ABSTRACT

The development of innovative medicine delivery methods is currently generating renewed interest. These innovative medication delivery technologies also include vesicular drug delivery system. Skin permeability, or TDDS, is extremely impermeable to macromolecules and hydrophilic medicines but permeable to small molecules and lipophilic medications. Recent methods have led to the creation of two vesicular carriers: ethosomes and transferosomes, which are incredibly elastic lipid-based vesicles. Transferosomes can pass both high & low molecular weight medications transdermally. This has been used to enhance the efficiency of material transferring across skin intact by the use of sonophoresis, colloidal carriers, among other methods. These methods have a number of main advantages over convenient routes, including the avoidance of the first pass metabolism, the predictable and the extended duration of the activity, minimization of undesired side effects, improved pharmacological response, minimization of undesirable side effects. It allows for better intact vesicle penetration because of its high deformability. Because they may formed of naturally occurred phospholipids and have a high efficiency entrapment, they may biocompatible and biodegradable. The preparation process was correspondingly refined and validated because the preparation factors depend on the manufacturing process used to make the formulation. It is possible to characterise transferosomes to learn about their drug content, entrapment...
effectiveness, size, morphology, ability to penetrate, in vitro drug release, the occlusion effect, surface charge. This improves the stability of the labile drugs and offers controlled release.

**KEYWORDS:** Novel Drug Delivery System, Optimisation, Transdermal drug delivery system, Transferosomes.

**INTRODUCTION**

The vesicular carrier systems for transdermal medication administration that have attracted the most attention in recent years are liposomes and niosomes. In order to improve medication delivery inside of vesicles' cavities and tag the vesicles for cell selectivity, researchers have investigated the features of vesicle structures. Vesicles are used in transdermal delivery due to the ability to act as penetration enhancers and drug carriers to transport drug molecules that are entrapped across the skin.[1] Additionally, in the case of topical formulations, these vesicles act as a reservoir for the gradual releasing of active ingredients, and in case of transdermal formulation, as a rate-limiting barrier for the controlled of systemic absorption. For many years, the vesicles' significance in celluarly communication and particle particle transportation has been well understood.

Rigid vesicles of the liposomes and niosomes and extremely deformable vesicles-transferosomes different type of liposomal formulations.[2]

The following are drawbacks of liposomes and niosomes:

- They are not appropriate for transdermal distribution because they may stuck in upper layers of the stratum layer, which prevent them from reaching the deeper layers of the skin.
- Though tailored distribution is ensured by vesicular systems, liposomal or niosomal category vesicles typically fall short of the needed transdermal penetration.[3-6] The "transferosomes," a novel vesicular derivative, have made it possible to reduce the poor transdermal oriented penetration of many medications,[7] A unique variety of liposome called a transferosome is made of phosphatidyl-choline plus an edge activator & are soft, pliable vesicle designed for improved active agent deliveries.

They are trademarked by the German business named IDEA AG, which uses them to describe its unique delivery system. The term, which translates as "carrying body," comes
from the Greek word "soma," which mean "body," and the Latin verb "transfere," which means "to carry across."\textsuperscript{[8]}

![Fig. 1: Structure of transferosomes.\textsuperscript{[9]}](image)

**Uses and advantages of Transferosomes**

Transferosomes can be accommodate medicinal molecule with wide spectrum of solubilities because its infrastructure combines hydrophobic and hydrophilic moieties. With no discernible loss, transferosomes can contract and travel through spaces that may five to ten times lower weight than their own diameter.\textsuperscript{[10-11]} This great deformability allows intact vesicles to penetrate more effectively.

