TRANSFEROSOME: AN OPPORTUNISTIC CARRIER FOR TRANSDERMAL DRUG DELIVERY SYSTEM

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ABSTRACT
Transdermal route of drug delivery system has received a great attention in pharmaceutical research and it has already proved its superiority in various respects than oral route, which has a number of problems in drug delivery system. However, the permeation of hydrophilic ionizable species of drug always has been denied by the intrinsic barrier or stratum corneum for providing local or systemic actions. Transferosomes are ultra deformable vesicles, elastic in nature, which can squeeze itself through a pore and it is more advantageous than the conventional liposome due to its high elasticity, which offers its penetration through narrow constrictions without measurable loss. The high permeability of transferosome across the skin also depends on its deformability and intermediate attachment sites for membrane fusion due presence of ripples in vesicles surface. Its infrastructure possesses both hydrophilic and hydrophobic moieties together and it can entrap both type of drug. They can act as a carrier for low as well as high molecular weight drugs e.g., analgesics, anesthetics, corticosteroids, sex hormones, anticancer drugs, insulin, gap junction proteins, albumin, etc.

KEY WORDS: Transferosome; Ultraformable; Vesicles; Transdermal; Drug delivery

INTRODUCTION
During last few decades, transdermal route has been tremendously focused in drug delivery than other routes as it reveals it superiority as convenient and safe route for drug administration. The transdermal route offers several potential advantages over conventional routes like avoidance of first pass metabolism, predictable and extended duration of activity, minimizing side effects, improving physiological and pharmacological responses, avoiding plasma-drug level fluctuations, inter- and intra-patient variations2-5. But, the application of transdermal drug delivery for a wider range of drugs is limited due to the significant barrier to penetration across the skin, which is related primarily with outermost stratum corneum layer of epidermis1-2. To overcome the problem associated with the stratum corneum barrier, various approaches can be adopted. Among various approaches investigated to overcome the skin barrier associated penetration, vesicular systems are gaining importance recently owing to their ability to act as a means of sustained release of drug molecules. Recently, the vesicular drug-carrier system, transferosome have been reported to enhance the transdermal delivery of drugs, when applied onto the skin non-occlusively6-8. Transferosomes are artificial vesicles, being several orders of magnitude more deformable than standard liposomes7-8. The deformability of liposomes for improved skin permeation of drug molecules can be achieved by using surfactants in appropriate ratio7. Transferosomes have ability to overcome the permeation difficulty by squeezing themselves along the inter-cellular sealing lipid of the stratum corneum10. The resulting flexibility of transferosomes membranes minimize the risk of complete vesicle rupture in the skin and allows transferosomes to follow the natural water gradient across the epidermis, after application on the skin.

The term “Transferosome” and the underlying concept were introduced in 1991 by Gregor Cevc. Transferosome is a term registered as a trademark by the German company IDEA AG, and used by it to refer to its proprietary drug delivery technology. The name means “carrying body”, and is derived from the Latin word ‘transferre’, meaning ‘to carry across’, and the Greek word ‘soma’, for a ‘body’. A Transferosomal carrier is an artificial vesicle and resembles the natural cell vesicle. Thus, it is suitable for targeted and controlled drug delivery. In functional terms, it may be described as lipid droplet of such deformability that permits its easy penetration through the pores much smaller than the droplets size. It is a highly adaptable and stress-responsive, complex aggregate. The current review deals with the trends and different aspects of transferosomes as a carrier system for transdermal drug delivery.

Figure 1 Schematic diagram describing interaction of the transferosome with skin tissue

Silent Features Of Transferosomes11-13
1. Transferosomes hold an infrastructure consisting of hydrophobic and hydrophilic moieties together and as a result can accommodate drug molecules with wide range of solubility.
2. Transferosomes can deform and pass through narrow constriction (from 5 - 10 times less than their own diameter) without measurable loss.
3. The high deformability of transferosomes give a better penetration of intact vesicles.
4. Transferosomes can act as a carrier for low as well as high molecular weight drugs, e.g., analgesics, anesthetics, corticosteroids, sex hormones, antineoplastics, and proteins.

