World Journal of Pharmaceutical and Life Sciences
WJPLS
www.wjpls.org
SJIF Impact Factor: 5.088

TRANSFEROSOMES: A CARRIER FOR DRUG DELIVERY- A REVIEW

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Article Received on 08/04/2018 **Article Revised on 29/04/2018** **Article Accepted on 20/05/2018**

ABSTRACT

Transdermal drug delivery appears to be the most vital drug delivery system because of its merit over conventional systems. Transport of the drug through skin is best route of drug delivery because of the skin is largest organ human organ with total weight 3 kg and a surface of 1.5 -2.0 m^2. Drug carries used in transdermal drug delivery. Various strategies can be used to augment the transdermal delivery which includes iontophoresis, electrophoresis, sonophoresis, chemical permeation enhancers, microneedles, and vesicular system (liposomes, niosomes, elastic liposomes such as ethosomes and transfersomes). Transfersomes penetrate through the pores of stratum corneum which are smaller than its size and get into the underlying viable skin in intact form. This is because of its deformable nature. The system can be characterized by in vitro for vesicle shape and size, entrapment efficiency, degree of deformability, number of vesicles per cubic mm. 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.

KEYWORDS: Transfersomes, permeability, Transdermal delivery, Phospholipids.

INTRODUCTION

Transdermal drug delivery systems offer a number of potential advantages over conventional methods such as injectable and oral delivery.[1] However, the major limitation of TDDS is the permeability of the skin, it is permeable to small molecules, lipophilic drugs and highly impermeable to macromolecules and hydrophilic drugs. The main barrier and rate-limiting step for diffusion of drugs across the skin is provided by the outermost layer of the skin, the stratum corneum.[2] Recent approaches in modulating vesicle compositions have been investigated to develop systems that are capable of carrying drugs and macromolecules to deeper tissues. These approaches have resulted in the design of two novel vesicular carriers, ethosomes and ultra flexible lipid-based elastic vesicles, transferosomes.[3] Transferosomes are ultra deformable vesicles possessing an aqueous core surrounded by the complex lipid bilayer. Interdependency of local composition and shape of the bilayer makes the vesicle both self-regulating and self-optimizing.[4] Transferosomes have recently been introduced, which are capable of transdermal delivery of low as well as high molecular weight drugs.[5] Transferosomes are specially optimized, ultra flexible lipid supra molecular aggregates, which are able to penetrate the mammalian skin intact and then act as a drug carrier for non-invasive targeted drug delivery and sustained release of therapeutic agents.[6] Each transferosomes 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.[7] Due to their deformability, transferosomes are good candidates for the non-invasive delivery of small, medium, and large sized drugs. Delivery via the transdermal route is an interesting option in this respect because a transdermal route is convenient and safe. This offers several potential advantages over conventional routes like avoidance of first pass metabolism, predictable and extended duration of activity, minimizing undesirable side effects, utility of short half-life drugs, improving physiological and pharmacological response, avoiding the fluctuation in drug levels, inter and intrapatient variations, and most importantly, it provides patients convenience. To date many chemical and physical 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 the use of colloidal carriers such as lipid vesicles (liposomes and proliposomes) and nonionic surfactant vesicles (niosomes and proniosomes). 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 Transferosomes 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. The term Transferosomes and the underlying concept were introduced in 1991 by Gregor Cevc. Numerous groups have since been working with similar carriers, frequently using different names (e.g., elastic vesicle, flexible vesicle, Ethosomes, etc.) to describe them.

Salient Features

Transferosomes possess an infrastructure consisting of hydrophobic and hydrophilic moieties together and as a result can accommodate drug molecules with wide range of solubility. Transferosomes 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, 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 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.[8]

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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. Transferosomes possess an infrastructure consisting of hydrophobic and hydrophilic moieties together and as a result can accommodate drug molecules with wide range of solubility.
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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.[11,12,13]

Limitations of Transferosomes

1. Transferosomes are chemically unstable because of their predisposition to oxidative degradation.
2. Purity of natural phospholipids is another criteria militating against adoption of transferosomes as drug delivery vehicles.
3. Transferosomes formulations are expensive.[10,12,13]

