ABSTRACT

Transfersomes is a carrying body for targeted transdermal drug delivery system. This are special types of liposomes, consisting of phosphatidylcholine and an edge activator. This system also takes advantage of phospholipids vesicles as transdermal drug carrier. It penetrate the stratum corneum by either intracellular route or the transcellular route by the generation of “osmotic gradient”. Advantages of Transfersomes are wide range of solubilities, better penetration, biocompatible and biodegradable etc. Advantages of Transfersomes are oxidative degradation, expensive, etc. The transfersomes were formulated by the conventional rotary evaporation sonication method. It contains phospholipids, surfactant and the drug were formulated. Evaluation parameters of transfersome are as Vesicle size distribution and zeta potential, Vesicle morphology, No. of vesicles per cubic mm, Entrapment efficiency, Drug content, Turbidity measurement, Degree of deformability or permeability measurement, Penetration ability, Occlusion effect, Surface charge and charge density, In-vitro drug release, in-vitro Skin permeation Studies, Physical stability. Transfersomes can be applied in controlled release, transportation of large molecules weight compounds, target delivery to peripheral subcutaneous tissues, transdermal immunization etc.

KEYWORDS: Transfersomes, Transdermal drug delivery system, Modified Transfersomes.

INTRODUCTION

Transfersome 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'. A Transfersome carrier is an artificial vesicle designed to exhibit the
characteristics of a cell vesicle or a cell engaged in exocytosis, and thus suitable for controlled and potentially, targeted drug delivery. Transfersomes are complex vesicles that have extremely flexible & self-regulating membranes, which make the vesicle very deformable. Transfersome vesicle can cross microporous barriers efficiently, even if the porous are much smaller than the vesicles size.

Drug Delivery via the route is an interesting option in this respect because transdermal route is convenient and safe. They offers several advantages over conventional drug delivery system like avoidance of first pass metabolism, predictable and extended duration of action, minimizing undesirable side effects, utility of short half-life drugs, improving physiological and pharmacological response, avoiding the fluctuation in drug levels, inter-and intra-patient variations and most importantly, it provides patients convenience. Despite major research and development efforts in transdermal systems and the advantages of these routes, low stratum corneum permeability limits the usefulness of topical drug delivery. To overcome this, various methods have been assessed to increase stratum corneum permeability. To date many physical and chemical approaches have been applied to increase the efficacy of the material to transfer across the intact skin, by use of the penetration enhancers, iontophoresis, iontophoresis and the use of colloidal carriers such as lipid vesicles (liposome and proliposomes) and non-ionic surfactant vesicles (noisome and proniosomes). Vesicular system used in transdermal drug delivery such as liposomes, niosomes, or microemulsions usually remains confined to the skin surface and therefore do not transport drugs efficiently through the skin. By using the concept of rational membrane design a special type of composite bodies, so-called Transfersomes have been developed, Which overcome the
filtration problem and penetrate the skin barrier along the transcutaneous gradient. Transfersomes is recent novel drug delivery system and are special types of liposome, consisting of phosphatidylcholine and an edge activator. This system also takes advantage of phospholipids vesicles as transdermal drug carrier. They are self-optimized aggregates, with the ultra flexible membrane, which deliver the drug reproducibly either into or through the skin. The system delivers the drug with high efficiency depending on the choice of administration or application. This system has several order magnitude of elasticity and flexibility over liposomal drug delivery which makes it favorable for efficient skin penetration and hence for the novel drug delivery system. They overcome the skin penetration difficulty by squeezing themselves along the intracellular sealing lipid of the stratum corneum. With the application of mechanical stress, they can enter through stratum corneum in self adapting manner because of their high vesicle deformability. Flexibility or elasticity of transfersomes membrane is achieved by mixing suitable surface-active components (edge activator) in the proper ratios. The resulting flexibility of transfersomes membrane minimizes the risk of complete vesicle rupture in the skin and allows them to follow the natural water gradient across the epidermis, when applied under nonocclusive condition. They can penetrate the intact stratum corneum spontaneously by either intracellular lipid or transcellular route. The high and self-optimizing deformability of typical composite bodies membrane, which are adaptable to ambient stress allow the ultra deformable transfersomes to change its membrane composition locally and reversibly, when it is pressed against or attracted into narrow pore. When applied on the skin, the carrier searches and exploits hydrophilic pathways or ‘pores’ between the cells, where it opens wide enough to permit the entire vesicle to pass through stratum corneum along with drug molecule, deforming itself extremely to accomplish this without losing its vesicular integrity. This enables them to cross various transport barriers efficiently.

