A Comprehensive approach into the Novel Drug carriers: Transferosomes

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Abstract

In recent year, research scenario is moving toward to the development of Novel drug delivery system with the aim of high therapeutic efficacy along with better patient compliance. Vesicular drug delivery system is also a part of these novel drug delivery systems. In TDDS permeability of the skin is important consideration, it is permeable to small molecules or lipophilic drug and particularly impermeable to the macromolecules and hydrophilic drugs. Recently various approached have been designed in the field of vesicular carriers system ,ethosome and transferosome (ultra flexible lipid based elastic vesicles).

Transferosomes have been introduced by the German company IDEA AG, refers to its proprietary drug delivery technology. Transferosomes consist of phospholipids and edge activator. It act as membrane softeners that facilates the ultra deformable property of transferosome. When Transferosomes reaches to the skin pores they change the membrane flexibility and passing through the skin pores spontaneously. This is called self-optimizing deformability. Transferosome offers several potential benefits over the conventional dosage form like underpass the first pass metabolism , expected and extended duration of activity, reduction in undesirable side effects, utilization of short half-life drugs, enhance physiological and pharmacological response and also have been applied to increase the efficiency of the material transfer across the intact skin by the use of permeation enhancer It is also suitable for targeted and controlled drug delivery system and it can serve drug molecules with wide range of solubility.

Due to its high deformability index it provides better penetration to the intact vesicles. They are biocompatible and biodegradable as they constituted from natural phospholipid , they have high entrapment efficiency . The process variables are depending upon the methods involved for the fabrication of transferosome .The characterization of transferosome can be done to know about the vesicle size , drug content, morphology, entrapment efficiency , permeation ability, ,surface

charge , In vitro drug release ,In vivo studies etc., Transferosomes in consequence differ from the conventional vesicles mainly by its softer, more defrmability , better adjustable artificial membrane.

Introduction

A novel form of medication delivery system is being developed in recent years with the goal of achieving great therapeutic efficacy and enhanced patient compliance. Since oral medication administration creates a hostile environment in the gastrointestinal tract (GIT), the majority of pharmaceuticals are broken down there in a variety of pH conditions, solubility problems, and most crucially, first pass metabolism. Due to a number of benefits, including a less invasive and painless method, the avoidance of first pass drug metabolism, gastrointestinal degradation, and enhanced patient compliance, topical drug delivery systems have gained significant attention in recent years. Here are a few crucial points to pay attention to

1.Even yet, there are certain drawbacks, such as the potential for localised skin irritation, erythema, and low stratum corneum permeability. The stratum corneum's permeability qualities are a significant barrier to this route.

2. Many technologies has been explored to overcome this problem including chemical permeation enhancers, electrophoresis, iontophoresis, sonophoresis, nano emulsions, apart of this utilization of vesicular systems such as liposomes, niosomes, ethosomes and transferosomes.

3. Among all formulation routes; transferosome appears as promising technique.

The German business IDEA AG registered the trademark Transferosomes to identify their unique drug delivery system. Edge activator (such as Tween 80, span80 and sodium cholate) and phospholipids make up transferosomes.Edge activator act as membrane softeners, facilitating the transferosome's ultra-deformable characteristic. Transferosomes change the membrane's pliability as they approach the skin pores and naturally pass through them.

