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Transferosomes Is a Novel Drug Delivery System for Percutaneous Drug Administration

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ABSTRACT

Transdermal drug delivery appears to be the most vital drug delivery system because of its merit over conventional systems. The drug carries used in transdermal drug delivery such as Liposomes, Niosomes, or Microemulsions have a problem that they remain mostly confined to the skin surface and therefore do not transport drugs efficiently through the skin. Among these strategies, transferosomes appear promising. Transferosomes possess an infrastructure consisting of hydrophobic and hydrophilic moieties together and as a result, can accommodate drug molecules with a wide range of solubility. Transferosomes can deform and pass through a narrow constriction (from 5 to 10 times less than their diameter) without measurable loss. Transferosomes is a type of carrier system which is capable of transdermal delivery of low as well as high molecular weight drugs. This is because of its deformable nature. This high deformability gives better penetration of intact vesicles [1-3].

INTRODUCTION

During the last few decades, the transdermal route has been tremendously focused on drug delivery than other routes as it reveals its superiority as a convenient and safe route for drug administration. The transdermal route offers several potential advantages over conventional routes like avoidance of first-pass metabolism, predictable and extended duration of the activity, minimizing side effects, improving physiological and pharmacological responses, avoiding plasma -drug level fluctuations. But the applications of transdermal drug delivery for a wider range of drugs are limited due to significant barriers to penetration across the skin, which is related primarily with the outermost stratum corneum layer of the epidermis. To overcome the problem associated with the stratum corneum barrier, various approaches can be adopted. Recently, the vesicular drug carrier system, transferosomes (which is composed of phospholipids, surfactant, and water) has been reported to enhance the transdermal delivery of drugs, when applied onto the skin non-occusively [1, 4].

The term “transferosomes” and the underlying concept were introduced in 1991 by “Gregor Cevc and his co-workers”. Transferosomes is a trademark registered by the German company IDEA AG, which refers to its proprietary drug delivery technology. The name means “carrying body” and is derived from the Latin word 'transferre', meaning “to carry across” and the Greek word 'soma', meaning “a body”[5]. Transferosomes are advantageous as phospholipids vesicles for transdermal drug delivery. Because of their self-optimized and ultra-flexible membrane properties, they can deliver the drug reproducibly either into or through the skin, depending on the choice of administration or application, with high efficiency. The vesicular transferosomes are more elastic than the standard liposomes and thus well suited for skin penetration. Transferosomes overcome the skin penetration difficulty by squeezing themselves along the intracellular sealing lipid of the stratum corneum [6].

A self-optimizing and a self-regulatory property are incorporated in the vesicle due to the composition of the bilayer and the Interdependency of the local composition. This property helps the vesicle is traversing the different transport barriers effectively and helps the carrier in targeted and sustained delivery of active constituents in a non-invasive manner. An artificial vesicle is designed in such a way that it acts like a cell involved in exocytosis which makes it appropriate for controlled and targeted drug delivery.

