



## A Review on Transfersomal Drug Delivery System

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### Abstract

Transfersomes is a carrying body for targeted transdermic drug delivery system. Transfersomes and also the elementary idea of transfersomes were launched by Gregor Cevc within the year 1991. It exists as associate ultra-deformable complex having a hydrous core enclosed by a fancy layer of macromolecule. It penetrate the corneum by either intracellular route or the transcellular route by the generation of "osmotic gradient". The carrier combination consists of a minimum of one amphipathic molecule (like phospholipids) that once value-added to binary compound systems self-assemble into a bilayer of lipid which eventually closes into a lipid sac and one bilayer softening agent which is generally a wetting agent that is chargeable for the flexibility of the vesicle.

The transfersomes were developed by the traditional rotary evaporation sonication method. analysis parameters of transfersome are as vesicle size distribution and zeta potential, sac morphology, No. of vesicles per isometric mm, entrapment potency, Drug content, turbidness measurement, Degree of deformability or porosity measurement, Penetration ability, Occlusion effect, Surface charge and charge density, In-vitro drug release, in-vitro Skin permeation Studies, Physical stability. Transfersomes offer the first advantage of upper entrapment efficiency along side a depot formation which releases the contents slowly. Transfersomes are often used for delivery of insulin, corticosteroids, proteins and peptides, interferons, anti-cancer medication, anaesthetics, NSAIDs and flavoring drugs

**Key words:** Transfersomes, Transdermal drug delivery system, Modified Transfersomes.

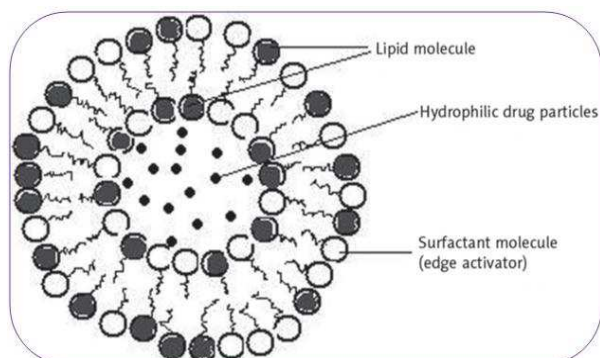
### Introduction

Transfersomes means that "carrying body" and comes from the Latin word 'transfere', which means 'to carry across' and also the Greek word 'oma', meaning 'a body'. A Transfersome carrier is a synthetic vesicle designed to exhibit the characteristics of a cell vesicle or a cell engaged in exocytosis, and so appropriate for controlled and potentially, targeted drug delivery. There are many blessings of the transdermic route over the opposite ancient routes like preventing the metabolism in liver, assuaging the untoward side effects, certainty and extended period of action, efficient delivery of medicine with a brief half-life, rising the physiological similarly as pharmacological response, lesser

fluctuation in blood levels of the medicine and last however the foremost important, improved patient compliance<sup>1,2</sup>. Vesicular drug delivery is most well-liked over different formulations due their definite characteristics of a much better capability of encapsulating hydrophilic and hydrophobic drugs, no toxicity, biodegradability, hyperbolic time of drug presence within the circulation because of encapsulation in the vesicular structure, ability to focus on different organs and tissues and an increased bioavailability.

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Permeability of corneum may be increased by the employment of penetration enhancers, iontotherapy, iontotherapy and also the use of mixture carriers like lipide vesicles (liposome and proliposomes) and non-ionic wetting agent vesicles (niosomes and proniosomes). Transfersomes overcome the filtration downside and penetrate the skin barrier on the body covering gradient. Transfersomes

may be a special sorts of vesicle, consisting of phosphatidylcholine and a position substance. With the applying of mechanical stress, they will enter through corneum in self adapting manner as a result of their high sac deformability. Flexibility of transfersomes membrane is achieved by combination appropriate active parts (edge activator) within the proper ratios. The ensuing flexibility of transfersomes membrane minimizes the chance of complete sac rupture within the skin and permits them to follow the natural water gradient across the cuticle, once applied below nonocclusive condition. once applied on the skin, the carrier searches and exploits deliquescent pathways or pores between the cells, wherever it opens wide enough to allow the complete sac to go through corneum beside drug molecule, deforming itself very to accomplish this while not losing its sac integrity. this allows them to cross numerous transport barriers with efficiency.