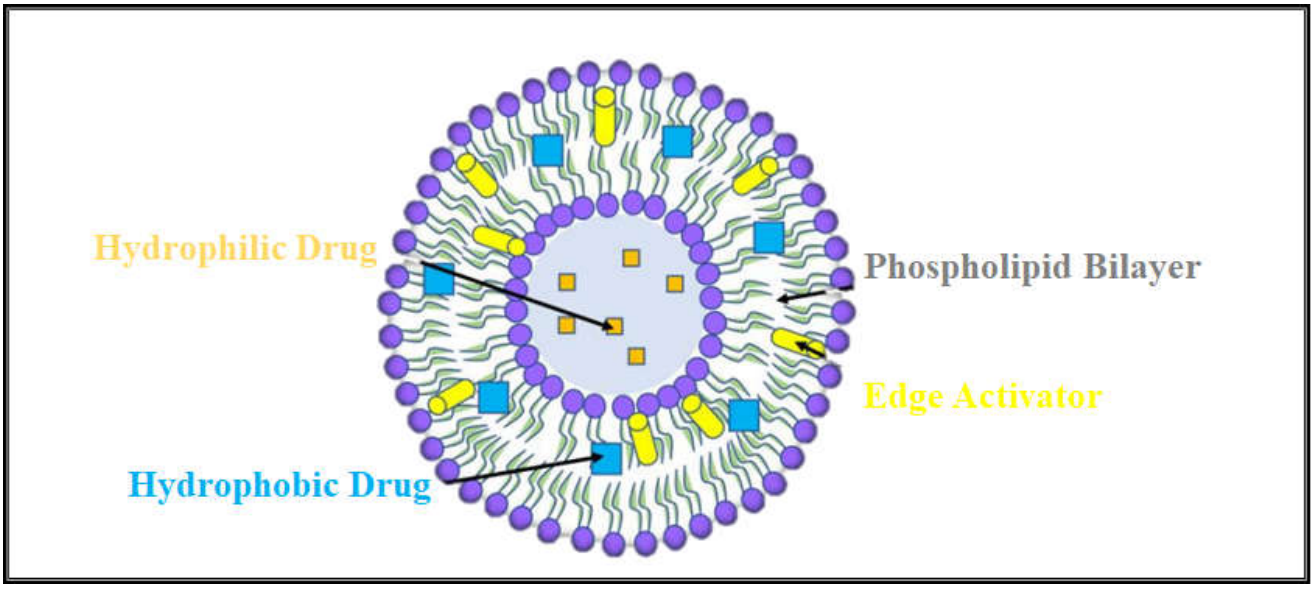

Fig -1 Structure of transferosome

Mechanism of action

It is yet unknown how exactly complete vesicles are transported outside of the stratum corneum. However, the creation of an osmotic gradient as a result of water evaporation is the foundation of the transferosome's mechanism. Water molecules are drawn to polar lipids. Thus, all lipid vesicles containing polar lipid vesicles shift from an adequate low water content to a high concentration. The lipid vesicles feel the osmotic difference and attempt to travel alongside the gradient when transferosomes are applied to skin that is somewhat dehydrated as a result of water loss through evaporation.

As it consist edge activator which have high deformability and good rheological properties so they can easily cross through the narrow pores of skin.

Since the conventional liposomes are rigid in structure, they only retain on the skin surface where they dehydrate completely. So their penetration power is less than the transferosome(5)Transferosome by disrupting the intercellular lipid present in the stratum corneum , also facilitates the penetration of therapeutic agents and across the stratum corneum .(6) Transferosome when applied under suitable conditions can deliver 0.1mg of lipid per hour and square centimeter area across the intact skin (7)

