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Review Article

A NARRATIVE REVIEW ON TRANSFERSOMES: VESICULAR TRANSDERMAL DELIVERY SYSTEM FOR ENHANCED DRUG PERMEATION

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ABSTRACT

Transdermal administration of drug is generally limited by the barrier function of the skin vascular system are one of the most controversial method for transdermal delivery of active substance. transdermal drug delivery system is designed to deliver biological active agents through the skin, principally by diffusion for local internal if not systemic effects. The transdermal delivery system was relaunched after the discovery of elastic vesicles like transfersome, ethosome, cubosome, phytosome etc. Transfersomes are a form of elastic or deformable vesicle, which were introduced in the early 1990s. Elasticity is generated by incorporation of edge activator in lipid bilayer structure. Drug absorbed and distributed into organs and tissue and eliminated from the body it must pass through one or more biological membranes at various locations such movement of drug across the membrane is called as drug transport for the drug delivery to cross the body it should pass through the membrane barrier. This concept of drug delivery system was designed in attempt to concentrate the amount of drug in the remaining drug; therefore, the phospholipid-based carrier system is of considerable interest in the era.

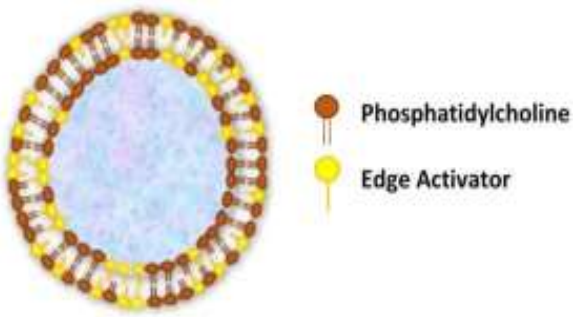
KEYWORDS: Transfersome, vesicles, Lecithin, Surfactant, membrane barrier.

INTRODUCTION

Since the last few years, the vesicular systems have been promoted as a mean of sustained or controlled release of drugs. The word “transfersome” and the underlying concepts were introduced in 1991 by Gregor Cevc. The name Transfero‟ is derived from the Latin word meaning to carry across and the Greek word „soma‟ for a body[1]. A transfersome is a highly adaptable and stress-responsive, complex aggregate. Its preferred form is an ultra-deformable vesicle possessing an aqueous core surrounded by the complex lipid bilayer. Vesicles are water-filled colloidal particles. The walls of these capsules consist of amphiphilic molecules (lipids and surfactants) in a bilayer conformation[2]. These vesicles serve as a depot for the sustained release of active compounds in the case of topical formulations, as well as rate-limiting membrane barrier for the modulation of systemic absorption in the case of transdermal formulations[3]. Transfersomes consist of a phospholipid’s component along with a surfactant mixture. The ratio of individual surfactants and total amount of surfactants control the flexibility of the vesicle. The uniqueness of this type of drug carrier system lies in the fact that it can accommodate hydrophilic, lipophilic as well as amphiphilic to drugs[4].

Transfersomes are applied in a non-occluded method to the skin and have been shown to permeate through the stratum corneum lipid lamellar regions as a result of the hydration or osmotic force in the skin. Transfersomes can deform and pass-through narrow constriction (from 5 to 10 times less than their own diameter) without measurable loss. Transfersomes can pass through even tiny pores (100mm) nearly as efficiently as water, which is 1500 times smaller[1].The transdermal route of drug delivery has gained great interest in pharmaceutical research, as it circumvents a number of problems associated with the oral route of drug administration. Recently, various strategies have been used to augment the transdermal delivery of bioactives. Mainly, they include electrophoresis, iontophoresis, chemical permeation enhancers, microneedles, sonophoresis, and vesicular systems like liposomes, niosomes, elastic liposomes such as ethosomes and Transfersomes. Among these strategies Transfersomes appear promising. A novel vesicular drug carrier system called Transfersomes, which is composed of phospholipid, surfactant, and water for enhanced transdermal delivery. Transfersomes are a form of elastic or deformable vesicles, which were first introduced in the early 1990s[5,6]. Transfersomes can penetrate the intact stratum corneum spontaneously along two routes in the intracellular lipid that differ in their bilayers properties[5]. The following figure shows possible micro routes for drug penetration across human skin intracellular and transcellular[7]. 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[8,9]. They also contain fewer double bonds than lecithin and, therefore, are less subjected to rancidity. For bilosomes, they are vesicles composed of nonionic

