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"Transfersomes: Pioneering Nanovesicles in Enhanced Drug Delivery Systems"

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Abstract: It is challenging to administer medications topically or transdermally, due to the fact that the skin serves as a barrier of protection. Most of the time, transdermal administering drugs is restricted by the skin's barrier function. The transdermal approach is regarded as the safest and most efficient because to its many benefits, which include identifiable and prolonged period for action, avoiding the first-pass metabolism, fewer side effects, etc. It also has several drawbacks, such as the inability to transport bigger molecules (>500D) and the inability to cross the stratum corneum barrier. Transfersomes was developed as an alternative to all of these issues because they had the advantages over other transdermal drug delivery systems and also had the ability to easily penetrate the barrier. They are novel vesicular drug delivery system for better transdermal absorption consisting of phospholipid, surfactant, and water. They include a high percentage of drug entrapment because to the natural phospholipids that build them up, and they are biocompatible and biodegradable. Using transfersomes, drugs that have low as well as high molecular weights can be transdermally administered. Transfersomes can deform and squeeze through extremely tiny openings since they are elastic by nature. The composition, preparation, and properties of transfersomes are discussed in detail in this review.

Keywords: Transfersomes, Transdermal drug delivery, Characterization, vesicular system, elastic vesicles, the transport mechanism.

1.INTRODUCTION

Transdermal drug delivery is currently becoming more significant because of issues with oral drug delivery methods. The effectiveness of a variety of novel approaches, including iontophoresis, electrophoresis, sonophoresis, chemical permeation enhancers in formulations, microneedles, and vesicular systems (liposome, transfersome, ethosome), has recently been demonstrated, successfully adopted for enhancing transdermal delivery of bioactive molecules and drugs, and the results are encouraging. Due to their outstanding physico-chemical properties, transfersomes as innovative drug carriers have already attracted a lot of attention.

Transfersomes were first recognised by Gregor Ceve in 1991. Transfersomes structure is made up of both hydrophobic and hydrophilic moieties, they can promote a variety of solubility levels in pharmaceutical compounds. They are highly effective at protecting encapsulated drug from metabolic degradation. The better skin penetration of the vesicle membrane, results in greater transdermal flow of drug that is encapsulated, due to the membrane's deformability. Drugs with low and high molecular weights can be delivered transdermally using transferosomes.

They are employed with a variety of active compounds and offer a versatile delivery method for enhancing stability. When used in non-occlusive situations, the vesicles are very deformable and can squeeze through pores in the stratum corneum that are smaller than one-tenth of their actual diameter because of their metastability, which makes the vesicle membrane extremely flexible. Intact skin can therefore be penetrated by even diameters up to 200–300 nm. The right surface-active ingredients are mixed in the right proportions to give transfersomes' membrane flexibility.

The transfersome membrane becomes more flexible after application under non-occlusive conditions, which reduces the risk of full vesicle rupture in skin and makes it possible for transfersomes to move along epidermis through the natural water gradient. When a carrier is introduced to the skin it actively seeks out and utilises hydrophilic routes or 'pores' amongst the cells, opening up sufficiently to allow the entire vesicle—including the drug molecule—pass through stratum corneum. To achieve this without compromising its vesicular integrity, it severely deforms itself. As a result, they can successfully overcome a variety of transportation difficulties.

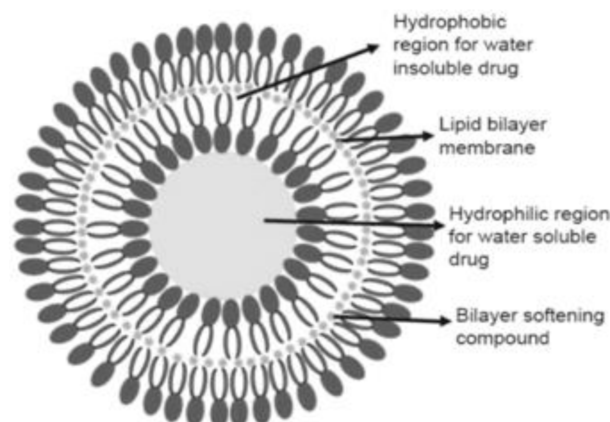

Fig 1: Structural Representation of Transfersome

1.1. Advantages

- Drug is successively delivered efficiently into or through the skin because to the self-optimized and ultra flexible membrane characteristics.
- Both low and large molecular weights can be transported by transfersomes, including analgesics, insulin, protein, anaesthetics, corticosteroids, sex hormones, anticancer drugs, and albumin.
- Its composition, which blends hydrophobic and hydrophilic moieties, can accept pharmacological molecules with a range of solubilities.
- They are also responsible for encasing the drug in phospholipid to protect it from enzymatic and other biological degradation.
- Enhance patient compliance through non-invasive delivery and painless administration.
- Easy and simple to scaleup that don't require lengthy procedures and unnecessary usage of pharmaceutically unacceptable additives.
- Transfersomes have a very high entrapment efficiency. when it comes to hydrophilic drugs, over 90% is the maximum allowed.