Transfersomes are ultra deformable, self optimized aggregates for transdermal application containing a mixture of lipids and biocompatible membrane softeners. Though basic organization is broadly similar to a liposome, the Transfersome differs by its softer, more deformable and better adjustable artificial membrane they posses. Transfersome penetrate the stratum corneum by either intracellular route or the transcellular route by the generation of “osmotic gradient” due to evaporation of water. Thus a transfersome vesicle, when applied on an open biological surface, such as non occluded skin, tends to penetrate its barrier and migrate into the water-rich deeper strata to secure adequate hydration. As the vesicles are
elastic, they can squeeze through the pores in stratum corneum (though these pores are less than one-tenth of the diameter of vesicles). Transfersome vesicles can transport molecules that are too big to diffuse through skin. Eg: systemic delivery of therapeutically meaningful amounts of macromolecules, such as insulin or interferon. Other applications include the transport of small molecule drugs which have certain physicochemical properties which would otherwise prevent them from diffusing across the barrier. Now a day, Transfersome can be used to target peripheral subcutaneous tissue. The Non-steroidal anti-inflammatory drug (NSAID) ketoprofen in a Transfersome formulation in the trade mark Diractin gained marketing approval by the Swiss regulatory agency (Swiss Medic) in 2007. Topical immunization using cationic transfersomes based DNA vaccine offers all the advantages of DNA vaccines and in addition overcome the disadvantages of classical invasive methods of vaccination. Liposomal as well as niosomal systems, are not suitable for transdermal delivery, because of their poor skin permeability, breaking of vesicles, leakage of drug, aggregation and fusion of vesicles. To overcome these problems, a new type of carrier system called "Transfersome", has recently been introduced, which is capable of transdermal delivery of low as well as high molecular weight drugs. Transfersomes are specially optimized, ultra deformable (ultra flexible) lipid supra molecular aggregates, which are able to penetrate the mammalian skin intact. Each Transfersome consists of at least one inner aqueous compartment. Which is surrounded by a lipid bilayer with specially tailored properties, due to the incorporation of "edge activators" into the vesicular membrane. Surfactants such as sodium cholate, sodium deoxycholate, span 80 and tween 80 have been used as edge activators. These novel carriers are applied in the form of semi-dilute suspension, without occlusion. Transfersomes are vesicles composed by phospholipids as the main ingredient (soya phosphatidylcholine, egg phosphatidylcholine, dipalmitylphosphatidylcholine, etc), 10-25% surfactants for providing flexibility (sodium cholate, tween 80, span-80), 3-10% alcohol as a solvent (ethanol, methanol) and hydrating medium consisting of saline phosphate buffer (pH 6.5-7). Transfersome is a term registered as a trademark by the German company IDEA AG, and used by it to refer to its drug delivery technology. The name means “carrying body”, and is derived from the Latin word 'transferrre', meaning “to carry across” and the Greek word “soma”, for a “body”. A Transfersome carrier is an artificial vesicle designed to be like a cell vesicle or a cell engaged in exocytosis, and thus suitable for controlled and potentially targeted, drug delivery.
Advantages of Transferosomes\cite{5,6}

