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A REVIEW ON TRANSFERSOMES

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Abstract:
Among the various drug delivery systems, transdermal drug delivery plays an important role. Iontophoresis, electrophoresis, sonophoresis, chemical permeation enhancers, microneedles, and vesicular constructs are different methods which supports transdermal drug delivery. Vesicular constructs includes liposomes, niosomes, virosomes, ethosomes and transfersomes. The transfersomal drug delivery system was much more efficient among all these types. Transfersomes can pass through narrow constriction of 5 to 10 times less than their own diameter, without any measurable drug loss. The transfersomal drug delivery system can be evaluated by in vitro for vesicle shape and size, entrapment efficiency, degree of deformability and number of vesicles. The deformability characteristic of transfersomes gives better drug permeability. They can act as a carrier for both low and high molecular weight drugs like insulin analgesics, anaesthetics, sex hormones, corticosteroids, etc.
Keywords: *Transfersomes, skin permeability, Thin film hydration technique*

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INTRODUCTION:

The term transferosome 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]. The underlying concept of transfersome was introduced in 1991 by Gregor Cevc. A transfersome is a highly adaptable and stress-responsive, complex aggregate, which is an ultra deformable vesicle 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-optimising. This helps the transfersome to cross various transport barriers efficiently. The transfersomal drug delivery system act as a drug carrier for non-invasive targeted drug delivery and sustained release of therapeutic agents, thus promising a convenient and safe drug delivery [2].

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 [3]. 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 [4].

Transfersomes were developed in order 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 with high efficiency either into or through the skin, depending on the choice of administration or application. 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 [5]. 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 nonocclusive condition.

Transfersomes can penetrate the intact stratum corneum spontaneously along two routes in the intracellular lipid that differ in their bilayers properties. The figure 1 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 [6]. 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.

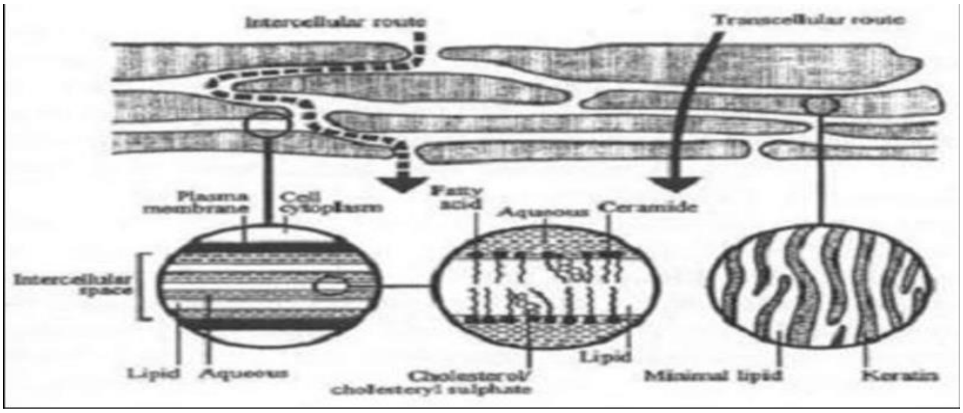

Fig 1: Schematic diagram of the two microroutes of penetration.

Features of transfersomes

The structure of transfersomes consists of both hydrophobic and hydrophilic moieties which results to accommodate drug molecules with wide range of solubility as shown in fig 2. 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 [7].

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 [8]. 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 [9].