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5. Transferosomes are biocompatible and biodegradable, as they are made from natural phospholipids similar to liposomes.
6. Transferosomes have capacity of high entrapment efficiency for wide range of biomolecules. In case of lipophilic drugs, this is near to 90%.
7. Transferosomes can protect the encapsulated drug from metabolic degradation.
8. Transferosomes act as depot, releasing their contents slowly and gradually.
9. Transferosomes can be used for both systemic as well as topical delivery of drug.
10. Easy to scale up, as procedure is simple, do not involve lengthy procedure and unnecessary use of pharmaceutically unacceptable additives.

**Mechanism Of Penetration Through Transferosomes**

The passage of transferosomes across the skin is a function of vesicle’s membrane flexibility, hydrophilicity and ability of the vesicle for retaining integrity. When transferosome vesicles in suspension form are applied on the skin surface, water is evaporated from the skin surface and the vesicles began to dry out due to strong polarity of transferosomes ingredient vesicles get attracted towards the area of higher water content in the narrow gaps between adjoining cells in the skin. This process along with the vesicles membrane deformability enables transferosomes aggregates to open the tiny pores temporarily through which water normally gets evaporated between the cells. Such newly activated intercellular channels can accommodate sufficiently deformable vesicles, maintaining their integrity and changing their shape to fit the channel reach region of high water content in the deeper skin layers in which the vesicles get distributed between the cells12.

The magnitude of the transport driving force, of course, also plays an important role.

**Flow = Area X (Barrier) Permeability X (Trans-barrier) force; Therefore;**

The chemically driven lipid flow across the skin always decreases dramatically when lipid solution is replaced by the some amount of lipids in a suspension12.

**Composition Of Transferosomes**

Transferosomes primarily consists of phospholipids and surfactant, where phospholipids self assembles into a lipid bilayer in aqueous environment and closes to form a vesicle. Surfactants soften the lipid bilayer structure and increase the flexibility and permeability of lipid bilayer. This second component is called as edge activator like sodium deoxycholate, which consists usually of single chain surfactant that causes destabilization of the lipid bilayer thereby increasing its fluidity and elasticity15-17. The newer elastic vesicles were introduced by Van den berg in 1998, consisting of non-ionic surfactant as the edge activator18. The flexibility and permeability of transferosome membrane depends on the ratio of surfactant and edge activator used, which make transferosome ultra deformable. Hence, flexibility also minimizes the risk of complete vesicle rupture in the skin and allows transferosome to penetrate through the skin. A list of different excipients used for the preparation of transferosomes is given in Table 1.

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<tr>
<th>Table 1: Different materials used in preparation of transferosomes</th>
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<td><strong>Type of material</strong></td>
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<td>Phospholipids</td>
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**Method Of Preparation**

Phospholipids, surfactants and the drug are dissolved in alcohol. The organic solvent is then removed by rotary evaporation under reduced pressure at 40°C. Final traces of solvent are removed under vacuum. The deposited lipid film is hydrated with the appropriate buffer by rotation at 60 rpm for 1 hour at room temperature. The resulting vesicles are swollen for 2 hours at room temperature. The multilamellar lipid vesicles (MLV) are then sonicated at first a thin film of phospholipids and surfactants is Prepared after dissolving it into the alcohol and removing of the organic solvent by rotary evaporation under reduced pressure at 40°C. Then the final traces of solvent are removed under vacuum. The thin lipid film is hydrated with the appropriate buffer by rotation at 60 rpm for 1 hour at room temperature. The resulting vesicles are swollen for 2 hours at room temperature. Either the multilamellar lipid vesicles (MLV) are then sonicated or extrusion, low shear mixing (for formation of unilamellar vesicles) or high shear mixing (for formation of multilamellar vesicles,) at room temperature22.

