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Transfersomes as versatile and flexible vesicular carriers in Transdermal drug delivery

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ABSTRACT

Transdermal drug delivery systems are a constant source of interest because of the benefits that they afford in overcoming many drawbacks associated with other modes of drug delivery (i.e. oral, intravenous). Because of the impermeable nature of the skin, designing a suitable drug delivery vehicle that penetrates the skin barrier is challenging. Encapsulating the drugs in transfersomes are one of the potential approaches to overcome the barrier function of the skin's outermost layer. They have a bilayered structure that facilitates the encapsulation of lipophilic and hydrophilic, as well as amphiphilic, drug with higher permeation efficiencies compared to conventional liposomes. Transfersomes are novel vesicular systems that are several times more elastic than other vesicular systems. These are composed of edge activator, phospholipids, ethanol, and sodium cholate and are applied in a non-occlusive manner. Transfersomes provide the primary advantage of higher entrapment efficiency along with a depot formation which releases the contents slowly. Transfersomes can be used for delivery of insulin, corticosteroids, proteins and peptides, interferons, anti-cancer drugs, anaesthetics, NSAIDs and herbal drugs.

Keywords : Transfersomes, Transdermal delivery, bilayered structure, non- occlusive.

I. INTRODUCTION

Transdermal delivery is an important delivery route that delivers precise amount of drug through the skin for local and systemic action. Transdermal route offers several potential advantages over conventional routes like avoiding first pass metabolism, predictable and extended duration of activity, minimizing undesirable effects, utility of short half-life drugs, improving physiological and pharmacological response, avoiding the fluctuation of drug levels, and most importantly, it provides patient convenience. But one of the major problems in transdermal drug delivery is the low penetration rate through the outer most layer of skin. As the outermost barrier of the skin, the stratum corneum is tightly connected and is the main obstacle and rate-limiting step for drug penetration into the skin.

In recent studies, to increase the penetration rate of drugs, some physical and chemical methods have been used in pharmacy such as the use of iontophoresis, microneedles, chemical penetration enhancers, nanocarriers, and liposomes to promote the drug through the skin barrier. However, these physicochemical methods also have potential disadvantages such as poor stability, a complicated preparation process and severe skin irritation.Lipid-based suspensions such as liposomes, niosomes, and microemulsions, have also been proposed as low- risk drug carriers, but they do not offer much value in transdermal drug delivery because they do not deeply penetrate the skin, but rather remain on the upper layers of skin strata.

Several researchers have developed novel elastic lipid vesicular systems in order to deeply and easily penetrate through the skin. Phospholipids, ethanol, bile salts and many surfactants have been used to prepare these elastic vesicles- such as Transfersomes, ethosomes etc.The high flexibility of vesicular membranes allows these elastic vesicles to squeeze themselves through the pores in stratum corneum, which are much smaller than their vesicular sizes.

Because of the impermeable nature of the skin, designing a suitable drug delivery vehicle that penetrates the skin barrier is challenging. Transdermal gels are designed to deliver sustained drug amounts, resulting in systemically consistent levels. They represent an improvement compared with transdermal delivery by patches because they offer more dosage flexibility, less irritation potential and a better cosmetic appearance. This gel technology has demonstrated to be efficient for many drugs, as shown in the preclinical and clinical pharmacokinetic studies presented in this technology evaluation. [1-2]

1.1 INTRODUCTION TO TRANSFERSOMES

The Transfersomes term was first introduced by Cevc and has been the subject of several patents and literature information since the 1990s (Transfersomes, a trademark of IDEA AG, Munich, Germany), and it represents the first generation of ultra-deformable vesicles. Transfersomes consist of both hydrophilic and hydrophobic properties and high deformability gives better penetration of intact vesicles. Transfersomes are vesicular carrier systems that are specially designed to have at least one inner aqueous compartment that is enclosed by a lipid bilayer, together with an edge activator. This aqueous core surrounded by a lipid bilayer makes ultra-deformable vesicles having both self-optimizing and self-regulating capabilities. In accordance with that, transferosomes are elastic in nature and can thereby deform and squeeze themselves as intact vesicles without a measurable loss through narrow pores or constrictions of the skin that are significantly smaller than the vesicle size. [2]

