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FROM FORMULATION TO FUNCTION: A REVIEW OF TRANSFEROSOMES AND THEIR PREPARATION METHODS

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ABSTRACT
Transferosomes 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 Transferosomes are wide range of solubilities, better penetration, biocompatible and biodegradable etc. This comprehensive review delves into the realm of transferosomes, lipid-based nanocarriers that hold immense potential in drug delivery. Beginning with an overview of their formulation, this paper explores the various methods employed in the preparation of transferosomes, ranging from thin film hydration to reverse-phase evaporation. A detailed analysis of their structural characteristics, including size, morphology, and membrane composition, is provided, shedding light on their remarkable ability to encapsulate both hydrophilic and hydrophobic drugs. Furthermore, the mechanisms underlying their enhanced transdermal and transmucosal delivery are elucidated, along with their applications in addressing various therapeutic challenges. Recent advancements in transferosome technology are discussed, along with future prospects in the field.

KEYWORDS: Transferosomes, Nanocarriers, Transdermal drug delivery, Transmucosal delivery.

INTRODUCTION
An efficacious, successful therapeutic treatment cannot be achieved in most cases, often due to many reasons, such as the occurrence of hepatic first-pass metabolism, adverse side effects, the rejection of invasive treatments and poor patient compliance.[1] The structure of the skin resembles as if stratum corneum cells are embedded in a pool of intercellular lipid lamella. The lamellae play a key role in imparting barrier properties to the stratum corneum. This limits the application of this route to only potent drugs. Several drug delivery systems have been developed and studied over the past decades to overcome these problems.

One promising approach is the use of transdermal delivery systems, as they are minimally invasive methods without first-pass effects. A new type of carrier system-namely, transfersomes-were introduced by Cevc et al. in the 1990s. The name means "carrying body", and derived from the Latin word 'transferre', meaning "to carry across", and the Greek word 'soma', for a "body". Transferosome carrier is an artificial vesicle and it is similar to the natural cell vesicle and it is appropriate for controlled and targeted drug delivery. The system is highly pliable and stress-responsive, complex aggregate. Transferosomes can cross various transport barriers efficiently and act as a drug carrier for non invasive targeted drug delivery and sustained release of therapeutic agents. Transferosomes are fabulous molecular entities which can pass through a permeability barrier and such that convey the material to the targeted site from the site of application.[2] Transferosomes boost the permeation of most of low as well as high molecular weight drugs. On a whole, a transferosomes is a self adaptable and optimized mixed lipid aggregate. They act as depot, releasing their content slowly and gradually. Transferosomes have been developed in order to take advantage of phospholipids vesicles as transdermal drug carrier. They are having self-optimizing deformability. Moreover, transferomes are extremely deformable; therefore, they easily cross even the very narrow pores.[3] These self-optimizing, highly

deformable lipid aggregates were successfully used in extensive preclinical tests, as well as for the transcutaneous delivery of peptides and proteins and the sustain release of desired therapeutic agents.[4]

Transferosomes

Composition

Transferosomes are vesicular 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, a membrane-softening agent (e.g., Tween 80, Span 80, and sodium cholate) that promotes the ultra-deformable property of the transfersomes by increasing the lipid bilayer flexibility and permeability.[5] This aqueous core surrounded by a lipid bilayer makes ultra-deformable vesicles having both self-optimizing and self-regulating capabilities.[6]

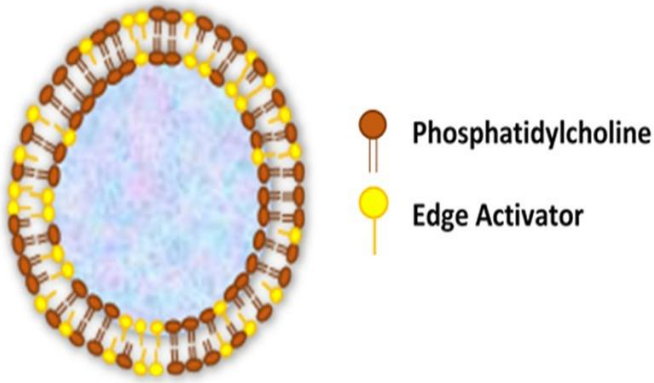

Figure 1: Schematic diagram of transferosome.

