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Transfersomes: An Emerging Approach for Enhanced Transdermal Drug Delivery

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ABSTRACT

Transdermal drug delivery has emerged as an effective alternative to conventional oral and parenteral routes because it enhances patient compliance while avoiding first-pass hepatic metabolism and gastrointestinal degradation. Among the various vesicular carrier systems developed for transdermal delivery, transfersomes have gained considerable attention owing to their exceptional flexibility and superior skin-penetrating ability. Transfersomes are ultradeformable lipid vesicles composed primarily of phospholipids and edge activators that enable them to traverse the narrow intercellular pathways of the stratum corneum without disrupting skin integrity. Their unique structural characteristics facilitate the efficient encapsulation and delivery of both hydrophilic and lipophilic therapeutic agents, thereby improving drug bioavailability and therapeutic efficacy. In recent years, transfersomes have been extensively investigated for the transdermal administration of a wide range of drugs, including anti-inflammatory agents, antivirals, anticancer drugs, proteins, peptides, and herbal compounds. This review summarizes the composition, mechanism of skin penetration, formulation approaches, characterization methods, advantages, limitations, and diverse pharmaceutical applications of transfersomes. Recent advances and future prospects of transfersome-based drug delivery systems are also discussed, highlighting their potential as promising nanocarriers for targeted and controlled transdermal therapy.

Keywords: Transfersomes, Transdermal drug delivery system, Ultradeformable vesicles, Nanocarriers, Skin permeation, Targeted drug delivery.

INTRODUCTION:

The transdermal drug delivery system (TDDS) has become an important strategy for administering therapeutic agents through the skin, offering a convenient, painless, and non-invasive alternative to oral and injectable dosage forms. Unlike conventional routes, transdermal administration bypasses hepatic first-pass metabolism and minimizes gastrointestinal degradation, resulting in improved bioavailability and more consistent plasma drug concentrations. In addition, sustained drug release from transdermal formulations reduces dosing frequency and enhances patient adherence, particularly in the long-term management of chronic diseases.¹

Despite these advantages, the outermost layer of the skin, the stratum corneum, acts as a highly effective barrier that restricts the permeation of most drug molecules. To overcome this limitation, several advanced drug delivery approaches have been developed, including chemical penetration enhancers, iontophoresis, sonophoresis, microneedles, and vesicular carrier systems. Among these, vesicular drug delivery systems have attracted considerable interest because they can encapsulate both hydrophilic and lipophilic drugs while protecting them from degradation and improving their penetration across biological membranes.²

Transfersomes represent one of the most promising vesicular carriers for transdermal drug delivery. These ultradeformable lipid vesicles are composed of phospholipids and edge activators that impart remarkable elasticity to the vesicular membrane. This unique property enables transfersomes to deform and migrate through intercellular spaces much smaller than their own diameter without losing structural integrity. Consequently, they deliver therapeutic agents into deeper layers of the skin and, when required, into systemic circulation with enhanced efficiency.³

The versatility of transfersomes has expanded their application to numerous therapeutic areas, including the delivery of antiviral, anti-inflammatory, anticancer, antifungal, cardiovascular, protein, peptide, and herbal drugs. Their ability to improve drug permeation, enhance bioavailability, reduce systemic adverse effects, and provide controlled drug release has made them an attractive platform for modern pharmaceutical research. Ongoing advances in nanotechnology and lipid-based drug delivery systems continue to strengthen the potential of transfersomes as an effective carrier for targeted and controlled transdermal therapy.

This review provides a comprehensive overview of transfersomes, including their composition, mechanism of action, formulation techniques, characterization methods, advantages, limitations, pharmaceutical applications, and future perspectives in transdermal drug delivery.⁴

Advantages of Transdermal Drug Delivery Systems⁵

1. Transdermal medication involves the constant delivery of an infusion of a drug over a long period of time. It is also possible to eliminate adverse effects or therapeutic failure that is often linked to intermittent dosing.
2. The combination of the simplified medication regimen results in a better patient compliance and less inter and intra-patient variability.
3. The preservation of the drug concentration in the diphasic may not be required at times. The best sequence of pharmacological effect is the result of application and removal of transdermal patch.
4. These systems can be self-administered.