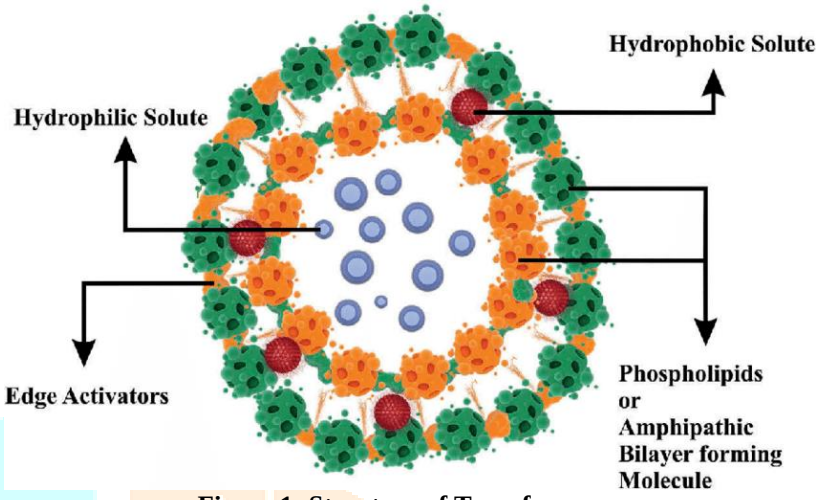

Figure 1: Structure of Transfersomes

Edge activators (EAs) function in an exceptional manner as membrane-destabilizing factors to increase the deformability of vesicle membranes, as well as ultra-flexible, which results in a higher permeation capability. Surfactants are one of many different compounds that act as edge activators and penetration enhancers.Deformability leads to better penetration of vesicles. It can act as a carrier for low also as high relative molecular mass drugs e.g: analgesic, anesthetic, corticosteroids, steroid hormone, anticancer, insulin, gap junction protein, albumin, interferons, NSAID's, pepties, herbal drugs.The combination of the transferosomal suspension with the gel matrix can lead to formulation of a transferosomal gel, which may prove to be more pertinent for transdermal drug delivery

According to various research publications, it is evidently known that transfersomes are capable of transporting low, as well as high, molecular weight ($200 \leq MW \leq 106$) bioactive molecules and hydrophilic and lipophilic molecules through the skin with a transport efficiency greater than 50%.

It was described in several published research papers that, due to vast skin-penetration capabilities, transfersomes are able to create skin drug depots for a sustained drug release, deliver therapeutic agents into deeper skin layers or transport drugs into the systemic circulation. [2]

1.2 ADVANTAGES

- Transfersomes are able to squeeze themselves through constrictions of the skin barrier that are very narrow, such as 5 to 10 times less than the vesicle diameter, owing to their ultra-deformability and elastic properties.
- High vesicle deformability facilitates the transport of drugs across the skin without any measurable loss in intact vesicles and can be used for both topical, as well as systemic treatments.
- Transfersomes carriers are very versatile and efficient in accommodating a variety of agents nearly independent of their size, structure, molecular weight or polarity.
- They are made up of natural phospholipids and EAs, therefore promisingly biocompatible and biodegradable.
- Transfersomes are an obvious choice for achieving a sustained drug release, as well as a predictable and extended duration of activity.
- They are capable of increasing the transdermal flux and improving the site specificity of bioactive agents.
- Avoiding the first-pass metabolism, which is a major drawback in oral drug administration, and result in optimized bioavailability of the drug.
- Minimize the undesirable side effects of the drug, as well as protect the drug from metabolic degradation; moreover, the utility of short half-life drugs.
- In most of the cases, a relatively high entrapment efficiency (EE) of nearly 90% of the lipophilic drug can be achieved by transfersomes. [3-5]

1.3 LIMITATIONS

- Transfersomes are considered as chemically unstable due to their tendency to oxidative degradation. The oxidation of transfersomes can be significantly decreased when the aqueous media is degassed and purged with inert gases, such as nitrogen and argon . Storage at a low temperature and protection from light will also reduce the chance of oxidation. Post-preparation processing, such as freeze-drying and spray-drying, can improve the storage stability of transfersomes .
- Another obstacle of utilizing transfersomes as a drug delivery system is the difficulty to achieve the purity of natural phospholipids. Therefore, synthetic phospholipids could be used as alternatives.
- The expensiveness of transfersomal formulations is associated with the raw materials used in lipid excipients, as well as the expensive equipment needed to increase manufacturing. Hence, the widely used lipid component is phosphatidylcholine, because it is relatively low in cost. [3,5,6]

II. MECHANISM OF ACTION

It is believed that the unimpeded passage of such carriers is based on two key factors: the high elasticity (deformability) of the vesicle bilayers and the reality of an osmotic gradient across the skin. [7] The transdermal water activity difference, which originates due to the natural transdermal gradient, creates a significantly strong force that acts upon the skin through transfersomes vesicles, which enforce the widening of intercellular junctions with the lowest resistance and thereby generate transcutaneous channels 20–30 nm in width,these created channels allow the transfer of ultra-deformable, slimed transfersomes across the skin with respect to the hydration gradient [9].