- Transfersomes possess an infrastructure consisting of hydrophobic and hydrophilic moieties together and as a result can accommodate drug molecules with wide range of solubilities. They can deform and pass through narrow constriction (from 5 to 10 times less than their own diameter) without significant loss.
- High deformability of this system gives better penetration of intact vesicles. They can act as a carrier for low as well as high molecular weight drugs e.g. analgesic, anaesthetic, corticosteroids, sex hormone, anticancer, insulin and albumin.
- They are biocompatible and biodegradable as they are made from natural phospholipids similar to liposomes.
- They have high entrapment efficiency, in case of lipophilic drug near to 90%.
- They protect the encapsulated drug from metabolic degradation example: protein and peptides.
- They act as depot, releasing their contents slowly and gradually & can be used for both systemic as well as topical delivery of drug. They are easy to scale up, as procedure is simple and avoid unnecessary use or pharmaceutically unacceptable additives.
- At first glance, transfersomes appear to be remotely related to lipid bilayered vesicle, liposomes. However in functional terms, transfersomes differ vastly from commonly used liposomes in that they are much more flexible and adaptable.
- The extremely high flexibility of their membrane permits transfersomes to squeeze themselves even through pores much smaller than their own diameter.
- Transfersomes possess an infrastructure consisting of hydrophobic and hydrophilic moieties together and as a result, can accommodate drug molecules with wide range of solubility.
- Transfersomes can deform and pass through narrow constriction (from 5 to 10 times less than their own diameter) without measurable loss. This high deformability gives better penetration of intact vesicles through tight junctions.
- 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. They are biocompatible and biodegradable as they are made from natural phospholipids similar to liposomes. They have high entrapment efficiency, in case of lipophilic drug close to 90%.
- They protect the encapsulated drug from metabolic degradation. They act as depot, releasing their contents slowly and gradually. They can be used for both systemic as well
as topical delivery of drug. Easy to scale up, as procedure is simple, do not involve lengthy procedure and unnecessary use or pharmaceutically unacceptable additives.

DISADVANTAGES\(^{[5-6]}\)

- Transfersomes are chemically unstable because of their predisposition to oxidative degradation.
- Purity of natural phospholipids is another criteria militating against adoption of transfersomes as drug delivery vehicles.
- Transfersomes formulations are expensive.

MECHANISM OF TRANSPORT\(^{[7-10]}\)

Transfersomes overcome the skin penetration difficulty by squeezing themselves along the intracellular sealing lipids of stratum corneum. At present, the mechanism of enhancing the delivery of active substances in and across the skin is not very well known. Two mechanisms of action have been proposed.

- Transfersomes act as drug vectors, remaining intact after entering the skin.
- Transfersomes act as penetration enhancers, disrupting the highly organized intercellular lipids from stratum corneum and therefore facilitating the drug molecules penetration in and across the stratum corneum.

The transfersomes vesicles usage in drug delivery consequently relies on the carrier’s ability to widen and overcome the hydrophilic pores in the skin. Intracellular drug transportation may involve diffusion of vesicle lipid bilayer with the cell membrane like normal endocytosis. The mechanism is thus complex and involves advanced principles of mechanics combined with material transport and hydration/osmotic force. Possible pathways for a penetrant to cross the skin barrier.

1. Across the intact horny layer,
2. Through the hair follicles with the associated sebaceaus glands, or
3. Via the sweat glands

MATERIAL FOR TRANSFEROSOMES\(^{[11-14]}\)

Transfersomes is a self adaptable and optimized mixed lipid aggregate and composed of phospholipids like phosphatidyl choline which self assembles into lipid bilayer in aqueous environment and closes to forma vesicle. A bilayer softening component (such as a
biocompatible surfactant or an amphiphile drug) is added to increase lipid bi layer flexibility and permeability. This second component is called as edge activator.

An edge activator consists usually of single chain surfactant that causes destabilization of the lipid bilayer thereby increasing its fluidity and elasticity. The newer elastic vesicles were introduced by Van den berg in 1998, consisting of non ionic surfactant as the edge activator. Flexibility of transfosomes membrane can be altered by mixing suitable surface active agents in the proper ratios. The resulting, flexibility and permeability optimized, transfosome vesicle can therefore adapt its shape to surrounding stress easily and rapidly, by adjusting local concentration of each bi layer component to the local stress experienced by the bi layer. This flexibility also minimizes the risk of complete vesicle rupture in the skin and allows transfosomes to follow the natural water gradient across the epidermis, when applied under non occlusive condition. Vesicles composed of phospholipids as the main ingredient (soya phosphatidylcholine, egg phosphatidylcholine, dipalmitylphosphatidylcholine, etc), 10-25% surfactant for providing flexibility (ethanol, methanol) and hydrating medium consisting of saline phosphate buffer (pH 6.5-7). Dye like Rhodamine 123, Nile red for Confocal Scanning Laser Microscopy.