**Table 1: Advantages and Disadvantages of Vesicular Systems**<sup>14</sup>

Methods	Advantages	Disadvantages
Liposomes	Phospholipid vesicle, biocompatible, biodegradable	Less skin penetration, less stable
Proliposome	Phospholipid vesicle, more stable than liposome	Less penetration, cause aggregation and fusion of vesicles
Niosomes Proniosomes	Non-ionic surfactant vesicles Convert to stable niosome in situ	Less skin penetration easy handling Cannot reach in the deeper layers of the skin
Transfersomes and Protransfersomes	High deforming ability which ensures deeper penetration in skin layers	Very few disadvantages
Colloidosomes	Can withstand high mechanical load	Insufficient locking of drug can lead to coalescence
Cubosomes	Targeted and controlled release of materials in a biodegradable manner	No disadvantage as such is reported

### Transfersomes for the skin

There are two routes through which the transfersomes can penetrate the corneum through the intracellular lipid and differ within the properties of the bilayer<sup>5</sup>. Since transfersomes are overlarge to diffuse through the skin, they have to seek out their own route through the organ. The magnitude of the drive can then be calculated using the subsequent formula: Flow = Area × (Barrier) permeability × (Trans-barrier) force. Hence flow of the lipid across the skin which is chemically driven, decreases drastically when the lipid in solution form is replaced by an equivalent amount of suspension of lipid.

### Features of Transfersome

1. They're ready to accommodate drugs of varying solubility thanks to presence of hydrophilic and hydrophobic moieties in its infrastructure.
2. High deformability of this technique gives better penetration of intact vesicles. They will act as a carrier for low also as high relative molecular mass drugs e.g. analgesic, anaesthetic, corticosteroids, steroid hormone, anticancer, insulin and albumin
3. They will be a carrier for drugs of any relative molecular mass
4. They're biocompatible and biodegradable as they're made up of natural phospholipids almost like liposomes.
5. Entrapment efficiency of transfersomes is extremely high. Almost the maximum amount as 90% when it involves hydrophilic drugs
6. They protect the encapsulated drug from metabolic degradation example: protein and peptides
7. They act as depot, releasing their contents slowly and gradually & are often used for both

systemic also as topical delivery of drug. They're easy to proportion, as procedure is straightforward and avoid unnecessary use or pharmaceutically unacceptable additives.

8. Useful for topical and systemic administration of medicine.

9. They will act as a carrier for low also as high relative molecular mass drugs e.g. analgesic, anesthetic, corticosteroids, steroid hormone, anticancer, insulin, gap junction protein and albumin. They're biocompatible and biodegradable as they're made up of natural phospholipids almost like liposomes. They need high entrapment efficiency, just in case of lipophilic drug on the brink of 90%.

10. No use of any pharmaceutically unacceptable additives

### Drawbacks of Transfersome

1. Susceptible to oxidative degradation which may render them unstable
2. Purity of natural phospholipids is another criteria militating against adoption of transfersomes as drug delivery vehicles
3. Manufacturing and processing is expensive<sup>8,9</sup>

### Composition of Transfersome

Two main aggregates structure the transfersome:

- Amphipathic molecule (e.g.: phosphatidyl choline) which is liable for self-assembly
- Bilayer softening agent (e.g.: Surfactant) which is liable for flexibility of the transfersome.

The main components of transfersome are phospholipids like soya phosphatidyl choline (Vesicle forming agent), surfactants like sodium cholate or spans and tweens and solvents like ethanol, methanol etc.<sup>10,11,12,13</sup>

**Table 2: Materials commonly used for the preparation of transfersomes are summarized:**

Ingredient	Examples	Functions
Phospholipid	Soya Phosphatidylcholine Egg Phosphatidylcholine Disteryl Phosphatidylcholine	Vesicle forming Component
Surfactant	Sodium Cholate Sodium deoxy Cholate Tween 80 Span 80	For Providing Flexibility

