The development of innovative medicine delivery methods is currently generating renewed interest. These innovative drug delivery technologies also include vesicular drug delivery systems. The permeability of the skin, 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. Recently developed transferosomes are able to deliver both high and low molecular weight medications transdermally. This has a number of potential benefits over conventional methods, including avoiding first pass metabolism, extending activity predictability, limiting negative side effects, and utilizing medicines with short half-lives.
because its infrastructure combines hydrophobic and hydrophilic moieties. With no discernible loss, transfersomes can contract and travel through spaces that are five to ten times smaller than their own diameter. This great deformability allows intact vesicles to penetrate more effectively. Drugs with both low and high molecular weights, such as analgesics, anesthetics, corticosteroids, sex hormone, anticancer, insulin, gap junction protein, and albumin, can be transported by them. Due to the fact that they are created from natural phospholipids, much like liposomes, they are biocompatible and biodegradable. They have a high entrapment efficiency, up to 90% in the case of lipophilic drugs. They guard against metabolic breakdown of the medication that is encapsulated. They serve as depots, gradually releasing their contents. They can be utilized for both topical and systemic medication delivery. Simple procedures that don't entail time-consuming steps, superfluous usage, or ingredients that aren't acceptable for use in medicines make them simple to scale up. [1].

**TRANSFERSOMES' BENEFITS AS A CARRIER**

1. Transfersomes can achieve high entrapment efficiencies of up to 90% for lipophilic medicines, and in the case of poor entrapment efficiencies, lipophilic encapsulation can be enhanced by adding a surfactant with a low HLB scale.
2. The use of transfersomes enhances bioavailability, patient compliance, and side effects reduction pharmaceutical additions.
3. It serves as a depot and delivers the medication gradually and steadily.
4. Because transfersomes contain natural phospholipids that are comparable to those in liposomes, they are biocompatible and biodegradable.
5. Transfersomes are employed for both topical and systemic medication delivery.
6. Transfersomes are simple to scale up and do not require time-consuming procedures or unnecessary.
7. They have a high entrapment efficiency, particularly for medicines that are lipophilic.
8. They have elastic properties due to which they deform themselves and squeeze themselves across the skin barrier without wastage of drug.
9. It comprises of both lipophilic and lipophobic moieties due to which they can accommodate drug with large range of solubility.
10. They are employed in the administration of numerous substances, including anesthetics, corticosteroids, NSAIDS, analgesics, peptides, protein, and insulin. [126-131]

**TRANSFERSOMES' DISADVANTAGES AS A CARRIER**

1. One disadvantage of using transfersomes is the challenge of obtaining pure phospholipids; as an alternative, synthesized phospholipids can be employed.
2. The cost of producing transfersomes is high due to the pricey machinery and raw materials required for lipid excipients.
3. The skin's function as a barrier change with aging, varies from person to person, and differs from one area of the skin to another within the same person.
4. Directional hypersensitivity and skin irritation are possible. [126-131]

**TRANSFEROSOME COMPOSITION**

Phospholipids such as phosphatidylcholine, an amphipathic component, and edge activator, a lipid bilayer component, are found in transfersomes and contribute to the vesicle's layout. The primary components of vesicles, such as soy phosphatidylcholine, egg phosphatidylcholine, and others, are phospholipids, which create the lipid bilayer within the vesicles.
For flexibility, 10–25% of a surfactant is used, along with various solvents like ethanol and methanol that contain a saline phosphate buffer (pH 6.5–7) and dyes like nile red and rhodamine. Phosphatidylcholine is a fatty substance that is largely an unsaturated fatty acid and can be found in both human and vegetable sources. Up to 70% of the total fatty acids in these unsaturated fatty acids are linoleic acid.

Edge activators (EA): Also referred to as "bilayer softening compound," edge activators are biocompatible surfactants. The permeability and flexibility of the lipid bilayer are increased by edge activators.

