Review Article
Transfersomes: Ultradeformable vesicles for Transdermal Drug Delivery
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ABSTRACTS
Objective: The present review is an attempt to summarized report relative to drug delivery through topical or transdermal system. Material and Method: Various research articles, review articles and short communication are collected and compiled. Results: Transdermal drugs delivery system is generally limited by the barrier function of the skin (stratum corneum). Vesicular systems are one of the means of transdermal applications of drug carriers such as liposome, niosomes, transfersomes etc. The interest in designing of topical delivery systems regained importance after the discovery of elastic vesicles known as transfersomes. Transfersomes are a form of elastic or deformable vesicle, which were first introduced in the early 1990 by Gregor Cevc. A Transfersome is a highly adaptable and stress-responsive, complex aggregate that are ultradeformable in nature and have the tendency of squeezing itself through the pores of the skin which is many times smaller than its size due to its elasticity and flexibility. They are usually made up of phospholipids component along with a surfactant mixture (edge activator). Conclusion: The uniqueness of this type of drug carrier system lies in the fact that it can accommodate hydrophilic, lipophilic as well as amphiphilic drugs. Peripheral drug targeting, transdermal immunization can also be achieved with this type of drug delivery system. Transfersome carriers can create a drug depot in the systemic circulation that is having a high concentration of drug.
Keywords: Transfersomes, Transdermal, liposomes, Ultradeformable vesicles

Introduction
Skin is considered as the largest organ of the body making up 16% of the body weight and consists of three functional layers: epidermis, dermis, and subcutis. It has many different functions. One major task of the skin is to protect the organism from water loss and mechanical, chemical, microbial and physical influences. The protective properties are provided by the outermost layer of the skin. Transdermal drug delivery system can be used as an alternative delivery of drug into the systemic circulation. Transdermal drug delivery offers many advantages as compared to traditional drug delivery better alternative to achieve constant plasma levels for prolonged periods of time, which additionally could be advantageous because of less frequent dosing regimens.

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Advantages claimed are increased patient acceptability, avoidance of first pass metabolism, predictable and extended duration of activity, minimizing side effects and utility of short half-life drugs, improving physiological and pharmacological response, avoiding the fluctuation in drug levels. The barrier function govern by stratum corneum is main problem for delivery of drugs across the skin. The stratum corneum consists of corneocytes surrounded by lipid layers, which play an essential role in the barrier properties of the stratum corneum (Tortara and Grabowski, 2000). Recently, various strategies have been used to augment the transdermal delivery of bioactives. Mainly, they include electrophoresis, iontophoresis, chemical permeation enhancers, microneedles, sonophoresis, and vesicular system like liposomes, niosomes, elastic liposomes such as ethosomes and transfersomes. Among these strategies transfersomes appear promising (Gupta et al., 2012). A novel vesicular drug carrier system called transfersomes, which is composed of phospholipid, surfactant, and water for enhanced transdermal delivery. Transfersomes are a form of elastic or deformable vesicle, which were first introduced in the early 1990s. Transfersomes are advantageous as phospholipids vesicles for transdermal drug delivery. Because of their self-optimized and ultra-flexible membrane properties, they are able to deliver the drug reproducibly either into or through the skin, depending on the choice of administration or application, with high efficiency (Irfan et al., 2012). The vesicles of transfersomes are more elastic than the standard liposomes and thus well suited for the skin penetration. Transfersomes overcome the skin penetration difficulty by squeezing themselves along the intracellular sealing lipid of the stratum corneum. Drug Delivery via the transdermal route is an interesting option in this respect because a transdermal route is convenient and safe (Loyd et al., 2005). They offers several advantages over conventional drug delivery system like avoidance of first pass metabolism, predictable and extended duration of action, minimizing undesirable side effects, utility of short half-life drugs, improving physiological and pharmacological response, avoiding the fluctuation in drug levels, inter-and intra-patient variations, and most importantly, it provides patients convenience (Nandha et al., 2005).