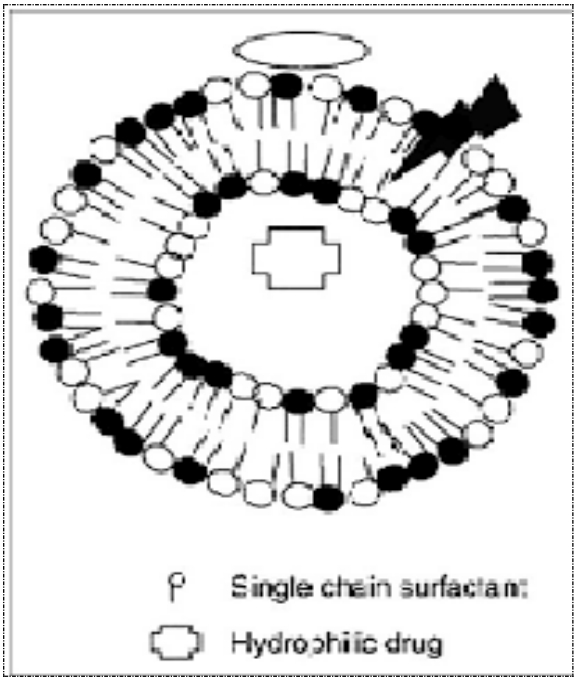

Fig 2: Structure of a transfersome

Human skin - Anatomy and Physiology

The skin is an important organ covers the entire external surface of the human body and it serves as a protective barrier that prevents internal tissues. Skin is a dynamic organ that undergoes continuous changes throughout life as outer layers are shed and replaced by inner layers. Skin also varies in thickness among anatomic location, sex, and age of the individual.

The skin is continuous, with the mucous membranes lining the body surface. The skin of an average adult body covers a surface area of approximately 2 m^2 and receives about one third of the blood circulating through the body and serves as a permeability barrier against the transdermal absorption of various chemical and biological agent. The skin separates the underlying blood circulation network from the outside environment. It serves as a barrier against physical, chemical and microbiological attacks. It acts as a thermostat in maintaining body temperature. It plays an important role in the regulation of blood pressure and protects the human body against the penetration of UV rays. Skin is the major factor in determining the permeation and absorption of drug across the dermis [10].

The structure of the skin is indicated by three distinct layers:

- The epidermis is the outermost layer of skin, which provides a waterproof barrier and creates our skin tone.
- The dermis is below the epidermis, which contains tough connective tissue, hair follicles, and sweat glands.
- The deeper subcutaneous tissue (hypodermis) is made of fat and connective tissue.

The epidermis is derived primarily from surface ectoderm but contains melanocytes are of neural crest origin, antigen-processing Langerhans cells of bone marrow origin, and pressure-sensing Merkel cells of neural crest origin. The dermis is derived primarily from mesoderm and contains collagen, elastic fibers, blood vessels, sensory structures, and fibroblasts (Figure 3).

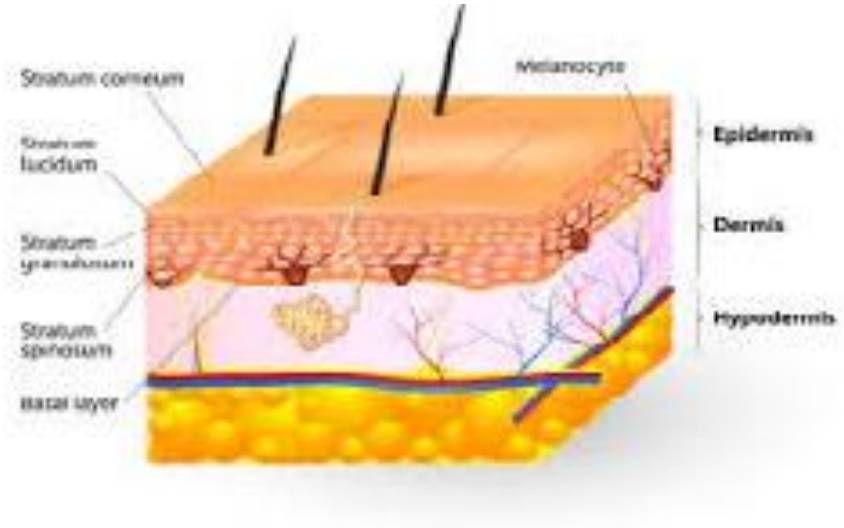

Fig. 3: Three layers of the skin.

Subcutaneous fat layer

The subcutaneous fat layer or hypodermis, bridges between the overlying dermis and the underlying body constituents. In most areas of the body this layer is relatively thick, typically in the order of several millimetres. This layer of adipose tissue principally serves to insulate the body and to provide mechanical protection against physical shock. The subcutaneous fatty layer can also provide a readily available supply of high-energy molecules, whilst the principal blood vessels and nerves are carried to the skin in this layer.