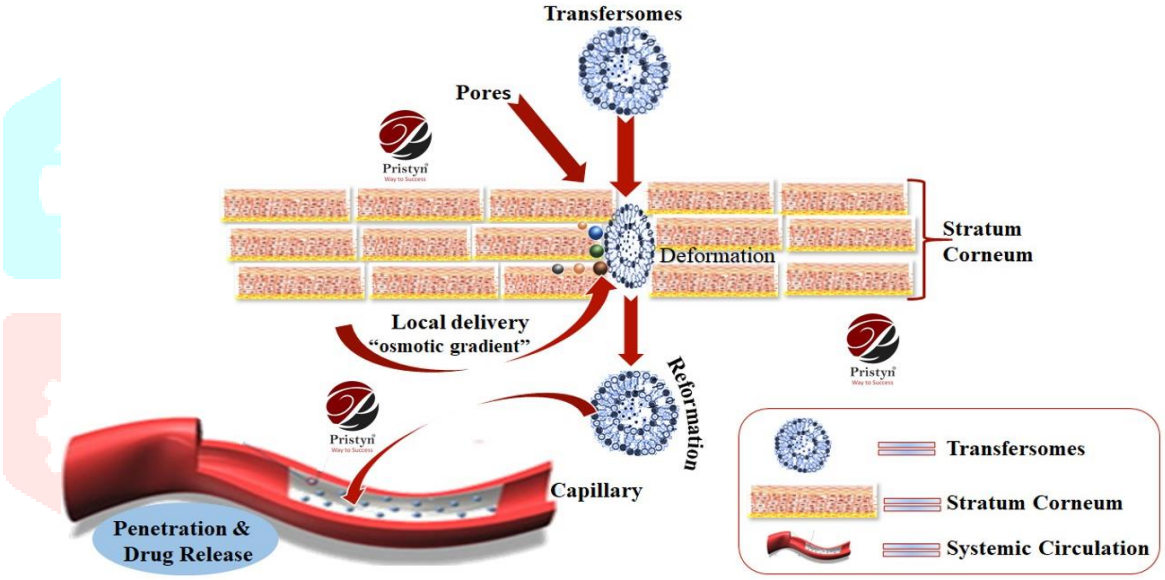

Figure 2: Mechanism of penetration of Transfersomes

Moreover, the osmotic gradient develops as a result of evaporation of the skin surface water due to body heat, which exerts its action as the driving force to facilitate the flexible transport across the skin to deliver therapeutic agents from the site of application to the target area for local or systemic treatments in effective therapeutic concentrations and minimum systemic toxicity [10] . When a transfersome reaches a pore, it is capable of changing its membrane work reversibly as an effect of its self-optimizing deformability. To go throughout the pore, the mechanism of the transfersome liable for its deformability starts accumulating at the site of tension, whereas the less elastic mechanism experiences dilution, which significantly reduces the active rate of membrane deformation and allows the highly elastic particles to go throughout the pores. [8] Their penetration ability depends on the deformability of the transfersomal membrane, which can be attributed to the vesicle compositions .[10]

III. COMPOSITION OF TRANSFERSOMES

The modified liposomal vesicular system (transfersomes) is composed of the phospholipid component and single-chain surfactant as an edge activator.The formulation of transfersomes includes-

1. The main ingredient, an amphipathic ingredient (e.g., soy phosphatidylcholine, egg phosphatidylcholine, etc.) that can be a mixture of lipids, which are the vesicle-forming components that create the lipid bilayer
2. 10–25% surfactants/edge activators; the most commonly used edge activators in transfersome preparations are surfactants as sodium cholates; sodium deoxycholate; Tweens and Spans (Tween 20, Tween 60, Tween 80, Span 60, Span 65 and Span

80) and dipotassium glycyrrhizinate, which are biocompatible bilayer-softening compounds that increase the vesicles' bilayer flexibility and improve the permeability.

