International Journal of Research in Engineering and Applied Sciences(IJREAS)
Available online at http://euroasiapub.org/journals.php
Vol. 7 Issue 6 , June-2017, pp. 189~198
ISSN (O): 2249-3905, ISSN(P): 2349-6525 | Impact Factor: 7.196

Transfersomes: A Novel Drug Delivery System

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Abstract: Transfersomes is a novel, elastic or ultra-deformable drug carrier system composes of phospholipid, surfactant & water for enhanced transdermal delivery. These are self optimised & have ultra flexible membrane properties; they are able to deliver a low & high molecular weight drug either into or through the skin depending upon the choice of administration or application. This review describes the composition, preparation, and characteristics of transfersomes. Transfersomes have been claimed to enhance significantly the local and systemic delivery of a wide range of compounds. This review also describes the mechanism of penetration, optimisation methods & application of transfersomes at various sectors.

Keywords: Transfersomes, Characterization, Interaction with skin.

Introduction

Transdermal drug delivery technology represents one of the most rapidly advancing as of the novel drug delivery. Transdermal drug delivery is an increasingly important method of drug administration. Transdermal drug delivery as a comfortable, covininent and non invasive alternative to other means of drug delivery. The systemic treatment of disorder via transdermal route is not a recent innovation, but in the past two decades, transdermal drug delivery has gain increasing interest. Although the transdermal delivery of drugs has been subject for more than 100 years the active development of transdermal products began to gain pace only in last 40 years. The first transdermal system transderm- scop developed in 1980 used the drug scopolamine for treatment of motion sickness. Although thousands of drugs could utilised in such delivery system only 8 hours and 25 transdermal system have been developed up to date. Current drugs utilised in transdermal drug delivery system include nicotine, nitroglycerin and various hormones such as estradiol and testosterone. In transdermal drug delivery systems, drugs are delivered from patch applied to skin. With gentle pressure, and can be easily removed without causing pain. Transdermal drug delivery system are typically composed of a polymeric layer is placed in contact with skin; the drug compound migrates through the polymer, partitions across the polymer/skin interface and then migrates into skin. [1]

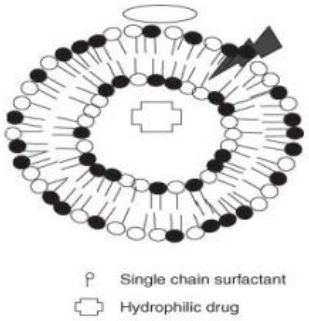

Figure: 1 Transfersome [11]

Advantages of transdermal drug delivery system

1. First pass metabolisms of drug get avoided.

2. Gastrointestinal incompatibilities get avoided.

3. Self medication is possible.

4. Duration of action gets extended & predictable.

5. Unwanted side effects get minimized.

6. Drug plasma concentration gets maintained.

7. Number of doses get reduces which improve patient compliance.

8. Therapeutic value of many drugs get increased by avoiding problems associated with drug like-lower absorption, GI irritation, decomposition due to hepatic first pass metabolism. [2]

Disadvantages of Transdermal drug delivery System

1. Chances of allergic reactions at the site of application like-itching, rashes, local edema etc.

2. Larger molecular size of drug (above 1000) creates difficulty in absorption.

3. Barrier function of skin varies from site to site on the same or different person.

4. Drug with hydrophilic character is less suitable as compare to drug with lipophilic character because of their low permeability. [2]

Transfersomes

Transfersomes have been defined as specially designed vesicular particles, consisting of at least one inner aqueous compartment surrounded by lipid bilayer with approximately tailored properties. Accordingly, transfersomes resemble lipid vesicles, liposomes in morphology but functionally, transfersomes are sufficiently deformable to penetrate pores much smaller than their own size. They are metastable, which makes the vesicles are highly deformable. It is chiefly the usually strong membrane adaptability that allows the transfersomes vesicles to accommodate to a confining pore

and thus trespass such a pore. Typical transfersomes are, therefore, characterized by least one order of magnitude. More elastic membrane than that of conventional lipid vesicles, liposomes. In order to change liposomes into transfersomes, one can incorporate one or more edge active substances into the vesicular membrane. [3]