Materials commonly used for the preparation of transfosomes are summarized in

**Table below:**

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Examples</th>
<th>Functions</th>
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<tbody>
<tr>
<td>Phospholipid</td>
<td>Soya Phosphatidylcholine</td>
<td>Vesicle forming Componet</td>
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<tr>
<td></td>
<td>Egg Phosphatidylcholine</td>
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<td></td>
<td>Disteryl Phosphatidylcholine</td>
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<tr>
<td></td>
<td>Phosphatidylcholine</td>
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</tr>
<tr>
<td>Surfactant</td>
<td>Sodium Cholate</td>
<td>For Providing Flexibility</td>
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<td></td>
<td>Sodium deoxy Cholate</td>
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<tr>
<td></td>
<td>Tween 80</td>
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<tr>
<td></td>
<td>Span 80</td>
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<tr>
<td>Alcohol</td>
<td>Ethanol</td>
<td>As a Solvent</td>
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<tr>
<td></td>
<td>Methanol</td>
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</tr>
<tr>
<td>Dye</td>
<td>Rhodamine-123</td>
<td></td>
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<tr>
<td></td>
<td>Rhodamine-DHPE</td>
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<tr>
<td></td>
<td>Flurescein-DHPE</td>
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<tr>
<td></td>
<td>Nil red</td>
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<td></td>
<td>6 Corboxy fluorescence</td>
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<tr>
<td></td>
<td>For Confocal Scanning Laser Microscopy (CSDLM) Study</td>
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<tr>
<td>Buffering Agent</td>
<td>Saline phosphate buffer (PH 6.5)</td>
<td>As a hydrating medium</td>
</tr>
<tr>
<td></td>
<td>7% v/v ethanol</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Tris buffer (PH 6.5)</td>
<td></td>
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</table>
METHOD OF PREPARATION[11-15]

A. Thin film hydration technique is employed for the preparation of transfersomes which comprised of three steps

1. A thin film is prepared from the mixture of vesicles forming ingredients that is phospholipids and surfactant by dissolving in volatile organic solvent (chloroform methanol).

Organic solvent is then evaporated above the lipid transition temperature (room temp. for pure PC vesicles, or 50°C for dipalmitoyl phosphatidyl choline) using rotary evaporator. Final traces of solvent were removed under vacuum for overnight.

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.

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.

A. Modified hand shaking, lipid film hydration technique is also founded for the preparation of transfersomes which comprised following steps

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

2. The film was then hydrated with phosphate buffer (pH 7.4) with gentle shaking for 15 minute at corresponding temperature. The transfersome suspension further hydrated up to 1 hour at 2-8°C

EVALUATION OF TRANSFEROSOMES[16-17]

1. Vesicle size distribution and zeta potential

Vesicle size, size distribution and zeta potential were determined by Dynamic Light Scattering system by Malvern Zeta sizer.
2. Vesicle 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 done by using photon correlation spectroscopy or dynamic light scattering (DLS) measurements. Transfersomes vesicles can be visualized by TEM, phase contrast microscopy, etc. The stability of vesicle 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.

3. No. 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 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.

4. Entrapment efficiency
The entrapment efficiency is expressed as the percentage entrapment of the drug added. Entrapment efficiency was determined by first separation of the un-entrapped drug by use of mini-column centrifugation method. After centrifugation, the vesicles were disrupted using 0.1% Triton X-100 or 50% n-propanol]. The entrapment efficiency is expressed as:
Entrapment efficiency = (Amount entrapped / Total amount added) ×100

5. 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.

6. Turbidity measurement
Turbidity of drug in aqueous solution can be measured using nephelometer.
7. 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.

8. Penetration ability

Penetration ability of Transfersomes can be evaluated using fluorescence microscopy.

9. Occlusion effect

Occlusion of skin is considered to be helpful for permeation of drug in case of traditional topical preparations. But the same proves to be detrimental for elastic vesicles. Hydrotaxis (movement in the direction) of water is the major driving force for permeation of vesicles through the skin, from its relatively dry surface to water rich deeper regions. Occlusion affects hydration forces as it prevents evaporation of water from skin.

10. Surface charge and charge density

Surface charge and charge density of Transfersomes can be determined using zeta sizer.