Disadvantages of Transdermal Drug Delivery Systems⁵

1. The drug should possess some desirable physicochemical characteristics of penetration, in the stratum corneum and in case the dose of the drug to achieve therapeutic value is above 10 mg/day, then transdermal delivery of the drug will be extremely challenging.
2. The only type of drugs that can be candidates of TDDS due to the natural constraints of drug entry by the skin impermeability are relatively potent drugs.
3. Contact dermatitis may occur at the place of application of some patients with one or more of the system components, requiring discontinuation.
4. Another field that must be looked into before deciding to come up with a transdermal product is clinical need.
5. The barrier role played by the skin varies between one point on the individual to the other, between people as well as with age.

Transferosomes⁶

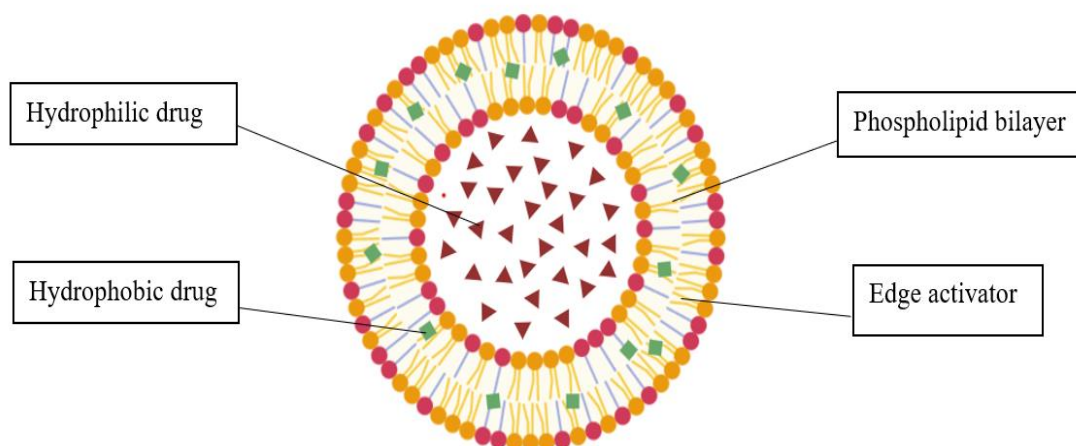
Transferosomes are highly deformable lipid-based nanovesicular carriers specifically developed to enhance the transdermal delivery of therapeutic agents across the skin barrier. The term *transferosome* is derived from the Latin word *transfere*, meaning "to carry across," and the Greek word *soma*, meaning "body." These vesicles were first introduced by Gregor Cevc in the early 1990s as an advanced modification of conventional liposomes to overcome the limited skin permeability associated with traditional vesicular systems.

Structurally, transferosomes consist of phospholipids forming a bilayer membrane along with an edge activator, which is generally a single-chain surfactant such as Tween 80, Span 80, sodium cholate, or sodium deoxycholate. The incorporation of edge activators imparts remarkable elasticity and flexibility to the lipid bilayer, enabling the vesicles to deform and traverse intercellular pores that are considerably smaller than their own diameter without compromising membrane integrity.

Unlike conventional liposomes, transferosomes possess the unique ability to respond to the natural hydration gradient across the skin. Following topical application under non-occlusive conditions, water evaporation from the skin surface generates an osmotic gradient that drives these ultradeformable vesicles through the stratum corneum into the deeper epidermal and dermal layers. This mechanism significantly enhances drug penetration and facilitates efficient systemic or localized drug delivery.

Transferosomes are capable of encapsulating hydrophilic drugs within their aqueous core while simultaneously incorporating lipophilic drugs into the phospholipid bilayer. This dual-loading capability makes them suitable for delivering a broad spectrum of therapeutic agents, including antiviral, anti-inflammatory, antifungal, anticancer, cardiovascular, peptide, protein, and herbal drugs. Furthermore, their biocompatibility, biodegradability, and ability to improve drug bioavailability have established transferosomes as one of the most promising nanocarrier systems in modern pharmaceutical research.

