Sarojini Naidu Vanita Pharmacy Maha Vidyalaya, Tarnaka, Secunderabad, India

\*Corresponding author: [sanjanardy28@gmail.com](mailto:sanjanardy28@gmail.com)

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### ABSTRACT

Transdermal delivery systems have gained popularity as a non-invasive method of drug administration that offers several advantages over other routes of drug delivery. They are noninvasive and self-administered delivery system which improves patient compliance and provide a controlled release of the drug. The greatest challenge of transdermal delivery systems is that in which the outermost layer of skin acts as a barrier function for transfer of therapeutic agent into the body. Molecules with high molecular weights do not pass through the skin. Therefore, only a limited number of drugs are administered by this route. So encapsulating the drugs in transfersomes is one of the best approaches to overcome this problem. Transferosomes are lipid based vesicular drug delivery systems which have a unique composition that allows them to overcome the limitation of conventional drug delivery system. They are composed of phospholipids and surfactants, which provide them with the ability to encapsulate both hydrophilic and hydrophobic drugs. They penetrate through stratum corneum by either intracellular route or the transcellular route by the generation of natural osmotic gradient. Compared to conventional drug delivery systems, transferosomes offer several advantages like avoidance of first pass metabolism, increasing bioavailability of drugs. Due to its high deformability it enhances the penetration of intact vesicles. Transferosomes vary from other conventional vesicles due to their softer, better adjustable and ultra deformable artificial membranes. This review summarizes the concept of transfersomes, including their structure, formation mechanism of action, different methods of preparation, advantages, limitations along with applications.

**Keywords:** Osmatic gradient, Stratum corneum, Transfersomes, Transdermal delivery system

### 1. INTRODUCTION

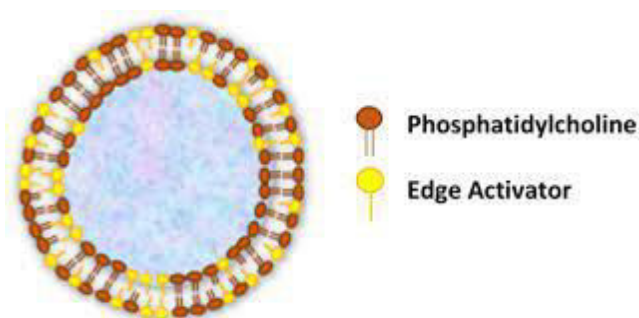
Drug delivery systems are crucial in the development and administration of pharmaceutical, with the aim of achieving a safe and effective therapeutic response. The design and development of drug delivery systems have been an area of reducing toxicity, and increasing patient compliance [1]. Therefore many drug delivery systems have been developed and studied over the past decades to overcome these problems. One of the promising approaches is the use of transdermal delivery systems, as they are less invasive methods without first-pass metabolism. Transdermal drug delivery system delivers medicine through the skin to systemic circulation at a predetermined rate and maintain effective concentrations over a prolonged period of time, they are noninvasive and self administered delivery system [2]. Delivery of drug through the transdermal route is convenient and safe this offers several advantages over conventional

systems. The major drawback of TDDS is the permeability of the skin, it is permeable to small molecules, lipophilic drugs and impermeable to macromolecules and hydrophilic drugs. The major disadvantage of transdermal drug delivery is the poor penetration of compounds across the skin. The major barrier and rate limiting step for diffusion of drug across is provided by the skin, stratum corneum. Many investigations are done to develop systems that are capable of carrying drugs and macromolecules into the deeper tissues. These approaches have resulted in developing of novel vesicular carriers like ethosomes and ultra flexible lipid based elastics vesicles transferosomes [3].

### 2. TRANSFEROSOMES [4-5]

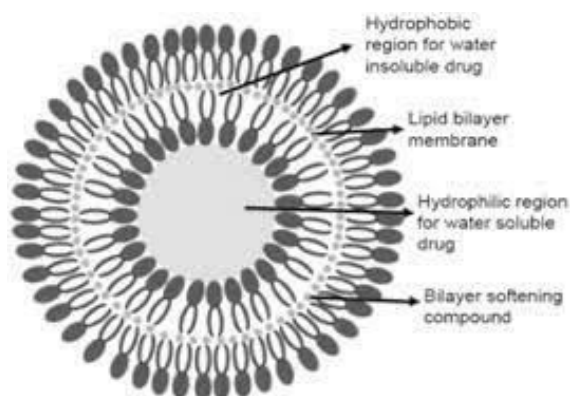
The name means carrying body, and is derive from the Latin word *Transferred* meaning across, and Greek word

*Soma* for a body. Transferosomes are a type of nanocarrier that has been developed as a novel drug delivery system. They are lipid vesicles that are flexible and deformable, which allows penetrating through stratum corneum, the outermost layer of the skin and delivers drugs to the deeper layers of skin. This is particularly useful for drugs that are poorly absorbed through the skin or have a high molecular weight as transferosomes can improve their permeability and enhance their bioavailability. They are composed of phospholipids, surfactants, which allow them to self assemble and from vesicles. They can also incorporate various types of drugs, including hydrophilic and lipophilic drugs, peptides, proteins and genes. Transferosomes can be prepared by various methods, including thin-film hydration, reverse-phase evaporation, and ether injection methods. Transferosomes have been used to deliver a range of drugs including anti-inflammatory agents, antibiotics, antifungal agents and anticancer drugs.