11. 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, transfersomes suspension is incubated at 320C and samples are taken at different times and the free drug is separated by mini column 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).

12. In-vitro Skin permeation Studies

Modified Franz diffusion cell with a receiver compartment volume of 50ml and effective diffusion area of 2.50 cm2 was used for this study. In vitro drug study was performed by using goat skin in phosphate buffer solution (pH 7.4). Fresh Abdominal skin of goat were collected from 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. Skin was kept in 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 donor compartment exposed to receptor compartment was 2.50cm² and capacity of receptor compartment was 50ml. The receptor compartment was filled with 50ml 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.

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 months. Samples from each ampoule were analyzed after 30 days to determine drug leakage. Percent drug lose was calculated by keeping the initial entrapment of drug as 100%.

APPLICATION OF TRANSFEROSOMES
1. 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.

2. 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. As protein and 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.

3. since transfersomes obtain similar bioavailability to subcutaneous injection. Human serum albumin was found to be effective in producing the immune response when delivered by transdermal route encapsulated in Transfersomes.

4. Peripheral drug targeting: the ability of transfersomes to target peripheral subcutaneous tissues is due to minimum carrier associated drug clearance through blood vessels in the subcutaneous tissue.
5. Transdermal immunization: Transcutaneous hepatitis-B vaccines have given good results. A 12 times higher AUC was obtained for zidovudine as compared to normal control administration. Selectivity in deposition in RES (which is the usual site for residence of HIV) was also increased.

6. NSAIDS are associated with number of GI side effects. These can be overcome by transdermal delivery using ultra deformable vesicles.

7. Transferosomes have been widely used as a carrier for the transport of proteins and peptides. Proteins and peptide are large biogenic molecules which are very difficult to transport into the body, when given orally they are completely degraded in the GI tract. These are the reasons why these peptides and proteins still have to be introduced into the body through injections. Various approaches have been developed to improve these situations. The bioavailability obtained from transferosomes is somewhat similar to that resulting from subcutaneous injection of the same protein suspension.

8. The transferosomal preparations of this protein also induced strong immune response after the repeated picutaneous application, for example the adjuvant immunogenic bovine serum albumin in transferosomes, after several dermal challenges is as active immunologically as is the corresponding injected proteo-transferosomes preparations.

9. Delivery of insulin by transferosomes is the successful means of non invasive therapeutic use of such large molecular weight drugs on the skin. Insulin is generally administered by subcutaneous route that is inconvenient. Encapsulation of insulin into transferosomes (transfersulin) overcomes these entire problems. After transfersulin application on the intact skin, the first sign of system ichypoglycemia are observed after 90 to 180 min, depending on the specific carrier composition.

10. 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.

11. Another most important application of transferosomes is transdermal immunization using transferosomes loaded with soluble protein like integral membrane protein, human serum albumin and gap junction protein. These approach offers at least two advantages, first they
are applicable without injection and second, they give rise to rather high titer and possibly, to relatively high IgA levels. Transferosomes have also used for the delivery of corticosteroids. Transferosomes improves the site specificity and overall drug safety of corticosteroid delivery into skin by optimizing the epicutaneously administered drug dose.

CONCLUSION

Transferosomes are specially optimized particles or vesicles, which can respond to an external stress by rapid and energetically inexpensive, shape transformations. Such highly deformable particles can thus be used to bring drugs across the biological permeability barriers, such as skin. When tested in artificial systems. Transferosomes can pass through even tiny pores (100 mm) nearly as efficiently as water, which is 1500 times smaller. Drug laden transfersomes can carry unprecedented amount of drug per unit time across the skin (up to 100mg cm2h-1). Transdermal drug delivery system is frequently used due to its several advantages over other routes drug delivery but the penetration of drug via the stratum corneum is a rate limiting step, its major limitations like, it cannot be able to transport the larger size molecule. That is why vesicular system like Transfersomes are developed to overcome these limitations. The elastic vesicles deform themselves to penetrate the skin through pores. It is more efficient & safer in composition then others. In this type of delivery, Drug release can also be controlled according to the requirement. Thus, this approach can overcome the problems which occur in conventional techniques.

REFERENCES