Recent developments in transferosomal technology have focused on improving vesicle stability, drug-loading efficiency, controlled drug release, and targeted delivery through the incorporation of novel phospholipids, surfactants, and polymeric components. These advances continue to expand the clinical potential of transferosomes for the treatment of dermatological disorders as well as systemic diseases requiring non-invasive drug administration.

Structure of transferosomes⁷**Fig no.1:** Structure of transferosomes**Advantages of transferosome⁸**

1. High efficiency to alter to pore size hence greater penetration capability.
2. Transport smaller and larger weighted molecules, without any loss being measurable.
3. Depot drug, the drug is released gradually and firmly.
4. Applied to the systemic and topical level.
5. Avoid first-pass metabolism, physicochemical degradation and offer protection to encapsulated drug.
6. Specific and augmented bioavailability.
7. Easy formulation and evaluation process.
8. Biodegradable and biocompatible.
9. Giving compliance to the patients and also suitable to unconscious patients.

Disadvantages of transferosome⁹

1. Transferosomes formulations have unstable lipids that are susceptible to oxidation.
2. These are highly expensive.
3. It was also one which needed a special method in the preparation of transferosome.

Limitations¹⁰

1. Chemically unstable, highly oxidatively degraded.
2. Formulations are expensive.

Composition of transferosomes¹¹

The lipidic vesicular carrier transferosome, consists of phospholipids that may be of natural origin or may be synthetic in nature and edge activators³⁰⁻³³. The lipids on entering in contact with the aqueous environment, self-assemble to create a bilayer and in the process, they also enclose a hydrophilic core in the centre. The edge activators or softening agents as they are also known as, put in the process of formulation, increase the flexibility and deformability of the lipidic vesicle by destabilizing the lipid bilayer. Their malleability gives them the capacity to squeeze even through the pores of the skin and membranes that are smaller than their own size without any tear. As transferosomes consist of lipids, any hydrophilic and lipophilic drug may be delivered by them. Transferosomes may be also loaded with imaging dyes i.e. Nile red, etc.

The components used in the formulation of transferosomes are compiled in the table 1.

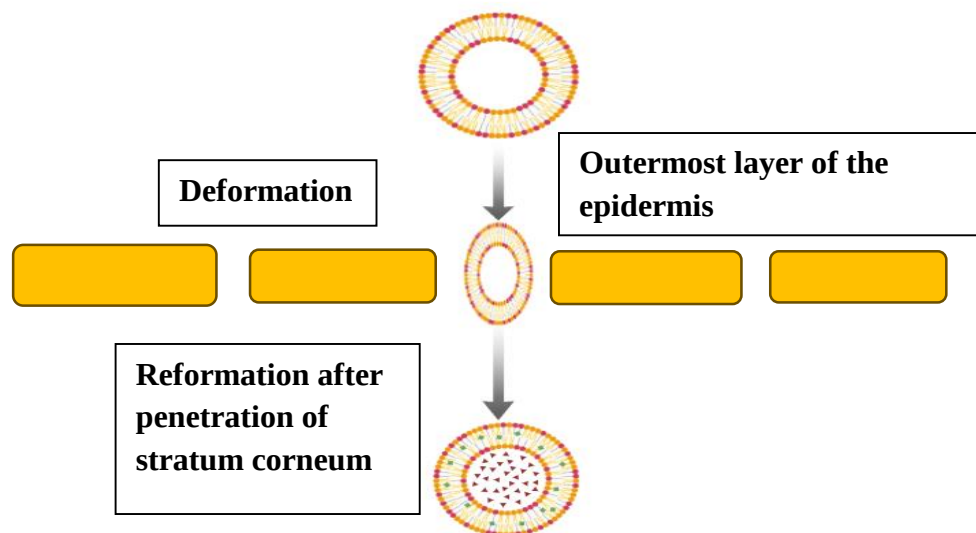
Table 1: Components used in the formulation of transfersomes