### 2.1. Structure of transferosome [6]

Transferosome is an artificial vesicle that has similar properties to a natural cell vesicle or a cell undergoing exocytosis, making it useful for controlled and possibly targeted drug delivery. They are complex vesicles that have a highly flexible and self regulating membrane which allows them to be deformable.



### 2.2. Composition of transferosomes [7]

**Amphipathic ingredient:** The main ingredient that can be amixture of lipids which are the vesicle-forming components that form the lipid bilayer structure in transferosomes.

**Surfactants/edge activators (10-25%):** These are surfactants that destabilize the lipid bilayer and increase its permeability.

**Alcohol (3-10%):** As the solvent.

**Hydrating medium:** Facilitate the formation of transferosomes by hydrating the lipid bilayer and promoting the self-assembly of the lipid molecules.

### 3. ADVANTAGES [8]

- They can encapsulate both hydrophilic and lipophilic drugs.
- It protects the drug product from degradation and metabolism.
- Transferosomes reduces systemic toxicity.
- Transferosomes enhances skin permeation and bioavailability of drugs.
- Transferosomes can improve patient compliance due to their non invasive route of administration.

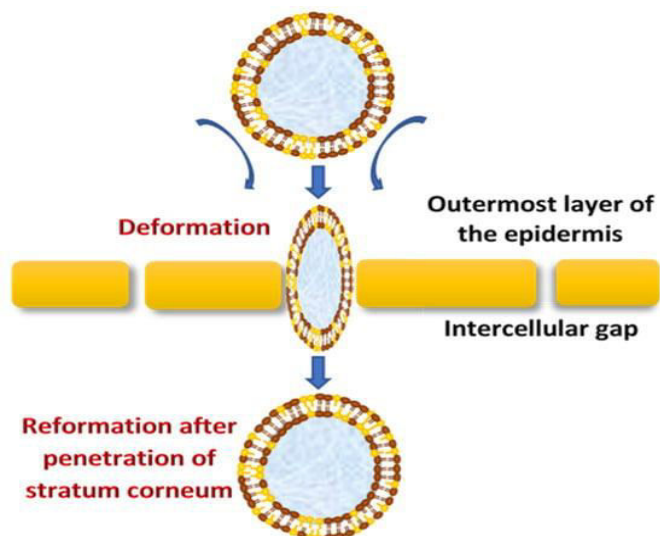
### 4. LIMITATIONS [9]

- Transferosomes have a tendency to aggregate and undergo structural changes which affect their stability and drug release properties.
- Transferosomes may have limited capacity for a drug loading compared to other drug delivery systems, which can limit their use for certain types of drugs.
- The use of surfactants and penetration enhancers can cause skin irritation and sensitization in some patients.
- Purity of natural phospholipids is another criterion which resists against adoption of transferosomes as drug delivery vehicles.
- Transferosomes are expensive.

### 5. MECHANISM OF ACTION OF TRANSFEROSOMES

- The interaction between the lipid residue and the proximal water makes the lipid to attract water molecules inducing hydration and the lipid vesicles move to the site of higher water concentration. This difference in water content across the skin stratum and epidermis develops transdermal osmotic gradient leading to penetration of transferosomes across the skin [10].

- Transferosomes act as permeation enhancers that disrupt the intercellular lipid form the stratum that ultimately widens the pores and facilitates the molecular interaction and penetration of system across the skin.
- Transferosomes by enforcing its own route induce hydration that widens the hydrophilic pores of the skin causing the gradual release of the drug that bind to the target organ [11].



## 6. METHODS OF PREPARATION [12-14]

### 6.1. Thin film hydration technique

A thin film is formed by dissolving the lipids, such as phospholipids and surfactant in organic solvent, such as chloroform or methanol. The solvent is then evaporated using a rotary evaporator or a vacuum pump to obtain a thin lipid on the walls of the flask. The lipid film is then hydrated with an aqueous solution containing the drug or active compound of interest, along with additives such as stabilizers, permeation enhancers or preservatives. The hydration process leads to the formation of multimaller vesicles, which are subjected to size reduction step, either by sonication or extrusion to obtain smaller vesicles.