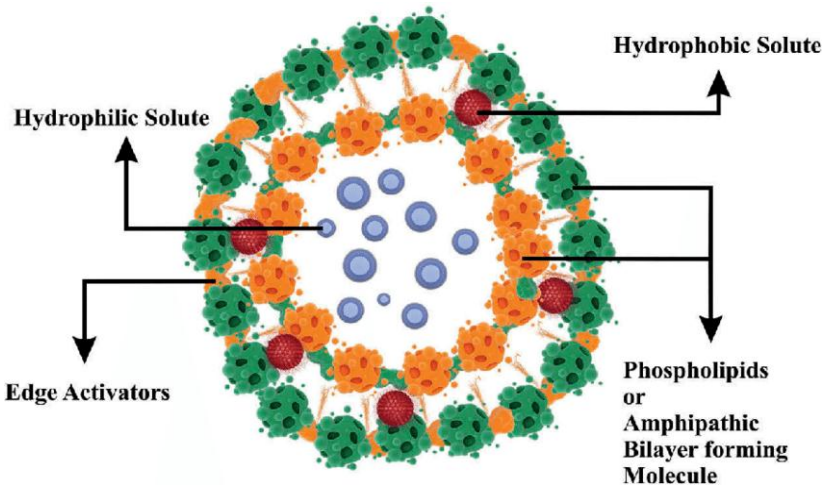

Figure No. 1: Structure of Transferosomes

The carrier aggregate is composed of at least one amphipathic molecule (like phospholipids) which when added to aqueous systems self-assemble into a bilayer of lipid which eventually closes into a lipid vesicle. A bilayer softening agent is generally added (a biocompatible surfactant) to improve the bilayer flexibility and permeability. This vesicle can then adapt its shape easily and quickly, by adjusting the concentration at the local level of every bilayer component to the anxiety or stress experienced. Transferosomes differ from liposomes in that they are much softer than liposomes and are deformable to a higher extent [7].

ADVANTAGES OF TRANSFEROSOMES

1) They have high entrapment efficiency, in the case of lipophilic drugs near 90%.

2) This high deformability gives better penetration of intact vesicles.

3) They can act as a carrier for low as well as high molecular weight drugs e.g. analgesic, anesthetic, corticosteroids, sex hormone, anticancer, insulin, gap junction protein, and albumin.

4) They are capable of deforming themselves and passing through narrow constrictions (5-10 times lesser than their diameter) without any significant losses.

5) They are made of natural phospholipids and are biocompatible.

6) They provide suitable protection to the encapsulated drug from degradation. This is specifically useful in the case of proteins and peptides.

7) Suitable for both systemic as well as topical delivery of drugs.

8) Biodegradability and lack of toxicity [8].

DISADVANTAGES OF TRANSFERSOMES

1) Transferosomes are chemically unstable because of their predisposition to oxidative degradation.

2) The purity of natural phospholipids is another criterion militating against the adoption of transferosomes as drug delivery vehicles.

3) Transferosomes formulations are expensive **[8, 9]**.

MECHANISM OF ACTION:

The mechanism behind the penetration of transferosomes is the development of "osmotic gradient" because while lipid suspension applies on skin surface water gets evaporated. Transferosomes have strong bilayer deformability and therefore they have increased affinity to bind and retain water. Dehydration does not happen in case an ultra deformable and highly hydrophilic vesicle; it is not identical to forwarding osmosis but may involve in the transport process related to forward osmosis. Upon application on the skin surface (non-occluded), it penetrates skin barrier and reaches the deeper strata (water-rich portion), where they get hydrated. Then, reach a deeper epidermal layer through dehydration of lipid vesicles within the stratum corneum by natural transepidermal activity. Therefore, transferosomes uptake is a function of the hydration gradient that exists across the epidermis, stratum corneum, and ambient atmosphere [10].

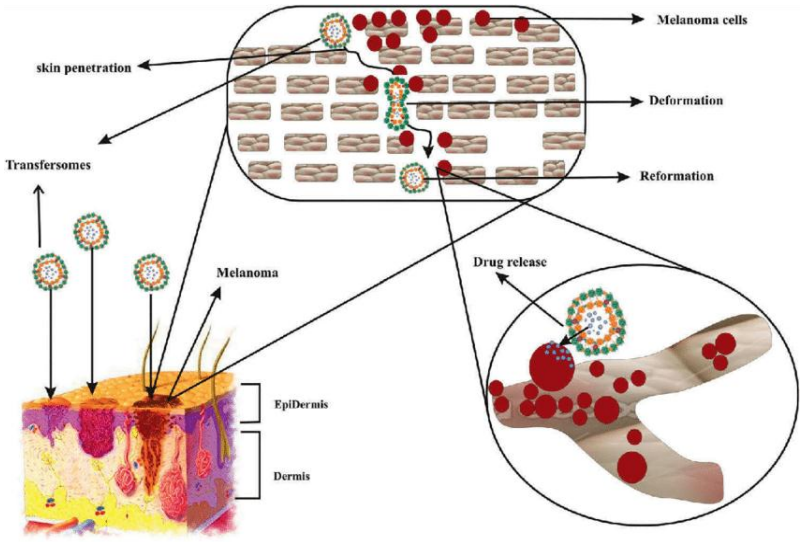

Figure No. 2: Mechanism of action of Transferosomes

Proposed mechanism of penetration

1. Transferosomes act as drug vectors, remaining intact after entering the skin.

2. Transferosomes act as penetration enhancers, disrupting the highly organized intercellular lipids from stratum corneum and therefore facilitating the drug molecule penetration in and across the stratum corneum.