Dermis

The dermis has numerous structures embedded within it: blood and lymphatic vessels, nerve endings, pilosebaceous units like hair follicles and sebaceous glands and sweat glands like eccrine and apocrine. It provides physiological support for the epidermis. It is typically 3–5 mm thick and is the major component of human skin. It is composed of a network of connective tissue, predominantly collagen fibrils providing support and elastic tissue providing flexibility, embedded in a mucopolysaccharide gel. In terms of transdermal drug delivery, this layer is often viewed as essentially gelled water and thus provides a minimal barrier to the delivery of most polar drugs, although the dermal barrier may be significant when delivering highly lipophilic molecules [11].

Epidermis

The epidermis is composed of 10–20 layers of cells. This pluristratified epithelium also contains melanocytes involved in skin pigmentation, and Langerhans' cells, involved in antigen presentation and immune responses. The epidermis, as for any epithelium, obtains its nutrients from the dermal vascular network.The epidermis is further classified into a number of layers. The stratum germinativum is the basal layer of the epidermis. Above the basal layer are the stratum spinosum, the stratum granulosum, the stratum lucidum and finally, the stratum corneum.

Stratum Corneum

The stratum corneum is a 10–20 μm thick, multilayer stratum of flat, polyhedral-shaped, 2 to 3 μm thick, non-nucleated cells named corneocytes. Corneocytes are composed primarily of insoluble bundled keratins surrounded by a cell envelope stabilized by cross-linked proteins and covalently bound lipids. Corneodesmosomes are membrane junctions connecting corneocytes and contributing to stratum corneum cohesion. The intercellular space between corneocytes is composed of lipids primarily generated from the exocytosis of lamellar bodies during the terminal differentiation of the keratinocytes. These lipids are required for a competent skin barrier function.The main source of resistance to penetration and permeation through the skin is the stratum corneum.

In the simplest sense, therefore, the skin may be represented as a bilaminated membrane; and to reach the dermal vasculature (and rapid systemic distribution), a penetrating molecule must traverse both, the lipophilic environment of the stratum corneum and the aqueous environment of the underlying viable epidermis and upper dermis.

Mechanism of action of transfersomes

The carrier aggregate is composed of one amphipathic polymer like phosphatidylcholine, which self-assembles in aqueous solvents into lipid bilayer that closes into a simple lipid vesicle. On addition of

a bilayer softening component like biocompatible surfactant or an amphiphile drug, lipid bilayer flexibility and permeability are increased. The resulting 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 4. Transfersome differs from other conventional vesicles by its softer, more deformable, and better adjustable artificial membrane [12].

Transfersomes has a beneficial consequence of strong bilayer deformability is the increased affinity to bind and retain water. An ultra deformable and highly hydrophilic vesicle always seeks to avoid dehydration; this may involve a transport process related to but not identical with forward osmosis. For example, a transfersome vesicle applied on an open biological surface, such as non-occluded skin, tends to penetrate its barrier and migrate into the water-rich deeper strata to secure its adequate hydration. Barrier penetration involves reversible bilayer deformation, but must not compromise unacceptably either the vesicle integrity or the barrier properties for the underlying hydration affinity and gradient to remain in place. Since it is too large to diffuse through the skin, the transfersome needs to find and enforce its own route through the organ.

The transfersome vesicles helps the carrier's ability to widen and overcome the hydrophilic pores in the skin or some other (e.g. plant cuticle) barrier. The subsequent, gradual agent release from the drug carrier allows the drug molecules to diffuse and finally bind to their target. Drug transport to an intracellular action site may also involve the carrier's lipid bilayer fusion with the cell membrane unless the vesicle is taken up actively by the cell in the process called endocytosis.

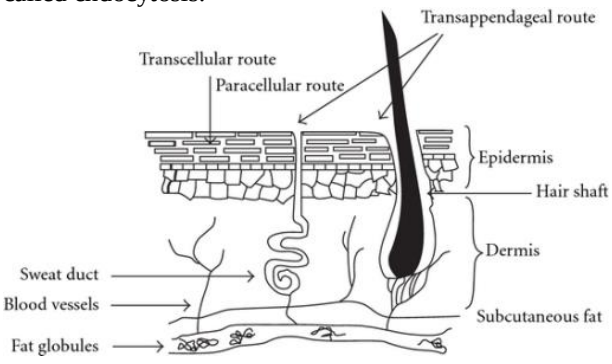

Fig 4: Diagrammatic representation of the intercellular and transcellular routes of penetration.