surfactants and bile salts (bile salts are incorporated into the niosome's membrane), which are considered as non-lipoidalbio carriers. These novel vesicles were developed for the purpose of vaccine oral delivery due to its resistance towards the enzymes and bile salts in the gastrointestinal tract. Bile salts are considered as endogenous surfactants that are comprehensively used as absorption enhancers to improve the drug permeation across biological membranes.



Transdermal drug delivery systems use the skin as the drug administration site. The administered drug is absorbed into the systemic circulation via blood vessels in the skin and then circulates around the body

ADVANTAGES OF VESICULAR SYSTEMS

- Liposomes: -Phospholipid vesicle, biocompatible, biodegradable.
- Proliposome: -Phospholipid vesicle, more stable than liposome.
- Niosomes: -Non-ionic surfactant vesicles
- Proniosomes: - Convert to stable niosomal in situ
- Protransfersomes: -High deforming ability which ensures deeper penetration in skin layers.
- Colloidosomes: - Can withstand high mechanical load.
- Cubosomes: -Targeted and controlled release of materials in a biodegradable manner[10].

DISADVANTAGES OF VESICULAR SYSTEM

- Liposomes: -Less skin penetration, less stable
- Proliposome: -Less penetration, cause aggregation and fusion of vesicles
- Niosomes: -Less skin penetration easy handling
- Proniosomes: -Cannot reach in the deeper layers of the skin
- Colloidosomes: -Insufficient locking of drug can lead to coalescence
- Cubosomes: -No disadvantage as such is reported[10].

MECHANISM OF TRANSFERSOMES

Transfersomes overcome skin penetration difficulty by squeezing themselves along the intracellular sealing lipids of the 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[11,12]. Transfersomes act as drug vectors, remaining intact after entering the skin. Transfersomes act as penetration enhancers, disrupting the highly organized intercellular lipids from stratum corneum and therefore facilitating the drug molecules penetration in and across the stratum corneum. The Transfersomes vesicles usage in drug delivery consequently relies on the carrier's ability to widen and overcome the hydrophilic pores in the skin. Intracellular drug transportation may involve diffusion of vesicle lipid bilayer with the cell membrane like normal endocytosis. The mechanism is this complex and involves advanced principles of mechanics combined with material transport and hydration/osmotic force. Possible pathways for penetrant to cross the skin barrier[1]. Across the intact horny layer[2], Through the hair follicles with the associated sebaceous glands[3], or Via the sweat glands.

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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:

• Carrier in-flow
• Carrier accumulation at the targets site
• 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 transcutaneous 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.

COMPOSITION OF TRANSFERSOMES

Transfersomes are ultradeformable vesicles possessing an aqueous core surrounded by the complex lipid bilayer. Transfersomes possess an infrastructure consisting of hydrophobic and hydrophilic moieties together and as a result can accommodate drug molecules with wide range of solubility[13]. Transfersomes can deform and pass-through narrow constriction (from 5 to 10 times less than their own diameter) without measurable loss. The transfersome is composed of two main aggregates namely. Firstly, an amphipathic ingredient (phosphatidylcholine), in which the aqueous solvents self-assemble into lipid bilayer that closes into a simple lipid vesicle. Secondly, a bilayer softening component (such as a biocompatible surfactant or amphiphile drug) that increases lipid bilayer flexibility and permeability. They differ from liposomes because of the presence of so-called edge-activators, and comprise phospholipids as the main ingredient with 10-25% surfactant (e.g. sodium cholate) and 3-10% ethanol. The surfactants are the "edge activators", which confer ultra-deformability on the transfersomes. The elasticity of the vesicle is correlated with the quantity and the structure of the incorporated surfactant. In comparison with liposomes, it has been claimed that transfersomes are able to deliver their "payload" deeper into the skin. The carrier aggregate is composed of at least one amphipathic (such as phosphatidylcholine), which

in aqueous solvents self-assembles into a lipid bilayer that closes into a simple lipid vesicle. By addition of at least one bilayer softening component (such as a biocompatible surfactant or an amphiphile drug) lipid bilayer flexibility and permeability are greatly increased. The resulting, flexibility and permeability optimized, 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. In its basic organization broadly similar to a liposome), the Transfersome thus differs from such more conventional vesicle primarily by its "softer", more deformable, and better adjustable artificial membrane.

