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SELF-ASSEMBLED ULTRADEFORMABLE PHOSPHOLIPID VESICLES WITH EDGE ACTIVATORS FOR DELIVERY OF TRANSCUTANEOUS BIOACTIVES

Ms. Namita G. Narvekar*, Mr. Mayuresh R. Redkar, Ms. Namita S. Bhosale
Yashwantrao Bhonsale College of Pharmacy, Sawantwadi, (MS), India, 416510.

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ABSTRACT

Molecules more than 500 Dalton normally do not permeable through skin. This prevents percutaneous delivery of the large molecular weight therapeutics as well as non-invasive transcutaneous immunization. The flexible or deformable vesicles are called as Transfersome which are derived from two words as 'Transferred' from Latin which means 'To carry across' and 'Soma' from Greek which means 'Body'. The word transfersome was first introduced by Gregor Ceve in 1991. Elasticity is produced by incorporation of an edge activator in the lipid bilayer structure. The vesicular transferosomes have several orders of magnitude more elastic than the standard liposomes and therefore well suited for skin penetration. Transfersomes are composed of phosphotidyl choline which is self assembles into lipid bilayer in aqueous environment and closes to form a vesicle. The flexibility of transferosomes membrane is achieved by mixing suitable surface-active components in the proper ratios. The conclusion of this review is transfersome technology is best suited for noninvasive delivery of therapeutic molecule across open biological barriers. Transfersomes are applied in a non-occluded method to the skin and have been shown to cross through the stratum corneum lipid lamellar regions as a result of the hydration or osmotic force in the skin. They have been used as drug carriers for a range of small molecules, peptides, proteins and vaccines, both in vitro and in vivo. The methods of preparation of transferosomes are rotary film evaporation, reverse-phase evaporation, vortexing sonication, ethanol injection and freeze-thaw method etc.

Corresponding author
Ms. Namita G. Narvekar
Yashwantrao Bhonsale College of Pharmacy,
Sawantwadi, (MS), India, 416510
mayuresh.redkar253@gmail.com

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INTRODUCTION

Delivery via the transdermal route is more convenient and safer. Transdermal route has 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 intra-patient variations, and most importantly, it provides patients convenience. Upto the present time 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, iontophoresis, sonophoresis and the use of colloidal carriers such as lipid vesicles (liposomes and proliposomes) and nonionic surfactant vesicles (niosomes and proniosomes). [1]

In the recent years, the vesicular systems have been used mostly as a mean of sustained or controlled release of drugs, because of their certain advantages, e.g. lack of toxicity, biodegradation, capacity of encapsulating both hydrophilic and lipophilic molecules, capacity of prolonging the existence of the drug in the systemic circulation by encapsulation in vesicular structures, capacity of targeting the organs and tissues, capacity of reducing the drug toxicity and increasing its bioavailability. [2]

A transfersome, is an entity which can travel spontaneously through a barrier and transport material from the application to the destination site. The flexible or deformable vesicles are called Elastic Vesicles or Transfersomes. Transfersome is a term derived from two words as 'transferred' from Latin which means 'to carry across' and 'soma' from Greek which means 'body'. It is a spectacular artificial vesicle which having structure as same as a normal biological cell vesicle. The word transfersome was introduced by Gregor Ceve in 19912. There is tremendous research is going on worldwide on these elastic vesicles which can also know with different titles like flexible vesicles, ethosome, etc. Transfersome is a term registered as a trademark by the German company IDEA AG, and used by it to refer to its proprietary drug delivery technology. [3]

A transfersome is a highly adaptable and stress-responsive, complex aggregate. Its most used form is an ultra-deformable vesicle possessing an aqueous core surrounded by the complex lipid bilayer. Because of interdependent nature of local composition and shape of the bilayer makes the vesicle self-regulating as well as self-optimizing which makes the transfersome to cross various transport barriers efficiently, and then act as a Drug carrier for non-invasive targeted drug delivery and sustained release of therapeutic agents.

