**Scholars Academic Journal of Pharmacy**
Abbreviated Key Title: Sch Acad J Pharm
ISSN 2347-9531 (Print) | ISSN 2320-4206 (Online)
Journal homepage: http://saspublishers.com

OPEN ACCESS

**Pharmacy**

# Transferosome- A Noval Drug Delivery System

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**DOI:** 10.36347/sajp.2024.v13i05.003 | **Received:** 05.04.2024 | **Accepted:** 12.05.2024 | **Published:** 17.05.2024

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**Abstract** **Review Article**

The skin's barrier function typically places restrictions on the transdermal administration of medications. One of the most contentious techniques for transdermal distribution of active ingredients is vesicular systems. After elastic vesicles such as transferosomes, ethosomes, cubosomes, phytosomes, etc. were discovered, there was a renewed interest in developing transdermal delivery systems. In order to provide active compounds transdermally, this paper describes the composition, penetration mechanisms, production processes, and characterization techniques of transferosomes. A medication must cross one or more biological membranes or barriers at different sites in order to be absorbed, distributed into organs and tissues, and removed from the body. Substance transport refers to the passage of a substance through a membrane in this manner. The medications must get through the membranous barrier in order to be absorbed by the body. In an effort to reduce the amount of medicine in the remaining tissues and concentrate the drug in the targeted tissues, several delivery systems were devised. As a result, the medication has no effect on the tissues nearby. Furthermore, medication loss does not occur. Furthermore, the localization of the drug prevents drug loss, resulting in the medication's optimum efficacy. As such, there is a lot of interest in phospholipid-based carrier systems nowadays.

**Keywords:** Lecithin, stratum corneum, surfactant, transferosomes, vesicles.



## INTRODUCTION

Liposome and niosomeare not suitable for transdermal delivery and cannot reach deeper skin layers as they are trapped in the upper stratum corneum layers. In most cases, the liposome and niosome category vesicles do not cause the desired transdermal penetration because of some issues with vesicular structures, such as bad permeability of the skin, vesicle breakage, drug leakage and aggregation, and vesicle fusion, in terms of drug delivery through transdermal route [1-5]. To overcome this problem Gregor Cevc launched the word Transfersome and the fundamental idea in year 1991.In the broadest sense, a transfersome is a extremely adaptable and stress-responsive, complicated aggregate with an aqueous vesicle is entirely enclosed by a lipid bilayer complex [1,6]. Local composition interdependence and bilayer shape make the vesicle both self-regulating and self-optimizing. Transfersome is an artificial vesicle intended to deliver drugs or genetic material to a cell. Transfersome consists of one natural phospholipid that tends to self-aggregate into vesicles, supplemented by at least one bilayer (biocompatible surfactant) softener [1, 6]. Transfersome's structural organisation is similar to lipid vesicle (liposome), but it differs from liposome as it is more flexible, having softened bilayer membrane is more permeable [8]. Transfersomes consisting of phospholipid, surfactant, and water to increase transdermal delivery [9]. Because of its lipid nature it's more effective in transdermal route. Due to their self-optimized and ultra-flexible membrane characteristics, they can deliver the drug to or through the skin reproducibly with high efficiency, depending on the selection of administration or application.

The vesicular transfersomes are more elastic than standard liposomes and therefore suitable for the penetration of the skin [1, 6]. The name transferosome implies body carrying and derives from the translated significance of the Latin term for a body and the Greek term soma. A transfersome carrier is an artificial vesicle intended to be like a cell vesicle or an exocytose cell and therefore appropriate for the controlled drug delivery and possibly targeted delivery of drugs [9, 10].

The biggest advantage of transferosome is that they can use in high molecular weight drugs as well as lower molecular drugs. Transfersomes overcome the trouble of skin penetration by squeezing themselves along the stratum corneum's intracellular locking lipid. The flexibility of the transfersome membrane is

controlled by the mixing with phospholipids of proper ratio of surface-active elements. The resulting transfersome membrane flexibility minimizes the danger of full skin vesicle rupture and enables transfersomes to follow the natural water gradient across the epidermis when applied in non-occlusive situation [11, 12].