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.[7,8] The modified liposomal vesicular system (Transfersomes) is composed of the phospholipid component and single-chain surfactant as an edge activator.[9] Edge activators (EAs) function in an exceptional manner as membrane-destabilizing factors to increase the deformability of vesicle membranes and, when combined in a proper ratio with an appropriate lipid, gives the optimal mixture, enabling the transfersomes to become deformable, as well as ultra-flexible, which results in a higher permeation capability.[10,11] Therefore, transfersomes overcome the major drawbacks of conventional liposomes and penetrate pores that are much smaller than their own diameters Once the transfersomes reach the skin pores, they can spontaneously change their membrane flexibility and pass through the pores, a phenomenon known as self-optimizing deformability.

Salient features of transferosome

- These vesicular systems acts as a carriers for drugs with different molecular weight, such as low as well as high molecular weight drugs e.g. analgesic, anesthetic, corticosteroids, sex hormone, anticancer, insulin, gap junction protein, and albumin.[12]
- Transfersomes are able to deform and can pass easily through the narrow constriction (from 5 to 10 times less than their own diameter) without measurable loss. This high deformability gives superior penetration of intact vesicles.
- Transfersomes contains both of hydrophobic and hydrophilic moieties together so that it can hold the drug molecules with wide or broad range of solubility.[13]
- The entrapment efficiency is very high, e.g. it the drug entrapped is lipophilic it have an entrapment efficiency up to 90%.
- They act as depot, releasing their contents slowly and gradually, so that can be used in the formulation of controlled drug delivery systems.

Advantages[14-17]

- 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.
- The entrapped drug is protected from the atmospheric degradation.
- Transfersomes carriers are composed of hydrophilic and hydrophobic moieties, which result in becoming a unique drug carrier system that can deliver therapeutic agents with wide range of solubility.
- They are easy to scale up as the procedure involved is simple.
- For systemic as well as topical delivery of drug, transferosomes can be used.
- They are made up of natural phospholipids and EAs, therefore promisingly biocompatible and biodegradable.
- They serve as depot preparations releasing their contents slowly.
- Transfersomes are an obvious choice for achieving a sustained drug release, as well as a predictable and extended duration of activity.

- Avoiding the first-pass metabolism, which is a major drawback in oral drug administration, and result in optimized bioavailability of the drug.
- They have easily deformable properties which make them easily squeeze out from the stratum corneum and the mechanism for penetration is the generation of 'osmotic gradient'
- Transferosomes penetrate the stratum corneum by either intracellular route or transcellular route.
- Transferosomes, can increase the transdermal flux, prolong the release and improve the site specificity of bioactive molecules.

Limitations of transferosomes[18-20]

- Transfersomes cannot offer chemical stability because of their predisposition 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.
- The Purity of the natural phospholipids
  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 Transferosome formulations are very expensive
  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.

Mechanism of action

Vesicles are known as colloidal particles, which are an aqueous compartment enclosed by a concentric bilayer that are made-up of amphiphilic molecules. They are very useful as vesicular drug delivery systems, which transport hydrophilic drugs encapsulated in the inner aqueous compartment, whereas hydrophobic drugs are entrapped within the lipid bilayer[21]. With regard to transfersomes, they are highly deformable (Ultra-flexible) and self-optimizing novel drug carrier vesicles, in which their passage across the skin is mainly associated with the membrane flexibility, hydrophilicity and the ability to maintain the vesicle's integrity.