The "lipid film hydration technique," a modified hand shaking method, is used in this procedure to produce the transferosomes. In ethanol, edge activator, lecithin (PC), and drug were dissolved. 877-881

4. Process of Centrifugation
In this procedure, alcohol is used to dissolve the medication, surfactants, and phospholipids. The solvent is then eliminated using rotary evaporation at a lower pressure and 40 °C. Under vacuum, the last remnants of the solvent are eliminated. Centrifuging at 60 rpm for an hour at room temperature hydrates the deposited lipid layer with the proper buffer 877-881

TRANSFEROSOMES MECHANISM
When used under the right circumstances, transferosomes may move roughly 0.1 mg of lipid per hour and cm² through undamaged skin. This number exceeds the transdermal concentration gradient's typical driving value by a wide margin. The "transdermal osmotic gradient" is the true cause of this increased flow rate. The skin penetration barrier keeps the skin's water content at 75% in the epidermis and at 15% in the stratum corneum, which is located near to the skin's surface, and prevents water loss across the skin.

Due to the interaction between hydrophilic lipid remnants and the water nearby, nearly all polar lipids pull some water. Lipid vesicles detect a "osmotic gradient" when a lipid transferosome suspension is applied to partially dried skin and attempt to cross it in order to avoid total drying. If they are sufficiently malleable to pass through the tiny skin pores, as opposed to transferosomes, which have high deformability due to their surfactant and hydration qualities.

Liposomes, which are less deformable than transferosomes and have less penetration control, completely dry out when applied to the skin. Transferosomes are subsequently modified to obtain maximum flexibility in order to fully take

➢ PREPARATION TECHNIQUE INCLUDE:
1. Vertexing-Sonication Method
This technique involves blending mixed lipids—phosphatidylcholine, EA, and the medicinal agent—in a phosphate buffer and vortexing them to create a milky suspension. After being sonicated, the suspension is extruded via polycarbonate membranes. 877-881

2. Process of Suspension Homogenization
In this method, transferosomes are created by combining an adequate amount of edge-activators, such as sodium cholate, with an ethanolic soybean phosphatidylcholine solution. A total lipid concentration is produced by mixing this prepared solution with Triethanolamine-HCl buffer. The resulting suspension undergoes two or three cycles of sonication, freezing, and thawing. 877-881

3. Modified Process for Shaking Hands

Fig :1 structure of transferosomes

➢ MODIFICATION PROCESS

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advantage of the transcutaneous osmotic gradient (water concentration gradient. 126-131

➢ Transcellular and Intracellular Penetration Routes

The carrier aggregation contains at least one amphiphatic (such as phosphatidyl choline), which self-assembles into a lipid bilayer in aqueous solvents and then closes into a straightforward lipid vesicle. By adapting the local concentration of each bilayer component to the local stress encountered by the bilayer, as shown in Fig. 3, the resulting, flexible and permeability optimized, Transfersomes vesicle can alter its shape to environment readily and quickly. The Transfersome varies from such more traditional vesicles chiefly by its "softer," more malleable, and better modifiable artificial membrane, although having a basic structure that is roughly similar to a liposome. Strong bilayer deformability also increases Transfersomes' affinity to bind and hold water, which is a positive side effect. An extremely deformable and highly hydrophilic vesicle will always try to prevent dehydration; this may entail a transport method similar to, but distinct from, forward osmosis. In order to ensure proper hydration, a Transfersomes vesicle put to an open biological surface, such as nonoccluded skin, tends to pass through its barrier and move into the water-rich deeper strata. Barrier penetration includes reversible bilayer deformation, yet for the underlying hydration affinity and gradient to persist, neither the vesicle integrity nor the barrier characteristics may be inadvertently compromised. The Transfersomes must determine and impose its own path because it is too big to diffuse through the skin. Penetration Propensity

Of course, the size of the driving force behind the conveyance also matters: Area x Barrier Permeability x Trans-Barrier Force equals Flow. Therefore, when lipid solution is replaced by a little amount of lipids in a suspension, the chemically driven lipid flow over the skin always falls considerably. [ ]

Fig: penetration mechanism of transfersomes

CHARACTERIZATION OF TRANSFEROSOMES

1. Entrapment Efficacy

Percentage entrapment efficiency (%EE) is the measurement of the amount of drug entrapped in the formulation. Through the use of both direct and indirect approaches, the entrapment efficacy is assessed by removing the unentrapped medication from the vesicles by minicolumn centrifugation.