Components	Examples	Purpose
Edge Activator	Span 80, Tween 80, Sodium deoxy Cholate, Sodium Cholate	To impart flexibility to formed vesicles
Phospholipid	Phosphatidylcholine, Soya Phosphatidylcholine, Dipalmitoyl phosphatidylcholine	To form self-assembled vesicles
Solvents	Chloroform, Methanol, Ethanol	Solvent system to dissolve different components
Hydrating Agent	Distilled Water or Saline phosphate buffer Distilled Water	To hydrate the lipid film formed after evaporation of the solvent
Active Pharmaceutical ingredient	Miconazole Nitrate, Itraconazole, Ketoprofen, Diclofenac Sodium	For providing pharmacological effect

Mechanism of Action of transfersome ¹²

Transfersomes can penetrate intact skin effectively, without the need of occlusion, under nonocclusive conditions, which develop trans epidermal osmotic gradient because of surface water evaporation. The gradient causes the vesicles to be pulled towards the deeper, moist layers of the skin through a process called hydrotaxis (xerophobia). The resulting transdermal water activity gradient yields enough force to dilate intercellular junctions to create temporary transcutaneous channels (2030 nm) via which ultra-deformable transfersomes move down the hydration gradient.

Transfersomes have high deformability through the addition of edge activators, resulting in high skin permeation as compared to conventional liposomes due to the presence of soft, flexible, and highly deformable lipid bi-layers. These vesicles are able to isolate hydrophilic, lipophilic and amphiphilic drugs and enter the stratum corneum to the dermis and the systemic circulation. Ethanol or propylene glycol are penetration enhancers that increase the fluidity of lipid bi layers to help in the process of permeation. All in all, the transfersomal drug delivery is regulated by osmotic-driven transport, membrane deformability and optimized vesicle composition.

**Fig no.2:** Mechanism of Action of transfersome**Formulation techniques for Transfersomes ¹¹**

The techniques widely used for the formulation of transfersomes are given below

a) Rotary Film Evaporation Method/ Modified Hand Shaking Method

Rotary Film Evaporation Process/ Alternated Hand Shaking Process. The most commonly adopted approach to making transfersomes is the Rotary Film Evaporation or Modified Hand Shaking Method since it is an effective method of delivering drugs. Under this method, phospholipids and edge activators are dissolved in a volatile organic solvent, and in case the drug is lipophilic then it is added to the mixture. This is sonicated until clear and homogenous

and transferred to a rotary evaporator where the solution is rotated under a vacuum at a constant temperature to a thin film of lipids forming on the walls of the flask. This film is then moistened in a water medium, which enables it to expand and it becomes vesicles of bilayers. It is possible to add hydrophilic drugs to the aqueous phase during the hydration process. Lastly, the vesicles are made uniform by sonication or extrusion methods of vesicles. The transferosomes resultant are very efficient in permeating the stratum corneum of the skin and transporting therapeutic agents to their places of action making the technique a powerful one in the study of drug delivery.