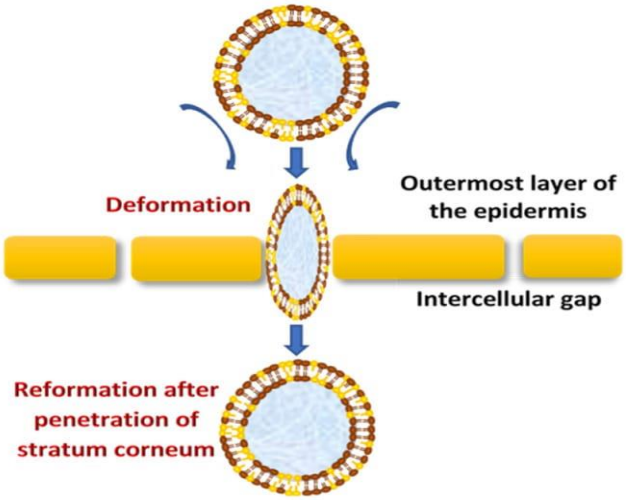

Figure 2: MOA of transferosome.

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.

Two mechanisms of action have been proposed[22]

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.

When the formulation (Lipid suspension (Transferosomes)) is applied on to the skin the water gets evaporated and there is a formation of "osmotic gradient", which is the major mechanism for transportation of transferosomes across the skin. They can only achieve this if they are sufficiently deformable to pass through the narrow pores in the skin because transferosomes composed of surfactant have more

suitable rheological and hydration properties than that responsible for their greater deformability; less deformable vesicles including standard liposomes are confined to the skin surface, where they dehydrate completely and fuse, so they have less penetration power than the transferosome. Transferosomes are optimized in this respect and thus attain maximum flexibility, so they can take full advantage of the transepidermal osmotic gradient (water concentration gradient). This osmotic gradient that is developed due to the skin penetration barrier prevents water loss through the skin and maintains a water activity difference in the viable part of the epidermis (75% water content) and nearly completely dry stratum corneum near to the skin surface (15% water content).[23,24,25] This gradient is very stable because ambient air is a perfect sink for the water molecule even when the transdermal water loss is unphysiologically high. All polar lipids attract some water. Most lipid bilayers spontaneously resist an induced dehydration. Consequently, all lipid vesicles made from the polar lipid vesicles move from the rather dry location to the sites with a sufficiently high water concentration.

MATERIALS AND METHOD

Materials which are widely used in the formulation of transferosomes are various phospholipids, Surfactants, alcohol, dye; buffering agent etc different additives used in the formulation of transferosomes are summarized in Table 1.

Table 1: Different additives used in formulation of transfersomes.

Ingredients	Examples	Functions
Phospholipid	Soya phosphatidylcholine Egg phosphatidylcholine Dipalmityl phosphatidylcholine Distearyl phosphatidylcholine	Vesicle forming component
Surfactant	Sodium cholate Sodium deoxy cholate Tween 80 Span 80	For providing flexibility
Alcohol	Ethanol Methanol	As a solvent
Dye	Rhodamine-123 Rhodamine-DHPE Fluorescein-DHPE Nile red 6 Carboxy fluorescence	For Confocal Scanning Laser Microscopy (CSLM) study
Buffering agent	Saline phosphate buffer (pH 6.5) 7% v/v ethanol Tris buffer (pH 6.5)	As a hydrating medium

Methodologies for the preparation of transferosomes

1. Thin film hydration method

In a round-bottom flask, the phospholipids and edge activator (the components that form vesicles) are dissolved using a mixture of volatile organic solvents (such as methanol and chloroform in an appropriate (v/v) ratio). The following step can include the addition of the lipophilic drugs. A rotary vacuum evaporator is used to evaporate the organic solvent above the lipid transition temperature under reduced pressure in order to generate a thin layer. Maintain it under vacuum to get rid of any remaining solvent residue.[26] After the thin film has been formed, it is hydrated by rotating it for the required quantity of time at the appropriate temperature using a buffer solution with a correct pH (example, pH 7.4). At this point, the hydrophilic drug incorporation can be done. For the production of small vesicles, the resultant vesicles are sonicated in a bath or probe sonicator after being swelled at ambient temperature. Extrusion across a sandwich of 200 nm to 100 nm polycarbonate membranes homogenizes the sonicated vesicles.