2. vesicle size and size distribution: Malvern Zeta Sizer's Dynamic Light Scattering System can be used to calculate these parameters

3. Vesicle density per cubic mm: The 0.9% sodium chloride nacl solution is multiplied by five times to dilute non-sonicated Transfersome formulations. Then, for more research, hemocytometer and optical microscope can be employed. 80 tiny squares containing transfersomes are counted, and the following formula is used to calculate them:

\[
\text{Total transfersomes per cubic millimetre} = \frac{(\text{Total transfersomes counted} \times \text{dilution factor 4.000})}{\text{Total squares counted}}
\]

4. Drug content: The following equation can be used to determine the drug content using UV spectroscopy.

\[
\text{Drug content} = \frac{\text{theoretical/practical drug content}}{100}
\]
5. **Measurement of turbidity**: A nephelometer can be used to assess the drug's turbidity.

6. **Surface Charge and Charge Density**: A zetasizer can be used to measure the surface charge and charge density of transfersomes.

7. **Penetration Capability**: Fluorescence microscopy can be used to assess Transfersomes' penetration capacity.

8. **Occlusion Effect**: In the case of topical preparations, occlusion of the skin is thought to be a useful criterion for drug permeation.

9. **Drug release**: In-vitro is carried out to ascertain the penetration rate. Transfersomes suspension is incubated at 320°C for the purpose of determining the drug release. Samples are taken at various intervals, and the free drug is separated using the micro column centrifugation method.

10. **Charge density and surface charge**

    Zetasizer can be used to assess the surface charge and charge density of transfersomes amount (100 percent entrapped and zero percent released) by the amount of drug entrapped.

11. **Physical stability**

    The formulation's initial drug concentration was calculated, and sealed glass ampoules were used to store the medicine. For at least three months, the ampoules were kept at 4°C (refrigeration), 25°C (room temperature), and 37°C (body temperature). After 30 days, samples from each ampoule were examined to assess medication leakage. The initial drug entrapment was used to compute the percent drug loss at 100%.

➢ **Transfersome applications**

    Transfersomes as drug delivery systems have the potential to increase the stability of labile pharmaceuticals and provide controlled release of the medication delivered. Transfersomes as drug delivery systems have the potential to increase the stability of labile pharmaceuticals and provide controlled release of the medication delivered. the creation of transfersomes carrying interleukin-2 and interferone for conceivable transdermal use. They claimed to have delivered IL-2 and INF- at concentrations suitable for immunotherapy that were trapped by transfersomes.

3. **Other Protein and Peptide Carrier**

    Other proteins and peptides have frequently been transported using transfersomes as a vehicle. Large biogenic molecules like proteins and peptides have a difficult time entering the body when taken orally since they are totally broken down in the GI tract, and their size makes transdermal distribution problematic. These are the explanations for why injections of these peptides and proteins are still necessary. Different strategies have been created to enhance these circumstances. Transfersomes' increased bioavailability is relatively comparable to subcutaneous injection of the same protein suspension. When administered
via a transdermal method and enclosed in Transfersomes, human serum albumin or gap junction protein was found to be effective in eliciting an immunological response. Certain drug molecules can be delivered even when their physical and chemical properties would otherwise hinder stratum corneum diffusion.

4. Drug Peripheral Targeting
Transfersomes' capacity to target peripheral subcutaneous tissues is a result of the minimal carrier-associated medication clearance through the subcutaneous tissue's blood arteries. Since these blood arteries lack fenestration and have tight connections between endothelial cells, vesicles cannot enter the bloodstream directly. This automatically raises local drug concentration and the likelihood that it will reach peripheral tissues.

5. Skin-to-Skin Immunization
Ultra deformable vesicles can carry big molecules, making them suitable for the topical delivery of vaccines. For this, transfersomes containing human serum albumin, gap junction protein, and integral membrane protein are employed. The avoidance of protein injection and the achievement of increased IgA levels are benefits of this strategy. The transcutaneous hepatitis-B vaccination has shown positive outcomes. Zidovudine was administered with a 12 times higher AUC than usual control medication.

