

A REVIEW ON TRANSDERMAL DRUG DELIVERY SYSTEM: TRANSFERSOMES

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Abstract: Transdermal drug delivery systems have been used as safe and effective drug delivery devices. Their potential role in controlled release is being globally exploited by the scientists with high rate of attainment. With oral and parenteral drug delivery systems, poor patient compliance is a frequent problem observed in daily clinical practice. Transport of drug across the skin is best route of drug delivery, because the skin is largest human organ with total weight 3 kg and a surface of 1.5 - 2.0 m². But the big hurdle in transdermal delivery of drug is the skin, the stratum corneum, the outermost envelop of the skin. Transferosomes possess an infrastructure consists 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. Transferosomes penetrate through the pores of stratum corneum which are smaller than its size and get into the underlying viable skin in intact form due to 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. 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 hormones, anticancer, insulin, gap junction protein, and albumin. The present review highlights the advantages and disadvantages, formulation method, characterization, and therapeutic applications of transferosomes.

Index Terms: Transdermal, drug delivery device, Transferosomes, Phospholipids edge activator

I. INTRODUCTION

Transdermal drug delivery system are topically administered medicaments in the form of patches that deliver drugs for systemic effects at a predetermined and controlled rate. Transdermal drug delivery system has been in existence for a long time. In the past, the most commonly applied systems were topically applied creams and ointments for dermatological disorders. ¹ Transdermal drug delivery is the non-invasive delivery of medications from the surface of skin-the largest and most accessible organ of human body-through its layers, to the circulatory system. TDDS offers many advantages over conventional injection and oral methods. Transdermal delivery not only provides controlled, constant administration of the drug, but also allows continuous input of drugs with short biological half-lives and eliminates pulsed entry into systemic circulation. The term transferosomes and the underlying concept were introduced in 1991 by Gregor Cevc.² In broadest sense, a transferosome is a highly adaptable and stress-responsive, complex aggregate possessing an aqueous core surrounded by a complex of lipid bilayer. Interdependency of local composition and shape of the bilayer makes the vesicle both self-regulating and self-optimizing. This enables the transferosomes to cross various transport barriers efficiently, and act as a drug carrier for non-invasive targeted drug delivery and sustained release of therapeutic agents. 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, involving physiological response, avoiding the fluctuation in drug levels, inter- and intra-patient variations, and most importantly it provides patient convenience. Transferosomes have a unique structure which is capable of entrapping hydrophilic and lipophilic amphiphilic drugs. Vesicles are colloidal particles having a water filled core surrounded by a wall of lipids and surfactants (amphiphiles) arranged in bilayer. If the proportion of water is increased, these amphiphiles can form one or more concentric bilayers. Hydrophilic drugs find a place in the internal aqueous environment while amphiphilic, lipophilic drugs get entrapped in the bilayered wall with electrostatic and/or hydrophobic forces. The flexible or deformable vesicles are called elastic vesicles or transferosomes.

II. SALIENT FEATURES AND LIMITATIONS OF TRANSFERSOMES

Transferosomes possess an infrastructure consisting of hydrophobic and hydrophilic moieties together and as a result can accommodate drug molecules with wide range of solubility as shown in fig 1. Transferosomes 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. 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.⁴

III. LIMITATIONS OF TRANSFERSOMES

Transfersomes are chemically unstable because of their predisposition to oxidative degradation. Purity of natural phospholipids is another criteria militating against adoption of transfersomes as drug delivery vehicles. Transfersomes formulations are expensive.⁵

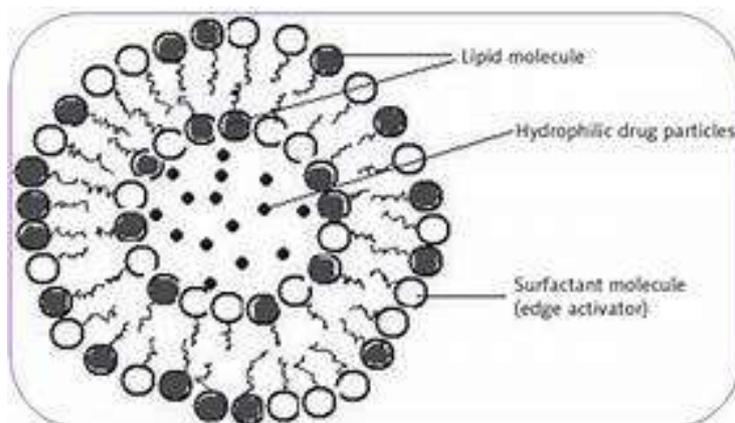


Fig 1. Transfersomes

IV. PREPARATION OF TRANSFERSOMES

Thin film hydration method

In this method a thin film is prepared from the mixture of vesicles forming ingredients that is phospholipids and surfactant by dissolving in volatile organic solvent (Chloroform-Methanol). Organic solvent is then evaporated above the lipid transition temperature or 50°C using rotary evaporator. Final traces of solvent were removed under vacuum for overnight. A prepared thin film is hydrated with buffer (pH 6.5) by rotation at 60 rpm for 1 hour at the corresponding temperature. The resulting vesicles were swollen for 2 hours at room temperature. To prepare small vesicles, resulting vesicles were sonicated at room temperature or 50°C for 30 min. using a bath sonicator or probe sonicated at 40°C for 30 min. The sonicated vesicles were homogenized by manual extrusion 10 times through a sandwich of 200 and 100 nm polycarbonate membranes.⁶