Transfersomes were developed to take the advantage of phospholipids vesicles as transdermal drug carrier. These self-optimized aggregates, with the ultra-flexible membrane, are capable to deliver the drug reproducibly either into or through the skin, which depends upon the choice of administration or application, with high efficiency. These vesicular transfersomes are several orders of magnitudes as they are more elastic than the standard liposomes and therefore well suitable for the skin penetration. Transferosomes overcome the skin penetration difficulty by squeezing themselves along the intracellular sealing lipid of the stratum corneum. Because of the high vesicle deformability, it allows the entry due to the mechanical stress of surrounding, in a self-adapting manner. Flexibility of transferosomes membrane is obtained by mixing suitable surface-active components in the appropriate ratios. 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 it is applied under non-occlusive condition. [4]

Transferosomes dose applied per unit area, rather than the total drug amount or concentration used. Transfersomes protects the encapsulated drug from metabolic degradation. They act as depot, releasing their content slowly and gradually. Transfersomes can penetrate the intact stratum corneum spontaneously with two routes in the intracellular lipid that differ in their bilayers properties. The Fig. 1 shows possible micro routes for drug penetration across human skin intracellular and transcellular. The high and self-optimizing deformability of typical composite transfersomes membrane, which are adaptable to ambient stress allow the ultra deformable transfersomes to change its membrane composition locally and reversibly, when it is pressed against or attracted into narrow pore. 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. This behavior is not limited to one type of pore and has been observed in natural barriers such as in intact skin. [5]

The present review is an attempt to summarized.

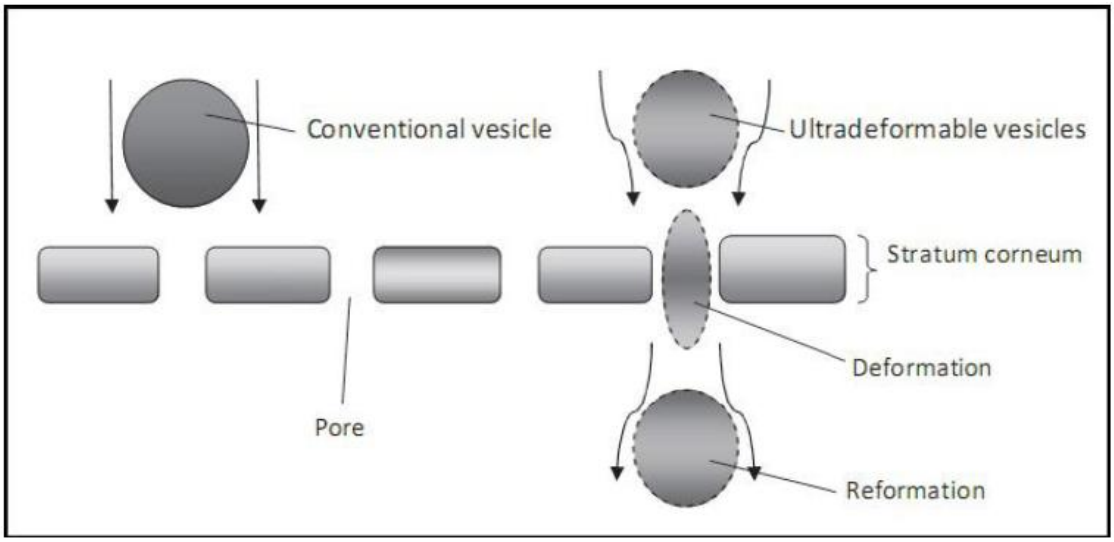

Fig 1: Schematic Diagram of the Two Microroutes of Penetration.

Advantages:

1. High entrapment efficiency, for lipophilic drug it is near to 90%.
2. Can encapsulate both hydrophilic and lipophilic moieties.
3. Suitable as a carrier for low as well as high molecular weight drugs e.g., analgesic, corticosteroids, hormones, anticancer drugs, insulin, proteins, etc.
4. Can deform and pass through narrow constriction (from 5 to 10 times less than their own diameter) without measurable loss.
5. Suitable for both systemic as well as topical delivery of drug.
6. Protect the encapsulated drug from metabolic degradation.
7. Biodegradability and lack of toxicity.

Limitations:

1. Chemically unstable, highly susceptible to oxidative degradation.
2. Formulations are expensive**.** [6]

Scope of Transfersomes:

Transfersome technology is best suitable for noninvasive delivery of therapeutic molecules across open biological barriers. The Transfersome vesicles can transport across the skin, for example, molecules that are large to diffuse through the barrier for examples, systemic delivery of therapeutically meaningful amounts of macromolecules, such as insulin or interferon, across intact mammalian skin. Other applications include the transport of small molecule drugs which have certain physicochemical properties which would otherwise prevent them from diffusing across the barrier. Another attraction of the Transfersome technology is the Carrie's ability to target peripheral, subcutaneous tissue. This ability relies on minimization of the carrier associated drug clearance through cutaneous blood vessels plexus: the non-fenestrated blood capillary walls in the skin together with the tight junctions between endothelial cells preclude vesicles getting directly into blood, thus maximizing local drug retention and propensity to reach the peripheral tissue targets. [7]

