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CURRENT STATUS AND FUTURE PROSPECTS OF TRANSFERSOMAL DRUG DELIVERY

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Abstract:

Vesicular systems have gained immense importance in the last few years as a means for sustained and efficient drug delivery. This article was designed to review all aspects of a novel class of vesicles, transfersomes. Transfersomes (elastic or ultraflexible liposomes) were a new class of lipid vesicles introduced. Transfersomes overcome the skin barrier by opening extracellular pathways between cells in the organ and then deforming to fit into such passages. In the process, Transfersomes undergo a series of stress-dependent adjustments of the local carrier composition to minimize the resistance of motion through the otherwise confining channel. It exists as an ultra-deformable complex having a hydrated core surrounded by a complex layer of lipid. 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 and one bilayer softening agent which is generally a surfactant which is responsible for the flexibility of the vesicle. Transfersomes provide the primary advantage of higher entrapment efficiency along with a depot formation which releases the contents slowly. The characterisation of transfersomes is similar to that of other vesicles like liposomes, niosomes and micelles. Transfersomes can be used for delivery of insulin, corticosteroids, proteins and peptides, interferons, anti-cancer drugs, anaesthetics, NSAIDs and herbal drugs.

Keywords: *Transfersomes, Transdermal, Skin barrier, Corticosteroids, Carrier aggregate.*

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INTRODUCTION:

The term is derived from Latin word 'transferre', meaning 'to carry across', and the Greek word 'soma', meaning 'a body'. A Transfersome is defined as 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 [1,2]. Transfersomes, a novel class of modified liposomes, was first reported by Cevc [3] and are variously described as deformable, highly deformable, elastic or ultra-flexible liposomes or vesicles [4]**.** They are claimed to improve *in vitro* transdermal delivery of a variety of drugs. The deformability possessed by transfersomes is the outcome of incorporation of an edge activator within the phospholipid bilayers and this improves elasticity by means of lipid bilayer destabilization [5]**.** Edge activators commonly used are single chain surfactants such as sodium cholate and tween 80 [6, 7]**.** Transfersomes are able to squeeze through conduits one-tenth the diameter of the vesicles, allowing them to spontaneous penetrate the stratum corneum [8].

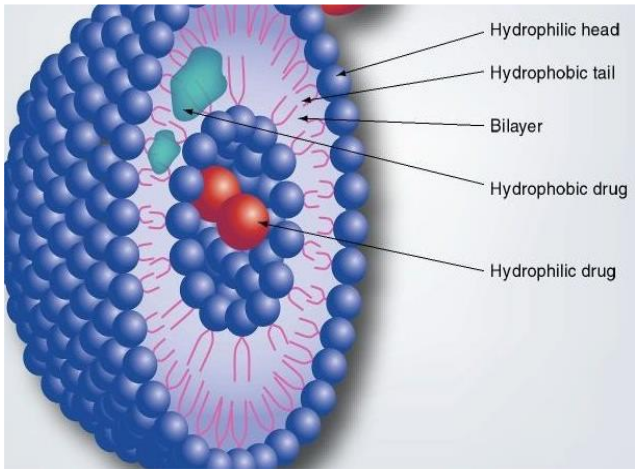

Figure 1: Structure of Transfersome

The transfersomal drug delivery system posses various potential advantages over conventional routes such as avoidance of first pass metabolism, predictable and extended duration of activity, utility of short half-life drugs, improving physiological and pharmacological response, minimizing undesirable side effects, avoiding the fluctuation in drug levels, inter-and intra-patient variations, and most importantly, it provides patients convenience [9]. In the field of medical research, several approaches have been applied to increase the efficacy of the material transfer across the intact skin, by use of the penetration enhancers, enhancers, iontophoresis, sonophoresis and vesicular constructs. Singh et al. used the expression "vesicular constructs" in common for liposomes, niosomes, virosomes, ethosomes and transfersomes [10].

Transfersomes were developed in order to take the advantage of phospholipids vesicles as transdermal drug carrier. Transfersomes overcome the skin penetration difficulty by squeezing themselves along the intracellular sealing lipid of the stratum corneum. There is provision for this, because of the high vesicle deformability, which permits the entry due to the mechanical stress of surrounding, in a self-adapting manner. The resulting flexibility of transfersome membrane minimizes the risk of complete vesicle rupture in the skin and allows transfersomes to follow the natural water gradient across the epidermis, when applied under non occlusive condition. [11].

Transfersomes can penetrate the intact stratum corneum spontaneously along two routes in the intracellular lipid that differ in their bilayers properties. The **Figure 2** shows possible micro routes for drug penetration across human skin intracellular and transcellular. The self-optimizing deformability of typical composite transfersomes membrane, adapts to ambient stress which allows the ultra-deformable transfersomes to change its membrane composition locally and reversibly, when it is pressed against or attracted into narrow pore [12]. The transfersomes components that sustain strong membrane deformation preferentially accumulate, while the less adaptable molecules are diluted at sites of great stress. This dramatically lowers the energetic cost of membrane deformation and permits the resulting, highly flexible particles, first to enter and then to pass through the pores rapidly and efficiently [12].