Transferosome are self-aggregate with incredibly flexi-membrane that transfer drugs into or through the skin in a consistent manner. Compared to typical liposomes, these vesicular arranged vesicle are a number of order of magnitude with more elastic. Transferosomes circumvent obstacle of skin penetration by squeezed along the corneum's internal arranged sealing lipids.\textsuperscript{[11]} Cevc and colleagues introduced the idea of transferosome as a vehicle for transdermal drug delivery in 1992.\textsuperscript{[12]}

Since then, numerous studies on the transferosomes and their active potential use as drug carrier have been conducted. Peptide delivery using transferosomes offers a highly effective method for the topical administration of high molecular weight medications like protein insulin. For a potential transdermal use, Hafer researched the formulation of the interleukin 2 and the interferon an incorporating transferosome.
A combination of the lipids and the biocompatible membrane softeners are present in transferosomes for the potential transdermal application. The ideal mix causes the elastic liposomal membranes to stretch and makes it possible for entry through epidermal channels that carriers have already opened. A transferosome is a supramolecular structure that has the potential to cross permeability barriers and transport materials from one location to another.\(^{[11-12]}\) The stratum corneum is easily squeezed out of them due to their easily malleable characteristics. The mechanism for the penetration is creation for a "osmotic active gradient" brought on by evaporation of the water while applying lipid suspension of the transferosomes to skin surface.\(^{[11]}\) Transcellular or intracellular pathways are used by transferosomes to enter the stratum corneum.\(^{[7,10,11]}\) With excellent distributions properties of the transferosomes, they have widely used as carrier for various of proteins, anti-cancer drugs, analgesics, anaesthetics, anti-fungal drugs, corticosteroids, insulin, albumin, sex hormone etc.\(^{[5,11,13]}\) Due to the fact that they may produced from the natural phospholipids, much like the liposomes, they are biocompatible and biodegradable. They may have a highly entrapment efficacy, which for a hydrophobic medication is close to about 90%. It guard against metabolic breakdown of the medication that is encapsulated.\(^{[13,14]}\) They serve as depots, slowly and gradually discharging their contents. They can be used to deliver medications topically or systemically. Thus, the complex lipid structures known as transferosomes can enhance the site specificity of bioactive compounds, prolong their release, and boost transdermal flow.

**Composition of Transferosomes**

1. Amiphicathic component (phosphatidyl-choline), in which aqueous solvents self-assembled into lipid bilayer that can close into straight forward lipid vesicle, makes up the first of the transfersome's two primary aggregates.

2. A bilayer softening element that improves the permeability and flexibility of the lipid bilayer, such as a biocompatible surfactant or medication.\(^{[15]}\)

As a result, the resulting flexible and permeability-optimized transferosome vesicle may quickly and readily change its form by matching the localized concentration of the each bilayer components to local stress it is under. The artificial membrane of the transferosome is therefore "softer," "more flexible," and "better adaptable" than that of such more traditional vesicles.
Table 1: Different types of additives used in the formulation of transfersomes.

<table>
<thead>
<tr>
<th>S.No.</th>
<th>Classes</th>
<th>Examples</th>
<th>Uses</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Phospholipid</td>
<td>Soya phosphatidyl choline, dipalmitoylphosphatidyl choline, egg phosphatidyl choline</td>
<td>Vesicle formed component</td>
</tr>
<tr>
<td>2</td>
<td>Surfactant</td>
<td>Sod.cholate, Tween-80, Span-80, Sod.deoxycholate, Tween 20</td>
<td>Vesicle formed component</td>
</tr>
<tr>
<td>3</td>
<td>Solvent</td>
<td>isopropyl alcohol, chloroform, Ethanol, methanol,</td>
<td>As a normal solvent</td>
</tr>
<tr>
<td>4</td>
<td>Buffering agents</td>
<td>Saline phosphate buffer, phosphate buffer, 7% V/V ethanol</td>
<td>As hydrating medium</td>
</tr>
<tr>
<td>5</td>
<td>Dyes</td>
<td>Rhodamine-DHPE, Fluorescein-DHPE, Rhodamine-123, Nile-red</td>
<td>For the CSLM study</td>
</tr>
</tbody>
</table>

Preparation Methodology

1. **Vortexing-sonication process**
   The medicinal drug, EA, and mixed lipids (such as phosphatidylcholine) are combined in the phosphate buffer and then it vortexed to create a thick milkified suspension. After being sonicated, the forming suspension is extruded via polycarbonate membranes.

2. **Suspension homogenization method**
   This method involves combining an appropriate quantity of edged active chemical, like sodium salt (cholate), with an ethanolic soybean phosphatidylcholine solution. A total lipid concentration is produced by mixing this is the prepared solution with Tri-ethanolamine with HCl buffer. The resulting suspensions undergoes two or three cycles of sonication, freezing, and thawing.