Cevc and coworkers proposed the first mechanism, suggesting that deformable liposomes penetrate the stratum corneum because of the transdermal hydration gradient normally existing in the skin, and then cross the epidermis, and enter the systemic circulation.

Recent studies propose that the penetration and permeation of the vesicles across the skin are due to the combination of the two mechanisms. Depending on the nature of the active substance (lipophilic or hydrophilic) and the composition of the transfersomes, one of the two mechanisms prevails [6, 7].

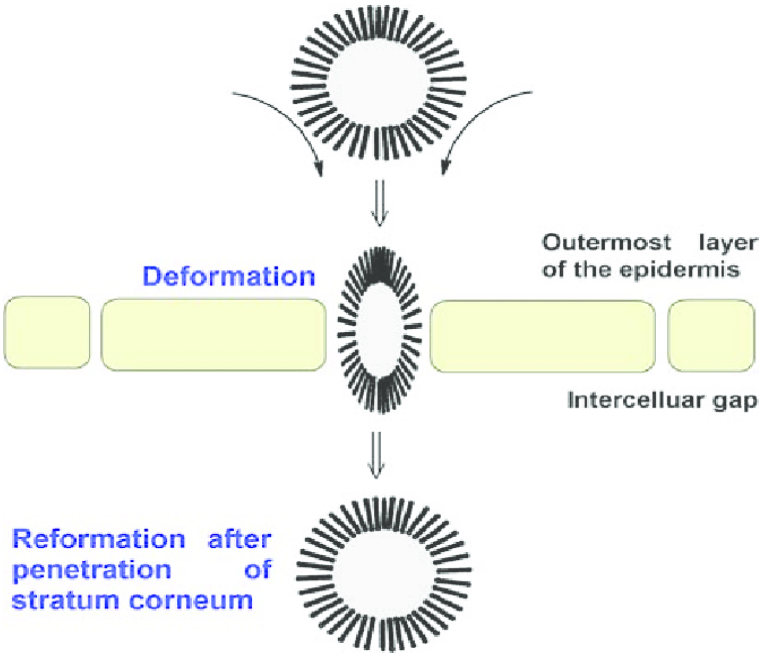

Figure No. 3: Mechanism of penetration of Transferrosome

Penetration of Transferosomes through the Skin

Transferosomes ensure penetration through the skin by getting squeezed through the lipid present in the cells of the stratum corneum. This is possible due to the ability of the vesicle to deform to a great extent which provides the mechanical stress needed to enter the skin.

The main point to be kept in mind to have optimum flexibility of transferosomes is to have a suitable mix of surface-active agents in proper ratios with phospholipids. This flexibility minimizes the possibility of complete rupture of the vesicle in the skin and helps the vesicles to follow a natural aqueous gradient across the outer layer of non-occluded skin.