3. About 3–10% alcohol (ethanol or methanol), as the solvent and, finally, hydrating medium consist with either water or a saline phosphate buffer (pH 6.5–7), [11-14]

IV. PREPARATION METHODS OF TRANFEROSOMES

1. Thin Film Hydration Technique/Rotary Evaporation-Sonication Method
2. Vortexing - Sonication Method
3. Modified Handshaking Process
4. Suspension Homogenization Method
5. Centrifugation Process
6. Reverse-Phase Evaporation Method
7. High-Pressure Homogenization Technique
8. Ethanol Injection Method

1. Thin Film Hydration Technique/Rotary Evaporation-Sonication Method

The phospholipids and edge activator (vesicle-forming ingredients) are dissolved in a round-bottom flask using a volatile organic solvent mixture (example: chloroform and methanol in a suitable (*v/v*) ratio). The lipophilic drug can be incorporated in this step. In order to form a thin film, the organic solvent is evaporated above the lipid transition temperature under reduced pressure using a rotary vacuum evaporator. Keep it under vacuum to remove the final traces of the solvent. The deposited thin film is then hydrated using a buffer solution with the appropriate pH (example: pH 7.4) by rotation for a respective time at the corresponding temperature. The hydrophilic drug incorporation can be done in this stage. The resulting vesicles are swollen at room temperature and sonicated in a bath or probe sonicator to obtain small vesicles. The sonicated vesicles are homogenized by extrusion through a sandwich of 200 nm to 100 nm polycarbonate membranes. [15]

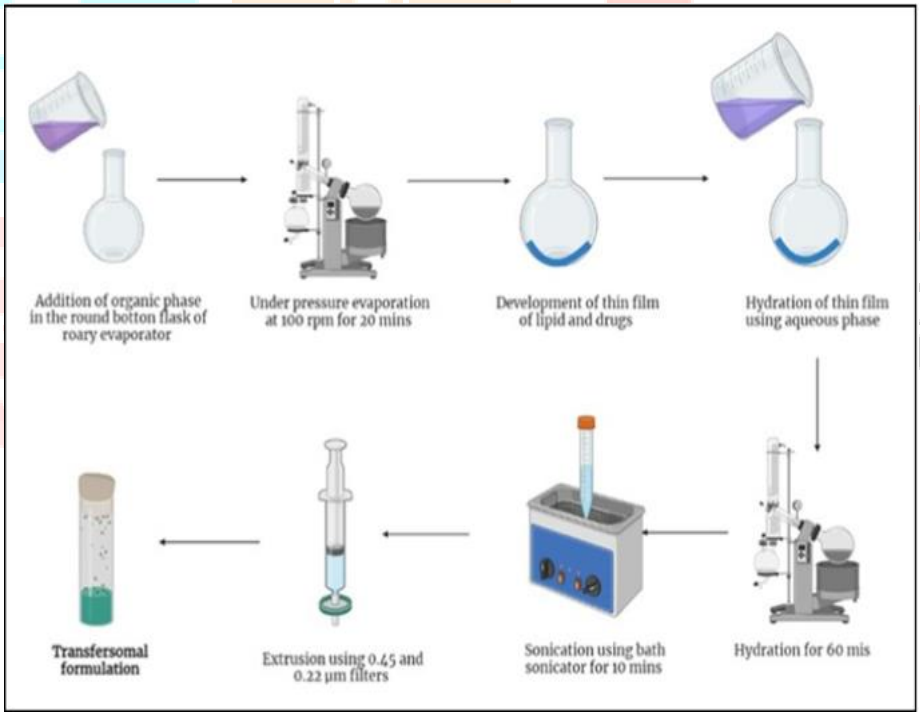

Figure 3 Thin Film Hydration Technique/Rotary Evaporation-Sonication Method

2. Vortexing sonication method

In the vortexing sonication method, mixed lipids (i.e. phosphatidylcholine, EA and the therapeutic agent) are blended in a phosphate buffer and vortexed to attain a milky suspension. The suspension is sonicated, followed by extrusion through polycarbonate membranes. Cationic transfersomes have also been set by this method, which involves mixing cationic lipids, such as DOTMA, with PBS to attain a concentration of 10 mg/ml followed by a count of sodium deoxycholate (SDC). The blend is vortexed and sonicated, followed by extrusion through a polycarbonate (100 nm) filter. [15]