**Advantages of Transfersomes as Drug Carrier**

- It consisting of hydrophobic and hydrophilic moieties together and as a result can accommodate drug molecules with wide range of solubility.
- Transfersomes are having elastic property and can pass through intracellular spaces by deforming itself.
- Deformability of transfersome gives better penetration of intact vesicles.
- They can act as a carrier for low as well as high molecular weight drugs e.g. analgesic, anesthetic, corticosteroids, sex hormone, anticancer, insulin, gap junction protein, and albumin.
- They are biocompatible and biodegradable as they are made from natural phospholipids similar to liposomes.
They have high entrapment efficiency, in case of lipophilic drug near to 90%.

They protect the encapsulated drug from metabolic degradation.

They act as depot, releasing their contents slowly.

They can be used for both systemic as well as topical delivery of drug.

Easy to scale up, as procedure is simple, do not involve lengthy procedure and unnecessary use of pharmaceutically unacceptable additives.

Limitations of Transferosomes

- Transfersomes are chemically unstable because these are prone to oxidative degradation.
- Purity of natural phospholipids is another criteria and influence against adoption of transfersomes as drug delivery vehicles.
- Transfersomes formulations are expensive.

Factors affects Transdermal Drug Delivery

The effective transdermal drug delivery can be formulated by considering three factors like as drug, skin and the vehicles. Mainly two factor involved; Biological factors and physiochemical factors (Prajapati et al., 2011).

(a) Biological factors:

(i) Skin condition: Acids and alkalis, many solvents like chloroform, methanol damage the skin cells and promotes penetration. Diseased state of patient also alters the skin conditions.

(ii) Age of Skin: The young stage skin is more permeable than older stage of skin. Children’s are more sensitive for skin absorption of toxins. Thus, skin age is one of the factor affecting penetration of drug in TDDS

(iii) Blood Flow: Changes in peripheral blood flow can affect the transdermal absorption of drug.

(iv) Site of skin: Thickness of skin, nature of stratum corneum and density of appendages vary site to site. These factors affect significantly penetration.

(v) Skin metabolism: Skin metabolizes steroids, hormones, chemical carcinogens and some drugs. So skin metabolism determines efficacy of drug permeated through the skin.

(vi) Species differences: The skin thickness, density of appendages and keratinization of skin vary species to species, so affects the penetration.

(b) Physiochemical factors:

(i) Hydration of Skin: In contact with water the permeability of skin increases significantly. Hydration is most important factor increasing the permeation of skin. Hence, humectant are generally used in transdermal delivery.

(ii) Temperature and pH: The permeation of drug is increase with temperature variation. The diffusion coefficient decreases as temperature decreases. Weak acids and weak bases dissociate depending on the pH and pKa or pKb values. The proportion of unionized drug determines the drug concentration in skin.

(iii) Partition coefficient: For molecules with intermediate partition coefficient (log K 1 to 3) and for highly lipophilic molecules (log K > 3), the intercellular route will be almost the pathway used to traverse the stratum corneum. However, for these molecules a further consideration is the ability to partition out of the stratum corneum into the aqueous viable epidermal tissues. For more
hydrophilic molecules \((\log K < 1)\), the transcellular route probably predominates. 

**(iv) The concentration of Drug:** The flux is proportional to the concentration gradient across the barrier and concentration gradient will be higher if the concentration of drug will be more across the barrier.

**(v) Molecular size and shape:** Drug absorption is inversely proportional to molecular size, small molecules penetrate faster than large ones. A second major factor in calculating the flux of a material through human skin is the size of the molecule. However, for simplicity, the molecular weight is generally taken as an approximation of molecular size. It has been suggested that an inverse relationship existed between transdermal flux and molecular weight of the molecule. However, most conventional therapeutic agents that are selected as candidates for transdermal delivery tend to lie within narrow range of molecular weight (100-500 Dalton).