Possible pathways for a penetrant to cross the skin barrier

(1) Across the intact horny layer/ stratum corneum

(2) Through the hair follicles with the associated sebaceous glands,

(3) Via the sweat glands

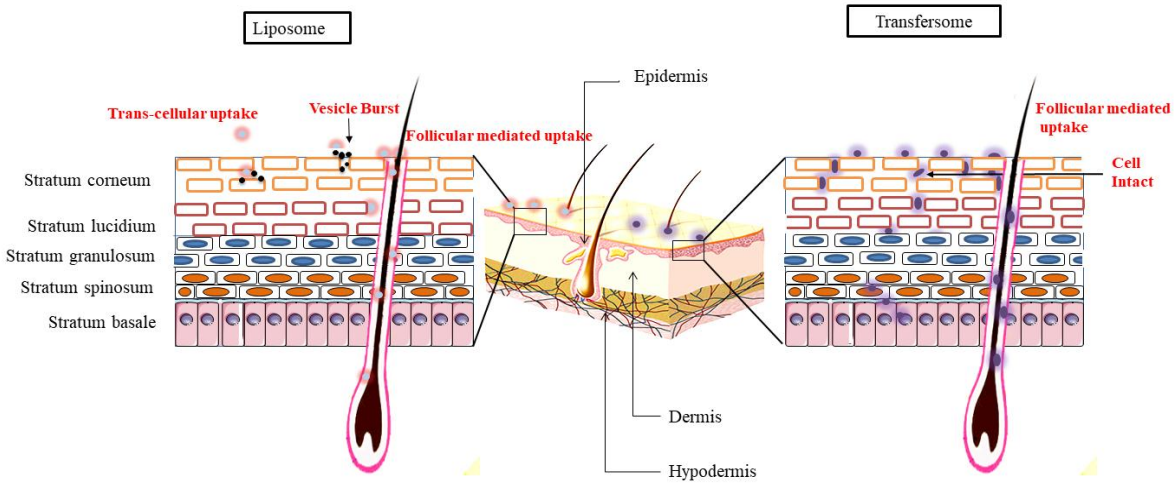

Figure No. 4: Comparison of Liposome and Transferrosome drug penetration through the skin

It has been proven through confocal microscopic studies that liposomes in the intact form cannot pass through the granular epidermis and remain as such on the upper layer of the stratum corneum. Changes in the composition of the vesicle and surface properties will make sure the appropriate rate of drug release and drug deposition. Thus, transferosomes are ideal candidates for vesicular delivery of drugs and bioactive through the transdermal and topical delivery routes.

The propensity of Penetration:

Transferosomes are too large to diffuse through the skin, they need to find their route through the organ. The magnitude of the driving force can then be calculated using the following formula:-

Flow = Area × (Barrier) permeability × (Trans-barrier) force.

Hence the flow of the lipid across the skin which is chemically driven decreases drastically when the lipid in solution form is replaced by the same amount of suspension of lipid.

Transferosomes, when applied under suitable conditions, can transfer 0.1 mg of lipid per hour and square centimeter area across the intact skin. This value is substantially higher than that typically driven by the transdermal concentration gradients [11, 12].

Materials used in the formulation of transferosomes

Materials which are widely used in the formulation of transferosomes are various phospholipids, surfactants, alcohol, dye, buffering agent, etc.

Phospholipids like phosphatidylcholine which self assembles into lipid bilayer in an aqueous environment and closes to form a vesicle.

A bilayer softening component (such as a biocompatible surfactant or an amphiphile drug) is added to increase lipid bilayer flexibility and permeability. This second component is called as edge activator [13].

Table No. 1: Different additives used in the formulation of transferosomes

Class	Example	Uses
Phospholipids	Soya phosphatidylcholine, Disteryl phosphatidylcholine, Egg-phosphatidylcholine, Dipalmitoylphosphatidyl choline	Vesicles forming agent
Surfactant	Sodium cholate, Sodium deoxycholate, Tween-80, Tween-20, Span-80	For providing flexibility
Alcohol/Solvents	Ethanol, Methanol, Isopropyl- alcohol, Chloroform	As a solvent
Buffering agent	Saline phosphate buffer(pH 6.4), Phosphate buffer (pH 7.4), 7% v/v ethanol, Tris buffer (pH 6.5)	As a hydrating medium
Dye	Rhodamine- 123, Rhodamine- DHPE, Fluorescein-DHPE, NBD-PE, Nile red, 6 Carboxy Fluorescein [14]	For CSLM study

METHOD FOR PREPARATION OF TRANSFERSOMES

A. Thin-film hydration technique

Thin-film hydration technique is employed for the preparation of transferosomes which comprised of three steps:-

Step-1: A thin film is prepared from the mixture of vesicles forming ingredients that are phospholipids and surfactants by dissolving in a volatile organic solvent (chloroform-methanol). The organic solvent is then evaporated above the lipid transition temperature (room temp. for pure PC vesicles, or 50°C for dipalmitoylphosphatidylcholine) using a rotary evaporator. Final traces of solvent were removed under vacuum overnight.

Step-2: A prepared thin film is hydrated with buffer (pH 6.5) by rotation at 60 rpm for 1 hr at the corresponding temperature. The resulting vesicles were swollen for 2 hr at room temperature.