**Characterization Of Transferosomes**

The different characteristics of transferosome vesicles like size, shape, diameter, surface texture, elasticity, penetrability, drug entrapment efficiency, in vitro drug release, drug content etc are determined for this purpose.

**Vesicle diameter:** 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 done by using photon correlation spectroscopy or dynamic light scattering (DLS) measurements.

**Vesicle shape and type:** Transferosomes vesicles can be visualized by TEM, phase contrast microscopy, etc. The stability of 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.
Confocal scanning laser microscopy (CSLM) study: This study is generally used to distinguish between the transferosome and liposomes or niosomes, and it reveals the mechanism of transferosome penetration. In this technique lipophilic fluorescence markers are incorporated into the transferosomes and the light emitted by these markers used for following purpose.

Different fluorescence markers used in CSLM study are fluorescein-DHPE [1, 2-dihexadecanoyl-sn-glycero-3-phosphoethanolamine-N-(5-fluoro dithiocarbamoyl), triethylammonium salt], rhodamine-DHPE [1, 2-dihexadecanoyl-sn-glycero-3-ogisotetradecanube-N-lissamine tmrhodamine B sulfonyl], triethanolamine salt], NBD-PE [1, 2-dihexadecanoyl-sn-glycero-3-phosphoethanolamine-N-(7-nitro- benz-2- oxa-1, 3-diazol-4-yl) triethanolamine salt], and Nile red [1, 3].

Degree of deformability or permeability measurement: Permeability or deformability is one of the most important characteristic of transfersomes vesicles and this parameter enables to differ from others. The transferosome preparation is passed through many filters between pore sizes 50 to 400 nm. Vesicles retained on each filter are studied for particle size and distribution using dynamic light scattering technique. The degree of deformability can be determined using the following formula,

\[ D = J^\ast(rv/rp), \]

where, J is the amount of the suspension extruded during 5 min, rv is the size of the vesicle and rp is pore size of the barrier [1, 3].

Drug entrapment efficiency: The drug entrapment efficiency can be determined by centrifugation method. The unentrapped drug is first separated out during centrifugation and then the vesicles can be disrupted using 0.1% Triton X-100 or 50% n-propanol [24]. The entrapment efficiency is expressed as:

\[ \frac{\text{Amount entrapped}}{\text{Total amount added}} \times 100 \]

Drug content: The drug content in transferosome can be determined using a modified high performance liquid chromatography method (HPLC) method using a UV detector, column oven, auto sample, pump, and computerized analysis program. This can be easily estimated using UV-VIS spectrophotometric analysis at maximum wavelength.

In vitro drug release: Transfersomes suspension is first incubated at 32°C using cellophane paper or various biological membranes as permeation membrane. The samples are withdrawn at different time intervals and free drug are separated by mini-column centrifugation. Detection is done by various analytical techniques using UV-VIS spectrophotometer, HPLC, and HPTLC. The amount of separated free drug is calculated. From this, the drug release is calculated [11].

Number of vesicle per cubic mm: This determination can be done by using haemocytometer and optical microscope. The transferosome formulations are first diluted in 0.9% w/w sodium chloride solution and then calculated using the following formula [11]:

\[ \text{Total number of transfersomes per cubic mm} = \frac{\text{Total number of transfersomes counted \times X dilution factor}}{X 4000}. \]

Penetration ability: Fluorescence microscopy is used to evaluate penetration ability of transfersomes.

Turbidity measurement: Turbidity of drug in aqueous solution can be measured using nephelometer.

Surface charge and charge density: Surface charge and charge density of transfersomes can be determined using Zetasizer.

Occlusion effect: Occlusion of skin is always considered helpful for drug permeation in case of traditional topical preparations. However, the same proves to be detrimental for elastic vesicles. Hydrotaxis (movement in the direction) of water is the major driving force for permeation of vesicles through the skin, from its relatively dry surface to water rich deeper regions [24].