**Composition of Transfersomes**

Transfersomes is a novel elastic or ultradeformable vesicular drug carrier system composed of phospholipid, surfactant and water for the enhancement of transdermal delivery. It crosses skin barrier by squeezing themselves along the intracellular space of the stratum corneum. Because of their self-optimised and ultraflexible membrane properties they are able to deliver a low and high molecular weight drugs either into or through the skin depending on the choice of application. Transfersomes is a self-adaptable and optimized mixed lipid aggregate and composed of phospholipids like phosphatidyl choline which self assembles into lipid bilayer in aqueous environment and closes to form a vesicle. Phosphatidylcholine of both human and vegetable origin shows a fatty acid composition, which is dominated by unsaturated fatty acids. The fatty acid contents of soy phosphatidylcholine, which is readily available and mostly used in various formulations, is characterized by a proportion of linoleic acid up to 70% of the total fatty acids. Consequently, soy phosphatidylcholine has a very low phase-transition temperature of less than zero°C in water-containing systems. This may be the reason behind its ability to fluidize the lipid bilayers of the horny layer, which can be determined by measuring the increase of the transepidermal water loss (TEWL) after application for a short while. The slight increase of TEWL coincides with the penetration of phosphatidylcholine and active agents, which are co-formulated with phosphatidylcholine. Also a lipid bilayer softening component (such as a biocompatible surfactant or an amphiphilic drug) is added to increase lipid bilayer flexibility and permeability. This second component is called as edge activator. An edge activator consists usually of single chain surfactant of non ionic nature that causes destabilization of the lipid bilayer thereby increasing its fluidity and elasticity. Flexibility of transfersomes membrane can be altered by mixing suitable surface active agents in the proper ratios. The resulting, flexibility and permeability optimized, transfersome vesicle can therefore adapt its shape to surrounding stress easily and rapidly, by adjusting local concentration of each bilayer component to the local stress experienced by the bilayer. The flexibility of this system minimizes the risk of complete vesicle rupture in the skin and allows them to follow the natural
water gradient across the epidermis, when applied under non occlusive condition. Vesicles composed of phospholipids as the main ingredient like soya phosphatidylcholine, egg phosphatidylcholine, dipalmityl phosphatidylcholine etc., 10-25% surfactant for providing flexibility, various solvents such as ethanol, methanol and hydrating medium consisting of saline phosphate buffer (pH 6.5-7). Dye like Rhodamine 123, Nile red is incorporated for Confocal Scanning Laser Microscopy evaluation studies.

Table-1: List of various additive used in preparation of Transfersome

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Additive</th>
<th>Examples</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Phospholipids</td>
<td>Soya phosphatidyl choline, Dipalmitoyl phosphatidyl choline, Distearoyl phoshatidyl choline</td>
<td>Vesicles forming component</td>
</tr>
<tr>
<td>2.</td>
<td>Surfactant</td>
<td>Sodium Cholate, Sodium deoxycholate, tween-80, Span80</td>
<td>provide flexibility</td>
</tr>
<tr>
<td>3.</td>
<td>Alcohol</td>
<td>Ethanol, methanol</td>
<td>As a solvent</td>
</tr>
<tr>
<td>4.</td>
<td>Buffering agent</td>
<td>Saline phosphate buffer (pH 6.4)</td>
<td>As a hydrating medium</td>
</tr>
<tr>
<td>5.</td>
<td>Dye</td>
<td>Rhodamine-123, Rhodamine-DHPE, Fluorescein-DHPE Nile red</td>
<td>For CSLM Study</td>
</tr>
</tbody>
</table>