PROPENSITY OF PENETRATION

Since Transfersomes is too large to diffuse through the skin, the Transfersome needs to find and enforce its own route through the organ. The magnitude of the transport driving force, can be calculated by: Flow = Area x (Barrier) Permeability x (Trans-barrier) force. Therefore, the chemically driven lipid flow across the skin always decreases dramatically when lipid solution is replaced by some amount of lipids in a suspension[14].

METHOD OF PREPARATION OF TRANSFERSOMES

A. Thin film hydration technique is employed for the preparation of transfersomes which consist 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 500C for dipalmitoylphosphatidyl choline) using rotary evaporator. Final traces of solvent were removed under vacuum for overnight.
2. A prepared thin film is hydrated with a buffer (pH 6.5) by rotation at 60 rpm for 1 hr at the corresponding temperature. The resulting vesicles were swollen for 2 hours at room temperature.
3.To prepare small vesicles, resulting vesicles were sonicated at room temperature or 500C for 30 min. using a bath sonicator or probe sonicated at 40C 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

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

STABILITY OF TRANSFERSOMES

Transfersomes are chemically unstable because of their predisposition to oxidative degradation. Purity of natural phospholipids is another criterion militating against adoption of Transfersomes as drug delivery vehicles.

CHARACTERIZATION OF TRANSFERSOMES

Determination of Entrapment Efficiency (EE %) One milliliter of MIC Transfersomes suspension was centrifuged at 15.000 rpm for 1 h to allow the separation of the entrapped drug from the un-entrapped drug. After removal of the supernatant, the sediment was lysed using methanol and then analyzed spectrophotometrically at 272 nm using a UV spectrophotometer, (Shimadzu, Kyoto, Japan)[15].

APPLICATIONS OF TRANSFERSOMES

Delivery of Insulin:

Insulin is generally administered by subcutaneous route that is inconvenient. Encapsulation of insulin into transfersomes (transfersulin) overcomes the problems of inconvenience, larger size (making it unsuitable for transdermal delivery using conventional method) along with showing 50% response as compared to subcutaneous injection[16].

Delivery of corticosteroids:

Transfersomes improves the site specificity and overall drug safety of corticosteroid delivery into skin by optimizing the epicutaneous 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[17].

Delivery of proteins and peptides:

Transfersomes have been widely used as a carrier for the transport of proteins and peptides. Proteins and peptides are large biogenic molecules which are very difficult to transport into the body, when given orally they are completely degraded in the GI tract and transdermal delivery suffers because of their large size[17].

Delivery of anticancer drugs:

Anti-cancer drugs like methotrexate were tried for transdermal delivery using transfersome technology. The results were favorable. This provided a new approach for treatment especially of skin cancer[17].

Delivery of anesthetics:

Transfersome based formulations of local anesthetics lidocaine and tetracaine showed permeation equivalent to subcutaneous injections, 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 transferosomal anesthetics last longer[17].

Delivery of herbal drugs:

Transfersomes can penetrate stratum corneum and supply the nutrients locally to maintain its functions resulting in maintenance of skin[17].

CONCLUSION

The use of the transdermal route has been well established in the past, and because of inherent advantage, new method for transdermal delivery is continuously being developed. It is clear that transfersome or elastic vesicle can deliver enhanced amount of both small and large therapeutic agents into and through the skin. they allow enhanced permeation of drug through skin. Their composition is safe, and the component are approved for pharmaceutical and cosmetic use, they can increase the transdermal flux, prolonging the release and improving the site specificity of bioactive molecules, they can accommodate drug molecule with a wide range of solubility the exact mechanism by which transport occurs remain to be elucidated and evidence for transport of intact vesicle beyond the stratum corneum is lacking. However, there are increasing application of enhanced delivery by elastic vesicle formulation that are being reported, with some product, such as transfersome, nearing the market.

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