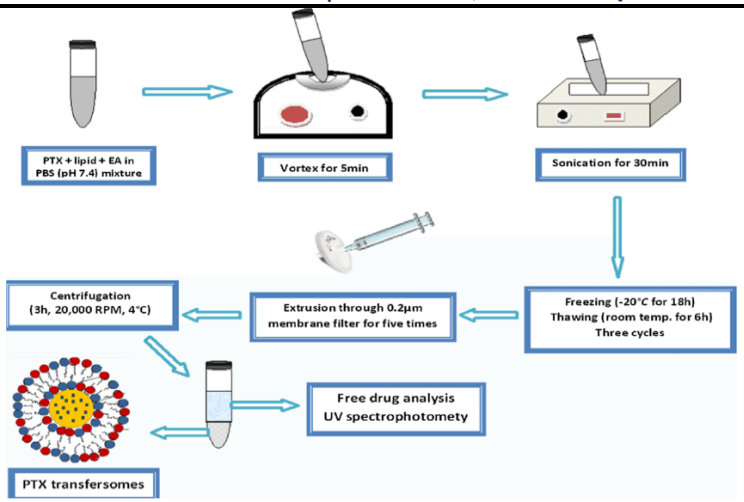

Figure 4 Vortexing sonication method

3. **Modified Handshaking Process**

The modified handshaking method has the same basic principle as the rotary evaporation-sonication method. In the modified handshaking process, the organic solvent, the lipophilic drug, the phospholipids and edge activator are added in a round-bottom flask. All the excipients should completely dissolve in the solvent and obtain a clear transparent solution. Then, the organic solvent is removed by evaporation while handshaking instead of using the rotary vacuum evaporator. In the meantime, the round-bottom flask is partially immersed in the water bath maintained at a high temperature (example: 40–60 °C). A thin lipid film is then formed inside the flask wall. The flask is kept overnight for complete evaporation of the solvent. The formed film is then hydrated with the appropriate buffer solution with gentle shaking at a temperature above its phase transition temperature. The hydrophilic drug incorporation can be done in this stage. [16]

4. **Suspension Homogenization Method**

Transfersomes are prepared by mixing an ethanolic phospholipid solution with an appropriate amount of edge activator. The prepared suspension is subsequently mixed with buffer to yield a total lipid concentration. The resulting formulation is then sonicated, frozen and thawed respectively two to three times . [17]

5. Centrifugation Process

The phospholipids, edge activator and the lipophilic drug are dissolved in the organic solvent. The solvent is then removed using a rotary evaporator under reduced pressure at the respective temperature. The remaining traces of solvent are removed under vacuum. The deposited lipid film is hydrated with the appropriate buffer solution by centrifuging at room temperature. The hydrophilic drug incorporation can be done in this stage. The resulting vesicles are swollen at room temperature. The obtained multilamellar lipid vesicles are further sonicated at room temperature. [18]

6. Reverse-phase evaporation method

At this point, the scheme will alter to a viscous gel followed by the arrangement of vesicles. The non-encapsulated material and residual solvents can be indifferentiable using dialysis or centrifugation . In this method, lipids dissolved in organic solvents are collected in a round-bottomed flask. Aqueous media containing EAs is added under nitrogen purging. The drug can be added to the lipid or aqueous medium based on its solubility character. The system formed is then sonicated, awaiting its conversion into a standardized dispersion, and should not separate for at least 30 min after sonication. The organic solvent is then removed under low pressure. [19]