Comparision of Transfersons V/s Other Carrier System

Transfersomes appear to be remotely related to lipid bilayers vesicle, liposomes. However in functional terms, transfersomes differ vastly from commonly used liposomes in that they are much more flexible and adaptable (Table 2). The extremely high flexibility of their membrane permits transfersomes to squeeze themselves even through pores much smaller than their own diameter. This is due to high flexibility of the transfersomes membrane and is achieved by judiciously combining at least two lipophilic/amphiphilic components (phospholipids plus bio surfactant) with sufficiently different packing characteristics into a single bilayer. The high resulting aggregate deformability permits transfersomes to penetrate the skin spontaneously. This tendency is supported by the high transfersomes surface hydrophilicity that enforces the search for surrounding of high water activity. It is almost certain that the high
penetration potential of the transfersomes is not primarily a consequence of stratum corneum fluidization by the surfactant because micellar suspension contains much more surfactant than transfersomes (PC/Sodium cholate 65/35 w/w %, respectively). Thus, if the penetration enhancement via the solubilisation of the skin lipids was the reason for the superior penetration capability of transfersomes, one would expect an even better penetration performance of the micelles. In contrast to this postulate, the higher surfactant concentration in the mixed micelles does not improve the efficacy of material transport into the skin. On the contrary, mixed micelles stay confined to the topmost part of the stratum corneum even they are applied non occlusively. Transfersomes differ in at least two basic features from the mixed micelles, first a transfersome is normally by one to two orders of magnitude (in size) greater than standard lipid micelles. Secondly and more importantly, each vesicular transfersome contains a water filled core whereas a micelle is just a simple fatty droplet. Transfersomes thus carry water as well as fat-soluble agent in comparison to micelles that can only incorporate lipoidal substances. To differentiate the penetration ability of all these carrier systems proposed the distribution profiles of fluorescently labelled mixed lipid micelles, liposomes and transfersomes as measured by the Confocal Scanning Laser Microscopy (CSLM) in the intact murine skin. In all these vesicles the highly deformable transfersomes transverse the stratum corneum and enter into the viable epidermis in significant quantity.

Table-2: Comparison of different vesicular carrier system used for drug delivery

<table>
<thead>
<tr>
<th>Method</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liposomes</td>
<td>Phospholipid vesicle, biocompatible, biodegradable</td>
<td>Less skin penetration less stable</td>
</tr>
<tr>
<td>Proliposome</td>
<td>Phospholipid vesicle, more stable than liposomes</td>
<td>Less penetration, cause aggregation and fusion of vesicles</td>
</tr>
<tr>
<td>Physical methods e.g. iontophoresis</td>
<td>Increase penetration of intermediate size charged molecule</td>
<td>Only for charged drugs, transfer efficiency is low (less than 10%)</td>
</tr>
<tr>
<td>Niosomes</td>
<td>Non-ionic surfactants vesicles</td>
<td>Less skin penetration easy handling But will not reach up to deeper skin layer</td>
</tr>
<tr>
<td>Proniosomes</td>
<td>Greater stability, Will convert into noisome in situ, stable</td>
<td>Less skin penetration easy handling But will not reach up to deeper skin layer</td>
</tr>
<tr>
<td>Transfersomes and Protransfersomes</td>
<td>More stable, high penetration due to high deformability, biocompatible and biodegradable, suitable for both low and high molecular</td>
<td>None, but for some limitations</td>
</tr>
</tbody>
</table>
weight and also for lipophilic as well as hydrophilic drugs and reach up to deeper skin layers.

**Mechanism of Penetration of Transfersomes:**

Transfersomes when applied under suitable condition can transfer 0.1 mg of lipid per hour and cm² area across the intact skin. This value is substantially higher than that which is typically driven by the transdermal concentration gradients. The reason for this high flux rate is naturally occurring "transdermal osmotic gradients" i.e. another much more prominent gradient is available across the skin. This osmotic gradient is developed due to the skin penetration barrier, prevents water loss through the skin and maintains a water activity difference in the viable part of the epidermis (75% water content) and nearly completely dry stratum corneum, near to the skin surface (15% water content). This gradient is very stable because ambient air is a perfect sink for the water molecule even when the transdermal water loss is unphysiologically high. All polar lipids attract some water this is due to the energetically favorable interaction between the hydrophilic lipid residues and their proximal water. Most lipid bilayers thus spontaneously resist an induced dehydration. Consequently all lipid vesicles made from the polar lipid vesicles move from the rather dry location to the sites with a sufficiently high water concentration. So when lipid suspension (transfersomes) is placed on the skin surface, that is partly dehydrated by the water evaporation loss and then the lipid vesicles feel this "osmotic gradient" and try to escape complete drying by moving along this gradient. They can only achieve this if they are sufficiently deformable to pass through the narrow pores in the skin, because transfersomes composed of surfactant have more suitable rheologic and hydration properties than that responsible for their greater deformability. Less deformable vesicles including standard liposomes are confined to the skin surface, where they dehydrate completely and fuse, so they have less penetration power than transfersomes. Transfersomes are optimized in this respect and thus attain maximum flexibility, so they can take full advantages of the transepidermal osmotic gradient (water concentration gradient). Transfersome vesicle can therefore adapt its shape to ambient easily and rapidly, by adjusting local concentration of each bilayer component to the local stress experienced by the bilayer shown in figure:1
Preparation of Transfersome:

*Thin film hydration technique is employed for the preparation of transfersomes which comprised of three steps:*

1. A thin film is prepared from the mixture of vesicles forming ingredients that is phospholipids and surfactant by dissolving in volatile organic solvent (chloroform or methanol). Organic solvent is then evaporated above the lipid transition temperature (room temp. for pure PC vesicles, or 50°C for dipalmitoyl phosphatidyl choline) using rotary evaporator. Final traces of solvent were removed under vacuum for overnight.

2. A prepared thin film is hydrated with buffer (pH 6.5) by rotation at 60 rpm for 1 hr at the corresponding temperature. The resulting vesicles were swollen for 2 hr at room temperature.

3. To prepare small vesicles, resulting vesicles were sonicated at room temperature or 50°C for 30 min. using a bath sonicator or probe sonicated at 4°C for 30 min. The sonicated vesicles were homogenized by manual extrusion 10 times through a sandwich of 200 and 100 nm polycarbonate membranes.

*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.

2. The thin film was kept overnight for complete evaporation of solvent. 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 2-8 degree celcius.
Table-3 List of drugs delivered using transfersomes as a delivery vehicle

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Inferences</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oestradiol</td>
<td>Improved transdermal flux</td>
</tr>
<tr>
<td>Norgesterol</td>
<td>Improved transdermal flux</td>
</tr>
<tr>
<td>Hydrocortisone</td>
<td>Biologically active at dose several times lower than currently used formulation.</td>
</tr>
<tr>
<td>Human serum albumin</td>
<td>Antibody titer is similar or even slightly higher than subcutaneous injection</td>
</tr>
<tr>
<td>Interferon-α</td>
<td>Controlled release, Overcome stability problem</td>
</tr>
<tr>
<td>Insulin</td>
<td>High encapsulation efficiency. Transfer across the skin with an efficiency of &gt;50%. Provide noninvasive means of therapeutic use.</td>
</tr>
<tr>
<td>Vincristine</td>
<td>Increase entrapment efficiency of and skin permeation</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>Improved transdermal flux</td>
</tr>
<tr>
<td>Triamcinolone acetonide</td>
<td>Used for both local and systemic delivery</td>
</tr>
<tr>
<td>Tetanus toxoid</td>
<td>For transdermal immunization</td>
</tr>
<tr>
<td>Indinavir sulphate</td>
<td>Improved influx for activity against acquired immune deficiency syndrome(AIDS)</td>
</tr>
<tr>
<td>Stavudine</td>
<td>Improved the in vitro skin delivery of stavudine for antiretroviral activity</td>
</tr>
</tbody>
</table>

**Optimization and characterization of Formulation containing Transfersomes**

There are various process variables which could affect the preparation and properties of the transfersomes. The preparation procedure was accordingly optimized and validated. The process variables are depending upon the procedure involved for manufacturing of formulation. The preparation of transfersomes involves various process variables such as,

1. Lecithin: surfactant ratio
2. Effect of various solvents
3. Effect of various surfactants
4. Hydration medium

Optimization was done by selecting entrapment efficiency of drug. During the preparation of a particular system, the other variables were kept constant.

**Characterization:**

The mechanical properties and transport ability of a vesicle can be studied by measuring stress or deformation dependent vesicle bilayer elasticity and permeability changes. For the proper Transfersome vesicles, “Penetrability” increases non-linearly (usually sigmoidally) with the flux driving force (head pressure) (Shen et al., 2007).

**Entrapment efficiency:** Entrapment efficiency can be determined by separating the unentrapped drug. After centrifugation (to separate the unentrapped drug), the vesicle can be ruptured.