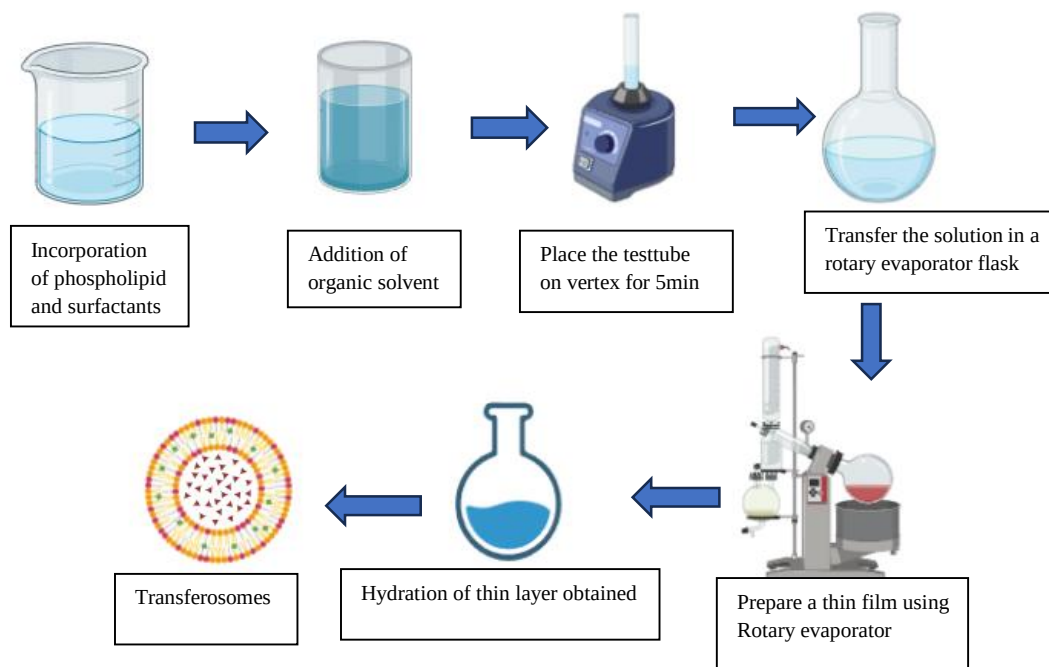


Fig no.3: Rotary Film Evaporation Method

b) Reverse Phase Evaporation Method:

In this method phospholipids are dissolved in an organic solvent, e.g. chloroform, methanol or ethanol and putting the dissolution in a flask³⁷. Nitrogen gas is purged in the flask with the addition of hydrophilic media, which is also a surfactant (EA). The drug is added either into the hydrophilic or lipophilic media depending on the solubility properties. The resulting mixture is sonicated until it is a clear dispersion that is homogeneous in nature and is followed by observing that this will need at least thirty more minutes after sonication to make sure that no separation takes place. Lastly, the sonicated mixture is processed at reduced pressure in order to eliminate the organic solvent in the preparation.

c) Vortex/Sonication Method:

The vortexing technique requires the mixing of the phospholipids, drug and edge activator in the phosphate buffer saline (PBS) solution and then vortexing of the mix until a suspension of a milky white in colour is attained. The product is then sonicated in a few minutes after which extrusion is done by using a membrane filter that is of polycarbonate whose size of the pores is 100nm.

d) Ethanol Injection Method:

Elastic liposomes have been formulated using the technique which is a popular technique. The first step in the process starts by dissolving the drug in an aqueous medium and then heating the mixture under a constant stirring temperature. Then, drop wise the solution of ethanol with edge activator and phospholipids are added to the aqueous medium. The mixing of the ethanolic solution of phospholipids and EA with the aqueous solution causes the precipitation of the lipid molecules that consequently causes the formation of bilayer structures.

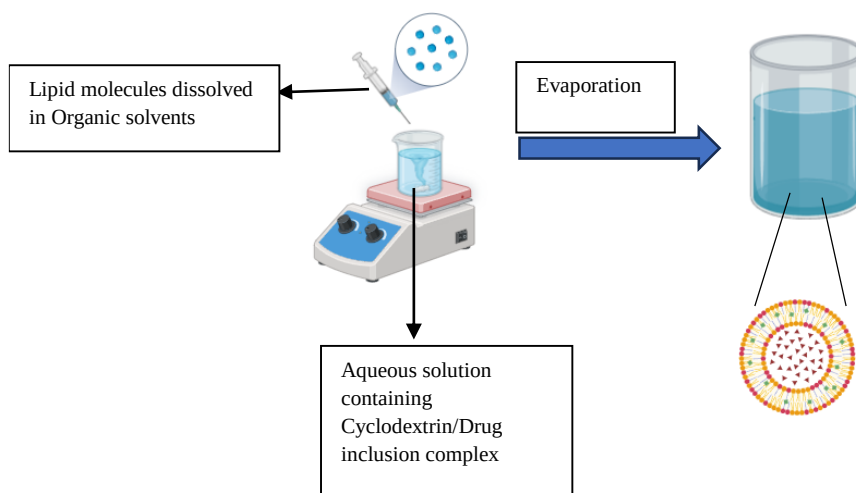


Fig no.4: Ethanol Injection Method

e) Freeze Thaw Method:

In order to come up with the transferosomal formulation, a process that incorporates freezing and heating alternately is utilized. The multilamellar vesicles (MLV) are subjected to extremely low temperatures by dipping during 30 s at -30°C (nitrogen bath) and then subjected to high temperatures in a water bath. The procedure is repeated a few times to generate the transferosomes which are desired.