Salient features of Transfersomes:

1. Transfersomes possess an infrastructure consisting of hydrophobic and hydrophilic moieties together and as a result can accommodate drug molecules with wide range of solubility.
2. Transfersomes can deform and pass through narrow constriction (from 5 to 10 times less than their own diameter) without measurable loss.
3. This high deformability gives better penetration of intact vesicles.
4. 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.
5. They are biocompatible and biodegradable as they are made from natural phospholipids similar to liposomes.
6. They have high entrapment efficiency, in case of lipophilic drug near to 90%.
7. They protect the encapsulated drug from metabolic degradation.
8. They act as depot, releasing their contents slowly and gradually.
9. They can be used for both systemic as well as topical delivery of drug.
10. Easy to scale up, as procedure is simple, do not involve lengthy procedure and unnecessary use or pharmaceutically unacceptable additives. [8]

Composition of Transferosomes:

Transferosomes composed of phospholipids like phosphatidyl choline which self assembles into lipid bi layer in aqueous environment and closes to form a vesicle. To increase lipid bi layer flexibility and permeability a bi layer softening component (such as a biocompatible surfactant or an amphiphile drug) is added. This second component is called as edge activator. An edge activator consists usually of single chain surfactant that responsible for destabilization of the lipid bi layer thereby increasing its fluidity and elasticity. The resulting, flexibility and permeability optimized. Transfersome vesicles can therefore adapt its shape to ambient easily and rapidly, by adjusting local concentration of each bi layer component to the local stress experienced by the bi layer. [9].

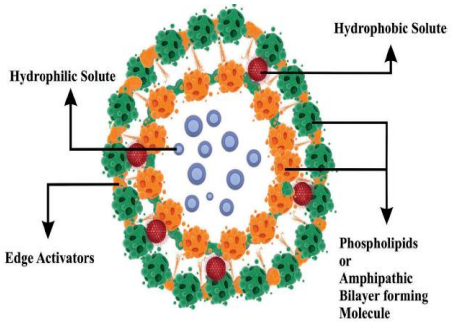

Fig 2 Undeformable Vesicle (Transfersome).

Table 1: shows the composition of a transfersome [10].

CLASS	EXAMPLE	USES
Phospholipids	Soya phosphatidyl choline, egg phosphatidyl choline, dipalmitoylphosphatidyl choline	Vesicles forming complexes
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, Nile red	for confocal scanning Laser microscopy (CSLM)

Mechanism of penetration of Transfersomes:

Transfersomes whenever applied under suitable condition can transfer 0.1 mg of lipid per hour and cm^2 area across the intact skin. This value is substantially greater than that which is 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 is developed due to the skin penetration barrier, which 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 more stable because ambient air is a perfect sink for the water molecule even when the transdermal water loss is physiologically high. Due to the energetically favorable interaction between the hydrophilic lipid residues and their proximal water all polar lipids attract some. Most of the lipid bilayers therefore 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, So when lipid suspension (transfersomes) is placed on the skin surface, that is partly dehydrated by the water evaporation loss and then 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 rheologic 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 transfersomes. Transfersomes are optimized in this respect and thus attain maximum flexibility, so they can take full advantages of the transepidermal osmotic gradient (water concentration gradient). Transfersome vesicle can therefore adapt its shape to ambient easily and rapidly, by adjusting local concentration of each bilayer component to the local stress experienced by the bilayer as shown in fig 3. [11,12].