2. Modified hand shaking method

A 1:1 mixture of ethanol and chloroform was utilized to dissolve the hydrophilic drug, lecithin (PC), and edge activator in a round bottom flask to obtain a clear transparent solution. Organic solvent was removed by evaporation while hand shaking above lipid transition temperature (43°C). In the meantime, the round bottom flask is partially immersed in the water bath maintained at a high temperature. With rotation, a thin lipid coating developed inside the flask wall. The thin coating was left overnight to allow the solvent to completely evaporate. After that, the film was hydrated using appropriate phosphate buffer (pH 7.4) with gentle shaking. Up to an hour at 2–8 0C, the transfersome suspension is further hydrated.[27]

3. Vortexing - Sonication method

The phospholipids, edge activator and the drugs are mixed in a phosphate buffer. The mixture is then vortexed until milky transferosomal suspension is obtained. It is then sonicated, for a respective time at

room temperature in a bath sonicator755+ and then extruded through polycarbonate membranes.[28,29]

4. Centrifugation process

The phospholipids, edge activator and drug are dissolved in the organic solvent. The solvent is then removed using a rotary evaporator under reduced pressure. The remaining traces of solvent are removed under vacuum. The lipid film deposited is hydrated with the appropriate buffer solution by centrifuging at room temperature. The resulting vesicles are swollen at room temperature. The obtained multilamellar lipid vesicles are further sonicated at room temperature.[30]

5. Ethanol injection method

This approach involves heating the drug and aqueous solution while stirring continuously and maintaining a constant temperature throughout the process. Phospholipids and edge activators are added to an ethanolic solution, which is then dropped gradually into an aqueous solution. When the solution makes touch with lipid molecules precipitate and form bilayered structures in aqueous environments. Compared to other approaches, this one has greater benefits.

6. Freeze thaw method

Using this technique, a suspension of produced multilamellar vesicles is subjected to repeated cycles of extremely low temperature for freezing and then extremely high temperature subjection. After the suspension is ready, it is poured into a tube and submerged for 30 seconds in a nitrogen bath (-30° C). It is placed in a water bath at a high temperature after freezing. This is done up to eight times over.

7. Suspension homogenization process

In this process, transfersomes are prepared by mixing an ethanolic soylecithin solution with an appropriate amount of edge-activator, 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.

8. Aqueous lipid suspension process

In this process, Drug-to-lipid ratio in the vehicles is fixed between 1/4 and 1/9. This would ensure the high flexibility of the vesicle membrane in comparison to the standard phosphatidylcholine vesicles in the fluid phase. Vesicles with the size ranging from 100-200 nm are prepared by using soylecithin deviation. This formulation could be prepared by suspending the lipids in an aqueous phase where the drug is dissolved.

9. High-Pressure homogenization technique

The phospholipids, edge activator and the drug are uniformly dispersed in PBS or distilled water containing alcohol and followed by ultrasonic shaking and stirred simultaneously. The mixture is then subjected to intermittent ultrasonic shaking. The resulting mixture is then homogenized using a high-pressure homogenizer. Finally, the transfersomes are stored in appropriate conditions.

10. Reverse-Phase evaporation method

In a round-bottom flask, the phospholipids and edge activator are combined with an organic solvent mixture (diethyl ether and chloroform, for example) and dissolved. At this stage the lipophilic drug can incorporated. The lipid films are then obtained by utilizing a rotary evaporator to evaporate the solvent. The organic phase, which mainly consists of isopropyl ether and/or diethyl ether and the lipid films are redissolved. The organic phase is then combined with the aqueous phase to create a two-phase system. At this point, the hydrophilic drug inclusion can be done. After that, this system is sonicated with a bath sonicator until a uniform w/o (water in oil) emulsion forms. Using a rotary evaporator, the organic solvent is gradually evaporated to create a thick gel that subsequently turns into a vesicular suspension.[31,32]

Characterization of transferosomes

The characterization of transfersomes is generally similar to liposomes, niosomes and micelles. The following characterization parameters have to be checked for transfersomes.