Step-3: To prepare small vesicles, resulting vesicles were sonicated at room temperature or 50°C for 30 min. using a bath sonicator or probe sonicated at 4°C for 30 min. The sonicated vesicles were homogenized by manual extrusion 10 times through a sandwich of 200 and 100 nm polycarbonate membranes.

B. Modified handshaking, lipid film hydration technique

Modified handshaking, lipid film hydration technique is also founded for the preparation of transferosomes which comprised the following steps:-

Step-1 Drug, lecithin (PC), and edge activator were dissolved in ethanol: chloroform (1:1) mixture. The organic solvent was removed by evaporation while handshaking above the lipid transition temperature (43°C). A thin lipid film was formed inside the flask wall with rotation. The thin film was kept overnight for the complete evaporation of the solvent.

Step-2 The film was then hydrated with phosphate buffer (pH 7.4) with gentle shaking for 15 minutes at the corresponding temperature. The transferosomes suspension further hydrated up to 1 hour at 2-8°C [15].

C. Reverse phase evaporation method

Phospholipids, surfactants, and the drug are used to dissolve in alcohol to form transferosomes. The organic solvent is then evaporated by rotary evaporation under reduced pressure at 40-45 ºC. The final residue of the solvent is removed under vacuum. The retainer lipid film is moderated with a separated buffer by rotation at 60 rpm for 1 hour at room temperature. The emerging cysts are inflated for 2 hours at room temperature. The

multilamellar lipid cysts are then scanted at room temperature. Scantination may be replaced by extrusion, low shear mixing, or high shear mixing [16].

D. Vortexing-Sonication Method:

In the Vortexing-sonication method, mixed lipids (i.e. phosphatidylcholine, Edge activator, 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 10. Cationic transferosomes have also been prepared by this method, which involves mixing cationic lipids, such as DOTMA, with PBS to obtain a concentration of 10 mg/ml followed by the addition of sodium deoxycholate (SDC). The blend is vortexed and sonicated, followed by extrusion through a polycarbonate (100-nm) filter [17].

E. Ethanol injection method

In this process, the aqueous solution containing the drug is heated with unremitting stirring at a constant temperature. The ethanolic solution of phospholipids and EAs is injected into an 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 [18].

F. Suspension homogenization process

In this process, transferosomes are prepared by mixing an ethanolic soybean phosphatidylcholine solution with an appropriate amount of edge-active molecule, e.g. sodium cholate. This prepared suspension is subsequently mixed with Triethanolamine-HCl buffer to yield a total lipid concentration. The resulting suspension is sonicated, frozen, and thawed for 2 to 3 times.

G. Aqueous lipid suspension process

In this process, the Drug-to-lipid ratio in the vehicles is fixed between 1/4 and 1/9. Depending upon the particular formulation type, the composition is preferred. This would ensure the high flexibility of the vesicle membrane in comparison to the standard phosphatidylcholine vesicles in the fluid phase. Specifically, vesicles with the size ranging from 100- 200 nm are prepared by using soya phosphatidylcholine with the standard

deviation of the size distribution (around 30%). This formulation could be prepared by suspending the lipids in an aqueous phase wherein the drug is dissolved [19].

OPTIMIZATION OF FORMULATION CONTAINING TRANSFEROSOMES

There are various process variables which could affect the preparation and properties of the transferosomes. The preparation procedure was accordingly optimized and validated. The process variables are depending upon the procedure involved in the manufacturing of formulation. The preparation of transferosomes involves various process variables such as,

1. Lecithin: surfactant ratio

2. Effect of various solvents

3. Effect of various surfactants

4. Hydration medium

Optimization was done by selecting the entrapment efficiency of drugs. During the preparation of a particular system, the other variables were kept constant [20].

CHARACTERIZATION OF TRANSFEROSOMES:

The characterization of transferosomes is generally similar to liposomes, niosomes, and micelles.

1. Vesicle size distribution and zeta potential

Vesicle size, size distribution, and zeta potential were determined by Dynamic Light Scattering system by Malvern Zetasizer. The sample was prepared by diluting with water and corresponding zeta potential measured using Malvern Zetasizer [12].