Transfersomes V/S Other Carrier Systems

At first glance, transfersomes appear to be remotely related to lipid bilayer 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. This is due to high flexibility of the transfersomes membrane and is achieved by judiciously combining at least two lipophilic/amphiphilic components (phospholipids plus bio surfactant) with sufficiently different packing characteristics into a single bilayer. The high resulting aggregate deformability permits transfersomes to penetrate the skin spontaneously. This tendency is supported by the high transfersomes surface hydro-philicity that enforces the search for surrounding of high water activity. It is almost certain that the high penetration potential of the transfersomes is not primarily a consequence of stratum corneum fluidization by the surfactant because micellar suspension contains much more surfactant than transfersomes (PC/Sodium cholate 65/35 w/w %, respectively). Thus, if the penetration enhancement via the solubilization of the skin lipids was the reason for the superior penetration capability of transfersomes, one would expect an even better penetration performance of the micelles. In contrast to this postulate, the higher surfactant concentration in the mixed micelles does not improve the efficacy of material transport into the skin. On the contrary, mixed micelles stay confined to the topmost part of the stratum corneum even they are applied non occlusively. Transfersomes differ in at least two basic features from the mixed micelles, first a transfersomes is normally by one to two orders of magnitude (in size) greater than standard lipid micelles. Secondly and more importantly, each vesicular transfersomes contains a water filled core whereas a micelle is just a simple fatty droplet. Transfersomes thus carry water as well as fat-soluble agent in comparison to micelles that can only incorporate lipoidal substances. To differentiate the penetration ability of all these carrier systems proposed the distribution profiles of fluorescently labelled mixed lipid micelles, liposomes and transfersomes as measured by the Confocal Scanning Laser Microscopy (CSLM) in the intact skin. In all these vesicles the highly deformable transfersomes transverse the stratum corneum and enter into the viable epidermis in significant quantity. [3]

Interaction of transfersomes with the skin

The proposed driving force for the putative penetration of transfersomes across the skin is the water activity gradient between the relatively dehydrated skin surface and the aqueous viable epidermis. Hence, when a transfersome formulation is applied on the skin under non-occlusive conditions, the evaporation of water from the vehicle drives the penetration of vesicles towards the viable epidermis to avoid their dehydration. It has been reported that transfersomes penetrate into the SC via two different hydrophilic pathways: (i) An intercluster route via the “gorge” between corneocytes clusters (formed by 3 to 10 individual corneocytes) which has a uniform width (≤ 4-6 μm) and depth (≤ 3-5 μm); this pathway has a relatively low penetration resistance and corresponds to ≤ 1% of the total skin surface area. (ii) The intercorneocyte pathway travels between the individual corneocytes in the cell clusters, and occupies an area greater than 3% of the total skin surface area. [12]

Composition of transfersomes:

The transfersome is composed of two main aggregates namely

1. Firstly, an amphipathic ingredient (Phosphatidylcholine), in which the aqueous solvents self-assemble into lipid bilayer that closes into a simple lipid vesicle.

2. Secondly, a bilayer softening component (such as a biocompatible surfactant oramphiphile drug) that increases lipid bilayer flexibility and permeability. The resulting, flexibility and permeability optimized, transfersome vesicle can therefore adapt its shape easily and rapidly, by adjusting local concentration of each bilayer component to the local stress experienced by the bilayer. Therefore, the transfersome thus differs from such more conventional vesicle primarily by its "softer", more deformable, and better adjustable artificial membrane. the bilayer Therefore, the transfersome thus differs from such more conventional vesicle primarily by its "softer", more deformable, and better adjustable artificial membrane. Materials which are widely used in the formulation of transfersomes are various phospholipids, surfactants, alcohol, dye, buffering agent etc; different additives are used.