A. Vesicle size, Shape and Charge[33,34, 35]

Dynamic light scattering (DLS) is one of the standard methods for measuring particle sizes in fluids. This method is based on the examination of random particle movement due to constant Brownian motion. Particle size and zeta potential were assessed by phase contrast microscopy, DLS and electrophoretic light scattering (ELS) using a dynamic light scattering nanoparticle size analysis (Malvern Zetasizer Nano ZS, Malvern Instruments Ltd., Malvern, UK). Prior to measurement, transfersomes are diluted with distilled water and filtered through a 0.2 mm membrane filter. Transmission electron microscopy (TEM) and optical microscopy can be used to view the morphology of the vesicles.

B. Vesicle morphology

Photon correlation spectroscopy or DLS method generally used for vesicle diameter determination. Prepared sample in distilled water was filtered through 0.2 mm membrane filter and diluted with filtered saline and then size measurement done using photon correlation spectroscopy or DLS measurements. Transmission electron microscopy (TEM) and phase contrast microscopy can be commonly used for visualization of transfersomes vesicles. For TEM measurement, 1% phototungustic acid is employed as a negative stain. Using an optical microscope and phase contrast microscopy, transfersomes without sonication can be visualized. After applying a cover slip and spreading a thin layer of transfersomes on a slide, the morphology of the vesicles is examined under an optical microscope. Zetasizer may be used to calculate the surface charge and

charge density of transfersomes. The stability of vesicle can be determined by assessing the size and structure of vesicles with respect to time. DLS and TEM used for mean size and structural changes, respectively.

C. NO. of vesicles per cubic mm

In order to optimize the composition and other process variables, this parameter is crucial. Transfersome formulations that are not sonicated are diluted five times using a 0.9% sodium chloride solution. Then, for further investigation, an optical microscope and hemocytometer might be employed. The following formula is used to count and compute the Transfersomes in 80 small squares.[1]

$$Total\ no.of\ transferosome\ per\ cubic\ mm = \frac{Total\ no.of\ transferosomes\ counted * dilution\ factor * 4000}{Total\ no.of\ squares\ counted}$$

D. Entrapment efficiency

Transferosomal suspensions (Total mount) were ultracentrifuged at 20,000 rpm and 10 °C for 30 min.The supernatant liquid is then collected and prper dilution of 1ml of suspension with 9ml of phosphate buffer, it is measured in UV-spectrophotometer or high performance liquid chromatography (HPLC) to determine the unencapsulated drug to calculate the EE. From the unentrapped drug, amount of medication entrapped in the vesicles is estimated using the following formula[2]

$$\%EE = \frac{Total\ amount\ of\ drug\ taken - free\ drug}{Total\ amount\ of\ drug\ taken} * 100$$

E. Drug content

The drug content is determined using one of the instrumental analytical methods such as a modified high performance liquid chromatography method using an ultraviolet detector, column oven, auto sample, pump, and computerized analysis program depending on the analytical method of the pharmacopoeial drug.

F. Degree of deformability

This parameter significant because it has an impact on how well the transfersomal formulation penetrates. Pure water is used as the a standard in the present study. The mixture is run through many microporous filters with known pore diameters ranging from 50 to 400 nm. DLS measurements are used to measure the particle size and size distribution following each pass.[36,37] The expression for the degree of deformability is:[3]

$$D = J * \frac{rv}{rp}$$

Where, D = degree of deformability, J = amount of suspension extruded during 5 min, rv is size of the vesicle and rp = pore size of the barrier.

G. *In vitro* drug release

A scientific method to optimize the transfersomal formulation can be made possible by the in vitro drug release profile, which can offer essential information on the formulation design as well as information on the release mechanism and kinetics. The study is performed using Franz diffusion cell method.[38]

The transferosomal formulation is placed on a cellophane membrane between the donor and receptor compartment, which consist the buffer. Samples are taken at specific intervals and replaced with fresh buffer each time to maintain sink conditions. The absorbance of the samples is measured, and the amount of drug released is determined.