Application of Transfersomes

For delivery of proteins and peptides: Transfersomes is nothing but a modified form of liposome and it has discovered to overcome the drawbacks of conventional liposomes. It provides controlled release of drug administration and increasing the stability of labile drug. In case peptides like insulin and interferon, is very difficult to diffuse into the skin due to their large molecular weights, but it can be transported across the skin with the help of transfersomes. Transdermal transferosomal delivery of insulin is the useful delivery for non-invasive therapeutic systems. It is already found that the insulin entrapped transferosome has showed 50% response as compared to subcutaneous injection [11, 25]. Transfersomes have also been used as a carrier for interferons like leukocyte derived interferon-α (IFN-α). The oral delivery of proteins and peptides is quite impossible as they are very sensitive in nature and cannot tolerate the harsh environment of gastrointestinal tract (GIT). Again, transdermal diffusion of these molecules is very low. However, transfersomal formulations through transdermal delivery have received a great attention for protein and peptide drug delivery.

Transdermal immunization: Transfersomes also take part in transdermal immunization like Tetaox toxoid-loaded transfersomes for topical immunization [26], and transcutaneous hepatitis-B vaccine [27].

Drug delivery for non-steroidal anti-inflammatory drugs (NSAIDs): Transdermal delivery of NSAID’s has been developed due to a number of side effects of NSAIDS in gastrointestinal tract. Studies have been carried out on diclofenac [26] and ketoprofen [27] for delivery through transfersomes. Ketoprofen in a transfersomal formulation have gained marketing approval by the Swiss regulatory agency (SwissMedic) in 2007; the product is expected to be marketed under the trademark Diractin.

Targeting peripheral tissue: The blood vessels of subcutaneous tissue possess tight junctions between endothelial cells thus do not allow the transferosome vesicles to enter directly into the blood stream and this way drugs are concentrated in peripheral tissue.

Others: Transfersomal formulations already have been developed for anti-HIV agent like zidovudine and a 12 times higher AUC was obtained for zidovudine as compared to normal control administration [25]. Transdermal permeation of indinavir was enhanced when it administered via transfersome [25]. The application of ethinylestradiol delivery through ultra deformable vesicle showed better anti-ovulatory effects in comparisons to plain drug for oral administration and liposomes for topical administration [24]. Transfersome based formulations of local anesthetics-lidocaine and tetracaine showed permeation equivalent to subcutaneous injections [26]. A new approach for treatment of skin cancer of topical delivery has been done on anticancer drug like methotrexate through transfersome formulations.
and it showed significant results\textsuperscript{11}. Some useful work has been on various drugs like ketotifen\textsuperscript{23}, estradiol\textsuperscript{12}, low molecular weight heparin\textsuperscript{33}, retinol\textsuperscript{34}, melatonin\textsuperscript{35}, curcumin\textsuperscript{36} etc.

**Limitations Of Transfersomes**

1. Transfersomes are chemically unstable because of their predisposition to oxidative degradation.
2. Purity of natural phospholipids is another criteria mitigating against adoption of transfersomes as drug delivery vehicles.
3. Transfersomes formulations are expensive.

**CONCLUSION**

Transfersomes are ultra deformable, flexible, elastic and inexpensive vesicles and they enable to pass the entrapped drug molecule through the intact skin due to its high deformability, which makes it differ to conventional liposome. Transfersomes can pass through even tiny pores (100 mm) nearly as efficiently as water, which is 1500 times smaller. It has been found that systemic drug availability reaches higher or at least 90-90 %, when given via transfersome. The biodistribution of radioactively labeled phospholipids applied in the form of transfersomes after 24 hours is essentially the same after an epicutaneous application or subcutaneous injection of the preparations. More over, transfersome can be a good alternative in contrast to oral and invasive drug delivery.

**REFERENCES**


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