Alcohol	Ethanol Methanol	As a Solvent
Dye	Rhodamine-123 Rhodamine-DHPE Fluorescein-DHPE Nil red 6 Corboxy fluorescence	For Confocal Scanning Laser Microscopy (CSLM) Study
Buffering Agent	Saline phosphate buffer (PH 6.5) 7% v/v ethanol Tris buffer ( PH 6.5)	As a hydrating medium

### Method of Preparation<sup>11-12</sup>

There are broadly two reported procedures for the transfersomes preparation

Thin Film Hydration Technique: This method has three steps:

1. The first step involves dissolution of phospholipids along with surfactants in an organic solvent (Chloroform-methanol) to get thin film of vesicles. The mixture is then subjected to heat above the transition temperature of the lipid, during a rotary evaporator to free the mixture of the organic solvents. Any remaining traces of the solvent are removed by placing over night in vacuum.

2. The formed film is then subjected to hydration with an appropriate buffer at 60 rpm for 1 h. The vesicles formed are left for two h to swell at temperature .

3. The tiny vesicles are then prepared by subjecting the prepared vesicles to sonication at temperature or at 50°C for 30 min employing a bath sonicator. In a probe sonicator, the vesicles are sonicated at 40 °C for 30 min. The desired vesicles are obtained by homogenizing the sonicated vesicles by manual extrusion 10 times through a sandwich layer of 200 and 100nm polycarbonate membranes yields<sup>14,15,2</sup>.

**Modified hand shaking, lipid film hydration technique is also founded for the preparation of transfersomes which comprised following steps-**

1. Drug, lecithin (PC) and edge activator were dissolved in ethanol: chloroform (1:1) mixture. Organic solvent was removed by evaporation while hand shaking above lipid transition temperature (43°C). A thin lipid film was formed inside the flask wall with rotation. The thin film

was kept overnight for complete evaporation of solvent.

2. The film was then hydrated with phosphate buffer (pH 7.4) with gentle shaking for 15 minute at corresponding temperature. The transfersome suspension further hydrated up to 1 hour at 2-8°C

### Evaluation of Transfersomes<sup>16-17</sup>

**1. Vesicle Size, Size Distribution and Vesicle Diameter:** Transmission electron microscopic studies are used to study the vesicular shape. The size of the vesicle and size distribution is generally determined using light scattering technique. The diameter of the vesicle is decided by photon correlation spectroscopy or dynamic light scattering DLS method. The samples are prepared using water , and diluted with filtered saline after passing through a membrane filter of 0.2 µm<sup>11</sup>

**2. Vesicle Shape and Type:** The visualization is administered using TEM. Also, they will be visualized by phase contrast microscopy without sonication using optical microscopy method. Dynamic light scattering technique can also be used.

**3. No. of vesicles per cubic mm**

This is a crucial parameter for optimizing the composition and other process variables. Non sonicated Transfersome formulations are diluted five times with 0.9% common salt solution. Haemocytometer and optical microscope can then be used for further study. The Transfersomes in 80 small squares are counted and calculated using the subsequent formula:

Total number of Transfersomes per cubic mm =

(Total number of Transfersomes counted  $\times$  dilution factor  $\times$  4000) / Total number of squares counted.

4. **Entrapment Efficiency:** It is expressed because the amount of the drug entrapped in percent of that what's added. It is determined by separating the untrapped drug by mini column centrifugation followed by disruption of the vesicles using 0.1% Triton X-100 or 50% n-propanol. The entrapment efficiency is expressed as:

Entrapment efficiency = (amount entrapped/ total amount added)\*100<sup>24</sup>

5. **Drug content**

The drug content are often determined using one among the instrumental analytical methods like modified high performance liquid chromatography method (HPLC) method employing a UV detector, column oven, auto sample, pump and computerized analysis program depending upon the analytical method of the pharmacopoeial drug.