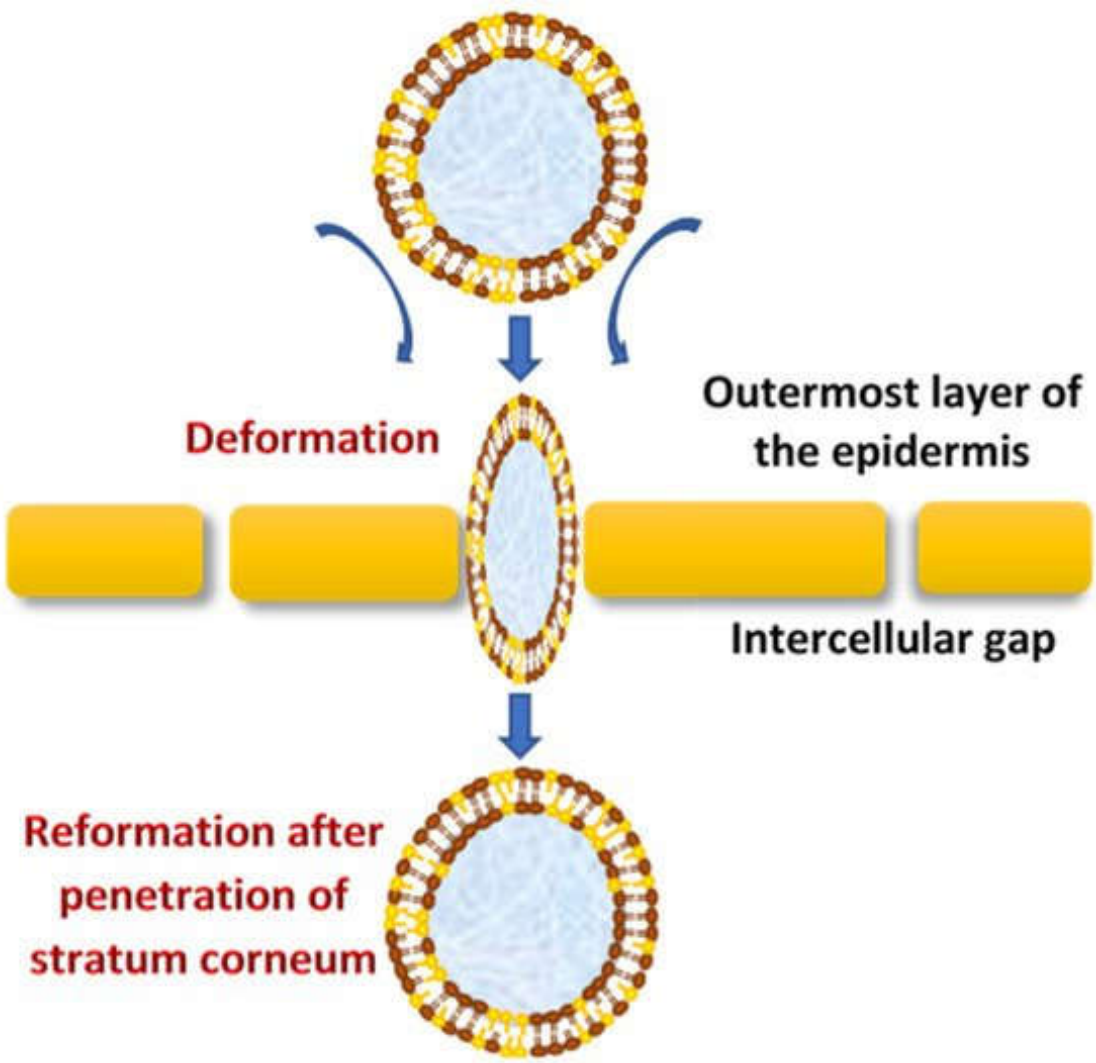

Fig 2: Mechanism of action of transferosome .