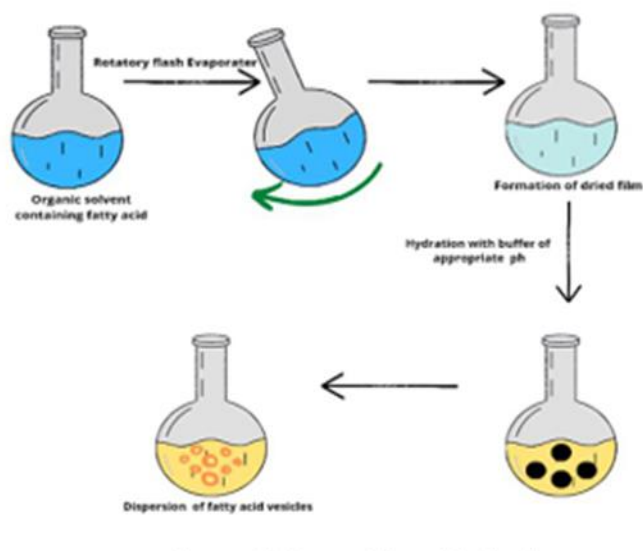


Fig no.6: Freeze Thaw Method

Characterization and evaluation of transferosomes¹³**1.Determination of vesicle diameter.**

One of the main problems when the transferosomes are being produced is their vesicle size. It provides significant data on the control of the preparation technique and could be used to optimise the processes. Vesicles below 40 nm are very small and can readily undergo fusion by virtue of the fact that the bilayer membrane is highly curved. Photon correlation spectrophotometry or dynamic light scattering (DLS) method can be used to determine it.

2.Vesicle shape and type of Transferosomes determination.

vesicles could be visualized with TEM, Phase contrast microscopy etc.

3. Vesicle size distribution determination and zeta potential determination.

Dynamic Light Scattering Method (DLS) was used to evaluate the size, size distribution and zeta potential of the vesicles by using a computerized inspection system on Malvern Zetasizer.

4. Quantification of number of vesicle per cubic mm.

This is a significant parameter when it comes to optimizing the composition and other variables of the process. The Dilution of non sonated transfersome formulations is done with 0.9% sodium chloride solution 5 times. Thereafter, further study can be done by using haemocytometer and optical microscope.

5. Entrapment efficiency determination.

The entrapment efficiency is defined as the percentage entrapment of the drug added. Entrapment efficiency can be obtained by separating that drug that is not entrapped. The vesicle may be torn apart after centrifugation (to get the unentrapped drug out).

6. Content determination of drug.

The instrumental analytical methods that can be applied to determine drug contents include modified high performance liquid chromatography method (HPLC) method with the use of a UV detector, column oven, auto sample, pump and computerized analysis program based on the analysis method of the pharmacopoeial drug.

7. Turbidity measurement

Nephelometer can be used in turbidity of drug in aqueous solution.

8. Surface charge and surface charge density.

To find surface charge and charge density of transfersomes, Zeta sizer is employed. Zetasizer can be used to determine the surface charge and Charge density of transfersomes.

9. Confocal scanning laser microscopy examination.

In this method lipophilic fluorescence markers are introduced into the transfersomes and the light generated by the markers utilized in the purpose of following: a) Investigation of the mechanism of dermal penetration of transfersomes. b) Identification of histological structure of the skin, forms and architecture of skin penetration pathway. c) Comparison and contrast of the mechanism of penetration of transfersomes verses that of liposomes, niosomes and micelles.

10. In-vitro drug release

In vitro drug release experiment is conducted in order to measure the rate of permeation. To find in vitro release of drug, beaker method is utilized where transfersomes suspension is incubated at 32 degree C with cellophane membrane and the samples are collected at various periods and then regulated by various analytical methods (UV, HPLC, HPTLC) and the free drug is centrifuged on mini column and then the quantity of drug release is given.