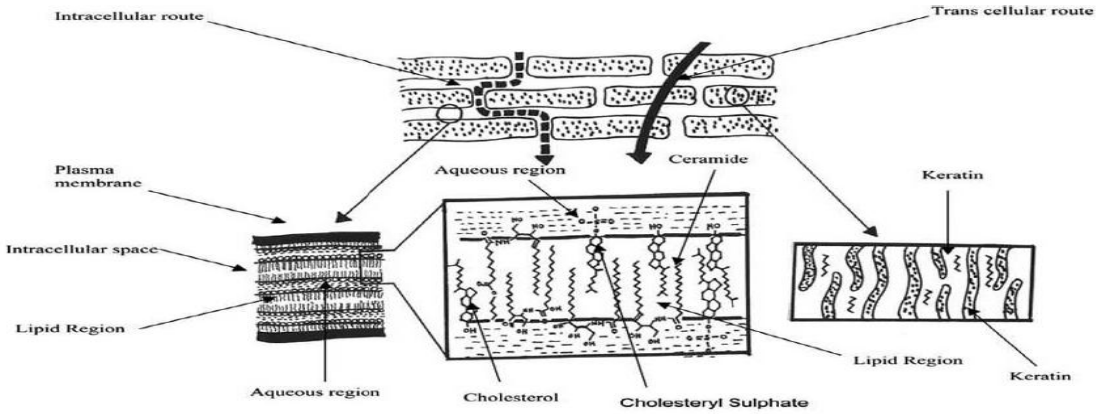

Fig 3: Diagrammatic Representation of the Stratum Corneum and the Intercellular and Transcellular Routes of Penetration.

Method of preparation:

Rotary film evaporation method:

This method is also called as the hand-shaking process, which was initially introduced by Bangham. In this process, the quantity needed of phospholipidsand surfactants (as EAs) is essential to organize a thin film. It is largely worn for the research of multilamellar vesicles. A solution of phospholipids and EAs is organized in a crude solvent such as a combination of chloroform and methanol. This prepared solution is transferred to a round-bottomed flask which is rotated at constant temperature (above the glass transition temperature of lipids) and reduced pressure. A film of lipids and EA is formed on the walls of the flask. The twisted film is then hydrated using aqueous media containing drug. This causes lipids to swell and form bilayer vesicles. Vesicles of desired size can be achieved by extrusion or by sonication of the superior vesicles.

Reverse-phase evaporation method:

At this point, the scheme will alter to a viscous gel followed by the arrangement of vesicles. The non-encapsulated material and residual solvents can be indifferentiable using dialysis or centrifugation. In this method, lipids dissolved in organic solvents in a round-bottomed flask. Aqueous media containing EAs is added under nitrogen purging. The drug can be added to the lipid or aqueous medium based on its solubility character. The system formed is then sonicated, awaiting its conversion into a standardized dispersion, and should not separate for at least 30 min after sonication. The organic solvent is then removed under low pressure.

Vortexing sonication method:

In the vortexing sonication method, mixed lipids (i.e. phosphatidyl choline, EA and the therapeutic agent) are blended in a phosphate buffer and vortexes to attain a milky suspension. The suspension is sonicated, followed by extrusion through polycarbonate membranes. Cationic transfersomes have also been set by this method, which involves mixing cationic lipids, such as DOTMA, with PBS to attain a concentration of 10 mg/ml followed by a count of sodium deoxycholate (SDC). The blend is vortexed and sonicated, followed by extrusion through a polycarbonate (100 nm) filter.

Ethanol injection method:

In this process, the aqueous solution containing drug is heated with unremitting stirring at constant temperature. Ethanolic solution of phospholipids and EAs is injected into aqueous solution drop wise. As the solution comes into contact with aqueous media the lipid molecules are precipitated and form bilayered structures. This process offers assorted advantages over other methods, which include simplicity, reproducibility, and scale-up.

Freeze–thaw method:

This method includes the exposure of multilamellar vesicles to alternate cycles of very low temperature for freezing followed by exposure to very high temperature. The geared-up suspension is transferred to a tube and dipped in a nitrogen bath (−30°C) for 30 s. After freezing, it is exposed to a high temperature in a water bath. This course is repeated eight–nine times. [13]

Characterization of Transfersomes:

The characterization of transfersomes is generally similar to liposomes, niosomes and micelles.

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-100or 50% n-propanol.

The entrapment efficiency is expressed as:

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

Drug content:

The drug content can be determined using one of the instrumental analytical methods such as modified high performance liquid chromatography method (HPLC).

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. [14]

Number of Vesicle per Cubic mm:

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

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 following purpose:

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.

Different fluorescence markers used in CSLM study are:

I. Fluorescein-DHPE (1, 2-dihexadecanoyl-Sn-glycero-3-phosphoethanolamine-N-(5-fluoresdenthiocarbamoyl), triethylammonium salt).
II. Rhodamine-DHPE (1,2-dihexadecanoyl-sn-glycero-3ogisogietgabikanube-N-LissamineTmrhodamine B sulfonyl), triethanolamine salt).
III. NBD-PE (1, 2-dihexadecanoyl-Sn-glycero-3-phosphoethanolamine-N-(7-nitro-Benz-2- oxa-1, 3-diazol-4-yl) triethanolamine salt).
IV. Nile red. [15]

Degree of Deformability or Permeability Measurement:

Degree of deformability is an important and unique parameter of transfersomal formulations because it differentiates transfersomes from other vesicular carriers like liposomes that are unable to cross the stratum corneum intact. 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. The degree of deformability was calculated by using the following formula:

$$D = J^{*} \left(r_v / r_p \right)^2$$

where,

D = deformability of vesicle membrane

J = amount of suspension, which was extruded during 5 min

r_v = size of vesicles (after passes)

r_p = pore size of the barrier

Propensity of penetration:

The magnitude of the transport driving force plays an important role:

Flow = Area x (Barrier) Permeabilityx (Trans-barrier) force

Therefore, the chemically driven lipidflow across the skin always decreases dramatically when lipid solution is replaced by some amount of lipids in a suspension. [16]

Turbidity measurement:

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

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

Penetration ability:
Penetration ability of Transfersomes can be evaluated using fluorescence microscopy. [17]

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. Hydro-taxis (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.

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^{0C} and samples are taken at different times and the free drug is separated by mini column centrifugation. The amount of drug released is then calculated indirectly from the amount of drug entrapped at zero times as the initial amount (100% entrapped and 0% released). [18]

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 hairswere 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 $0\text{-}40^0$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 ± 0.5^0C 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.

Physical stability:
The initial percentage of the drug entrapped in the formulation was determined and were stored in sealed glass ampoules. The ampoules were placed at 4 ± 2^0C months. Samples from each ampoule were analyzed after 30 days to determine drug leakage. Percent drug lose was calculated by keeping the initial entrapment of drug as 100%. [19]

***In Vivo* Fate of Transfersomes and Kinetics of Transfersomes Penetration:**
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 favorable 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 anesthesia 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 6hr. depending on the details of drug formulation. Molecules that do not diffuse readily fromthe 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 extentby 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. [20]

Applications of Transfersome:

Delivery of Insulin:

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 transferosome (transfersulin) overcomes these entire problems. After transfers insulin application on the intact skin, the first sign of systemic hypoglycemia are observed after 90 to 180 min, depending on the specific carrier composition.

Delivery of Corticosteroids:

Transferosome improves the site specificity and overall drug safety of corticosteroid delivery into skin by optimizing the epicutaneously administered drug dose. Transferosome based corticosteroids are biologically active at dose several times lower than the currently used formulation for the treatment of skin diseases. [21]

Delivery of proteins and peptides:

Transfersomes have been widely used as a carrier for the transport of proteins and peptides also safely given by means of transfersome technology. Proteins and peptide has problem is, it is difficult to transfer into the body, are large biogenic molecules, GI tract degradation is problem arise when given orally. That's the reason why these peptides and proteins still given by means of injectables. A number of approaches have been developed to improve this condition. Transfersome is somewhat identical to that resulting from subcutaneous injection of protein suspension in terms of bioavailability. On repeated epicutaneous application, transfersome preparation of protein also induced a strong immune response. For example, the adjuvant immunogenic serum albumin in transfersomes, after several dermal challenges, is as active immunologically as is the corresponding injected proteo-transfersomes preparations.

Delivery of interferon (INF):

INF also delivered using transfersome as a carrier, for example, leukocyte-derived INF-α is a naturally occurring protein having antiviral, antiproliferative, 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 transfersome containing interleukin-2 (IL-2) and INF-α for potential transdermal application. They reported delivery of IL-2 and INF-α promising by transfersomes insufficient concentration for immunotherapy. [22]

Delivery of Anticancer Drugs:

Anti-cancer drugs like methotrexate were tried fortransdermal delivery using transfersome technology. The results were favorable. This provided a newapproach for treatment especially of skin cancer.

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 paininsensitivity is nearly as strong (80%) as that of a comparable subcutaneous bolus injection, but the effect of transferosomal anesthetics last longer.

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.

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. [23,24]

Future direction:

No drug delivery system has been perfected in a single step. Likewise, the Transfersome® technology is expected to evolve further. This relates to potential use of self-regulating, ultra deformable carriers in devices (patches; electrically controlled percutaneous reservoirs), and in design of formulation with additional special features, allowing, e.g., targeting of cellular subsets. The nearest term goal that remains to be reached is expansion of the positive experiences with NSAID targeting into peripheral tissues to other drugs with similar therapeutic demands.

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 cm2h-1). The systemic drug availability thus mediated is frequently higher than, or at least approaches 80-90%. The biodistribution 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.

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Competing Interests:

The all authors declared that no conflict of interest.

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