6. **Confocal Scanning Laser Microscopy Study:** Conventional methods of sunshine microscopy and microscopy have problems when it involves fixing, sectioning and marking the sample. There is an incompatibility generally observed between the sample and therefore the processing techniques. The misinterpretations that arise from such studies are often corrected by using Confocal Scanning Laser Microscopy (CSLM). This technique involves the utilization of lipophilic fluorescence markers and therefore the light emitted by these markers is then used for:

- Understanding the mechanism by which the transfersomes penetrate the skin
- Determining the arrangement of the skin and therefore the organization of the skin penetration pathway
- Understanding the similarities and dissimilarities within the mode of penetration of transfersomes with other vesicles like liposome, noisome, micelles etc.

**The fluorescence markers that are generally used are:**

- Fluorescein- DHPE (1, 2- dihexadecanoyl- sn-glycero- 3- phosphoethanolamine- N- (5fluore-sdenthiocarbamoyl), triethyl- ammonium salt)

- Rhodamine- DHPE (1, 2- dihexadecanoyl- sn-glycero- 3ogisogietgabikanube Lissamine Tmr hodamine-B- sulfonyl), triethanol- amine salt)

- NBD- PE (1, 2- dihexadecanoyl- sn-glycero- 3-phosphoethanolamine- N- (7-nitro- Benz- 2- xa- 1,3- diazol- 4- yl) triethanolamine salt)

- Nile red<sup>25</sup>.

**7.Turbidity measurement:**

Turbidity of drug in solution are often measured using nephelometer.

**8. Surface Charge and Charge Density:** A zeta sizer is employed to work out the surface charge and charge density.

**9.Penetration Ability:** This is often generally evaluated using microscopy<sup>15</sup>.

**10. Degree of deformability or permeability measurement:**

In the case of transfersomes, the permeability study is one of the important and unique parameter for characterization. The deformability study is completed against the pure water as standard. Transfersomes preparation is skilled an outsized number of pores of known size (through a sandwich of various micro porous filters, with pore diameter between 50 nm and 400 nm, counting on the starting transfersomes suspension). Particle size and size distributions are noted after each travel by dynamic light scattering (DLS) measurements.

**11. Occlusion effect:**

Occlusion of skin is taken into account to be helpful for permeation of drug just in case of traditional topical preparations. But the same proves to be detrimental for elastic vesicles. Hydrotaxis (movement within the direction) of water is that the main drive for permeation of vesicles through the skin, from its relatively dry surface to water rich deeper regions. Occlusion affects hydration forces because it prevents evaporation of water from skin.

**12.In-vitro Drug Release:** Determined by calculating the permeation rate. The formulation is incubated at 32 °C. The free drug from the samples which are drawn at regular intervals is obtained by mini column centrifugation. The calculation for amount of drug released is completed indirectly from the quantity of drug that was entrapped at zero time as 100%<sup>2</sup>

### 13. In-vitro Skin permeation Studies

Modified Franz diffusion cell with a receiver compartment volume of 50ml and effective diffusion area of 2.50 cm<sup>2</sup> was used for this study. In vitro drug study was performed by using goat skin in phosphate solution (pH 7.4). Fresh Abdominal skin of goat were collected from slaughter house and utilized in the permeation experiments. Abdominal skin hairs were removed and therefore the skin was hydrated in normal saline. The fat layer of the skin was removed by rubbing with a cotton swab. Skin was kept in isopropanol solution and stored at 0-40°C.

To perform skin permeation study, treated skin was mounted horizontally on the receptor compartment with the corneum side facing upwards towards the donor compartment of Franz diffusion cell. The effective permeation area of donor compartment exposed to receptor compartment was 2.50cm<sup>2</sup> and capacity of receptor compartment was 50ml. The receptor compartment was crammed with 50ml of phosphate buffer (pH 7.4) saline maintained at 37 ± 0.5°C and stirred by a magnetic bar at 100RPM. Formulation (equivalent to 10mg drug) was placed on the skin and therefore the top of the diffusion cell was covered.

**Skin Deposition Studies of Optimized Formulation:** After the top of permeation study (at the top of 24 h), the goat skin surface is washed five times with an answer containing ethanol: PBS (pH 7.4) within the ratio 1:1 and therefore the excess drug present on the surface should be removed by giving washings with water.

The skin is subjected to homo-genisation after it's dig small pieces with an equivalent ethanol and pH 7.4 solution and is then left at room temperature for six hour. After shaking it for five min then centrifuging it for 5 min at 5000 rpm, the drug content is analysed using appropriate dilutions with phosphate solution (pH 7.4). The result's compared, employing a student's t test, thereupon of the control<sup>2</sup>.