Preparation of transfersomes

Thin film hydration method

In this method 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 or 50°C 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 hour at the corresponding temperature. The resulting vesicles were swollen for 2 hours 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 40°C for 30 min. The sonicated vesicles were homogenized by manual extrusion 10 times through a sandwich of 200 and 100 nm polycarbonate membranes.

Modified hand shaking, lipid film hydration technique

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. The film was then hydrated with phosphate buffer (pH 7.4) with gentle shaking for 15 minute at corresponding temperature. The transfersome suspension was further hydrated up to 1 hour at 2-80°C. [4]

Class	Example	Uses
Phospholipids	Soya phosphatidyl choline, Egg phosphatidyl choline	Vesicles forming component
Surfactant	Sod. Cholate, Sod. Deoxycholate, Tween 80, Span 80	For providing flexibility
Alcohol	Ethanol, methanol	As a solvent
Buffering agent	Saline phosphate buffer (Ph 6.4)	As a hydrating medium
Dye	Rhodamine- 123, Rhodamine- DHPE Fluorescein-DHPE Nile- red	For CSLM study

Table: 1 Additives used in formulation of Transfersomes [11]

Mechanism of penetration of transfersomes:

Transfersomes, when applied under suitable condition, can transfer 0.1 mg of lipid per hour and square centimetre area across the intact skin. This value is substantially higher than that typically driven by the transdermal concentration gradients. The reason for this high flux rate is naturally occurring "transdermal osmotic gradients", i.e. another much more prominent gradient is available across the skin. 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).This gradient is very stable because ambient air is a perfect sink for the water molecule even when the transdermal water loss is un-physiologically high. All polar lipids attract some water. This is due to the energetically favourable interaction between the hydrophilic lipid residues and their proximal water. Thus, most lipid bilayer spontaneously resists 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. So, when lipid suspension (transfersome) is placed on the skin surface that is partly dehydrated by the water evaporation loss, the lipid vesicles feel this "osmotic gradient" and try to escape complete drying by moving along this gradient. They can only achieve this if they are sufficiently deformable to pass through the narrow pores in the skin because transfersomes 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 transfersome. Transfersomes are optimized in this respect and thus attain maximum flexibility, so they can take full advantage of the transepidermal osmotic gradient (water concentration gradient). 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:

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

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. The 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. [5]

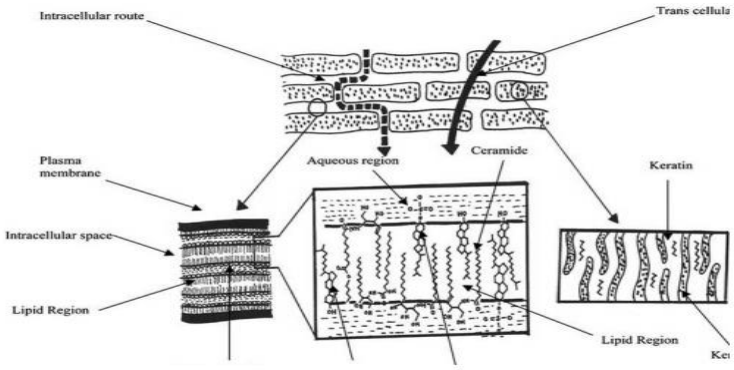

Figure: 2 Diagramatic representation of stratum corneum The Intercellular & Transcellular Routes of penetration. [11]

Characterization

The characterization of transfersomes is generally similar to liposomes, niosomes and micelles. Following characterization parameters have to be checked for transfersomes. [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 minicolumn centrifugation method. After centrifugation, the vesicles were disrupted using 0.1% Triton X-100 or 50% n-propanol. [4]

The entrapment efficiency is expressed as:

$$EE = \frac{\text{Amount entrapped} \times 100}{\text{Total amount added}}$$

Vesicle size distribution and zeta potential

Vesicle size, size distribution and zeta potential were determined by Dynamic Light Scattering Method (DLS) using a computerized inspection system by Malvern Zetasizer. [4]

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]

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. [3]

Confocal Scanning Laser Microscopy (CSLM)

Study Conventional light microscopy and electron microscopy both face problem of fixation, sectioning and staining of the skin samples. Often the structures to be examined are actually 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 transfersomes and the light emitted by these markers used for investigating the mechanism of penetration of transfersomes across the skin for determining 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 transfersomes with liposomes, niosomes and micelles. [6]

Degree of deformability or permeability measurement:

The Transfersome preparation is passed through many filters between pore size 50 to 400 nm. Vesicle retained on each filter is studied for particle size and distribution using Dynamic light scattering technique.