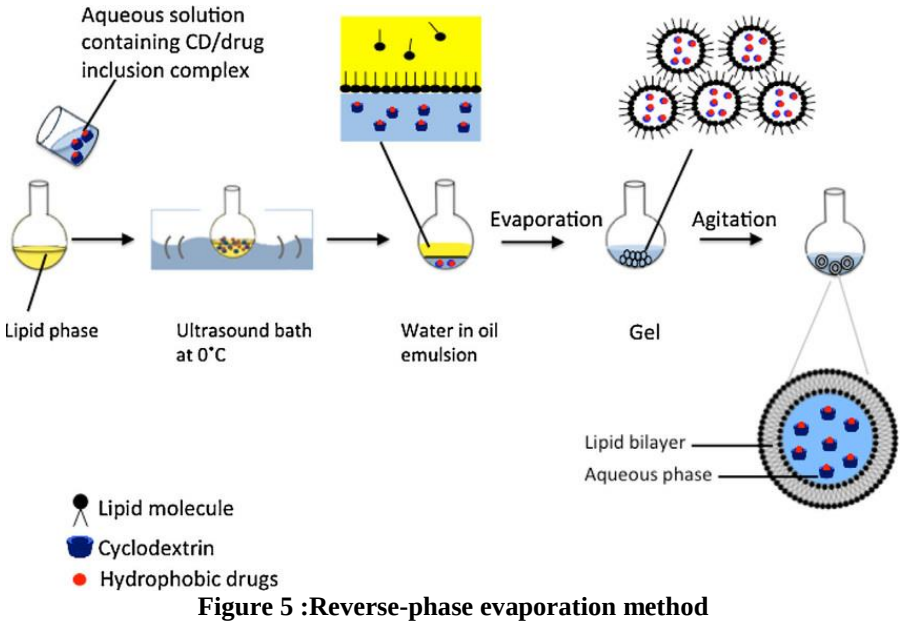

Figure 5 :Reverse-phase evaporation method

7. Ethanol injection method

In this process, the aqueous solution containing drug is heated with unremitting stirring at constant temperature. Ethanolic solution of phospholipids and EAs is injected into aqueous solution dropwise. As the solution comes into contact with aqueous media the lipid molecules are precipitated and form bilayered structures. This process offers assorted advantages over other methods, which include simplicity, reproducibility, and scale-up. [20-21]

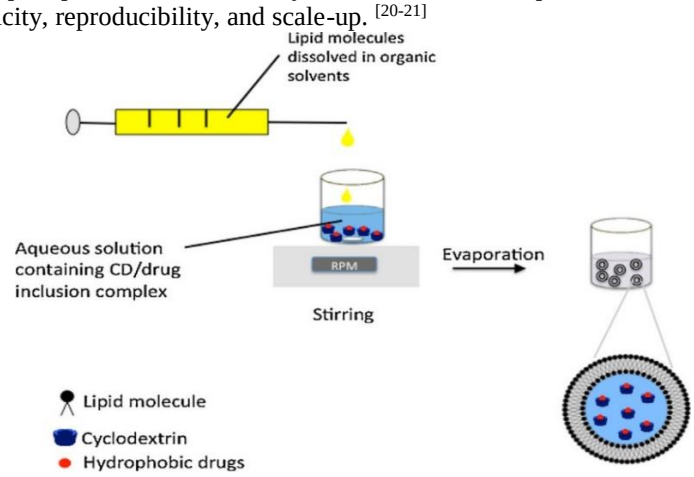

Figure 6 : Ethanol injection method

V. CHARACTERIZATION OF TRANSFERSOMES

1. Vesicle Size and morphology

The vesicle size is one of the important parameters during transfersome preparation, batch-to-batch comparison and scale-up processes.

Generally, the dynamic light scattering (DLS) method or photon correlation spectroscopy (PCS) can be used to determine the vesicle diameter. The vesicle's suspension can be mixed with an appropriate medium, and the vesicular size measurements can be obtained in triplicate. Moreover, as another approach, the sample can be prepared in distilled water and filtered through a 0.2 mm membrane filter. The filtered sample is then diluted with filtered saline to measure the size of the vesicles by DLS or PCS. Moreover, the DLS method-associated computerized inspection system by Malvern Zetasizer can be used for the determination of the vesicle size and size distribution, whereas the structural changes are observed by transmission electron microscopy (TEM).[22]

- **Zeta potential**

The zeta potential is measured by the *electrophoretic mobility technique* using Malvern Zetasizer. The *visualization* of transfersome vesicles can be done by using the phase contrast microscopy or TEM .

2. Number of vesicles per cubic mm

This is an important parameter for optimizing the composition and other process variables. Non- sonicated Transfersome formulations are diluted five times with 0.9% sodium chloride solution. Haemocytometer and optical microscope can then be used for further study. The transfersomes with a vesicle size of more than 100 nm can be observed by optical microscope. The Transfersomes in 80 small squares are counted and calculated using the following formula:

Total number of Transfersomes per cubic mm = (Total number of Transfersomes counted × dilution factor × 4000) / Total number of squares counted.[23]