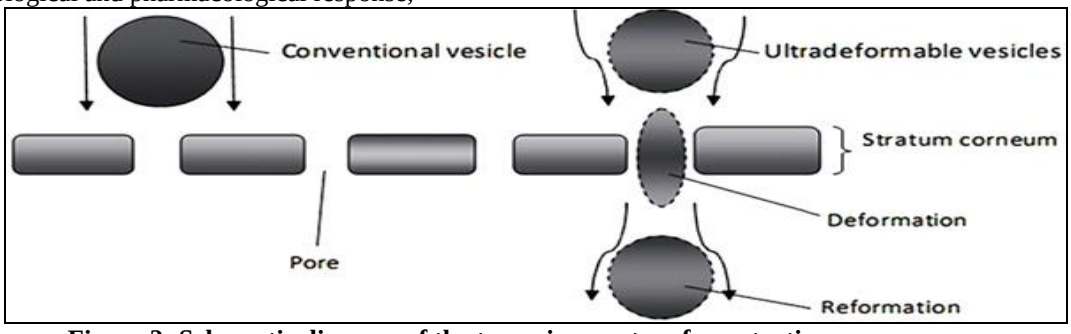

Figure 2: Schematic diagram of the two microroutes of penetration.

SALIENT FEATURES OF TRANSFERSOMES

Transfersomes possess an infrastructure consisting of hydrophobic and hydrophilic moieties together and as a result can accommodate drug molecules with wide range of solubility as shown in fig 3. 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. They can act as a carrier for low as well as high molecular weight drugs e.g. analgesic, anaesthetic, 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 near 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 [13].

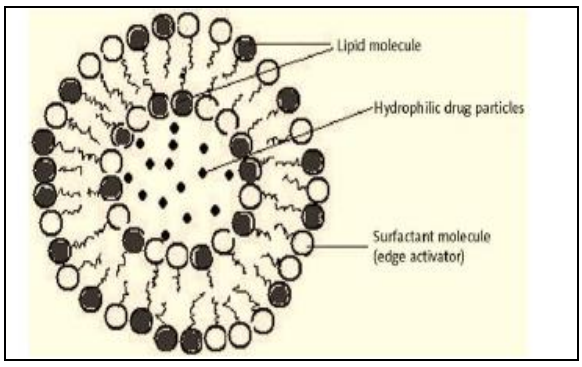

Figure 3: Structural representation of one transfersome unit Salient features of Transfersomes

Advantages of Transfersomes

Transfersomes can deform and pass through narrow constriction (from 5 to 10 times less than their own diameter) without measurable loss.

1. They have high entrapment efficiency, in case of lipophilic drug near to 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. Transfersomes possess an infrastructure consisting of hydrophobic and hydrophilic moieties together and as a result can accommodate drug molecules with wide range of solubility.
5. They act as depot, releasing their contents slowly and gradually.
6. They can be used for both systemic as well as topical delivery of drug.
7. They are biocompatible and biodegradable as they are made from natural phospholipids similar to liposomes.
8. They protect the encapsulated drug from metabolic degradation.
9. Easy to scale up, as procedure is simple, do not involve lengthy procedure and unnecessary use or pharmaceutically unacceptable additives.
10. Biodegradability and lack of toxicity.
11. 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.
12. The extremely high flexibility of their membrane permits transfersomes to squeeze themselves even through pores much smaller than their own diameter [14, 15].

Limitations of transfersomes

1. Transfersomes are chemically unstable because of their predisposition to oxidative degradation.
2. Purity of natural phospholipids is another criteria militating against adoption of transfersomes as drug delivery vehicles.
3. Transfersomes formulations are expensive [16].

MECHANISM OF TRANSPORT

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 comlplex and involves advanced principles of -mechanics combined with material transport and hydration/osmotic force. Possible pathways for apenetrant to cross the skin barrier.

(1) Across the intact horny layer,

(2) Through the hair follicles with the associated sebaceaous glands, or
(3) Via the sweat glands [16, 18].