The degree of deformability,

$D = J X (rv/rp)$

Where, J- the amount of the suspension extruded during 5 min; rv - the size of the vesicle; rp - pore size of the barrier. [7]

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 32°C using cellophane membrane. The samples are withdrawn at different intervals. 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. Detection is done by various analytical techniques like U.V., HPLC and HPTLC). [7]

Vesicle shape and type:

Transmission electron microscopic (TEM) techniques are used to visualise transfersomes with an applied voltage of 100 k. A sample drop of transfersomes was treated with carbon coated grid. A thin film was formed on a carbon coated grid and allowed the film to be dried. After drying, the film was now negatively strained with 1% phototungustic acid; a film was now mixed with excess of straining solution and drained off grid with filter paper. View the dried grid on TEM. Transfersomes without sonication can also be viewed by phase contrast microscopy and optical microscope. [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]

Turbidity Measurement

Turbidity of drug in aqueous solution can be measured using nephelometer. [11]

Surface Charge and Charge Density

Surface charge and charge density of Transfersomes can be determined using zetasizer. [10]

- Visualization of transfersomes can be performed using transmission electron microscopy (TEM) and scanning electron microscopy (SEM).

- Particle size and size distribution can be determined by dynamic light scattering (DLS) and photon correlation spectroscopy (PCS).
- The drug entrapment efficiency by transfersomes can be measured by the ultracentrifugation technique.
- Vesicle stability can be determined by assessing the size and structure of the vesicles over time, and drug content can be quantified by high performance liquid chromatography (HPLC) or Spectrophotometric methods.
- *In vitro* drug release can be measured using a diffusion cell or a dialysis method. [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). [4]

Optimization of 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,

1. Lecithin: surfactant ratio

2. Effect of various solvents

3. Effect of various surfactants

4. Hydration medium

Optimization was done by selecting entrapment efficiency of drug. During the preparation of a particular system, the other variables were kept constant. [3]

Application of Transfersomes

Transfersomes 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 bioavaibility obtained from transfersomes is somewhat similar to that resulting from subcutaneous injection of the same protein suspension. The transfersomal preparations of this protein also induced strong immune response after the repeated epicutaneous application, for example the adjuvant immunogenic bovine serum albumin in transfersomes, after several dermal challenges is as active immunologically as is the corresponding injected proteo-transfersomes preparations. Delivery of insulin by transfersomes 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 transfersomes (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. Transfersomes 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. Transfersomes 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 transfersomes for potential transdermal application .they reported delivery of IL-2 and INF- α trapped by transfersomes in sufficient concentration for immunotherapy. Another most important application of transfersomes is transdermal immunization using transfersomes 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. Transfersomes have also used for the delivery of corticosteroids. Transfersomes improves the site specificity and overall drug safety of corticosteroid delivery into skin by optimizing the epicutaneously administered drug dose. Transfersomes beased corticosteroids are biologically active at dose several times lower than the currently used formulation for the treatment of skin diseases. Application of anesthetics in the suspension of highly deformable vesicles, transfersomes, 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 transfersomal anesthetics last longer. Transfersomes has also been used for the topical analgesics, anaesthetics agents, NSAIDS and anti-cancer agents. [11]

Conclusion

Transfersomes are specially optimized particles or vesicles, termed as novel drug delivery system, which can respond to an different stress conditions which are put on the skin externally, by rapid and energetically inexpensive, shape transformation, thus, referring as deformable vesicles. These highly deformable particles can thus be used to bring drugs across the biological permeability barriers.

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