3. Entrapment efficiency

The entrapment efficiency (%EE) is the amount of drug entrapped in the formulation. The EE is determined by separating the unentrapped drug from the vesicles using various techniques, such as mini-column centrifugation. The transfersomal sample is subjected to centrifugation for 15 min .After ultracentrifugation, the direct approach would be removing the supernatant followed by disrupting the sedimented vesicles using a suitable solvent that is capable of lysing the sediment. Subsequently, the resulting solution can be diluted and filtered using a syringe filter (0.22–0.45 µm) to remove the impurities. The drug content is determined by UV spectroscopy. The entrapment efficiency was calculated using the following equation: Entrapment efficiency

Entrapment efficiency = (Amount entrapped / Total amount added) ×100 [24]

4. Drug content

The drug content can be determined using one of the instrumental analytical methods such as modified high performance liquid chromatography method (HPLC) method using a UV detector, column oven, auto sample, pump and computerized analysis program depending upon the analytical method of the pharmacopoeial drug

5. Turbidity Measurement:

Turbidity of the drug is measured in the solution from using a nephelometer

6. **Degree of deformability or permeability measurement**
In the case of transfersomes, the permeability study is one of the important and unique parameter for characterization. The deformability study is done against the pure water as standard. Transfersomes preparation is passed through a large number of pores of known size (through a sandwich of different micro porous filters, with pore diameter between 50 nm and 400 nm, depending on the starting transfersomes suspension). Particle size and size distributions are noted after each pass by dynamic light scattering (DLS) measurements.
The degree of deformability is expressed as:

$$D=J(rv/rp)$$

where D = degree of deformability, J = amount of suspension extruded during 5 min, rv = size of the vesicle and rp = pore size of the barrier.[25]

7. ***In Vitro* Drug Release-** Franz diffusion cells are employed in the in vitro drug release study. The donor chamber is fixed to the receptor chamber by means of adhesive tape. The fluid in the receptor chamber is constantly stirred by a magnetic bar.
As normal skin surface temperature is approximately 32 °C , therefore, in the release study, the temperature of the receptor fluid should be kept at the in vivo skin surface temperature of 32 ± 1 °C . A mixed cellulose ester membrane of an average pore size of 0.45 µm is used. The membranes are soaked in the release media (phosphate buffer) at room temperature overnight in order to allow the membrane pores to swell. The aliquots of 1 mL of the receptor medium are withdrawn at appropriate time intervals (such as 0, 0.5, 1, 2, 3, 4, 5 and 6 h), and simultaneously, the receptor medium is replaced by an equal volume of the fresh PBS to maintain the sink conditions. The obtained samples were analyzed for drug content using UV spectrophotometer at specific wavelength. [26]

8. ***In-Vitro* skin permeation studies.**
The **in-vitro permeation studies** were done using **Franz Diffusion cell.**
The selected membranes are horizontally mounted on the receptor compartments as the side, indicating the stratum corneum facing upwards toward the donor compartments. The receptor compartments of the Franz diffusion cells are filled with phosphate buffer saline solution, which is stirred by a magnetic bar. , and the temperature of the receptor fluid should be kept at 37 ± 0.5 °C. An appropriate amount of the testing formulation is added into each donor compartment as it is placed on the membrane, and the top of the diffusion cell is opened to mimic non-occluded conditions. Specific volumes of aliquots of the receptor medium are withdrawn at appropriate time intervals, and simultaneously, the receptor medium is replaced by an equal volume of the fresh receptor medium to maintain the sink conditions. The obtained samples can be analyzed using UV spectrophotometer at specific wavelength [27-28]

9. **Stability of Transfersomes**
Stability of the transfersomes is generally determined by TEM visualization at 4 °C and 37 °C. DLS size measurement can also be used at different time intervals (30, 45, and 60 days), following vesicles preparation. The initial entrapment is considered as 100 % and the percent drug loss is calculated.. The optimized transfersomal formulations can be stored in tightly sealed amber vials at different temperature conditions. According to ICH (International Conference on Harmonization) guidelines, under the stability testing of new drug substances and products, the general case for the storage condition is described as, for the long term, 25 ± 2 °C/60% relative humidity (RH) ± 5% RH or 30 ± 2 °C/65% RH ± 5% for 12 months and, for accelerated testing, 40 ± 2 °C/75% RH ± 5% for six months. Drug products intended for refrigeration should be subjected to long-term storage at a condition of 5 ± 3 °C for 12 months and accelerated study for 25 ± 2 °C/60% RH ± 5% RH for six months. A significant change for the drug product is defined as the failure to meet its specifications.[29]