6. Provision of NSAIDS
NSAIDS have been linked to a variety of GI adverse effects. Transdermal delivery employing extremely deformable vesicles can get over these problems. Research has been done on ketotifen with diclofenac. The Swiss regulatory body gave ketoprofen in a Transfersomes formulation marketing authorisation; the drug is anticipated to be sold under the trade name Diractin. According to IDEA AG, further therapeutic treatments based on the transfersomes technology are in the clinical development stages.

7. Steroidal hormone and peptide delivery
Corticosteroids have also been delivered using transfersomes. By maximizing the medication dose applied epicutaneously, transfersomes enhance the site specificity and overall drug safety of corticosteroid delivery into the skin. Corticosteroids based on transfersomes are physiologically active at doses several times lower than the formulation currently used to treat skin conditions. The anti-ovulatory effects of flexible ethinyl estradiol vesicles were significantly greater than those of conventional liposomes applied topically and the oral administration of the medication as is. Numerous studies have been conducted on different medications, such as hormones and peptides like estradiol, low molecular-weight heparin, retinol, and melatonin, among others.

8. Administration of anesthetics
Lidocaine and tetracaine formulations based on transfersomes demonstrated penetration comparable to subcutaneous injections. The maximum amount of pain insensitivity that results is almost as powerful (80%) as that of a comparable subcutaneous bolus injection, but transfersomal anesthetics have a longer-lasting impact.

9. Drug delivery for cancer treatment
Utilizing transfersome technology, anti-cancer medications like methotrexate were tested for transdermal delivery. The outcomes were positive. This offered a fresh method of treating cancer, particularly skin cancer.

10. Providing herbal medicines
As a result, Xiao-Yin created transfersomes of capsaicin, which exhibit better topical absorption than pure capsaicin. Transfersomes can penetrate the stratum corneum and supply nutrients locally to maintain its functions, resulting in maintenance of skin.
Some examples of application of transferosomes as a transdermal delivery system; IC VALUE:5.16; ISI VALUE:2.286

<table>
<thead>
<tr>
<th>DRUG</th>
<th>Indication</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Curcumin</td>
<td>NSAID</td>
<td>Enhance bioavailability and permeability</td>
</tr>
<tr>
<td>sertraline</td>
<td>Anti-depressant</td>
<td>Permeability improved</td>
</tr>
<tr>
<td>Meloxicam</td>
<td>NSAID</td>
<td>Skin permeation increases</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>Anticancer drug</td>
<td>Skin permeation increases</td>
</tr>
<tr>
<td>Insulin</td>
<td>Hypoglycemic</td>
<td>Encapsulation efficiency increases</td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>vitiligo</td>
<td>Targeted drug delivery and safety</td>
</tr>
<tr>
<td>Repaglinide</td>
<td>Anti diabetic agent</td>
<td>Topical delivery enhances and targeted action</td>
</tr>
<tr>
<td>Ibuprofen</td>
<td>NSAID</td>
<td>Stability enhance</td>
</tr>
<tr>
<td>Lidocaine</td>
<td>Local anesthetic</td>
<td>Improved permeation through skin</td>
</tr>
<tr>
<td>Oestradiol</td>
<td>estrogen</td>
<td>Transdermal flux increases</td>
</tr>
<tr>
<td>5-fluorouracil</td>
<td>Antineoplastic drug</td>
<td>Enhance skin penetration and skin deposition</td>
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CONCLUSION
Due to the stratum corneum layer of the skin's barrier qualities, high molecular weight therapeutic agents and medicines cannot be delivered via the transdermal route. These Transferosomes are specialized vesicles that can respond to stress from the environment by forcing their way through skin pores that are much smaller than they are, increasing the flux of medicinal substance. Transferosomes have several advantages over other vesicular systems, including greater stability, the ability to release drugs systemically, and higher deformability than other vesicular systems like niosomes, ethosomes, etc. These features will ensure consistent and effective transcutaneous carrier and drug transport. Transferosomes can accommodate medicinal molecules with a wide spectrum of solubilities because its infrastructure combines hydrophobic and hydrophilic moieties. an they are, increasing the transdermal flux of medicinal substances.

REFERENCES
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