1.2. Disadvantages:

- It is impossible to provide drugs that need high blood levels.
- The product's cost is a significant barrier to the transfersomes widespread acceptability.
- Transfersomes are prone to oxidative degradation, which makes them chemically unstable.
- Many medications, especially those having hydrophilic moieties, penetrate the dermis too gradually to be of medicinal benefit.

2. Mechanism of Action

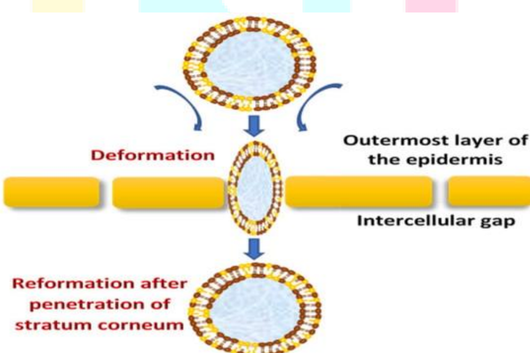

Fig 2: Mechanism of action of Transfersome

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In order to penetrate the stratum corneum's intracellular sealing lipids, transfersomes must squeeze along them. [8]"Osmotic gradient or transdermal gradient" has been reported as the primary mechanism for transfersomes' penetration through the skin. Transfersomes transport medicines intracellularly or transcellular via the stratum corneum. When applied to the skin's non-occluded surface, it permeate the skin's protective layer and advances to the deeper strata, then it finds the water-rich region, and hydrates the skin. the stratum corneum's lipid vesicles are then naturally dehydrated by transepidermal activity to reach the

deeper epidermal layer. A water hydration gradient develops between the layers of skin as a result of the excessive quantity of water that is present in the deeper layers of skin (about 75%) compared to the surface layers, which only contain 15% water. The transfersome vesicles can pass through deeper tissues of skin because of their amphiphilic shape. Upon hydrating dry skin, lipids penetrate deeper layers of skin.

3. Composition of transfersomes

Table 1: Composition of transfersomes

Class	Examples	Uses
Phospholipids	Soya phosphatidylcholine, Dipalmitoyl phosphatidylcholine	Vesicle forming components
Surfactant or edge activator	Sod. cholate, Sod. deoxycholate, Tween-80, Span80, Tween	For providing flexibility
Buffering agent	Saline phosphate buffer (pH 6.4), Phosphate buffer (pH 7.4)	For hydrating medium
Solvent	Ethanol, methanol	As a solvent

4. Preparation of Transfersomes

4.1. Thin Layer Hydration Technique

This approach generates thin films by dissolving vesicle-forming substances like phospholipids and surfactants in volatile organic solvents (methanol, chloroform, etc.). Rotary evaporator is used to evaporate an organic solvent above the lipid transition temperature, and a little amount of solvent is then removed overnight while under vacuum. The created film is hydrated by being rotated for one hour at 60 rpm while it's immersed in a buffer solution. The resulting vesicles were allowed to swell for two hours at room temperature. The resulting carriers were sonicated for 30 minutes at 50 °C or at ambient temperature in a bath sonicator.

4.2. Modified Hand Shaking

In ethanol:chloroform (1:1), the drug, lecithin (PC), and edge activator were dissolved. Above the lipid transition temperature (43°C), organic solvent was evaporated while being held in a shaking hand. Inside the flask wall, a thin lipid coating developed during rotation. The thin coating was left overnight so that the solvent would have enough time to completely evaporate. The film was then submerged in phosphate buffer (pH 7.4) and gently shaken for 15 minutes at the suitable temperature. Subsequent hydration of the transfersome suspension occurs for an hour at 2-80°C.