3. **Modified handshaking Method**
   The "lipid film based hydration technique," a modified method of hand shaking method, is used in this procedure to prepare the transfersomes. The drug, the PC, and edged activator were dissolved in a iso-molar mixture of ethanol and chloroform. Hand shaking was used for the evaporatio of the organic solvent while it was above lipid based transition temperature. Rotation caused a thin layered lipid coating to develop on the flask wall. For the solvent to completely evaporate, the thin film was left on all night. The film was then gently shaken for 15 minutes at the appropriate temperature while being hydrated with the phosphate buffer of pH 7.4.
4. **Aqueous lipid suspension method**

The vehicles used in this procedure have a predetermined Drug : Lipid between 1/4 to 1/9. Their composition is favoured based on the specific formulation type. As opposed to typical PC vesicles in fluid phase, this would guarantee the great flexibility of vesicle membrane. Particularly, soyphosphatidylcholine is used to create vesicles with a size distribution with a standard deviation of 100–200 nm (around 30–40 percent). The lipids could be suspended in an aqueous phase in which the medication is dissolved to create this formulation.

5. **Centrifugation method**

In this procedure, alcohol is used to dissolve the medication, surfactants, and phospholipids. The solvent is then eliminated using rotary evaporation at 40°C under reduced pressure. Under vacuum, the last remnants of the solvent are eliminated. Centrifuging done at 60 rpm with an hour at normal room temperature hydrates deposited lipid layer with the proper buffer. The resultant vesicles swell for two hours at normal room temperature. That resulting multi-lamellar layered lipid vesicles are sonicated again at normal room temperature.\[16-18\]

**Mechanism of Action**

Because water evaporates when the lipid suspension can applied to their skin surface, an osmotic gradient is created, which is mechanism by which the transfersomes can penetrate the skin. Transfersomes have a higher propensity to bind and hold water because of their great bilayer deformability. In the event of an ultra deformable and very hydrophilic vesicle, dehydration does not occur; however, it may be involved in a transport process linked to forward osmosis. The deeper strata (water-rich section) are reached after application to the non-occluded skin surface, where they are hydrated. Then, use natural transepidermal activity to dehydrate lipid vesicles inside the stratum corneum to reach the deeper epidermal layer. As a result, the stratum corneum of the epidermis's moisture gradient affects transfersome uptake.\[19-20\]

**Optimization of formulation containing transfersomes**

The Lecithin, the surfactant ratio, the effect of different solvent, the impact of different surfactant, and the hydration medium may a few examples of process variables. This might have an impact on how the transfersomes are made and their characteristics. Accordingly, the transfersome preparation process will be optimised and validated. The manufacturing process for formulation affects the processing variables. These instrument employed for optimization
is the drug's entrapment efficiency. When creating a specific system, other variables were held constant.\textsuperscript{[21]}

**Characterisation method**

Transfersomes are typically described in a way that is comparable to that of liposomes, niosomes, and micelles. For transfersomes, the following characterised criterion must be examined.

1. **Vesicle size and its distribution and zeta potential**
   Malvern Zetasizer's automated inspection system and the dynamic light scattering method (DLS) were utilised to measure the vesicle size and its distribution, and zeta potential.

2. **Vesicle morphological structure**
   DLS or photon correlated spectroscopical method are typically employed to measure vesicle diameter. The prepared sample was diluted with filtered saline after being filtered through a 0.2 mm membranous filter, and the size was then determined using photon correlated spectroscopical or DLS measurements. Transfersome vesicles are frequently seen using phase related contrast and transmission electron microscopical method (TEM). Analyzing how vesicles change in size and shape over time can reveal information about a vesicle's stability. For mean size and structural changes, respectively, DLS and TEM are used.