**Vesicle diameter:** The size of the vesicle is one of the key issues during the manufacturing process of transfersomes. It gives important information about the
control of the preparation technique and can be utilised for process optimisation. Particle size measurement is performed on routine base for batch to batch comparison and plays an important role in scaling up processes. During storage of colloidal dispersions the control over particle size is an important variable in terms of physical stability. Very small vesicles (smaller than 40 nm) are prone to fusion processes due to the high curvature of their bilayer membrane. For larger, electroneutral transfersomes aggregation through van der Waals forces due to the greater area of membrane contact is described. Particle size influences the ability of transfersomes to incorporate/encapsulate drug compounds. For lipophilic and amphiphilic compounds a high lipid to core ratio, is preferred, while a bigger aqueous core volume, is desired for the encapsulation of hydrophilic compounds Vesicle diameter can be determined using Photon correlation spectroscopy or Dynamic light scattering (DLS) method. For vesicles size measurement, vesicular suspension was mixed with the appropriate medium (7% v/v ethanol) and the measurements were conducted in triplicate.

**Confocal scanning laser microscopy (CSLM) studies:** In this technique lipophilic fluorescence markers are incorporated into the transfersomes and the light emitted by these markers used for following purpose (Schatzlein and Cevc, 1998 & Schatzlein and Cevc, 2005).

- For investigating the mechanism of penetration of transfersomes across the skin.
- For determining histological organization of the skin (epidermal columns, interdigitation), shapes and architecture of the skin penetration pathways.

- For comparison and differentiation of the mechanism of penetration of transfersomes with liposomes, niosomes and micelles.

Different fluorescence markers used in CSLM study are as –

1. Fluorescein- DHPE (1, 2-dihexadecanoyl- sn- glycerol- 3-phosphoethanolamine- N- (5 -fluorescentisothiocyanate), triethylammonium salt)
2. Rhodamine- DHPE (1, 2-dihexadecanoyl- sn- glycero-3nisothiocyanate)
3. NBD- PE (1, 2- dihexadecanoyl- sn-glycerol- 3-phosphoethanolamine- N- (7-nitro- Benz- 2- oxa- 1, 3- diazol- 4- yl) triethanolamine salt)
4. Nile red. This study enables comparison of transfersomes with liposomes, niosomes, etc. and study of mechanism of transferosome penetration. This emitted light is used for further detection.

**Degree of deformability or permeability measurement:** The Transferosome preparation is passed through many filters between pore size 50 to 400 nm. Vesicle retained on each filter is studied for particle size and distribution using Dynamic light scattering technique. The degree of deformability, \( D = J \times \frac{rv}{rp} \)

Where, \( J \)- the amount of the suspension extruded during 5 min; \( rv \) - the size of the vesicle; \( rp \) - pore size of the barrier.
In vitro drug release: In vitro drug release study is performed for determining the permeation rate. Time needed to attain steady state permeation and the permeation flux at steady state and the information from in vitro studies are used to optimize the formulation before more expensive in vivo studies are performed. For determining drug release transfersomes suspension is incubated at 32°C using cellophane membrane. The samples are withdrawn at different intervals. 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. Detection is done by various analytical techniques like U.V., HPLC and HPTLC).

Vesicle shape and type: Transfersomes vesicles can be visualized by TEM, Phase contrast microscopy, etc.

Number of vesicle per cubic mm: Non-sonicated transfersome formulations are diluted five times with 0.9% sodium chloride solution. Total number of transfersomes per cubic mm = total number of transfersomes counted 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. Regarding the zeta potential measurements, all colloidal dispersions have a negative surface charge, containing Tween 80 which is a non ionic surfactant while sodium cholate is anionic surfactant. It is speculated that the hydrocarbon tail of Tween 80 might be able to penetrate into the lipid bilayer, thus leaving the polyethylene oxide groups on the surface of the vesicles thereby introducing a stearic barrier on the surface of the transfersomes, which might decrease liposome fusion. Thus, the incorporation of negative zeta potential increases the stability of the transfersomes.

Drug content: The drug content 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.