APPLICATION OF TRANSFEROSOMES ¹⁴

1. Delivery of insulin

Transfersome is one of the successive ways to deliver such large molecular weight drugs on the skin. Insulin is generally administered by subcutaneous route that is inconvenient for patient. Encapsulation of insulin in transfersome (transfersulin) overcomes all problems arises with conventional insulin delivery. After application of transfersulin on the intact skin, therapeutic effect observed after 90-180 min, depending on the carrier composition.

2. Delivery of corticosteroids

Problems arise with corticosteroids delivery is mask by incorporation it into transfersomes. Site specificity and overall drug of corticosteroid delivery into skin by optimizing the epicutaneously administered drug dose safety is achieved by transfersome encapsulation. Dose required for biological activity of corticosteroid is less by use of transfersomes technology

3. Delivery of proteins and peptides

Transfersomes have been widely used as a carrier for the transport of proteins and peptides also safely given by means of transfersome technology. Proteins and peptide has problem is it is difficult to transfer into the body, are large biogenic molecules, GI tract degradation is problem arise when given orally. That's reasons why these peptides and proteins still given by means of injectables. A number of approaches have been developed to improve this condition. Transfersome is somewhat identical to that resulting from subcutaneous injection of protein suspension in terms of bioavailability. On repeated epicutaneous application, transfersome preparation of protein also induced a strong immune response. For example, the adjuvant immunogenic serum albumin in transfersomes, after several dermal challenges, is as active immunologically as is the corresponding injected proteo-transfersomes preparations.

4. Delivery of interferon (INF)

INF also delivered using transfersome as a carrier, for example, leukocyte-derived INF- α is a naturally occurring protein having antiviral, antiproliferative, and some immunomodulatory effects. Transfersomes 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 transfersome containing interleukin-2 (IL-2)

and INF- α for potential transdermal application. They reported delivery of IL-2 and INF- α promising by transferosomes insufficient concentration for immunotherapy.

5. Delivery of anticancer drugs

Transferosome technology provides a new approach for cancer treatment, especially skin cancer. Result found to be favorable when methotrexate was tried for transdermal delivery using transferosome technology.

6. Delivery of anesthetics

Application of transferosome containing anesthetics induces a topical anesthesia, under suitable conditions, within 10 min. Effect when we said in case of pain in sensitivity is nearly as strong (80%) as of a comparable subcutaneous bolus injection, but transferosomal anesthetics preparation has last longer effect.

7. Delivery of herbal drugs

Herbal drug also delivered by transferosome approach. XiaoYing et al. who shows the better topical absorption of transferosomes of capsaicin in comparison to pure capsaicin.

FUTURE PERSPECTIVES ¹⁵

Transferosomes have emerged as one of the most promising nano vesicular carriers for transdermal drug delivery because of their exceptional deformability, high drug-loading capacity, and enhanced skin penetration. Recent advances in nanotechnology, lipid engineering, and surface modification are expected to further improve the stability, targeting ability, and controlled drug release of transferosomal formulations. Future research is focused on the development of stimuli-responsive transferosomes, ligand-targeted delivery systems, and combination therapies for the treatment of chronic skin disorders, cancer, and systemic diseases. Furthermore, large-scale manufacturing, long-term stability studies, regulatory approval, and well-designed clinical trials are essential for the successful commercialization of transferosome-based pharmaceutical products.

CONCLUSION ¹⁶

Transferosomes are highly deformable lipid vesicles capable of traversing skin pores much smaller than their own diameter, enabling efficient penetration through the stratum corneum. Their unique flexibility enhances the transdermal and dermal delivery of a wide range of therapeutic agents, resulting in improved bioavailability, targeted drug delivery, and reduced systemic adverse effects. Owing to their ability to encapsulate both hydrophilic and lipophilic drugs, transferosomes have emerged as promising nanocarriers for the treatment of various dermatological disorders and systemic diseases. Furthermore, they have demonstrated potential in the topical delivery of anticancer agents for conditions such as melanoma, actinic keratosis, squamous cell carcinoma, Kaposi's sarcoma, and basal cell carcinoma. Although encouraging results have been obtained in preclinical and clinical studies, further large-scale clinical trials and commercialization efforts are required to establish transferosomes as a widely accepted drug delivery system.

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