Materials and methods

Materials which are widely used in the formulation of transfersomes are various phospholipids, surfactants, alcohol, dye, buffering agent etc. Phospholipids, the vesicles forming agents, used are Soya phosphatidylcholine, egg phosphatidylcholine, dipalmitoyl phosphatidylcholine, etc.Some of the surfactants used for providing flexibility are sodium cholate, sodium deoxycholate, Tween-80, Span-80, etc. Solvents like ethanol or methanol can be used. Saline phosphate buffer (pH 6.4) is used as hydrating medium [13].

Preparation of Transfersomes

a) 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 [14].

b) Modified hand shaking method:

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. 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 performed for entrapment efficiency, vesicle diameter, number of vesicles per mm, degree of deformability or permeability measurement, turbidity measurement, surface charge and charge density, penetration ability, in vitro drug release and in vivo fate of transfersomes and kinetics of transfersomes penetration [15].

Entrapment efficiency

Entrapment efficiency was determined by first separation of the unentrapped drug by use of mini-column centrifugation method. After centrifugation,

the vesicles were disrupted using0.1% 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.

Number of vesicle per cubic mm

For calculation of number of vesicles per mm transfersome 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

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 are measured using nephelometer.

Surface charge and charge density

Surface charge and charge density of transfersomes are determined using zeta sizer.

Penetration ability

Penetration ability of transfersomes 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 cm^2 was used for this study. In vitro drug study was performed by using goat skin in phosphate buffer solution (pH 7.4). To perform skin permeation study, treated goat 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 2.50 cm^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. The samples were analyzed by any instrumental analytical technique.

In vivo fate of transfersomes and kinetics of transfersomes penetration

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 passage. The most important single factors in this process are carrier in-flow, carrier accumulation at the targets site and 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 or water activity gradient. The rate of carrier passage across the skin is chiefly determined by the activation energy for the carrier deformation.

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.

Application of Transfersomes

- Encapsulation of insulin into transfersomes (transfersulin) overcomes the problem of inconvenience of administration by subcutaneous route [16].
- Transfersomes based corticosteroids are biologically active at dose several times lower than the currently used formulation for the treatment of skin diseases.
- The transfersomal preparations of the protein induced strong immune response after the repeated epicutaneous application, for example the adjuvant immunogenic serum albumin in transfersomes, after several dermal challenges, was active immunologically.
- Transfersomes as drug delivery systems have the potential for providing controlled release of the administered drug and increasing the stability of labile drugs like interleukin-2 and interferone-α.
- The anti-cancer drug, methotrexate, when tried for transdermal delivery using transfersomes technology, produced favourable results [17].
- The effect of transfersomes induced anaesthetics lasted longer when compared to conventional vesicles.
- Ketoprofen, an NSAID, in a transfersomes formulation gained marketing approval by the Swiss regulatory agency (Swiss Medic) in 2007.
- The transfersomes of capsaicin has been reported to show better topical absorption in comparison to pure capsaicin.

Future of transfersomes

Since transfersomes can pass through narrow constriction of the skin without any measurable loss they are unique systems. They can be produced synthetically and in large quantities. Since well-characterized transfersomes are available surge of activities, they can be performed in developing a pharmaceutically-acceptable transdermal drug carrier. Numerous clinical trials are ongoing in the designing and development of transfersomes as drug delivery systems.

CONCLUSION:

Transfersomes are potential carriers of various drugs that could be used for therapeutic applications. There are many factors which contribute to their success as drug delivery vehicles. The highly deformable particles can be used to bring drugs across the biological permeability barriers using transfersomes. The drugs, like insulin, which are difficult to administer by conventional dosage form can be administered as transfersomes. They easily pass through the skin making ease the drug delivery. By slowly releasing the drug in the body, transfersomes can prolong the drug action. 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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