H. *In vitro* skin permeation studies

The purpose of this study is to evaluate the transdermal flux of the medicines, which is commonly expressed in units of µg/cm2 /h,[39] as well as the transport efficiencies of the transdermal delivery systems. This is an ideal method for assessing a proposed formulation's ability to permeate is to use human skin. However, the human skin is less desirable for the permeation study because to its restricted availability, ethical issues, and religious boundaries. Many animal models have been proposed as more approachable alternatives to human skin, including rat, mouse, ape, porcine, guinea pig, and snake skins. It should be remembered, that percutaneous absorption through different animal skin types may vary greatly from the findings using human skin models.[40]

I. Stability studies

By following the guidelines from International Conference on Harmonization (ICH), stability testing of new drug substances and products is subject to general cases for storage conditions. These cases include 25 ± 2 ℃/60% relative humidity (RH) 5% RH or 30 ± 2 ℃/65% RH ±5% for a period of 12 months, and 40 ± 2 ℃/75% RH 5% for accelerated testing. It is recommended that drug items meant for refrigeration undergo long-term storage at 5 ±3℃ for a duration of 12 months, followed by an accelerated study at 25± 2 ℃/60% RH ± 5% RH for a period of 6 months. Failure to meet the drug product's standards is considered a significant alteration.[1]

Application of transfersomes

Delivery of interferons

Transferosomes have also been used as a carrier for interferons, for example leukocytic derived interferone-α (INF-α) is a naturally occurring protein having antiviral, antiproliferive 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. Hafer et al studied the formulation of interleukin-2 and interferone-α containing transferosmes for potential transdermal application. they reported delivery of IL-2 and INF- α trapped by transferosomes in sufficient concentration for immunotherapy.

Delivery of corticosteroids

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. Transferosomes based corticosteroids are biologically active at dose several times lower than the currently used formulation for the treatment of skin diseases.

Delivery of anesthetics

Application of anesthetics in the suspension of highly deformable vesicles, transferosomes, induces a topical anesthesia, under appropriate conditions, with less than 10 min. 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.

Delivery of anticancer drugs

Anti cancer drugs like methotrexate were tried for transdermal delivery using transfersome technology. The results were favorable. This provided a new approach for treatment especially of skin cancer.

Delivery of herbal drugs

Transfersomes can penetrate stratum corneum and supply the nutrients locally to maintain its functions resulting maintenance of skin in this connection the Transfersomes of Capsaicin has been prepared by Xiao-Ying et al. which shows the better topical absorption in comparison to pure capsaicin.

Delivery of NSAIDS

NSAIDS are associated with number of 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 Transfersome formulation gained marketing approval by the Swiss regulatory agency (SwissMedic) in 2007; the product is expected to be marketed under the trademark Diractin. Further therapeutic products based on the Transfersome technology, according to IDEA AG, are in clinical development.[41-43]

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 systemic hypoglycemia are observed after 90 to 180 min, depending on the specific carrier composition.[27]

Future perspectives

The high tolerability and efficiency of these vesicular systems open vast potential therapeutic uses. These nanocarriers might offer advanced local and systemic new therapies with agents that are unable to efficiently penetrate the stratum corneum via passive diffusion. The non steroidal anti-inflammatory drug (NSAID), ketoprofen, in a transferosome formulation gained marketing approval by the Swiss regulatory agency (SwissMedic). The product is expected to be marketed under the trademark Diractin. Further therapeutic products based on the transferosome technology, according to IDEA AG, are in clinical development.

Nano lipid carriers are exceedingly investigated and practiced applied science for transdermic and transcutaneous delivery. The deformability characteristic is due to the exixtence of a surfactant in transferosomes.

CONCLUSION

Transfersomes are a novel drug delivery system and are special types of liposomes. They provide improved drug penetration via the skin; their ingredients are safe and authorized for use in cosmetic and pharmaceutical products. The tranferosomal (Highly deformable vesicles) drug delivery system may be a better alternative for the conventional therapy. They can handle therapeutic molecules with a broad range of solubility, bioavailability, SAFETY; they can boost the transdermal flow, prolonging the release and enhancing the site specificity of bioactive compounds. Therefore, the future of transfersomes in transdermal medication administration appears bright and promising.

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