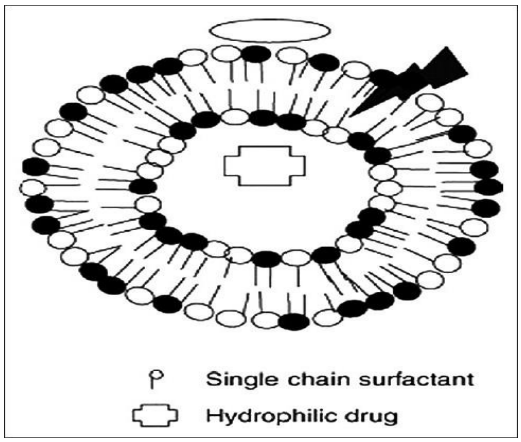


**Figure 1: Ultra Deformable Vesicle**

**ADVANTAGE OF TRANSFEROSOME [12-17]**

1. They have big trap effectiveness, nearly 90 percent of lipophilic drugs.
2. This strong deformability provides intact vesicles a better penetration.
3. They are biocompatible and biodegradable because they are produced from liposome-like natural phospholipids.
4. Transdermal medication provides a drug with a constant infusion over a long period of time.
5. They can work as a carrier for small and high molecular weight medicines such as analgesic, anesthetic, corticosteroids, sex hormone, anticancer, insulin, protein from the gap junction, and albumin.
6. They stop metabolic degradation of the encapsulated drug.
7. Transfersomes together have an infrastructure composed of hydrophobic and hydrophilic molecules and can therefore accommodate drug molecules with a broad spectrum of solubility. They function as a distribution centre, slowly and gradually releasing their content.
8. Easy to scale, as the method is easy, do not require long procedures and unnecessary use or additives that are pharmaceutically unacceptable.
9. An equal therapeutic effect with a reduced daily dose of the drug than is essential can be elicited via transdermal drug input.
10. Increased convenience for administering drugs that would require frequent dosage otherwise.
11. Improved patient compliance and convenience through implementation that is non-invasive, painless and easy.

**DISADVANTAGE OF TRANSFEROSOME [12]**

1. Many drugs with hydrophilic structures in particular permeate the skin too slowly to be beneficial for therapy.
2. The skin's barrier function varies on the same man, from man to man, and also with age, from one site to another.
3. Irritation of the skin and leads to hypersensitivity may arise.
4. Because of oxidative degradation, transfersomes are chemically volatile.
5. Drug molecule must be powerful because the amount of patch size that can be delivered must be limited.
6. Another criterion for adopting transfersomes as drug delivery cars is the purity of natural phospholipids.
7. In addition to these limitations, the product's elevated price is also a significant drawback to this product's broad adoption.

**LIMITATION OF TRANSFEROSOME [12]**

- Because of their tendency to oxidation, they are chemically unstable.
- It is difficult to achieve purity of natural phospholipids; therefore, the world is opposed to the adoption of transfersomes as vehicles for drug delivery.
- These are costly formulations.

**MECHANISM OF TRANSFEROSOME FOR SKIN [5, 18-21]**

Transfersomes are advantageous for transdermal drug delivery as phospholipids vesicles. Due to their self-optimized and ultra-flexible membrane characteristics, they can deliver the drug to or through the skin reproducibly with great effectiveness, depending on the selection of administration or application. The vesicular transfersomes are more porous than the standard liposomes and are therefore suitable for the penetration of the skin. Transfersomes overcome the challenge of skin penetration by squeezing along the stratum corneum's intracellular locking lipid. These are characteristic of transfersomes in a self-adapting way

owing to the elevated vesicle deformability that allows entry owing to the surrounding mechanical stress. The flexibility of the transfersome membrane is controlled by the mixing with phospholipids of appropriate surface-active agents. The resulting transfersome membrane flexibility minimizes the danger of full skin vesicle rupture and enables transfersomes to follow the natural water gradient across the epidermis when applied in non-occlusive situation. Transfersomes can spontaneously enter the intact stratum corneum along two intracellular lipid paths that vary in the characteristics of their bilayers. Confocal microscopic studies have shown that intact liposomes cannot penetrate into the epidermis granular layer, but instead stay on the upper stratum corneum layer. Changing the vesicular composition or surface characteristics can adjust the rate of release and deposition of the drug to the target site [20].