2. Vesicle Diameter or morphology

Vesicle diameter can be determined using photon correlation spectroscopy or dynamic light scattering (DLS) method. Samples were prepared in distilled water, filtered through a 0.2 mm membrane filter and diluted with filtered saline, and then size measurement is done by using photon correlation spectroscopy or dynamic light scattering (DLS) measurements. Transferosomes vesicles can be visualized by TEM, phase contrast microscopy, etc. The

stability of vesicles can be determined by assessing the size and structure of vesicles over time. Mean size is measured by DLS and structural changes are observed by TEM [21].

3. Number of Vesicle per Cubic mm

This is an important parameter for optimizing the composition and other process variables. Transferosomes formulations (without sonication) can be diluted five times with 0.9% of sodium chloride solution and studied with optical microscopy by using hemocytometer [22]. The Transferosomes in 80 small squares are counted and calculated using the following formula:-

Total number of Transferosomes per cubic mm = (Total number of Transferosomes counted × dilution factor × 4000) / Total number of squares counted

4. Entrapment Efficiency

The entrapment efficiency is expressed as the percentage entrapment of the drug added. Entrapment efficiency was determined by the first separation of the unentrapped drug by the use of the mini-column centrifugation method. After centrifugation, the vesicles were disrupted using 0.1% Triton X-100 or 50% n-propanol [23].

The entrapment efficiency is expressed as:-

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

5. Turbidity Measurement

The turbidity of drugs in aqueous solutions can be measured using a nephelometer. The transferosomes were diluted with distilled water to give a total lipid concentration of 0.312 mm. After rapid mixing by sonication for 5 min, the turbidity was measured with the help of UV- visible spectrophotometer at 274nm [16].

6. Surface Charge and Charge Density

Surface charge and charge density of transferosomes can be determined using zeta sizer [4].

7. Penetration Ability:

The penetration ability of transferosomes can be evaluated using fluorescence microscopy.

8. Drug content

The drug content can be determined using one of the instrumental analytical methods such as a 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 [10].

9. Degree of deformability or permeability measurement

In the case of transferosomes, the permeability study is one of the important and unique parameters for characterization. The deformability study is done against pure water as standard. Transferosomes preparation is passed through a large number of pores of known size (through a sandwich of different microporous filters, with pore diameter between 50 nm and 400 nm, depending on the starting transferosomes suspension). Particle size and size distributions are noted after each pass by dynamic light scattering (DLS) measurements [24].

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

Where, D= degree of deformability

J = amount of suspension extruded for 5 min.

rv = size of vesicle

rp = pore size of barrier

10. *In-vitro* drug release

In-vitro drug release study is performed for determining the permeation rate. Time needed to attain steady-state permeation and the permeation flux at steady-state and the information from *in-vitro* studies are used to optimize the formulation before more expensive in vivo studies are performed. For determining drug release, transferosomes suspension is incubated at 32°C, and samples are taken at different times and the free drug is separated by minicolumn centrifugation. The amount of drug released is then calculated indirectly from the amount of drug entrapped at zero times as the initial amount (100% entrapped and 0% released).

11. *In-vitro* skin permeation Release

Modified Franz diffusion cell with a receiver compartment volume of 50ml and an effective diffusion area of 2.50 cm^2 was used for this study. In vitro drug study was performed by using goatskin in phosphate buffer solution (pH 7.4). Fresh Abdominal skin of goat was collected from the slaughterhouse and used in the permeation experiments. Abdominal skin hairs were removed and the skin was hydrated in normal saline solution. The adipose tissue layer of the skin was removed by rubbing with a cotton swab. The skin was kept in an isopropyl alcohol solution and stored at 0-40˚C.

To perform skin permeation study, treated skin was mounted horizontally on the receptor compartment with the stratum corneum side facing upwards towards the donor compartment of Franz diffusion cell. The effective permeation area of the donor compartment exposed to the receptor compartment was 2.50cm^2 and the capacity of the receptor compartment was 50ml. The receptor compartment was filled with50ml of phosphate buffer (pH 7.4) saline maintained at 37 ± 0.5˚C and stirred by a magnetic bar at 100RPM. Formulation (equivalent to 10mg drug) was placed on the skin and the top of the diffusion cell was covered. At appropriate time intervals, 1 ml aliquots of the receptor medium were withdrawn and immediately replaced by an equal volume of fresh phosphate buffers (pH 7.4) to maintain sink conditions. Correction factors for each aliquot were considered in the calculation of the release profile. The samples were analyzed by any instrumental analytical technique [25].