### 6.2. Modified hand shaking Process

The modified handshaking method has the same basic principle as the rotary evaporation-sonication method. In the modified handshaking process, a lipid mixture is prepared by dissolving the lipids, such as phospholipids and surfactants, in a suitable organic solvent, such as chloroform or methanol. A solution of the drug or active compound of interest is prepared separately in an aqueous solvent, such as distilled water or phosphate -

buffered saline. The lipid mixture is then added to the drug solution drop wise and the mixture is shaken vigorously by hand to form milky suspension. The shaking process is repeated for a few minutes to ensure uniform mixing and entrapment of the drug in the lipid bilayer. The milky suspension is then subjected to sonication to obtain smaller vesicles.

### 6.3. Vortexing-sonication method

The phospholipids, surfactants and the drug are mixed in a phosphate buffer. The mixture is then vortexed until a milky transfersomal suspension is obtained. The milky suspension is subjected to sonication, either by using a probe sonicator or bath sonicator, to obtain smaller vesicles.

### 6.4. Suspension homogenization method

Transferosomes are prepared by dissolving the phospholipids and surfactants, in a suitable organic solvent such as chloroform or ethanol. The prepared suspension is subsequently mixed with buffer and the mixture is stirred continuously to form coarse suspension. The coarse suspension is then homogenized, either by using a high pressure homogenizer or a microfluidizer, to obtain smaller vesicles.

### 6.5. Centrifugation process

The phospholipids, edge activator and the lipophilic drug are dissolved in the organic solvent. The solvent is then removed using a rotary evaporator or vacuum pump to obtain lipid film on the walls on the flask. The lipid film is then hydrated with the appropriate buffer solution and then subjected to ultracentrifugation. During this process, the transferosomes move to the top of the gradient, where they can be collected and washed with an appropriate buffer.

### 6.6. Reverse -phase evaporation Method

The phospholipids and edge activator are added to a round-bottom flask containing organic solvent mixture such as diethyl ether and chloroform. The lipophilic drug can be incorporated in this step. Then, the solvent is evaporated using rotary evaporator to form concentrated lipid films. The lipid films are rehydrated by dissolving in the organic phase mostly composed of isopropyl ether and or diethyl ether the aqueous phase is added to the organic phase, which leads to formation of two-phase system. The hydrophilic drug incorporation can be done in this stage. This system is then subjected to sonication using a bath sonicator until a homogeneous w/o (water oil) emulsion is formed. The organic solvent is slowly

evaporated using rotary evaporator to form a viscous gel, which then becomes a vesicular suspension.

### 6.7. High-pressure homogenization Technique

The phospholipids, edge activator and the drug are uniformly dispersed in phosphate-buffered saline or distilled water containing alcohol and followed by ultrasonic shaking and stirred simultaneously. The mixture is then subjected to intermittent ultrasonic shaking. The resulting mixture is then homogenized using a high-pressure homogenizer. The homogenizer applies high pressure to the suspension to break down the lipid bilayers and form smaller vesicles.

### 6.8. Ethanol injection method

The organic phase is prepared by dissolving the phospholipid, edge activator and the lipophilic drug in ethanol with magnetic stirring for the respective time, until a clear solution is obtained. The aqueous phase is produced by dissolving the water-soluble substances in the phosphate buffer. The hydrophilic drug incorporation can be done in this stage. Both solutions are heated up to 45-50°C. Afterwards, the ethanolic phospholipid solution is injected drop wise into the aqueous solution with continuous stirring for the respective time. The addition of ethanol causes the formation of smaller lipid aggregates which fuse to form larger vesicles. The mixture is then stirred for a sufficient period of time to allow for the complete removal of the ethanol and then subjected to sonication for particle size reduction.

## 7. EVALUATION OF THE TRANSFERSOME [15-16]

The characterization of transfersomes is an important step in evaluating their physicochemical properties and performance. The following are some of the commonly used methods for the characterization of transfersomes:

### 7.1. Vesicle size, size distribution and zeta potential

These parameters can be determined by Dynamic Light scattering system by Malvern zeta sizer.

### 7.2. Vesicle morphology

Vesicle diameter can be determined using photon correlation spectroscopy or dynamic light scattering (DLS) method.

### 7.3. Entrapment efficiency

Entrapment efficiency of transfersomes is determined using various techniques, such as ultracentrifugation,

dialysis and centrifugation. The entrapment efficiency can be given by following equation:

Entrapment efficiency =  $\frac{[\text{Total amount of the drug added} - \text{Amount of the free drug}]}{\{\text{Total amount of the drug added}\}} \times 100$

### 7.4. Drug content

The drug content can be determined by disrupting the vesicles and measuring the drug concentration using various analytical techniques such as HPLC, UV spectroscopy.