VI. APPLICATIONS OF TRANSFERSOMES AS THE TRANSDERMAL DELIVERY SYSTEM

- Transfersomes have the potential for the controlled release of the administered drug and increasing the stability of labile drugs due to the incorporation of phospholipids
- **Delivery of Anticancer Drugs**
A research conducted by Jiang et al. in 2018 was associated with the topical chemotherapy of melanoma by transfersome-embedded oligopeptide hydrogels containing paclitaxel prepared by the thin-film dispersion method. Transfersomes composed of phosphatidylcholine, tween80 and sodium deoxycholate were shown to effectively penetrate into tumor tissues

Topical delivery of 5-FU for the treatment of AK and non-melanoma skin cancer

5-FU showed poor percutaneous permeation, thus reducing its anticancer effectiveness after topical administration. The *in vivo* results concluded that vesiculization of 5-FU not only improves the topical delivery, but also enhances the cytotoxic effect of 5-FU. An instance of transfersomal gel containing 5-FU provided efficient results against the treatment for AK and non-melanoma skin carcinoma, which showed up to a two fold increase of transdermal release in contrast to other marketed formulations. [30,31]

- **Delivery of Corticosteroids**
Transfersomes are used for delivery of corticosteroids due to site specificity and over all drug safety when applied to the skin by optimization of the administered dose. Steroids which are administered using transfersomes are biologically active at doses much lesser than the doses required in other conventional formulation techniques
The biological activity and characteristics of halogenated corticosteroid triamcinolone-acetonide-loaded transfersomes prepared by the conventional thin-film hydration technique were studied by Cevc and Blume in 2003 and 2004. The results

showed that transfersomes had increased the biological potency and prolonged effect, as well as the reduced therapeutic dosage [32,33]

- **Delivery of Proteins and Peptides**
  Large molecules weight compounds can be easily transported across the skin with the help of transfersomes.
  For example, insulin, interferon like leukocytic derived interferon (INF) can be delivered through mammalian skin. They have been widely used as a carrier for the transport of other proteins and peptides. [23]
  As protein sand peptides are large biogenic molecules difficult to transport into the body and degraded in the GI tract and transdermal suffers due to their large size and they get degraded completely when given by the oral route. The bioavailability of proteins using transfersomes is almost similar to that of the bioavailability obtained after a subcutaneous injection of a suspension of proteins. The transfersome preparation also induced strong immune responses when repeatedly applied epicutaneously. An example of this is an adjuvant immunogenic serum albumin which in spite of several dermal challenges is active immunologically using transfersome carrier and also injected proteotransfersome preparations. [34]
- Transferosomes have also been used as a carrier for interferons, for example INF-α is a naturally occurring protein having antiviral, anti proliferive and some immunomodulatory effects. Transferosomes as drug delivery systems have the potential for providing controlled release of the administered drug and increasing the stability of labile drugs.[35]
- **Delivery of NSAIDs**: The typical problems associated with NSAIDs like GI irritation can be overcome by transdermal delivery using transfersomes. Some drugs like diclofenac and ketoprofen are already studied for their efficacy using tranfersomes and ketoprofen formulation is already approved by Swiss regulatory agency.[36]
- **Delivery of Anti-Inflammatory Drugs**
  Diclofenac sodium, celecoxib, mefenamic acid and curcumin-loaded transfersomes were developed and studied for the purpose of topical administration by several research groups. Research findings suggested that transfersomes could improve the stability and efficacy of the anti-inflammatory drugs.[37]

VII. CONCLUSION

Transfersomes are ultra-deformable carriers that facilitate the delivery of a diverse array of drug molecules across the skin barrier with superior efficacy compared to the conventional vesicular systems. Transfersomes can penetrate the intact stratum corneum spontaneously along two routes in the intracellular lipid that differ in their bilayers properties.It is clear that transfersomes can deliver enhanced amounts of both small and large therapeutic agents into and through the skin. Transfersomes can be used for the delivery of various active compounds, including proteins and peptides, insulin, corticosteroids, interferons, anesthetics, NSAIDs, anticancer drugs and herbal drugs. In this type of delivery, Drug release can also be controlled according to the requirement. Importantly, transferosomes are specifically designed vesicular systems that need to be optimized in accordance with individual cases of drugs of interest to achieve the most effective formulations and ultimate pharmacological responses. Further scientific studies associated with transfersomes may lead to novel promising therapeutic approaches against many types of diseases. It is likely that a number of transfersome products for dermal and transdermal applications will be developed in the future.

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