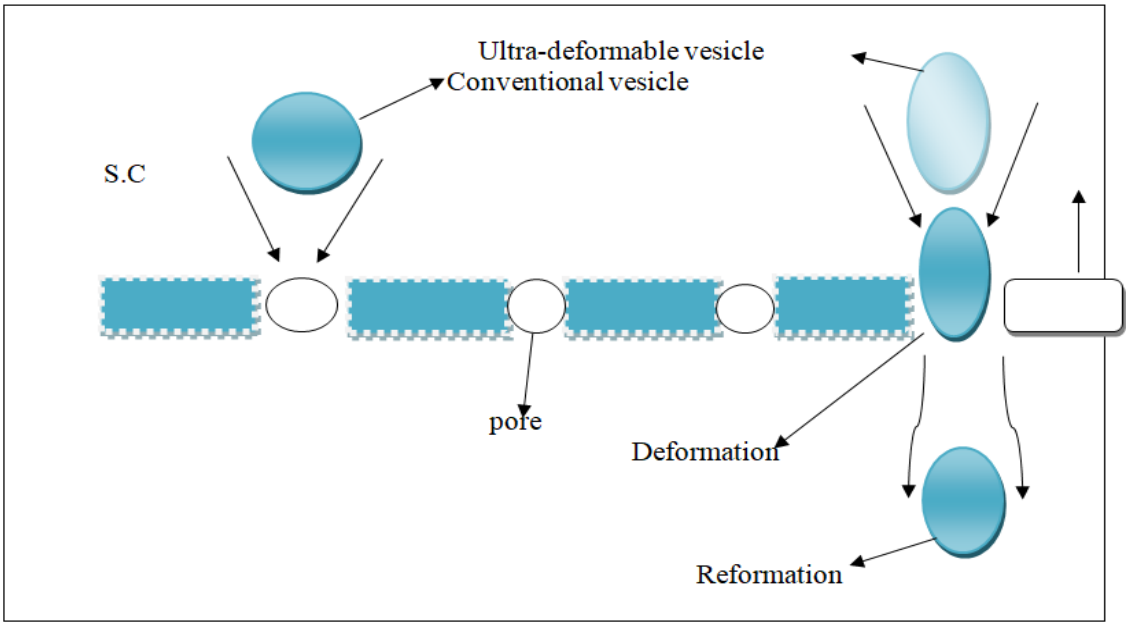


**Figure 2: Deformability of transfersomes in to skin pores**

## MECHANISM OF PENETRATION OF TRANSFEROSOME [12, 21, 22]

Transfersomes can pass 0.1 mg of lipid per hour and cm2 of region across the intact skin when applied under appropriate condition. The penetration mechanism is the generation of "osmotic gradient" due to water evaporation while applying lipid suspension (Transfersomes) to the surface of the skin. Transfersomes are highly bilayer deformable and thus have enhanced affinity to bind and maintain water. Because of the skin penetration barrier, this osmotic gradient avoids water loss through the body and retains a water activity gap in the feasible portion of the epidermis (75% water content) and almost entirely dry stratum corneum near the skin surface (15% water content). The hydration gradient that passes through the epidermis, stratum corneum, and ambient environment drives transfersome absorption. Barrier penetration includes reversible deformation of the bilayer, but must not inadmissibly compromise either the integrity of the vesicle or the barrier characteristics to maintain the fundamental hydration affinity and gradient. In this respect, transfersomes are optimized to achieve maximum flexibility so that they can take full advantage of the trans-epidermal osmotic gradient.

## PROPENSITY OF PENETRATION

Transfersomes are too big to spread through the skin, and the Transfersomes need to discover and implement their own organ path. The magnitude of the driving force of transport can be calculated by force: Flow = Area x (Barrier) Permeability x (Trans-barrier).

The chemical lipid flow through the skin therefore always reduces dramatically when lipid solution is exchanged by some lipids in a suspension.

## COMPOSITION OF TRANSFEROSOME

The transfersome consists of two primary components:

1. First, an amphipathic substance (phosphatidylcholine), in which the aqueous solvents are self-assembled into a lipid bilayer closing into a straightforward vesicle of lipids.
2. Second, a bilayer softening element (such as a biocompatible surfactant or amphiphilic medication) which improves the flexibility and permeability of lipid bilayers [23].

Therefore, the resulting transfersome vesicle, optimized in flexibility and permeability, can readily and quickly adapt its shape by adapting the local concentration of each bilayer element to the local stress experienced by the bilayer. Consequently, the

transfersom differs from such a more standard vesicle mainly through its weaker, more deformable and better adjustable artificial membrane.