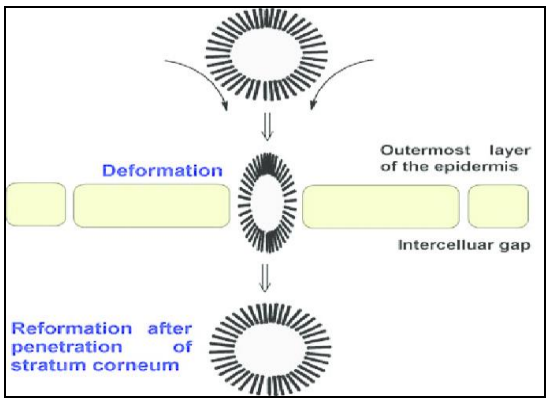

Figure 4: Penetration pathway of transfersomes

MATERIALS REQUIRED FOR PREPARATION OF THE TRASNSFERSOMES:

1. Phospholipids – (Vesicles forming component) Ex. - Soya phosphatidyl choline, egg phosphatidyl choline,
2. Surfactant – (Providing flexibility). Ex. - Sod.deoxycholate, Tween-80, Span-80
3. Alcohol – (As a solvent). Ex. - Ethanol, methanol
4. Buffering agent – (As a hydrating medium) Ex. - Saline phosphate buffer (pH 6.4)
5. Dye - {for Confocal scanning laser microscopy (CSLM)} Ex. – Rhodamine [19].

METHODS OF PREPARATION [17, 20].

Transfersomes 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.

1. Vortexing-sonication method: In this method, mixed lipids (i.e. phospha-tidylcholine, EA and the therapeutic agent) are blended in a phosphate buffer and vortexed to attain a milky suspension. The suspension is sonicated, followed by extrusion through poly-carbonate membranes.

2. Suspension homogenization process: In this process, transfersomes 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.

3. Modified handshaking process: In this process, the transfersomes are prepared by modified hand shaking, lipid film hydration technique. Drug, lecithin 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. The film was then hydrated with phosphate buffer (pH 7.4) with gentle shaking for 15 minutes at corresponding temperature.

4. Aqueous lipid suspension process: In this process, 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 soyphosphatidylcholine with the standard deviation of size distribution (around 30%). This formulation could be prepared by suspending the lipids in an aqueous phase wherein the drug is dissolved.

5. Centrifugation process: In this process, phospholipids, surfactants and the drug are dissolved in alcohol. Then the solvent is removed by rotary evaporation under reduced pressure at 40oC. Final traces of solvent are removed under vacuum. Then the deposited lipid film is hydrated with the appropriate buffer by centrifuging at 60 rpm for 1 hour at room temperature. At room temperature, the resulting vesicles are swollen for 2 hours. The multi-lamellar lipid vesicles obtained [20].

6. Thin film hydration technique: 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 vesicles, or 50°C for dipalmitoyl phosphatidyl choline) using rotary evaporator. Final traces of solvent were removed under vacuum for overnight. 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. 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 [17].

Optimization of Formulation Containing Transfersomes

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

- Lecithin: surfactant ratio
- Effect of various solvents
- Effect of various surfactants
- Hydration medium

Optimization was done by selecting entrapment efficiency of drug. During the preparation of a Particular system, the other variables were kept constant **[21].**

CHARACTERIZATION OF TRANSFERSOMES [20, 22, 23].

The characterization of Transfersomes is generally similar to liposomes, niosomes and micelles. Following characterization parameters have to be checked for Transfersomes. [12].

1. Determination of Vesicle shape and type

Transfersomes vesicles can be visualized by TEM, Phase contrast microscopy, etc.

2. Vesicle size distribution and zeta potential

Vesicle size, size distribution and zeta potential were determined by Dynamic Light Scattering system by Malvern Zetasizer.

3. 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.

4. Number of vesicles per cubic mm

This is an important parameter for optimizing the composition and other process variables. Non sonicated Transfersomes formulations are diluted five times with 0.9% sodium chloride solution. Haemocytometer and optical microscope can then be used for further study. The Transfersomes in80 small squares are counted and calculated using the following formula

$$\text{Total number of Transfersomes per cubic mm} = \frac{\text{Total number of Transfersomes counted} \times \text{dilution factor} \times 4000}{\text{Total number of square counted.}} \times 100$$

5. 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

$$\text{Entrapment efficiency} = \frac{\text{Amount entrapped}}{\textit{Total amount added}} \times 100$$

6. 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.

7. Turbidity measurement

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

8. 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 microporous 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.

9. Penetration ability

Penetration ability of Transfersomes can be evaluated using fluorescence microscopy.

10. 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 towater rich deeper regions. Occlusion affects hydration forces as it prevents evaporation of water from skin.

11. Surface charge and charge density

Surface charge and charge density of Transfersomes can be determined using zetasizer.

12. *In-vitro* Skin permeation Studies

Modified Franz diffusion cell with a receiver compartment volume of 50ml and effective diffusion area of 2.50 cm^2 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

slaughter house 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 2.50cm^2 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. 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 calculation of release profile. The samples were analyzed by any instrumental analytical technique.

APPLICATIONS OF TRANSFERSOMES [24].

Transfersomes use in percutaneous drug delivery systems has the implied for contributing restrained release of the contributing drug and developing the establishment of capable drugs.