#### Physical stability

The initial percentage of the drug entrapped in the formulation was determined and were stored in sealed glass ampoules. The ampoules were placed at 4 ± 20°C for month. Samples from each ampoule were analyzed after 30 days to work out

drug leakage. Percent drug lose was calculated by keeping the initial entrapment of drug as 100%.

#### Applications of Transfersome:

1. Transfersomes have the potential for the controlled release of the administered drug and increasing the steadiness of labile drugs thanks to the incorporation of phospholipids.

2. Large molecules weight compounds are often easily transported across the skin with the assistance of transfersomes. for instance, insulin, interferon like leukocytic derived interferon (INF) are often delivered through mammalian skin. They need been widely used as a carrier for the transport of other proteins and peptides. As protein sand peptides are large biogenic molecules difficult to move into the body and degraded within the alimentary canal and transdermal suffers thanks to their large size.

3. Since transfersomes obtain similar bioavailability to injection. Human albumin was found to be effective in producing the immune reaction when delivered by transdermal route encapsulated in Transfersomes.

4. Peripheral drug targeting: The power of transfersomes to focus on peripheral subcutaneous tissues is thanks to minimum carrier associated drug clearance through blood vessels within the subcutaneous tissue.

5. Transdermal immunization: Transcutaneous hepatitis-B vaccines have given good results. A 12 times higher AUC was obtained for zidovudine as compared to normal control administration. Selectivity in deposition in RES (which is that the usual site for residence of HIV) was also increased.

6. NSAIDS are associated with number of GI side effects. These are often overcome by transdermal delivery using ultra deformable vesicles

7. Transfersomes are widely used as a carrier for the transport of proteins and peptides. Proteins and peptide are large biogenic molecules which are very difficult to maneuver into the body, when given orally they're completely degraded within the alimentary tract. These are the reasons why these peptides and proteins still got to be introduced into the body through injections. Various approaches are developed to reinforce these situations. The bioavailability obtained from

transfersomes is somewhat almost like that resulting from injection of an equivalent protein suspension.

**8.** The transfersomal preparations of this protein also induced strong immune reaction after the repeated percutaneous application, for instance the adjuvant immunogenic bovine albumin in transfersomes, after several dermal challenges is as active immunologically as is that the corresponding injected proteo-transfersomes preparations.

**9.** Delivery of insulin by transfersomes is that the successful means of non invasive therapeutic use of such large relative molecular mass drugs on the skin. Insulin is usually administered by subcutaneous route that's inconvenient. Encapsulation of insulin into transfersomes (transfersulin) overcomes these entire problems. After transfersulin application on the intact skin, the first sign of system is hypoglycemia are observed after 90 to 180 min, depending on the specific carrier composition.

**10.** Transfersomes have also been used as a carrier for interferons, for example INF- $\alpha$  is a naturally occurring protein having antiviral, anti proliferive and some immunomodulatory effects. Transfersomes as drug delivery systems have the potential for providing controlled release of the administered drug and increasing the steadiness of labile drugs.

**11.** Another most vital application of transfersomes is transdermal immunization using transfersomes loaded with soluble protein like integral membrane protein, human albumin and gap junction protein. These approach offers at least two advantages, first they are applicable without injection and second, they give rise to rather high titer and possibly, to relatively high IgA levels. Transfersomes have also used for the delivery of corticosteroids. Transfersomes improves the location specificity and overall drug safety of corticosteroid delivery into skin by optimizing the epicutaneously administered drug dose.

### Conclusion

Ultra-deformable vesicles like transfersomes are capable of providing a perfect solution to all or any transdermal delivery and transport related problems. They are especially useful for delivery of troublesome molecules like peptides and

proteins. The exceptional quality of transfersomes to deform themselves counting on the environmental stress thanks to the presence of surfactants, often mentioned as "edge activators" makes them very flexible for delivery of an honest range of molecules also having a good scope for targeted delivery. Transfersomes, thus, hold a bright and promising future in transdermal drug delivery of medicine.

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