Composition of Transfersome

Materials which are widely used in the formulation of transfersomes are various phospholipids, surfactants, alcohol, dye, buffering agent etc.; different additives used in the formulation of transfersomes are summarized in Table No.1.⁷

Modified hand shaking, lipid film hydration technique

Drug, lecithin (PC) and edge activator were dissolved in ethanol: chloroform (1:1) mixture. Organic solvent was removed by evaporation while hand shaking above lipid transition temperature (43°C). A thin lipid film was formed inside the flask wall with rotation. The thin film was kept overnight for complete evaporation of solvent. The film was then hydrated with phosphate buffer (pH 7.4) with gentle shaking for 15 min at corresponding temperature. The transfersome suspension was further hydrated up to 1 hour at 2-80°C.⁸

V. CHARACTERIZATION

- Transmission electron microscopy (TEM) and scanning electron microscopy (SEM).
- Particle size and size distribution can be determined by dynamic light scattering (DLS) and photon correlation spectroscopy (PCS).
- The drug entrapment efficiency by transfersomes can be measured by the ultracentrifugation technique.⁹
- Vesicle stability can be determined by assessing the size and structure of the vesicles over time, and drug content can be quantified by high performance liquid chromatography (HPLC) or Spectrophotometric methods.
- In vitro drug release can be measured using a diffusion cell or a dialysis method.¹⁰

Table no 1: Different Additives Used in Formulation of Transfersomes

CLASS	EXAMPLE	USES
Phospholipids	Soya phosphatidyl choline, egg phosphatidyl choline, dipalmitoyl phosphatidyl choline	Vesicles forming component
Surfactant	Sod. cholate, Sod. deoxycholate, Tween-80, Span-80	For providing flexibility
Alcohol	Ethanol, methanol	solvent
Buffering agent	Saline phosphate buffer (pH 6.8)	A hydrating medium
Dye	Rhodamine-123 Rhodamine-DHPE Fluorescein-DHPE Nile-red	For CSLM study

VI. OPTIMIZATION OF FORMULATION CONTAINING TRANSFERSOMES:

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

The characterization of transferosomes is generally similar to liposomes, noisome and micelles.¹¹

Entrapment Efficiency

The entrapment efficiency is expressed as the percentage entrapment of the drug added. Entrapment efficiency was determined by first separation of the untrapped 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. ¹³

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. Transferosomes 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

Vesicle size distribution and zeta potential

Vesicle size, size distribution and zeta potential were determined by Dynamic Light Scattering Method (DLS) using a computerized inspection system by Malvern Zetasizer.¹⁵

Drug content

The drug content can be determined using one of the instrumental analytical methods such as modified high-performance liquid chromatography method (HPLC).¹⁶

Number of Vesicle per Cubic Mm

This is an important parameter for optimizing the composition and other process variables. Transferosome formulations (without sonication) can be diluted five times with 0.9% of sodium chloride solution and studied with optical microscopy by using hemocytometer.¹⁷

Turbidity measurement

Turbidity of drug in aqueous solution can be measured using nephelometer.¹⁷

Degree of deformability or permeability measurement

The permeability study is one of the important and unique parameters for characterization. The deformability study is done against the pure water as standard. Transferosomes preparation is passed through a large number of pores of known size. Particle size and size distributions are noted after each pass by dynamic light scattering (DLS) measurements.¹⁸

Confocal scanning laser microscopy study

Both the conventional light microscopy and electron microscopy techniques faces 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 transferosomes and the light emitted by these markers used for following purpose:¹⁹

- To investigate the mechanism of penetration of transferosomes across the skin.
- To determine histological organization of the skin (epidermal columns, interdigitation), shapes and architecture of the skin penetration pathways.
- To compare and differentiate the mechanism of penetration of transferosomes with liposomes, noisome and micelles.²⁰

Penetration ability

Penetration ability of transferosomes can be evaluated using fluorescence microscopy.