**Table 1: List of ingredients used in transferosome formulation [24-27]**

| INGREDIENT | EXAMPLES | USE |
|---|---|---|
| Phospholipids | Soya phosphatidyl choline, egg phosphatidyl choline, Dipalmitoylphophatidyl choline | Vesicle forming component |
| Surfactants | Sodium cholate, sodiumdeoxycholate, Tween-80, span -80, Tween 20 | Vesicles forming componenet |
| Solvents | Ethanol, methanol, isopropyl alcohol, chloroform | As a solvent |
| Buffering agents | Saline phosphate buffer (pH 6.4), phosphate buffer pH 7.4 | As a hydrating medium |
| Dye | Rhodamine-123, Rhodamine- DHPE, Fluorescein-DHPE, Nile-red | For CSLM Study |

## METHOD OF PREPRATION OF TRANSFEROSOME

### 1. Thin film hydration technique [28-30]

In this method, phospholipids, surfactants and the drug is dissolved inside organic solvent. Then the solvent is removed under decreased pressure at 40ºC by rotary evaporation. Keep this film under vacuum overnight forremoval of the final trace of liquid. The deposited lipid film is then hydrated by centrifuging at 60 rpm for 1 hour at room temperature with the suitable buffer. The resulting vesicles will be swollen for 2 hours at room temperature. The multi-lamellar lipid vesicles produced at room temperature are further sonicated to produce small lamellar lipid vesicles. Using a bath sonicator or probe sonicator at 40ºC for 30 minutes, the emerging vesicles can be sonicated at temperature 50ºC for 30 minutes to develop small vesicles. A sandwich of 200 and 100 nm polycarbonate membranes will homogenize the sonicated vesicles 10 times by manual extrusion.

### 2. Modified hand shaking method [28-30]

Transferosome is prepared by hand shaking in this method. Where, drug, phospholipid and surfactant are dissolved within organic solvent with a ratio of 1:1. Then both the mixture is completely mixed together by shaking the flask. By hand shaking, organic solvents are evaporated at $45^0$C after mixing. A thin layer of film is created at the flask wall. This film will be held overnight for the full removal of organic solvent. Then the film was hydrated with a suitable buffer and shaking at room temperature for 15 min. The transferosome preparation is further hydrated at 2-8oC for up to 1 hour.

### 3. Reverse phase evaporation method [31-33]

To prepare transferosome, phospholipids, surfactants and the drug are used to dissolve into alcohol. The organic solvent is then evaporated under decreased pressure at 40-45ºC by rotary evaporation. Under vacuum, the final solvent residue is removed. At room temperature, the retainer lipid film is hydrated by rotation with a separate buffer at 60 rpm for 1 hour. The developing vesicles are overstated for 2 hours at room tempreture. The multilamellar lipid vesicles are then sonicated. Extrusion, low shear blending or high shear blending can replace sonication method.

## OPTIMIZATION OF FORMULATION CONTAING TRANSFEROSOME [34-36]

There are different process factors that could influence the transfersomes' preparation and characteristics. The training process was optimized and validated accordingly. The process factors depend on the formulation manufacturing method concerned. Transfersomes preparation includes different process variables, such as,

- Lecithin: surfactant proportion
- Effect of different solvents
- Effect of different surfactants
- Hydration medium

Optimization was accomplished by choosing drug trap effectiveness. The other variables were held constant during the preparing of a specific scheme.

## EVALUATION PARAMETER OF TRANSFEROSOME

Transfersomal characterization is usually comparable to liposomes, niosomes and micelles [23, 36]. For transfersomes, the following characterization parameters must be checked.

### 1. Distribution of vesicle size and zeta potential [13]

In Dynamic light scattering technique (DLS) using Malvern Zetasizer's computerized examine system is used to determine vesicle size, size distribution, and zeta potential.

### 2. Entrapment Efficiency [13]

The efficiency of trapping is expressed as the drug's percentage of trapping added. Entrapment efficiency was determined using the mini-column centrifugation method by first separation of the unentrapped drug. Using 0.1 percent Triton X-100 or 50 percent n-propanol, the vesicles were interrupted after centrifugation. The effectiveness of encapsulation is expressed as: Efficiency of encapsulation = (complete quantity of encapsulated / amount of drug added)*100

### 3. Morphology of the vesicles [13, 37]

Spectroscopy of photon correlation or DLS technique usually used to determine vesicle diameter. Using photon correlation spectroscopy or DLS measurements, the prepared sample in distilled water was filtered through a 0.2 mm membrane filter and diluted with filtered saline. Transmission electron microscopy (TEM) and phase contrast microscopy can frequently be used for transfersome vesicle visualization. Vesicle stability can be determined by evaluating the time-related size and structure of the vesicles. DLS and TEM, respectively, were used for mean size and structural modifications.