Occlusion effect: Occlusion of skin is considered to be helpful for permeation of drug in case of traditional topical preparations. Occlusion affects hydration forces as it prevents evaporation of water from skin.

Application of transfersomes

1. Delivery of insulin: By transfersomes is the successful means of non-invasive therapeutic use of such large molecular weight drugs on the skin. Insulin is generally administered by subcutaneous route that is inconvenient. Encapsulation of insulin into transfersomes (transfersulin) overcomes these entire problems. After transfersulin application on the intact skin, the first sign of systemic hypoglycemia are observed after 90 to 180 min, depending on the specific carrier composition.

2. Delivery of corticosteroids: Transfersomes have also used for the delivery of corticosteroids. Transfersomes improves the site
specificity and overall drug safety of corticosteroid delivery into skin by optimizing the epicutaneously administered drug dose. Transferosomes based corticosteroids are biologically active at dose several times lower than the currently used formulation for the treatment of skin diseases.

3. Delivery of proteins and peptides: Transferosomes have been widely used as a carrier for the transport of proteins and peptides. Proteins and peptide are large biogenic molecules which are very difficult to transport into the body, when given orally they are completely degraded in the GI tract. These are the reasons why these peptides and proteins still have to be introduced into the body through injections. Various approaches have been developed to improve these situations. The bioavailability obtained from transferosomes is somewhat similar to that resulting from subcutaneous injection of the same protein suspension. The transferosomal preparations of this protein also induced strong immune response after the repeated epicutaneous application, for example the adjuvant immunogenic serum albumin in transferosomes, after several dermal challenges is as active immunologically as is the corresponding injected proteo-transferosomes preparations.

4. Delivery of interferons: Transferosomes have also been used as a carrier for interferons, for example leukocytic derived interferone-α (INF-α) is a naturally occurring protein having antiviral, antiproliferive and some immunomodulatory effects. Transferosomes as drug delivery systems have the potential for providing controlled release of the administered drug and increasing the stability of labile drugs. Hafer et al studied the formulation of interleukin-2 and interferone-α containing transferosomes for potential transdermal application. They reported delivery of IL-2 and INF-α trapped by transferosomes in sufficient concentration for immunotherapy.

5. Delivery of Anticancer Drugs: Anticancer drugs like methotrexate were tried for transdermal delivery using transfersome technology. The results were favorable. This provided a new approach for treatment especially of skin cancer.

6. Delivery of anesthetics: Application of anesthetics in the suspension of highly deformable vesicles, transferosomes, induces a topical anesthesia, under appropriate conditions, with less than 10 min. Maximum resulting pain insensitivity is nearly as strong (80%) as that of a comparable subcutaneous bolus injection, but the effect of transferosomal anesthetics last longer.

7. Delivery of NSAIDS: NSAIDS are associated with number of GI side effects. These can be overcome by transdermal delivery using ultra-deformable vesicles. Studies have been carried out on Diclofenac and Ketoprofen. Ketoprofen in a Transfersome formulation gained marketing approval by the Swiss regulatory agency (SwissMedic) in 2007; the product is expected to be marketed under the trademark Diractin. Further therapeutic products based on the Transfersome technology, according to IDEA AG, are in clinical development (Cevc and Blume, 2001).

8. Delivery of Herbal Drugs: Transferosomes can penetrate stratum corneum and supply the nutrients locally to maintain its functions resulting
maintenance of skin in this connection the Transfersomes of Capsaicin has been prepared by Xiao-Ying et al. 2006, and showed the better topical absorption in comparison to pure capsaicin.

**Conclusion**

Transfersomes are specially optimized particles or vesicles, which can respond to an external stress by rapid and energetically inexpensive, shape transformations. Such highly deformable particles can thus be used to bring drugs across the biological permeability barriers, such as skin. When tested in artificial systems transfersomes can pass through even tiny pores (100 mm) nearly as efficiently as water, which is 1500 times smaller. They are free from the rigid nature of conventional vesicles and can transport even the large molecules. This technology hold great prospective in delivery of huge range of drug substances which includes large molecules like peptides, hormones and antibiotics, drugs with poor penetration and could provide an effective tool for non-invasive therapy.

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