Surface charge and charge density

Surface charge and charge density of Transferosomes can be determined using zetasizer²²

VII. Mechanism of Penetration of Transferosomes.

Transferosomes, when applied under suitable condition, can transfer 0.1 mg of lipid per hour and square centimeter area across the intact skin. This value is substantially higher than that typically driven by the transdermal concentration gradients.²³ The reason for this high flux rate is naturally occurring “transdermal osmotic gradients”, i.e. another much more prominent gradient is available across the skin. This osmotic gradient that is developed due to the skin penetration barrier prevents water loss through the skin and maintains a water activity difference in the viable part of the epidermis (75% water content) and nearly completely dry stratum corneum near to the skin surface (15% water content). This gradient is very stable because ambient air is a perfect sink for the water molecule even when the transdermal water loss is unphysiologically high. All polar lipids attract some water. This is due to the energetically favorable interaction between the hydrophilic lipid residues and their proximal water. Thus, most lipid bilayers 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 (transferosome) is placed on the skin surface that is partly dehydrated by the water evaporation loss, the lipid vesicles feel this “osmotic gradient” and try to

escape complete drying by moving along this gradient.²⁴ They can only achieve this if they are sufficiently deformable to pass through the narrow pores in the skin because transferosomes composed of surfactant have more suitable rheological and hydration properties than that responsible for their greater deformability; less deformable vesicles including standard liposomes are confined to the skin surface, where they dehydrate completely and fuse, so they have less penetration power than the transferosome. Transferosomes are optimized in this respect and thus attain maximum flexibility, so they can take full advantage of the transepidermal osmotic gradient (water concentration gradient). Transferosomes overcome the skin penetration difficulty by squeezing themselves along the intracellular sealing lipids of stratum corneum.²⁵

Stability of Transferosomes

Transferosomes are chemically unstable because of their predisposition to oxidative degradation. Purity of natural phospholipids is another criterion militating against adoption of transferosomes as drug delivery vehicles. Transferosome formulations are expensive.²⁶

Applications of Transferosomes

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 transferosomes (transfersulin) overcomes these entire problems.²⁷ After Transfersulin application on the intact skin, the first sign of systemic hypoglycemia observed after 90 to 180 min, depending on the specific carrier composition.

Delivery of corticosteroids

Transferosomes have also used for the delivery of corticosteroids. Transferosomes improves the site specificity and overall drug safety of corticosteroid delivery into skin by optimizing the epicutaneously administered drug dose. Transferosomes based corticosteroids are biologically active at dose several times lower than the currently used formulation for the treatment of skin diseases.²⁸

Delivery of proteins and peptides

Transferosomes have been widely used as a carrier for the transport of proteins and peptides. Proteins and peptide are large biogenic molecules which are very difficult to transport into the body, when given orally they are completely degraded in the GI tract. These are the reasons why these peptides and proteins still have to be introduced into the body through injections. Various approaches have been developed to improve these situations. The bioavailability obtained from transferosomes is somewhat similar to that resulting from subcutaneous injection of the same protein suspension.²⁹ The transferosomal preparations of this protein also induced strong immune response after the repeated epicutaneous application.

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.³⁰

Delivery of Anticancer Drugs

Anti-cancer drugs like methotrexate were tried for transdermal delivery using transferosome technology.^{31,32} The results were favorable. This provided a new approach for treatment especially of skin cancer.

Future Perspectives

The high tolerability and efficiency of these vesicular systems open vast potential therapeutic uses. These nanocarriers might offer advanced local and systemic new therapies with agents that are unable to efficiently penetrate the stratum corneum via passive diffusion.³³ The non-steroidal anti-inflammatory drug (NSAID), ketoprofen, in a transferosome formulation gained marketing approval by the Swiss regulatory agency (Swiss Medic). The product is expected to be marketed under the trademark Diractin. Further therapeutic products based on the transferosome technology, according to IDEA AG, are in clinical development.³⁴

Conclusion

Transferosomes are highly significant in the design of transdermal drug delivery system because of their small size, greater penetration through stratum corneum and few systemic side effects.³⁵ Further research has to be carried out to minimize the side effects of drugs by avoiding fluctuations in drug levels. As seen, the effort to produce these new drug carrier systems is clearly high. Undoubtedly, those carriers provide the hope to treat and diagnose several diseases. Several technologies have advanced into clinical studies and are nowadays market products that have been shown favorable results.³⁶ The use of the transdermal route has been well established in the past, and because of its inherent advantages, new methods for transdermal delivery are continuously being developed.³⁸ The introduction of ultra-deformable vesicles, transferosomes, will thus surely become an important step in relaunching the researches regarding the use of vesicles as transdermal drug delivery systems.³⁹ In comparison to other transdermal delivery systems, the use of elastic vesicles has certain advantages: They allow enhanced permeation of drug through skin; their composition is safe and the components 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 molecules with a wide range of solubility. Hence, enhanced delivery of bioactive molecules through the skin by means of an ultra-deformable vesicular carrier opens new challenges and opportunities for the development of novel improved therapies.

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