- **Delivery of Insulin**
  In the broad sense molecules are inadequate of distribution into the skin such can be conveyed beyond the skin with using Transfersomes. For example, insulin, consignment of insulin by Transfersomes is the prosperous channel of non-forward therapeutic use of such comprehensive molecular weight drugs on the skin. Insulin is commonly executed by subcutaneous route that is inappropriately.
- **Carrier for Interferons & Interlukin**
  This is considered that the formulation of interleukin-2 and interferone-α accomodate Transfersomes for probable percutaneous application, leukocytic imitates interferon-α (INF-α) which is a generally existing protein having antiviral, anti-proliferive and some immune-modulatory effects.
- **Carrier for Other Proteins & Peptides**
  Transfersomes have been extensively approved as a transporter for the delivered of other proteins and peptides. Proteins and peptides are enormous biogenic molecules which are very ambitious to deliver into the body, when given orally they are absolutely attenuated in the GI tract and percutaneous delivery deteriorates being of their extensive size. Delivery of certain drug molecules that have physicochemical which is differently avert them from distributing cross stratum conium can be transferred.
- **Peripheral Drug Targeting**
  Subcutaneous tissue possesses tight junctions between endothelial cells which are not allowing vesicles to enter directly into the blood stream. This naturally increases drug concentration narrowly along with the expectation of drug allow to peripheral tissues due to transferosome.
- **Transdermal Immunization**
  By the reason of ultradeformable cysts have the ability of transferring the enormous particle; they can be utilized to convey vaccines topically. Transfersomes consists of proteins like intrinsic sheath protein, human serum albumin, difference attachment protein is used for this aspiration. Improvement of this accession are interjecting the protein can be averted and greater IgA elevation are promoted. Percutaneous hepatitis-B vaccine has accustomed positive conclusion.
- **Delivery of NSAIDs**
  NSAIDS are correlated with numeral of GI concomitant. These can be conquered by percutaneous distribution using ultra-deformable cysts. The consideration has been bringing out on Diclofenac and Ketoprofen. Ketoprofen in a transferosome production improved marketing recommendation. Another beneficial compound based on the transferosome automation, acceding to IDEA AG, is in analytical advancement.
- **Delivery of steroidal hormones and peptides**
  Transfersomes have as well as utilized for the transmission of corticosteroids. Transfersomes upgrade the location particularity and comprehension drug assurance ofcorticosteroid consignment into skin by developing the epicutaneously executed drug dose.
- **Delivery of Anesthetics**
  Superlative appering pain dispassion is approximately as active (80%) as that of a commensurate subcutaneous bolus injection, but the consequence of eq-lidocaine, tetracaine transferosomal anesthetics concluding longer.
- **Delivery of Anticancer Drugs**
  To administer a new advance entrance medication exclusively of skin cancer, anticancer drugs like methotrexate were demonstrated for percuteaneously delivery using transferosome automation. The outcome was agreeable.
- **Delivery of Herbal Drugs**
  Transfersomes can permeate stratum conium and accumulation the supplements narrowly to continue its activity proceeding allowance of skin. The current acquaintance of

Transfersomes of Capsaicin has been processed, which appearance the superior percutaneous absorption in correlation to natural capsaicin.

Drug	Inference
Oestradiol	Improved transdermal flux
Norgesterol	Improved transdermal flux
Hydrocortisone	Biologically active at dose several times lower than currently used formulation
Human serum albumin	Antibody titer is similar or even slightly higher than subcutaneous injection.
Interferon-α	Controlled release, Overcome stability problem.
Insulin	High encapsulation efficiency. Transfer across the skin with an efficiency of >50%. Provide noninvasive mea

Table 1: List of drugs used for Transfersomes

FUTURE OF TRANSFERSOMES

Since transfersomes can pass through narrow constriction of the skin without any measurable loss they're distinctive systems. they will be created synthetically and in massive quantities. Since well-characterized transfersomes ar out their surge of activities, they will be performed in developing a pharmaceutically-acceptable stratum drug carrier. Varied clinical trials are current within the planning and development of transfersomes as drug delivery systems.

CONCLUSION:

Transfersomes 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. Transfersomes 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 cm 2h-1). The systemic drug availability thus mediated is frequently higher than, or at least approaches 80-90%. The bio-distribution of radioactively labeled phospholipids applied in the form of transfersomes after 24 h is essentially the same after an epicutaneous application or subcutaneous injection of the preparations. When used under different application conditions, transfersomes can also positioned nearly exclusively and essentially quantitatively into the viable skin region. Though many transfersomes have already been discovered and registered there is greater promise in future for marketing of highly stabilized and more sophisticated transfersomal formulations. The future of transfersomes drug delivery system will be revolutionized with wide application especially in the treatment of diabetes, tumour and various disorders.

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