3. **Entrapment efficiency**
   Usually quantified in terms of the percentage of drugs entrapped. The unentrapped medication is first separated using a minicolumn centrifugation technique in this procedure. The vesicles were then broken up with either 50\% of n-propanol (0.1\% Triton X-100). The formula for entrapment efficiency can be:
   \[
   \text{Entrapment efficiency} = \left( \frac{\text{Amount of the entrapped amount}}{\text{Total amount added}} \right) \times 100.
   \]

4. **Measurement of Drug contents**
   Depending on analytical methods of the pharmacopoeial drugs, the drug contents can determined applying one of instrumental analytical method, such as modified high performance liquid chromatography (HPLC) method using UV detector, columnated oven, automated sample, the pump, and computerised analytical programme.
5. **Degree of the deformability(permeability measurement)**

To study the crucial and distinctively identified characteristics to transferosome characterisation is the permeability study. When doing the deformability investigation, pure water is used as the reference. Depending on the beginning transferosomes suspension, the transfersomes preparation is passed through a variety of knownly-size pore (via overlapping of several microporous related filters having pore size diameter of 50-400 nm). After each of pass, the DLS measurement are used to record the particle size & its distributions.

6. **Occlusive Effect**

In case of conventional topically medicines, occlusion of skin is thought to beneficial for the drug permeation. Their blockage, however, also turns out to bad for the elastic vesicles. The main mechanism for the vesicle permeation through skin is quiet hydrotaxis, or the flowable of water from skin's comparatively more dry surface to deeper, water-riched regions. As they stop water from the skin from evaporating, it has an impact on hydration forces.

7. **In-vitro release of drug**

To calculating the penetration rate, an in-vitro release study is conducted. Before it more costly in vivo related investigations are carried out, formulation is optimised based on the time required to reach steady state permeation rate, the permeation flux rate at steady state, and data from the in-vitro study. Transferosomes suspensions are incubated at temperature of 32°C, samples that are obtained at various intervals, and the free drugs are separated by the mini-column centrifugation to determine release. Amount of the released is then determined indirectly using multiplication of the initial quantity (100 % entrapping amount and 0 % releasing amount) by amount of the drug entrapped at 0 times.

8. **In vitro skin permeation studies**

For this work, a modified Franz discovered diffusion cell with effective diffusing area of about 2.50 cm² and a receiver part of volume 50 ml was applied. Goat peeling dermis was used for an in-vitro investigation in buffer of phosphate solution (pH 7.4). Goat abdomen skin that had just been removed from the abattoir was used in the permeation tests. Hairs on the abdominal skin were plucked, and ordinary saline solution was used to moisturise the area. A cotton swab was used to massage the skin's adipose tissue layer away. Dermis was preserved isopropyl alcohol between 0-40 degrees Celsius. In order to conduct skin permeation investigation, the treated dermis was put horizontally on receptor part of the Franz discovered diffusion cell, with stratum corneum sidely pointed upward toward the donor part. Volume of
receptor part was 50 ml, and the effectively permeated area of the donor part exposing to the receptor part was 2.50 cm². A magnetic stir bar operating at 100 revolutions per minute stirred 50 ml of phosphate containing buffered solution (pH 7.4) in the receptor part, which kept at normal body temperature. On the skin, formulation (10 mg of the drug) was applied, and top of diffusion cell was completely covered. To maintain sink conditions, 1 ml of aliquots of receptor solution taken out at the proper intervals and promptly replaced with a same amount of brand-new phosphate buffer. In order for calculate the release profile, many correction related factor for each of aliquot were taken into account. Any instrumental analytical method was used to analyse the materials.

9. Physical stability
A sealed glass ampoule was used to store the initial amount of medication that was contained (in percent) in the formulation. For a minimum of three months, the ampoules were stored at four degrees below freezing, twenty-five degrees above ambient temperature, and 37 degrees below body normal temperature. After about 30 days, samples from each of ampoule were examined for assess medication leakage. By retaining the initial drug entrapment percent at about 100 percent, percentage of drug loss that was measured.[22]

Utilisation of Transferosome

1. Delivery of the proteins like insulin
The method for successively delivering such high weight medications to surface of skin is transfersome. Insulin (protein) is typically administered using a subcutaneous method, which is uncomfortable for the patient. Traditional insulin delivery issues are resolved by cause encapsulating the insulin in a transfersome called the transfersulin. Depending on carrier compositions, therapeutic effect is seen 90 to 180 minutes following the applying transfersulin solution to undamaged layer of skin.