**4. Vesicle number per Cubic mm**

This is an significant parameter to optimize the structure and other factors of the method. Transferosome formulations (without sonication) can be diluted five times with 0.9% of the solution of sodium chloride and studied with optical microscopy using haemocytometer. Transfersomes are numbered and calculated in 80 tiny squares using the formula below:

Total number of transfersomes per cubic mm = (Total transfersomes vesicle counted × D.F × 4000) /total squares counted

**5. Confocal scanning laser microscopy (CSLM) [14]**

Conventional light microscopy and electron microscopy both face the issue of skin samples being fixed, selected and stained. The structures to be examined are often in fact inconsistent with the respective processing methods, which lead to misinterpretation but can be minimized by Confocal Scanning Laser Microscopy (CSLM). Fluorescence markers are used for the following purposes in the transfersomes and the light emitted by these markers;

- To investigate the mechanism of transfersome penetration across the skin.
- To determine skin histology organisation (epidermal columns, interdigitation), skin penetration pathways forms and architecture.
- To compare and differentiate the transfersome penetration mechanism with liposomes, niosomes and micelles

Various fluorescence markers used in the research of CSLM;

1. Nile red.
2. Rhodamine- DHPE
3. Fluorescein- DHPE

**6. Content of drug [38]**

Depending on the analytical technique of the pharmacopoeial medication, the substance content can be determined using one of the instrumental analytical techniques such as modified high-performance fluid chromatography (HPLC) technique using a UV sensor, column oven, auto sample, pump, and computerized evaluation program.

**7. Determination of turbidity [38]**

Nephelometer can be used to measure the turbidity of the drug in aqueous solution

**8. Degree of deformation or measurement of permeability [13, 37]**

The research of permeability is one of the significant and distinctive parameters for characterization in the situation of transfersomes. The conventional analysis of deformability is performed against pure water. Transfersomes preparation is carried through a big amount of pores of known size (through a sandwich of various microporous filters, with pore diameter between 50 nm and 400 nm, depending on the suspension beginning transfersomes). Distributions of particle size and size are observed after the measurements of dynamic light dispersion (DLS).

**9. Capacity of penetration [37]**

Transferosome penetration capability can be measured using fluorescence microscopy.

**10. Surface load and density load [40]**

A zetasizer can be used to calculate surface charge and density charge of transferosome.

**11. Effect of occlusion [13]**

In traditional topical preparations, skin occlusion is regarded to be useful for drug permeation. But the same demonstrates harmful to elastic vesicles. Water hydrotaxis (motion in the direction) is the main driving force for vesicle permeation through the skin, from its comparatively dry surface to deeper water-rich areas. Occlusion impacts the hydration forces because it prevents body water from evaporating.

**12. Physical stability [1, 35]**

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 ± 20C (refrigeration), 25 ± 20C (room temp), and 37 ± 20C (body temp) for at least 3 months. Samples from each ampoule were analyzed after 30 days to determine drug leakage.The percentage of drug loss was calculated by maintaining the original drug trap as 100%.

**13. *In-vitro*drug release**

The study of in vitro drug release is conducted to determine the rate of permeation. Time required to achieve steady state permeation and permanent permeation flux and information from in-vitro studies are used to optimize the formulation before more expensive in vivo studies are conducted. Transfersomes suspension is incubated at $32^0$C to determine drug release and samples are taken at separate times and the free drug is divided by centrifugation with minicolumns. The quantity of drug produced is then calculated indirectly as the original quantity (100 percent trapped and 0 percent

released) from the quantity of drug caught at zero moments [13].