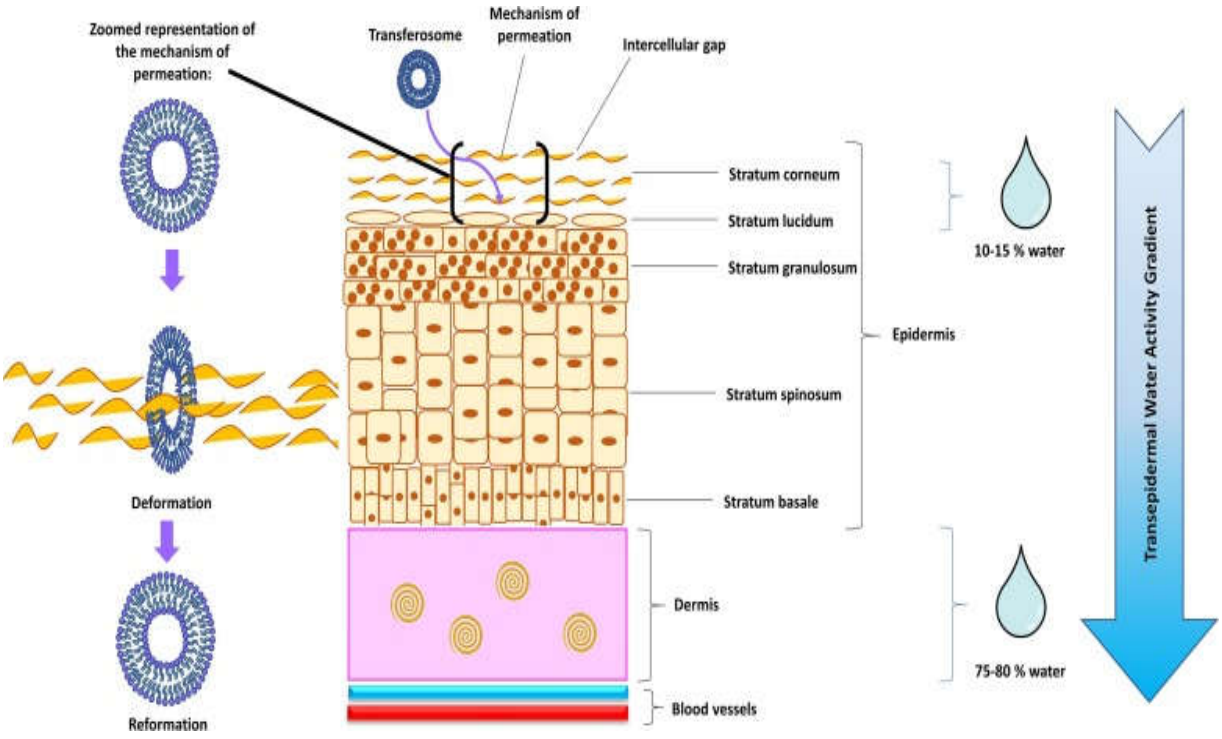

Figure 3: **Detailed MOA of Transferosomes**

Advantages

Transdermal drug delivery system delivers a steady infusion of a drug over an extended period of time.

- An equivalent therapeutic response can be achieved via transdermal drug inputs with a low daily dose of the drug than is required
- Self-administration is feasible with these systems.
- They can be used for drugs with narrow therapeutic range.
- They are capable of increasing the transdermal flux and improve the site specificity of bioactive agent.
- Due to the short and simple production process, it is easy to scale –up.
- They are easily and quickly identified in emergencies (eg. Unconscious or unresponsive patient) because of their physical presence, features and identifying markings.
- Reduction in dosing frequency because of longer duration of action.
- Improved bioavailability.
- More uniform plasma level and maintain plasma concentration of potent drug.
- Improved patient compliance via painless and non-invasive and ease of application
- Reduced side effects and improved therapy due to maintenance of plasma levels up to the end of the dosing interval.

  Disadvantages-

- Transferosome are considered as chemically unstable because of oxidative degeneration. Theoxidation can be significantly decreased when the aqueous media is degassed and exclude from inert gases.8Purity of natural phospholipids is another criterion for achieve for adoption of transferosome as drug delivery system.
- The expensiveness of transferosomal formulation is because of the raw material s used in lipid excipient as well as expensive equipmentneeded to increase manufacturing . so the widely used lipid component is phosphatidylcholine ,because it is relatively low in cost.9.

Materials for their formulations:

Despite TFS's enhanced stability capabilities, a number of components make up the majority of thisdeformableNano system. Some are essential for maintaining its structural integrity like edge activator and Phospholipids.In Table I, TFS fabrication is listed.

Surfactant–Engrossed as edge activator. Surfactants, often referred to as edge activators, give Transferosome the capacity to deform and enhance their ability to fit through stratum corneum pores that are five times smaller than their diameter (25). Edge activator are monomers which comprises a hydrophobic and a hydrophilic area. Edge activators included sodium cholate, sodium deoxycholate, Span 60, Span 65, Span 80, Tween 20, and Tween 80. The hydrophilic/lipophilic balance (HLB) value, entrapment effectiveness, and elasticity are the main factors considered while choosing an edge activator. According to reports in the literature, Tween 80 gives vesicles more flexibility when compared to span 80. (10

Phospholipid – Main ingredient to design lipid vesicles. Phospholipid are amphipathic mean it contain both hydrophilic and hydrophobic region and to create vesicles, phospholipids arrange themselves into a lipid bilayer in aqueous solvents .11 .Both hydrogenated and un-hydrogenated phospholipids are present, with phosphatidyl-choline constituting the majority of them (12) . Table I provides a summary of TFS's makeup (13,14). Hydrophilic medications are trapped in the core region of the vesicles facing the head portion, while hydrophobic drugs are entrapped in the tail portion of the phospholipid bilayer structure (15). Under the same conditions of preparation and energy input, the fatty acid chains of phospholipids promote the creation of bilayers and produce different vesicle sizes (16)

Table -1 main components of transferosome and their uses.