MECHANISM OF ACTION

Mechanism behind the penetration of transfersome is the development of osmotic gradient because while lipid suspension applies on skin surface water gets evaporated. Transfersomes have strong bilayer deformability and therefore they have increased affinity to bind and retain water. Dehydration is not happened in case an ultradeformable and highly hydrophilic vesicle; it is not identical to forward osmosis but may involve in transport process related to forward osmosis. Upon application on skin surface (non-occluded), it penetrates skin barrier and reaches at the deeper strata (water rich portion), where they get hydrated. Then, reach at deeper epidermal layer through dehydration of lipid vesicles within the stratum corneum by natural transepidermal activity. Therefore, transfersome uptake is a function of hydration gradient that exists across the epidermis, stratum corneum, and ambient atmosphere.[14-17]

MATERIALS

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 no. 1.[18]

Class	Example	Uses
Phospholipids	Soya phospholipids, egg phosphatidylcholine, diaplmitoyl phosphatidylcholine.	Vesicle forming agent
Surfactant	Sod,chocolate,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

Preparation of Transfersomes

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 dipalmitoylphosphatidylcholine) 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.

B. 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 handshaking 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.

Characterization of Transfersomes

The characterization of transfersomes is generally similar to liposomes, niosomes and micelles (Nanda et al., 2005, Jain et al., 1998).

Entrapment Efficiency

The entrapment efficiency is expressed as the percentage entrapment of the drug added. Entrapment efficiency was determined by first separation of the unentrapped 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.

Vesicle Diameter

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 (Gamal et al., 1999).

Number of Vesicle per Cubic Mm

This is an important parameter for optimizing the composition and other process variables. Transferosomes formulations (without sonication) can be diluted five times with 0.9% of sodium chloride solution and studied with optical microscopy by using haemocytometer.

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.

Turbidity Measurement

- Turbidity of drug in aqueous solution can be measured using nephelometer.
- Surface Charge and Charge Density.
- Surface charge and charge density of transferosomes can be determined using zeta sizer.

Penetration Ability

Penetration ability of transferosomes can be evaluated using fluorescence microscopy.

In vitro Drug Release

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 was2.50cm2 and capacity of receptor compartment was 50ml. The receptor compartment was filled with50ml of phosphate buffer (pH 7.4) saline maintained at 37 ± 0.5˚C and stirred by a magnetic bar at 100RPM. Formulation (equivalent to 10mg drug) was placed on the skin and the top of the diffusion cell was covered. At appropriate time intervals 1 ml aliquots of the receptor medium were withdrawn

and immediately replaced by an equal volume of fresh phosphate buffers (pH 7.4) to maintain sink conditions. Correction factors for each aliquot were considered in calculation of release profile. The samples were analyzed by any instrumental analytical technique.[19-21]

In Vivo Fate of Transfersomes and Kinetics of Transfersomes Penetration[22-23]

After having penetrated through the outermost skin layers, transfersomes reach the deeper skin layer, the dermis. From this latter skin region they are normally washed out, via the lymph, into the blood circulation and through the latter throughout the body, if applied under suitable conditions. Transfersomes can thus reach all such body tissues that are accessible to the subcutaneously injected liposomes. The kinetics of action of an epicutaneously applied agent depends on the velocity of carrier penetration as well as on the speed of drug (re) distribution and the action after this passage. The most important single factors in this process are:

1. Carrier in-flow
2. Carrier accumulation at the targets site
3. Carrier elimination.

The onset of penetration-driving force depends on the volume of the suspension medium that must evaporate from the skin surface before the sufficiently strong trans-cutaneous chemical potential chemical potential or water activity gradient is established. Using less solvent is favourable in this respect. The rate of carrier passage across the skin is chiefly determined by the activation energy for the carrier deformation. The magnitude of the penetration driving force also plays a big role. This explains, for example, why the occlusion of an application site or the use of too strongly diluted suspension hampers the penetration process. Carrier elimination from the subcutis is primarily affected by the lymphatic flow, general anaesthesia or any other factor that affects this flow, consequently, is prone to modify the rate of transcutaneous carrier transport. While it has been estimated that approximately 10% of the cardiac blood flow pass through each gram of living skin tissue, no comparable quotation is available for the lymph. Further, drug distribution is also sensitive to the number of carrier used, as this may affect the rate of vehicle degradation and / or filtration in the lymph nodes. The lag between the time of application and the time of drug appearance in the body, therefore, is always quite long, complex and strongly sensitive to the type of drug and formulation administration. In the best case, the skin penetration lag amounts to approximately 15 min. if rapidly exchanging agents such as local analgesics are detected right under the skin permeability barrier. Less rapidly exchanging molecules or molecules measured in the blood compartment are typically detected with a lag time between 2 and 6 hr. depending on the details of drug formulation. Molecules that do not diffuse readily from the carriers or agents delivered with the suboptimal carriers normally fall in this category. The kinetics of vesicle penetration into and across the skin can be controlled to a large extent by fixing the physicochemical characteristics of the drug carrier suspension. Kinetics of the transfersomes penetration through the intact skin is best studied in the direct biological assays in which vesicle associated drugs exert their action directly under the skin surface. Local analgesics are useful for this purpose, for determining the kinetics of penetration, various lidocaine loaded vesicles were left to dry out on the intact skin.

Corresponding subcutaneous injection is used as control. The animal's sensitivity to pain at the treated site after each application was then measured as a function of time. Dermally applied standard drug carrying liposomes or simple lidocaine solution have never caused any analgesic effect. It was necessary to inject such agent preparations to achieve significant pain suppression. In contrast to this, the lidocaine-loaded transfersomes were analgesically active even when applied dermally. Maximum analgesic effect with the latter type of drug application was typically observed 15 minutes after the drug application. A marked analgesic effect was still noticeable after very long time. The precise reach as well as kinetics of transfersomes penetration through the skin are affected by: drug carrier interaction, application condition or form, skin characteristics, applied dose.

Transfersomes vs Other Carrier Systems.[24]

At first glance, transfersomes appear to be remotely related to lipid bilayers 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 biosurfactant) 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 hydrophilicity 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 nonexclusively. The reason for this is that mixed

micelles are much less sensitive to the trans-epidermal water activity gradient than transfersomes. 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 (Gompper et al., 1995, Wearner et al., 1988). To differentiate the penetration ability of all these carrier systems (Rand et al., 1989) 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 murine skin. In all these vesicles the highly deformable transfersomes transverse the stratum corneum and enter into the viable epidermis in significant quantity.

APPLICATION OF TRANSFERSOMES[25]

1. Delivery of insulin

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.

2. Delivery of corticosteroids

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

3. Delivery of proteins and peptides

Transfersomes have been widely used as a carrier for the transport of proteins and peptides. Protein 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. The transferosomal preparations of this protein also induced strong immune response after the repeated epicutaneous application, for example the adjuvant immunogenic serum albumin in transferosomes, after several dermal challenges is as active immunologically as is the corresponding injected protea-transferosomes preparations.

4. 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, antiproliferative and some immunomodulatory effects. Transferosomes as drug delivery systems have the potential for providing controlled release of the administered drug and increasing the stability of labile drugs. Hafer et al studied the formulation of interleukin-2 and interferone-α containing transferosmes for potential transdermal application .they reported delivery ofIL-2 and INF- α trapped by transferosomes insufficient concentration for immunotherapy.

5. Delivery of Anticancer Drugs

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

6. Delivery of anaesthetics

Application of anaesthetics in the suspension of highly deformable vesicles, transfersomes induces atopical anaesthesia, 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 transfersomes anaesthetics last longer.

7. 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 transfersomes formulation gained marketing approval by the Swiss regulatory agency (Swiss Medic) in 2007; the product is expected to be marketed under the trademark Diractin. Further therapeutic products based on the transfersomes technology, according to IDEA AG, are in clinical development.

8. 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.

CONCLUSION

Ultra-deformable vesicles can provide the novel solution for the transport related problems. 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. They are free from the rigid nature of conventional vesicle and can transport even the large molecules. They work on number of mechanisms working together to provide an excellent carrier system for the drug transport. 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 loaded transfersomes can carry unprecedented amount of drug per unit time across the skin (up to 100mg cm^2h deformable vesicles hold great prospective in delivery of huge range of drug substances which includes large molecules like peptides, hormones and antibiotics, drugs with poor penetration due to unfavorable physicochemical characters, drugs for quicker and targeted action, etc.

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