12. Confocal Scanning Laser Microscopy (CSLM) Study:

Conventional light microscopy and electron microscopy both face the problem of fixation, sectioning, and staining of the skin samples. Often the structures to be examined are incompatible with the corresponding processing techniques; these give rise to misinterpretation but can be minimized by Confocal Scanning Laser Microscopy (CSLM). In this technique, lipophilic fluorescence markers are incorporated into the transferosomes and the light emitted by these markers used for investigating the mechanism of penetration of transferosomes across the skin for determining the histological organization of the skin (epidermal columns, interdigitation), shapes and architecture of the skin penetration pathways for comparison and differentiation of the mechanism of penetration of transferosomes with liposomes, niosomes and micelles [17].

13. Physical stability

The initial percentage of the drug entrapped in the formulation was determined and were stored in sealed glass ampoules. The ampoules were placed at 4 ± 20C (refrigeration), 25 ± 20C (room temp), and 37 ± 20C (body temp) for at least 3 months. Samples from each ampoule were analyzed after 30 days to determine drug leakage. Percent of drug loss was calculated by keeping the initial entrapment of drug as 100%.

APPLICATIONS OF TRANSFEROSOMES

1. Delivery of insulin

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

2. Delivery of corticosteroids

Transferosomes improves the site-specificity and overall drug safety of corticosteroid delivery into the skin by optimizing the epicutaneously administered drug dose. Transferosomes based corticosteroids are biologically active at dose several times lower than the currently used formulation for the treatment of skin diseases.

3. Delivery of proteins and peptides

Transferosomes have been widely used as a carrier for the transport of proteins and peptides. Proteins and peptides are large biogenic molecules that are very difficult to transport into the body, when given orally they are completely degraded in the GI tract and transdermal delivery suffers because of their large size. These are the reasons why these peptides and proteins still have to be introduced into the body through injections. The bioavailability obtained from transferosomes is somewhat similar to that resulting from subcutaneous injection of the same protein suspension [26].

4. Delivery of anticancer drugs

Anticancer drugs like Methotrexate were tried for transdermal delivery using transferosomes technology. The results were favorable. This provided a new approach for treatment especially of skin cancer.

5. Delivery of NSAIDs

NSAIDs are associated with some GI side effects. These can be overcome by transdermal delivery using ultra-deformable vesicles. Studies have been carried out on Diclofenac and Ketoprofen. Ketoprofen in a transferosomes formulation gained marketing approval by the Swiss regulatory agency (Swiss Medic) in 2007; the product is expected to be marketed under the trademark direction. Further therapeutic products based on transferosomes technology, according to IDEA AG, are in clinical development.

6. Delivery of herbal drugs

Transferosomes can penetrate stratum corneum and supply the nutrients locally to maintain its functions resulting in maintenance of skin [27].

7. Delivery of interferons

Transferosomes have also been used as a carrier for interferons, for example, leukocytic derived interferon-α (INF-α) is a naturally occurring protein having antiviral, antiproliferative 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.

8. Delivery of anesthetics

Transferosomes based formulations of local anesthetics lidocaine and tetracaine showed permeation equivalent to subcutaneous injections, with less than 10 min. The maximum resulting pain insensitivity is nearly as strong (80%) as that of a comparable subcutaneous bolus injection, but the effect of transferosomal anesthetics last longer effect [28].

9. Controlled release and stability enhancement

Transferosomes as drug delivery systems have the potential for providing controlled release of the administered drug and increasing the stability of labile drugs.

10. Utilization of high molecular weight drugs

Very large molecules incapable of diffusing into the skin as such can be transported across the skin with the help of transferosomes. For example, insulin interferon can be delivered through mammalian skin. Insulin is generally administered by a subcutaneous route that is inconvenient. Encapsulation of insulin into transferosomes overcomes the problem of inconvenience and the largest size. Transferosomes have been used as a carrier for interferons like leukocytic derived interferon-α (INF-α) [29].