4.3. Centrifugation Process

The phospholipids and lipophilic drugs with edge activator must be dissolved with in the alcohol. The solvent should then evaporate at the desired temperature and under reduced pressure. The solvent residues should also be eliminated under vacuum pressure. The resulting lipid film is then centrifuged at room temperature and hydrated with the proper stream solution. This stage the incorporation of hydrophilic drugs to obtain lipid and swollen and also allows for further sonication to produce multilamellar lipid vesicles

4.4. Freeze Thaw method

Involves the cycling of multilamellar vesicles that have formed between very low and very high temperatures. The prepared suspension needs to be collected in a tube and submerged for 30 seconds in a nitrogen bath (-300 C). This cycling process needs to be repeated about 8–9 times.

4.5. Vortexing-Sonication method

This procedure involves combining mixed lipids (such as phosphatidylcholine, EA, and the medicinal drug) in phosphate buffer and vortexing them to create milky suspension. Polycarbonate membranes are used to extrude and then sonicate the suspension.

4.6. Ethanol Injection method

The phospholipid, edge activator, and lipophilic drug in ethanol, and the organic phase is produced by stirring the mixture for a predetermined period of time. The water-soluble substances that make up the aqueous phase are dissolved by phosphate buffer. The hydrophilic drug should be used at this time. At 45–50 °C, both solutions are heated. After that, the aqueous solution is continuously stirred for a predetermined amount of time while being injected dropwise with the ethanolic phospholipid solution. The resulting dispersion is then put into a vacuum evaporator and subjected to sonication to reduce the particle size in order to remove the ethanol.

4.7. Lipid suspension in an aqueous phase

There are vehicles in this cycle with drug-to-lipid ratios between 1/4 and 1/9. The mixture is recommended depending on the specific type of formulation. As compared to regular phosphatidylcholine vesicles, this will make sure that the vesicle's membrane is highly flexible in the fluid phase. To be more precise, vesicles with size range of 100- 200 nm are made using soya-phosphatidyl choline, which has a typical size deviation of about 30%. An aqueous environment where the drug is dissolved can be used to process the lipids.

4.8. Reverse-phase evaporation method

Depending on the drug's solubility, it can be introduced into either the lipid or aqueous phases. In round bottom flask, dissolve the phospholipid in an organic solvent. Add an aqueous surfactant or edge activator solution to the phospholipid organic solvent, under nitrogen purging. After that, the mixture is sonicated for 15 minutes with a probe sonicator at 100°C in an ice bath. After sonication, keep this system in place for 30 minutes. The organic solvent evaporates under lower pressure, resulting in the formation of a homogeneous, viscous gel that contains transfersome vesicles.

4.9. Hi-pressure homogenization

Continuous mixing of the drug and the phospholipids, edge activator constantly in distilled water or PBS including alcohol. After that, an ultrasonic shaker is used to stir the mixture. The resulting mixture is then homogenized under intense pressure. The transfersomes are then stored properly.

5. Evaluation and Characterization of Transfersomes

5.1. Vesicle Morphology

5.1.1. Vesicle Diameter

To figure out the vesicle diameter, employ dynamic light scattering or photon correlation spectroscopy. For research using photon correlation spectroscopy or dynamic light scattering (DLS), samples are produced in distilled water, filtered through a 0.2 mm membrane filter, and then diluted with filtered saline. Analysing vesicle size and structure provides insight into the stability of vesicles.

5.1.2. Vesicle Size, Size Distribution and Zeta Potential

Malvern Zetasizer's computerised inspection system is typically used to measure the size of the vesicle, the size distribution, and the zeta potential utilising Dynamic Light Scattering Method (DLS).

5.1.3. Vesicle Shape and Type

Transmmision electron microscopy, which accelerates electrons at a voltage of 100 kV, can be used to see transfersome vesicles. Without using sonication, phase contrast microscopy with an optical microscope can be used to identify transfersome vesicles.

5.1.4. Number of Vesicle per Cubic mm

Along with other process factors, it is a crucial component of the formulation composition. Transfersome formulations (without sonication) can be diluted five times in 0.9% sodium chloride solution for optical microscopy by using hemocytometer.

5.2. Entrapment efficiency

The percentage of drug added successfully trapped represents entrapment efficiency. Entrapment efficiency was assessed by first using minicolumn centrifugation method to separate drug that was unentrapped. The vesicles were disrupted after centrifugation using either 0.1% Triton X-100 or 50% n-propanol.

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5.3. Turbidity and Surface Charge Measurement

5.3.1. Turbidity
Drug that is present in form of an aqueous solution can have its turbidity assessed using nephelometer.

5.3.2. Surface Charge and Charge Density
A zetasizer is used to measure surface charge and charge density of transfersomes.