### 7.5. Turbidity measurement

Turbidity of the drug can be measured by using nephelometer.

### 7.6. Surface charge and Charge Density

Surface charge and charge density of transfersomes can be determined using a zeta sizer.

### 7.7. Penetration Ability

Penetration ability of transfersomes can be evaluated by using techniques such as franz diffusion cells, confocal laser scanning microscopy, and tape -stripping.

### 7.8. Occlusion Effect

Occlusion of the skin is considered to be helpful parameter for the permeation of drug in case of topical preparations.

### 7.9. In-vitro drug Release

It is performed for determining the permeation rate. For determining the drug release, transfersomes suspension is incubated at 32°C and samples are taken at different times and the free drug is separated by mini column centrifugation method. 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).

### 7.10. In-vitro Skin Permeation Studies

The franz diffusion cell is a tool used to study drug release, it consists of two compartments a donor and a receptor. The receptor compartment has a volume of 50 ml and an effective diffusion area of 2.5cm. The abdominal skin is prepared by removing hair and hydrating it with saline solution. The adipose tissue layer is removed with a cotton swab. Then the treated skin is mounted horizontally with stratum corneum facing upwards the donor compartment of the Franz diffusion cell. The donor compartment has an area of 250cm and

the receptor compartment contains 50ml of phosphate buffer with pH of 7.4 at  $37 \pm 5^\circ$  C stirred at a magnetic bar for 100rpm. A formulation equivalent to 10mg is placed on the skin and covered. At appropriate intervals, 1ml aliquots are withdrawn and immediately replaced with fresh volume to maintain sink conditions. The obtained samples can be analyzed by HPLC method or spectroscopic method.

## 8. APPLICATIONS OF TRANSFEROSOMES [17-18]

Over the past few years, applications of the transfersomes in the field of transdermal drug administration have been extensively studied. Some of these applications are as given below.

### 8.1. Delivery of proteins and peptides

Transfersomes are frequently used to deliver proteins and peptides because these large molecules are typically hard to transport into the body when taken orally, as they can be degraded in the gastrointestinal tract. This is why they are usually introduced into the body through injections. When proteins and peptides are delivered through transfersomes, their bioavailability is comparable to what is achieved through subcutaneous injection of the same protein suspension.

### 8.2. Delivery of insulin

Transfersomes are a successful way to deliver large drugs non-invasively through the skin. Insulin is usually given through inconvenient subcutaneous injections. By encapsulating insulin into transfersomes, called transfersulin, these issues can be overcome.

### 8.3. Delivery of corticosteroids

Transfersomes can be used to deliver corticosteroids to the skin. By optimizing the dose of the drug given through the skin, transfersomes can improve the specificity and safety of corticosteroid delivery. The use of transfersomes can allow for lower dose of the drug to be used while still being in treating skin diseases.

### 8.4. Transdermal immunization

Transfersomes can be used to deliver proteins for transdermal immunization. This approach has two benefits: it does not require injection, and it can result in high level of antibodies, including IgA. Some of the proteins that can be delivered using transfersomes include integral membrane protein, human serum albumin, and gap junction protein.

### 8.5. Delivery of anti-inflammatory drugs

Transfersomes have been studied as a means of delivering anti-inflammatory drugs such as diclofenac sodium, celecoxib, mefenamic acid, and curcumin through topical administration. Studies have found that using transfersomes can enhance the stability and efficacy of these drugs.

### 8.6. Delivery of anticancer drugs

Researchers have studied the use of transfersomes to deliver anti-cancer drugs such as methotrexate, through the skin. The results were positive, suggesting that this approach could be useful for treating skin cancer and offering a new treatment option.

### 8.7. Delivery of herbal drugs

Transfersomes can be used to deliver herbal drugs through the skin and provided nutrients to support the function of the stratum corneum. Curcumin and capsaicin are examples of herbal drugs that have been delivered topically using transfersosomal formulations.

### 8.8. Delivery of NSAIDs

NSAIDs are known to cause gastrointestinal side effects. However, these side effects can be avoided by using transdermal delivery through ultra deformal vesicle

## 9. CONCLUSION

Transfersomes are a type of drug carrier that can deliver a variety of drug molecules across the skin barrier with superior efficacy compared to conventional vesicular systems. They are ultra-deformable and can pass through tiny pores as efficiently as water, creating a highly concentrated drug depot in the systemic circulation. Transfersomes have several advantages over other vesicular systems, such as site specificity, sustained release, higher penetration power across skin, high deformability, and the ability to encapsulate high molecular weight compounds. They are emerging technology with promising potential for transdermal drug delivery.

### Conflict of interest

None declared

### Source of funding

None declared

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