Ingredients	Examples	Importance
Phospholipids	Soya phosphatidylcholine Egg phosphatidylcholine Distearoylphosphatidylcholine Dipalmitoylphosphatidylcholine	vesicle forming substance

Edge activators	Span60, span 65, span80 Tween 20, tween 60, tween 80 Sodium cholate Sodium deoxycholate	Providdefoarmable properties
Solvents	Methanol Chloroform Ethanol	Used as solvent
Buffering agent	Phosphate buffer pH7.4 Phosphate buffer Ph 6. 4	Hydrating agent
Dyes	Rhodamine -123 Rhoamoine –DHPE Texas Red –DHPE Coumarine -6 Nile Red	Used for visualization of transferosome penetration with the help of confocal laser scanning microscope(CLSM)

Method of fabrication -

1. **The vortex-sonication technique**

The medicinal drug, EA, and mixed lipids (such as phospha-tidylcholine) are combined in a phosphate buffer and vortexed to create a milky suspension. After being sonicated, the suspension is extruded via polycarbonate membranes.

2. **Suspension homogenization technique**

An suitable quantity of an edge-active chemical, such as sodium cholate, is added to an ethanolic soybean phosphatidylcholine solution to create transfersomes. A total lipid concentration is produced by mixing this prepared solution with Triethanolamine-HCl buffer. The resultant suspension is then twice or three times sonicated, frozen, then thawed.

3.**Modified handshaking technique**

The "lipid film hydration technique," a modified hand shaking method, is used in this procedure to prepare the transfersomes. The drug, lecithin (PC), and edge activator were dissolved in a 1:1 mixture of ethanol and chloroform. Hand shaking was used to evaporate the organic solvent while it was above the lipid transition temperature (43°C). A thin lipid film was formed inside the flask wall with rotation. For the complete evaporation of solvent, the thin film was kept overnight. The film was hydrated with phosphate buffer (pH 7.4) with gentle shaking of 15 minutes at the corresponding temperature.

4. **Aqueous lipid suspension technique**

In this process, Drug –to- lipid ratio in the vehicle is fixed between ¼ and 1/9. The composition is preferred based on the specific formulation type.This would ensure the high flexibility of the vesicle membrane in comparison to the standard phosphatidylcholine vesicles in the fluid phase. Specifically, vesicles with the size ranging from 100-200 nm are prepared by using soyphosphatidylcholine with the standard deviation of size distribution (around 30%). This formulation could be prepared by suspending the lipids in an aqueous phase wherein the drug is dissolved.

5. The centrifugal process

In this process, alcohol is used to dissolve the drug, surfactants, and phospholipids. The solvent is then evaporated by rotary evaporation at 40°C under reduced pressure.The last remnants of solvent are removed undervacuum. Centrifuging at 60 rpm for an hour at room temperature hydrates the deposited lipid layer with the appropriate buffer. The resultant vesicles swell for two hours at room temperature. The resulting multi-lamellar lipid vesicles are then sonicated at room temperature .

6. Ethanol Injection method

In this technique an ethanolic solution contain a phospholipid , edge activator and drug was injected into an aqueous solution dropwise under homogenizer mixing. As the ethanolic solution comes into the direct contact with the aqueous solution, lipid molecules orient themselves and formed bilayer vesicles.[17,18,19]

Characterization parameter of Transferosome-

Transferosomes are often described similarly to liposomes, niosomes, and micelles. Transferosomes need to be screened for in the following characterization criteria.

1. Vesicle size dispersion and zeta potential

Malvern Zetasizer's dynamic light scattering (DLS) technology is used to determine vesicle size, size distribution, and zeta potential through a computerized inspection system.

2. Vesicle morphology

DLS or photon correlation spectroscopy are typically employed to measure vesicle diameter. The prepared sample was diluted with filtered saline after being filtered via a 0.2 mm membrane filter, and the size was then determined using photon correlation spectroscopy or DLS measurements. Transfersome vesicles may frequently be seen using phase contrast and transmission electron microscopy (TEM). By analysing the size and structure of vesicles with respect to time, it is possible to estimate the stability of a vesicle. For mean size and structural changes, respectively, DLS and TEM are employed.

3.Vesicle count per cubic millimetre

For the optimization of composition and other process factors, this parameter is crucial. Unsonicatedtransfersome formulations are diluted five times in 0.9% sodium chloride solution. For additional research, hemocytometer and optical microscope are employed.The following formula is used to count and compute the transfersomes in 80 small squares:

Total numbertransfersomes per cubic millimetre = (Total number of transfersomes counted x dilution factor x 4000)/Total squares counted.