5.3.3. Penetration Ability
To assess transfersome penetration, fluorescence microscopy is generally used.

5.4. Stability of Transfersomes
Vesicular suspension is transferred to glass ampoules, sealed, and exposed to various temperatures 4^0C, 25^0C, and 37^0C for at least three months to determine the stability of transfersomes. After 30 days, samples were checked for drug leakage while assuming that 100% of the drug was initially entrapped.

5.5. Degree of deformability or permeability measurement
One of the essential and distinguishing elements for transfersome characterisation is permeability study. Taking pure water as reference, the deformability study is conducted. Depending on the initial suspension of transfersomes, the preparation of transfersomes is carried out through a variety of known-size pores (through a sandwich of several microporous filters with pore diameters between 50 and 400 nm). DLS measurements are used to keep track of the particle size and size distribution for each pass.
The degree of deformability is expressed as:

$$D = j \; rv/rp$$

where, D = Degree of deformability
J = amount of suspension extruded within 5 min,
rv = size of vesicle
rp = barrier pore size

5.6. Occlusion effect
In case of conventional topically applied procedures, occlusion of skin may help with drug permeation. The hydrotaxis of water is primarily responsible for vesicles' penetration of skin from its comparatively dry surface to its more water-rich deeper regions. Occlusion interferes with the skin's ability to evaporate water, which influences hydration forces.

5.7. *In-vitro* Drug Release
Determined by calculating permeation rate found out by computing the penetration rate. At 32 °C, formulation is incubated. Free drug is separated from samples taken at regular intervals using a mini column centrifuge. The amount of drug entrapped at zero time is utilised as a stand-in for the amount of drug released, which is calculated as 100%.

6. Applications

6.1. Insulin supply

These large molecular drugs can be applied to the skin in a therapeutic and non-invasive manner using transfer drugs. Usually, insulin is administered by a painful subcutaneous method. These two issues are resolved via insulin encapsulation, or transfersulin. Depending on the particular carrier material, On the untreated skin, transfersulin was administered then after 90 to 180 minutes, early symptoms of systemic hypoglycemia were noticed.

6.2. Peripheral drug targeting

Transfersomes can target peripheral subcutaneous tissues because of the minimal carrier-associated medication removal through the blood vessels in subcutaneous tissue. Vesicles prevent enter the circulation directly in these blood vessels since they don't have fenestration and have tight connections between endothelial cells. This automatically raises local drug concentration and the probability that it will reach peripheral tissues.

6.3. Delivery of Corticosteroids

By optimising the drug dose administered epicutaneously, transfersomes have the potential to increase the skin's site specificity and overall drug safety margin when delivering corticosteroids. Transfersomes-based corticosteroids are physiologically active at levels that are considerably smaller compared to those used to treat skin problems today.

6.4. Delivery of anticancer drugs
A novel strategy to treating cancer, particularly skin cancer, is provided through transfersome technology. When methotrexate was administered transdermally utilizing transfersome technology, the results were favorable.

7. Conclusion

Although we were able to transmit large vesicles via the topical and transdermal drug delivery systems, we introduced transfersomes (elastic vesicles), which exhibit improved penetration for both small and large vesicles. Transfersomes are particularly made vesicles that may respond to stress by passing via skin pores that are considerably smaller than their own, thereby enhancing the transdermal passage of the therapeutic substances. Drug release in this form of delivery can also be controlled to meet requirements. As a result, this strategy can overcome the issues that exist with conventional techniques.

8. Future Prospects

Due to its many advantages over alternative ways to administer drugs, transdermal system for delivery of drugs are frequently used; But the penetration of the drug through the stratum corneum is a rate-limiting step. The best application for transfersome technology is the non-invasive delivery of drugs across permeable cellular barriers. For instance, compounds that are too large to diffuse across the barrier can be transported across the skin via transfersome vesicles. Targeting peripheral, subcutaneous tissue is another intriguing aspect of the transfersome method. This capability depends upon minimizing the drug clearance through the plexus of the cutaneous blood vessels connected with the carrier. Tight connections between endothelial cells and non-fenestrated blood capillary walls in the skin prevent vesicles from entering the circulation directly, maximising local drug retention and increasing possibility that drug will reach the peripheral tissue targets. The vesicular system will play a key role in advanced delivery of medications in the future by combining numerous methodologies, particularly in sick cell sorting, diagnostics, gene and genetic materials, safe, targeted, and effective *in vivo* distribution.

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