**14. *In-vitro* Skin permeation Studies [34, 38]**

For this analysis, a modified Franz diffusion cell with a 50ml reception compartment volume and an efficient 2.50 $cm^2$ diffusion region was used. Using goat skin in phosphate buffer solution (pH 7.4) was conducted in vitro drug research. From the slaughterhouse, fresh abdominal goat skin was gathered and used in the permeation experiments. Abdominal skin hairs were separated and in ordinary saline solution the skin was hydrated. Rubbing with a cotton swab separated the skin's adipose tissue layer. Skin was placed at $40^0$ C in isopropyl alcohol solution. For the research of skin permeation, treated skin was horizontally installed on the receptor compartment with the stratum corneum side facing upwards towards the Franz diffusion cell donor compartment. The efficient donor cell permeation region subjected to the receptor compartment was 2.50$cm^2$ and the receptor compartment capability was 50ml.The receptor compartment was packed with 50ml of phosphate buffer (pH 7.4) saline kept at 37 ± 0.5 μC and stirred at 100RPM with a magnetic bar. Formulation was placed on the skin (equivalent to 10mg drug) and coated the top of the diffusion cell. At suitable intervals 1 ml receptor medium aliquots were removed and substituted instantly by an equivalent quantity of new phosphate buffers (pH 7.4) to preserve sink conditions. In calculating the release profile, correction factors for each aliquot were regarded. Any instrumental analytical technique has evaluated the samples.

**APPLICATION OF TRANSFEROSOME**

Transferosomes as drug delivery systems have the ability to deliver the administered drug regulated release and increase the strength of labile drugs.

**1. Delivery of Insulin [41]**

By transferosomes, such big molecular weight drugs on the skin are the effective means of non-invasive therapeutic use. Insulin is usually administered by an inconvenient subcutaneous path. Insulin encapsulation into transferosomes (transfersulin) overcomes all of these issues. Depending on the particular carrier structure, the first sign of systemic hypoglycemia is noted after 90 to 180 min after transfersulin application on the intact skin.

**2. Delivery of corticosteroids [42]**

Transferosomes also used in corticosteroid delivery. Transferosomes enhances the site specificity and general drug safety of delivering corticosteroids to the skin by optimizing the epicutaneous dosage of the drug. Corticosteroids based on transferosomes are biologically active in a dose that is several times smaller than the formulation presently used to treat skin diseases.

**3. Delivery of proteins and peptides [43-45]**

Transfersomes were commonly used as a carrier for protein and peptide transportation. Proteins and peptides are large biogenic molecules that, when given orally, are completely degraded in the GI tract, are very difficult to transport into the body. These are the reasons why injections still require these peptides and proteins to be brought into the body. To enhance these circumstances, various methods have been created. The bioavailability of transferosomes is somewhat comparable to that of subcutaneous injection of the same protein suspension. After repeated epicutaneous implementation, this protein's transferosomal preparations also caused powerful immune response.

**4. Delivery of interferons [45]**

Transferosomes have also been used as an interferon carrier, such as interferon-α leukocytic derived (INF-α) is a naturally occurring protein with antiviral, antiproliferative and some immunomodulatory impacts. Transferosomes as drug delivery systems have the ability to deliver the administered drug regulated release and increase the strength of labile drugs. Hafer *et al*., studied for prospective transdermal implementation the formulation of interleukin-2 and interferone-α containing transferosmes. They revealed a adequate concentration of IL-2 and INF-α trapped by transferosomes for immunotherapy.

**5. Delivery of anesthetics [45]**

The number of GI side effects associated with NSAIDS. Using ultra-deformable vesicles, these can be overcome by transdermal delivery. Studies on Diclofenac and Ketotifen have been conducted. Ketoprofen is anticipated to be marketed under the trademark Diractin in a formulation of Transferosomes obtained marketing permission by the Swiss regulatory authority. According to IDEA AG, further therapeutic products are in clinical development based on the transferosome technology.

**6. Delivery of Anticancer Drugs [**45]

Anti-cancer drugs such as methotrexate have been attempted using transdermal technology for transdermal delivery. The findings were positive. This given a fresh strategy to treating skin cancer in particular.

**7. Delivery of Herbal Drugs [46, 47]**

Transfersomes 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*., which shows the better topical absorption in comparison to pure capsaicin.

**8. Delivery of NSAIDS [48]**

The number of GI side effects associated with NSAIDS. Using ultra-deformable vesicles, these can be overcome through transdermal delivery. Studies on Diclofenac and Ketoprofen were conducted. In 2007, the Swiss regulatory agency (SwissMedic) obtained

marketing approval for ketoprofen in a Transfersome formulation; the product is expected to be marketed under the trademark Diractin. According to IDEA AG, additional therapeutic products based on the Transfersome technology are being clinically developed.

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