REGULATORY ASPECTS

Recently, advances in pharmaceutical science and skill have made available a range of new excipients, such as lipids, surfactants, and solvents; though of late, there have been reservations within the scientific community regarding the dullness of excipients and that they in some capacity have unfavorable effects. The selection of excipients throughout the research of a transferosomes-based formulation is limited by safety and toxicity concerns associated with these excipients. Hence, a small range of excipients is obtainable for planning any highly porous drug deliverance system. Thus, inert excipients are usually measured when developing a transferosomes-based formulation and these are used as vesicle-forming agents, surfactants, EAs, and solvents. Mitigating the safety concerns, a narrow range of excipients are obtainable for crafting any highly porous drug delivery system, such as a transferosomes [30]. Different national regulatory agencies (WHO, International Pharmaceutical Excipients Council, US Food and Drug Administration (FDA), Japanese Ministry of Health and Welfare, and International Conference on Harmonization of Technical necessities for the muster of Pharmaceuticals for Human Use) have maintained a confidential list of excipients as ‘Generally Regarded as Safe’ (GRAS), which have been clinically categorized not to be toxic. The FDA keeps a record entitled ‘Inactive Ingredient Guide’, which includes a catalog of permitted excipients. This document provides information about the excipients with a value of their utmost dosage stage by a fastidious route of direction or dosage form. A phospholipid is a crucial element for the formation of a transferosomes-based drug delivery system. It is also roughly always true that the fluid-chain vesicles with a rather elastic bilayer

promote drug transport across skin obstruction better than the more rigid liposomes. Therefore, nearly all the common phosphatidylcholine (PC) used to organize stretchy liposomes is unsaturated PC (i.e. soybean phosphatidylcholine (SPC) or egg phosphatidylcholine (EPC)). SPC is a GRAS-listed Phospholipid and also complies with specifications of the Food Chemicals Codex. Edge activator is generally a kind of surfactant which destabilizes the lipid bilayer of the elastic liposomes and increases the elasticity of the bilayer concurrently. Amid EAs, sodium cholate, sodium deoxycholate, Span-80, Tween-80, and Tween-20 were normally used. Biju et al. recommended that some chemical penetration enhancers such as oleic acid can be used as well as edge activator to replace the normally used surfactant. The survival of mixed micelles also leads to lower drug trap due to their higher inflexibility and smaller size.

Edge activator plays an important role in determining the skin permeation behavior of elastic liposomes. An overview of the differences among EAs is helpful for the selection of an ideal EA for optimal formulation. Sodium deoxycholate is a water-soluble ionic surfactant. Valsartan-loaded elastic liposomes containing sodium deoxycholate as the EA were then investigated. Similarly, sodium cholate, which is used as an EA, is reported to be non-toxic but has been kept in the hazardous category as it causes skin and eye irritations as well as respiratory sensitization. Surfactants can cause severe gastrointestinal discomfort when used above certain concentrations; the maximum safe limit of surfactant concentration is 10–25%. Ethanol is known to act as an efficient skin-penetration enhancer. It can interact with the polar head group region of the lipid molecules, resulting in a reduction of the melting point of the stratum corneum lipids, thereby increasing their fluidity and cell membrane permeability [31].

CONCLUSION:

From above discussion and research work carried out by the various researcher, it can be concluded that transferosomes is one of the promising novel drug delivery systems concerning its stability, biocompatibility, reduce toxicity, and extended controlled delivery of drug which generally plays an important role in case of topical or transdermal delivery. Transferosomes are ultra deformable, flexible, elastic, and inexpensive vesicles and they enable to pass the entrapped drug molecule through the intact skin due to its high deformability, which makes it different from conventional liposomes. Transferosomes can pass through even tiny pores (100 mm) nearly as efficiently as water, which is 1500 times

smaller. It has been found that systemic drug availability reaches higher or at least 80-90% when given via transferosomes. The bio-distribution of radioactively labeled phospholipids applied in the form of transferosomes after 24 h is essentially the same after an epicutaneous application or subcutaneous injection of the preparations. Moreover, transferosomes can be a good alternative in contrast to oral and invasive drug delivery.

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