4.Entrapment effectiveness

Normally it is expressed in terms of drug entrapment percentage. In this procedure, the unentrapped drug is initially separated using a minicolumn centrifugation technique . The vesicles were then broken up with either 0.1% Triton X-100 or 50% n-propanol. The equation for the entrapment efficiency is: Entrapment efficiency = (Amount entrapped/Total amount added) x100.

5. Drug content

Depending on the analytical method of the pharmacopoeial drug, the drug content is determined using one of the instrumental analytical methods, such as a modified high-performance liquid chromatography method using an ultraviolet detector, column oven, auto sample, pump, and computerised analysis programme.

6. Turbidity analysis

One technique that is frequently used for determining the turbidity of an aqueous solution is the Nephelometer.

7. Measurement of the degree of permeability or deformability

Permeability study is one of the crucial and distinctive characteristics for characterisation in the case of transfersomes. Pure water is used as the reference for the deformability investigation. A mixture of known-sized pores is passed through with the transfersomes preparation (through a sandwich of different microporous filters, with pore diameter between 50 and 400 nm, depending on the starting transfersomes suspension). After each run of the DLS measurements, the particle size and size distributions are recorded.

8. Penetration ability

For the evaluation of penetration ability of transferosome fluorescence microsopy is generally used.

9. Occlusion effect

In the case of conventional topical medicines, occlusion of the skin is thought to be beneficial for drug penetration. The occlusion, however, also turns out to be bad for elastic vesicles. The primary mechanism for vesicle penetration through the skin is hydrotaxis, or the flow of water from the skin's comparatively dry surface to deeper, water-rich areas. As it stops water from the skin from evaporating, it has an impact on hydration forces.

10 . Charge density and surface charge

Zetasizer may be used to determine the surface charge and charge density of transfersomes.

11. In –vitro Drug release

For the purpose of calculating the penetration rate, an in vitro drug release study is conducted. Before more costly in vivo investigations are carried out, the formulation is optimized based on the time required to reach steady state permeation, the permeation flux at steady state, and the data from in vitro study. Transferosomes suspension is incubated at 32°C, samples are obtained at various intervals, and the free drug is separated by minicolumn centrifugation to determine drug release. The amount of drug released is then determined indirectly by multiplying the original amount (100 percent entrapped and zero percent released) by the amount of drug entrapped.

12. In vitro skin permeation studies

For this work, a modified Franz diffusion cell with an effective diffusion area of 2.50 cm2 and a receiver compartment capacity of 50 ml was employed. Goat skin was used for an in vitro drug investigation in phosphate buffer solution. Goat abdomen skin that had just been removed from the slaughterhouse was used in the permeation tests. Hairs on the abdominal skin were plucked, and ordinary saline solution was used to hydrate the area. A cotton swab was used to rub the skin's adipose tissue layer away. Skin was preserved in isopropyl alcohol solution between 0 -40 degrees Celsius. The stratum corneum side of the treated skin was positioned horizontally on the receptor compartment, facing up toward the donor, to conduct the skin permeation investigation.

The volume of the receptor compartment was 50 ml, and the effective permeation area of the donor compartment exposed to the receptor compartment was 2.50 cm2. A magnetic stir bar operating at 100 revolutions per minute swirled 50 ml of phosphate buffered saline (pH 7.4) in the receptor compartment, which was kept at 37 0.5°C. On the skin, formulation (10 mg of the medication) was applied, and the top of the diffusion cell was covered. To maintain sink conditions, 1 ml aliquots of the receptor solution were taken out at the proper intervals and promptly replaced with an equivalent volume of brand-new phosphate buffers (pH 7.4). In order to calculate the release profile, correction factors for each aliquot were taken into account. Any instrumental analytical method was used to examine the materials.