2. Delivery of corticosteroids
Corticosteroid delivery issues are concealed by incorporating them into transfersomes. Transfersome encapsulation is used to optimise the safety of the epicutaneously delivered medication dose while improving site targeted specificity and total drug amount of corticosteroid that delivery into skin. By using transfersomes technology, the dose amount of corticosteroid necessary for biological activity is reduced.
3. Delivery of the proteins and peptides
Proteins and related peptides can 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. For these reasons, injectables are still used to provide peptides and proteins. Many strategies have been created to help this issue. In terms of bioavailability, transfersome is having same action to that produced by subcutaneously administered injection of the protein solution. Transfersome formulation of protein also elicited a potent immune response upon repeated epicutaneous administration. After multiple cutaneous challenges, the adjuvant related immunogenical serum albumin in transfersomes are just as immunologically activated compound as the correspondingly injected proteo-transfersomes.

4. Delivery of interferon (INF)
Leukocytes based derived INF, for instance, is naturally occurred protein with antiviral properties, antiproliferative properties, and some of the immunomodulatory properties. INF is also given via transfersome as a carrier. The application of transfersomes as delivery systems has potential for increase stability of labile pharmaceuticals and provide regulated release of the medication delivered. For possible transdermal use, Hafer investigated formulation of the transfersome comprising interleukin-2 and INF. They reported that the concentration of transfersomes used to deliver IL-2 and INF was insufficient for the immunotherapy.

5. Delivery of the anticancer drugs
Novel method of treating cancer, especially skin cancer, is made possible using transfersome technology. When methotrexate drug explored for transdermally distribution using the transfersome technologies, the results were positive.

6. Delivery of the anesthetics
With right circumstances, the applications of transfersome containing anaesthetics causes topical anaesthetic within 10 minutes. Impact in cases of the pain sensitivity almost as powerful as that of comparable subcutaneously injected bolus administration, but the transferosomal anaesthetics formulation has a longer and lasting efficacy.

7. Delivery of the non-steroidal anti-inflammatory drugs
Numerous Gastro intestinal adverse effects may issues that most non-steroidal anti-inflammatory drugs have. These drugs can be avoided by utilising transfersome for the
transdermal delivery system. Diclofenac and Ketoprofen have both been studied. The Swiss regulatory body approved the sale of ketoprofen drugs in a transfersome formulation in 2007. The medication will likely be sold under trade name of "Diractin." IDEA AG group claims that other therapeutics items basically related on the transfersome technologies are in the clinically development stage.

8. Delivery of herbal drugs

The transfersome technique is often used to deliver herbal drugs. According to XiaoYing et al., transfersomes of capsaicin have better topical absorption than pure capsaicin.[23-29]

Safety considerations

After repeated epicutaneous delivery, phospholipid solutions containing liposomes that have been reported to safe and non-irritated to the skin; they might even have extra beneficial cosmetical effects. These primary components of transfersome is often soy PC, which is typically considered safely used because it has been used as emulsifier in preparation of Microemulsion for parenterally administered nutrition and it is also employed in the form of injectable medication informations. Soy phosphatidylcholine must be at least 95% pure.[30] These findings suggest that the transfersome product will be quite safe for carriers.[30]

CONCLUSION

The transdermal route has a long history of use, and because of its many benefits, new transdermal administration techniques are always being developed. Thus, the development of transfersomes, which are ultradeformable vesicles, will undoubtedly be a key step in resuming research on the application of vesicles as transdermal delivery systems. The usage of elastic vesicles provides a few benefits over other transdermal administration methods, including: They may boost the transdermal related flux, extending the releasing and improving the site targeted specificity of bioactive molecules, and they can be accommodate medicinal molecule with wide ranges of solubility. Their whole composition is safer, and components are authorised for the pharmaceutical and cosmetic use.

Consequently, improved distribution of the bioactive compounds through surface of skin using ultra-deformable vesicular carriers creates another difficulties, this potential for creation of newer, enhanced therapeutics. Since transfersomes are specially designed, optimised vesicles with the ability to respond to an external stress by quick, energy-efficient
shape changes, it may be inferred that novel, ultra-flexible drug carriers that is the transferosomes may resolve all issues related to transdermal distribution.

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