13. Physical Stability

The initial drug entapped (%) in the formulation was determined and was stored in sealed glass ampoules.For at least three months, the ampoules were stored at 4±2°C(refrigeration), 25±2°C (room temperature), and 37±2°C(body temperature.. After 30 days, samples from each ampoule were examined to assess drug leakage. Keeping the initial drug entrapment at 100% 32, the percentage of drug loss was computed.[20]

Scientific Applications of Transferosome in Nanomedical Sector

1.Delivery of NSAIDS - The majority of NSAIDs have a number of GI side effects, which can

be problematic. This can be avoided by utilisingtransfersome for transdermal delivery. Ketoprofen and diclofenac have both been studied. The Swiss regulatory body (Swissmedic) approved the sale of ketoprofen in a transfersome formulation in 2007. The medication will likely be sold under the trade name "Diractin." IDEA AG claims that other therapeutic items based on the transfersome technology are in the clinical development stage.21

2.Delivery of Anti -cancer drugs- A novel method of treating cancer, especially skin cancer, is made possible using transfersome technology. When methotrexate was explored for transdermal distribution utilisingtransfersome technology, the results were positive.22

Delivery of Anesthetic drugs-Application of transferosome that containing ansesthetic drugs induces a topical anesthesia , under the suitable condition within 10 minutes. Pain sensitivity is nearly as strong (80%) as comparable of subcutaneous bolus injection. Transferosomal anesthetics formulation has longer effect .23

Delivery of insulin - One method of successively delivering such high molecular weight medications to the skin is transfersome. Insulin is often given using a subcutaneous method, which is uncomfortable for the patient. Traditional insulin delivery issues are resolved by encapsulating insulin in a transfersome (transfersulin). Depending on the carrier composition, the therapeutic effect of transfersulin applied to undamaged skin is visible within 90 to 180 minutes.24

Delivery of Corticosteroid- Corticosteroid delivery issues are concealed by incorporating them into transfersomes. Transfersome encapsulation is used to optimise the safety of the epicutaneously delivered medication dosage while improving site specificity and total drug of

corticosteroid administration into skin. By using transfersomes technology, the dosage necessary for corticosteroid biological action is reduced.25

Delivery of protein and peptides- Proteins and peptides may be safely administered using transfersome technology and have been transported using transfersomes on a large scale. Because they are huge biogenic molecules and have a trouble entering the body, proteins and peptides are problematic for oral administration. This is the reason why injectables are still used to provide these peptides and proteins. Various strategies have been created to help this issue. In terms of bioavailability, transfersome is similar to that produced by subcutaneous injection of protein solution. Transfersome formulation of protein also elicited a potent immune response with repeated epicutaneous administration. For instance, following many cutaneous exposures, the adjuvant immunogenic serum albumin in transfersomes is just as immunologically active as the corresponding injected proteo-transfersomes preparations.26

Deliveryof herbal drug - Herbal drugs also be delivered via transfersometechnology . According to Xiao-Ying et al., transfersomes of capsaicin have superior topical absorption than pure capsaicin.[27]

Table-2

DRUG NAME	MAJOR FINDINGS
Sulforaphane	Anti-proliferative action against skin carcinoma(28)
5-flurouracil	Improved permeation and bioavailability against skin cancer (29).
Paclitaxel –modified TFS	Effectively retard the growth of melanoma (30).
Celecoxib –loaded TFS	Better permeation and anti-inflammatory activity (31).
Lornoxicam- loaded TFS	Suitable means for noninvasive treatment for acute or chronic pains on direct application (32).
Miconazole –loaded TFS	Effective for the treatment of superficial fungal infection .(33)
Nystatin	Enhanced solubility and antifungal activity (34).
Clindamycin phosphate loaded - TFS	Evaluated for *ex-vivo*permeation and *in-vitro* release study (35)
Retinyl Palmitate	Reduce hetatoxicity and teratogenicity in comparision of oral route (36)
Adapalene and ascorbic acid co-loaded –TFS	TFS showed significantly good deformability as compared to Adiffaqs gel for the treatment of acne vulgaries.(37)
Baicalin and Berberine –loaded TFS	TFS showed eminent photoprotective and antioxidant effect (38)

Future Scenario

TFS have brought up new possibilities for the transdermal mode of medication administration. By pushing through the internal lipid of the stratum corneum, they can transport medicinal compounds with both low and large molecular weights. The TFS has a number of benefits over conventional vesicular delivery methods, including decreased toxicity, biocompatibility, and sustained or regulated drug administration. This led one to the conclusion that the limitations of the transdermal drug delivery system may be solved by new generation ultra-deformable liposomes. In contrast to traditional liposomes, TFS displayed high steady-state flow and permeability coefficient.

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