

TRANSFEROSOME: THE DRUG LOADED ULTRADEFORMABLE VESICLES FOR TRANSDERMAL DRUG DELIVERY

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ABSTRACT

Now a days, The novel drug delivery system is creating a new interest in development of drug deliveries. Vesicular drug delivery system is also a part of this novel drug delivery system which is designed according to the recent demands of treatment like sustain release of drug in systemic circulation, definite dosing interval. Transferosomes are part of this vesicular drug delivery system which are altered deformable vesicles used to enhance skin penetration. It is also a controlled & targeted drug delivery system which is used to increase the existence of drug in systemic circulation & decrease the toxicity. Transferosomes are proposed for variety of applications in humans like as carrier for insulin & vaccines. In this review, we mainly focus on transferosome with its applications, limitations, advantages & preparation.

KEYWORDS: Transferosomes, Transdermal, Deformables,

INTRODUCTION

Transdermal drug delivery system is formulation that is applied to the body surface and is designed to deliver the active drug across the skin, into the systemic circulation.¹ 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,

Advantage Of Transdermal Drug Delivery

- ❖ Sustained delivery of drugs to provide a steady plasma profile, particularly for drugs with short half-lives, control input kinetics and hence reduced systemic side effects
- ❖ Reducing the typical dosing schedule to once daily or even once weekly
- ❖ Potential for improved patient compliance
- ❖ Avoidance of the first-pass metabolism effect for drugs with poor oral bioavailability
- ❖ Convenient, patient-friendly option for drug delivery with the potential for flexibility, easily allowing dose changes according to patient needs and the capacity for self-regulation of dosing by the patient
- ❖ TDD can be used in situations requiring minimal patient cooperation, that is, in situations involving administration of drugs by someone other than the patient
- ❖ The non-invasive character of TDD makes it accessible to a wide range of patient populations and a highly acceptable option for drug dosing.²

Limitations Of Transdermal Drug Delivery

- ❖ Possibility that a local irritation at the site of application
- ❖ Erythema, itching, and local edema can be caused by the drug, the adhesive, or other excipients in the patch formulation.³

Vesicular systems are gaining importance recently owing to their ability to act as a means of sustained release of drugs. These systems have several advantages: they can encapsulate both hydrophilic and lipophilic moieties, prolong half lives of drugs by increasing duration in systemic circulation due to encapsulation, ability to target organs for drug delivery, biodegradability, and lack of toxicity. Vesicles have a unique structure which is capable of entrapping hydrophilic, lipophilic, amphiphilic and charged hydrophilic 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.⁴

Transferosomes were developed by Ceve and coworkers in 1992. Transferosomes are modified liposomes i.e. they are liposomes with edge activators. They are ultra-deformable up to 105 times that of an unmodified liposome. Transferosome 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. The name means carrying body, and is derived from the Latin word 'transferre', meaning 'to carry across', and the Greek word soma, for a body. A Transferosome carrier is an artificial vesicle and resembles the natural cell vesicle. Thus it is suitable for targeted and controlled drug delivery. In functional terms, it may be described as lipid droplet of such deformability that permits its easy penetration through the pores much smaller than the droplets size. When applied to the skin, the carrier searches and exploits hydrophilic pathways or 'pores' between the cells in the skin, which it opens wide enough to permit the entire vesicle to pass through together with its drug cargo, deforming itself extremely to accomplish this without losing its vesicular integrity. Transferosome penetrate the stratum corneum by either intracellular route or the transcellular route.⁵

Silent features and Limitations of Transferosomes

Silent Features

Transferosomes possess an infrastructure consisting of hydrophobic and hydrophilic moieties together and as a result can accommodate drug molecules with wide range of solubility. Transferosomes can deform and pass through narrow constriction (from 5 to 10 times less than their own diameter) without measurable loss. This high deformability gives better penetration of intact vesicles. They can act as a carrier for low as well as high molecular weight drugs e.g. analgesic, 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. 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 of pharmaceutically unacceptable additives.⁶

Limitations Of Transferosomes

Transferosomes 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.⁷

Propensity of penetration

The magnitude of the transport driving force, of course, also plays an important role: $\text{Flow} = \text{Area} \times (\text{Barrier}) \text{ Permeability} \times (\text{Trans-barrier}) \text{ force}$. Therefore, the chemically driven lipid flow across the skin always decreases dramatically when lipid solution is replaced by the same amount of lipids in a suspension.⁸

Mechanism of Penetration of Transfersomes

Transfersomes when applied under suitable condition can transfer 0.1 mg of lipid per hour and 2 cm area across the intact skin. This value is substantially higher 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, 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 favourable interaction between the hydrophilic lipid residues and their proximal water. Most lipid bilayers thus spontaneously resist an induced dehydration.⁹

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 (transfersome) 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. 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 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 transfersome. Transfersomes are optimized in this respect and thus attain maximum flexibility, so they can take full advantage of the transepidermal osmotic gradient (water concentration gradient). Transfersomes overcome the skin penetration difficulty by squeezing themselves along the intracellular sealing lipids of stratum corneum.¹⁰

Composition of Transfersomes

Transfersomes are composed of phospholipids like phosphatidyl choline which self assembles into lipid bilayer in aqueous environment and closes to form a vesicle. A bilayer softening component (such as a biocompatible surfactant or an amphiphile drug) is added to increase lipid bilayer flexibility and permeability. This second component is called as edge activator 18, 21, 22. An edge activator consists usually of single chain surfactant that causes destabilization of the lipid bilayer thereby increasing its fluidity and elasticity.

The newer elastic vesicles were introduced by Van den berg in 1998, consisting of non ionic surfactant as the edge activator 23. Flexibility of transfersomes membrane can be altered by mixing suitable surface active agents in the proper ratios. The resulting, flexibility and permeability optimized, Transfersome vesicle can therefore adapt its shape to surrounding stress easily and rapidly, by adjusting local concentration of each bilayer component to the local stress experienced by the bilayer. This flexibility also 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 non occlusive condition.¹¹

Preparation of Transfersomes

Various published and patented procedure are available for the preparation of transfersome. Generally phosphatidylcholine is mixed in ethanol with sodium cholate or some other biocompatible surfactant. Subsequently a suitable buffer is added to yield a total lipid concentration of 10% w/w. the suspension is then sonicated, frozen, and thawed 2-3 times to catalyze vesicle growth and is finally brought to the preferred vesicle size by pressure homogenization, ultrasonication, or some other mechanical method. Final vesicle size, as determined dynamic light scattering, is approximately 120 nm for a typical transfersome preparation containing 8.7% by weight SPC, 1.3% by weight sodium cholate, and up to 8.5% by volume ethanol. The best carrier composition has to be found experimentally and for each drug separately to obtain appropriate transfersome carriers with maximum deformability and stability. There are some additives which are used are mentioned in Table.1¹³

Characterization of Transfersomes

The characterization of transfersomes is generally similar to liposomes, niosomes and micelles which is shown in Table.2:

Application of Transfersomes

Transfersomes 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 transfersomes is some what similar to that resulting from subcutaneous injection of the same protein suspension. The transfersosomal preparations of this protein also induced strong immune response after the repeated epicutaneous application, for example the adjuvant immunogenic bovine serum albumin in transfersomes, after several dermal challenges is as active immunologically as is the corresponding injected proteo-transfersomes preparations.

Delivery of insulin by transfersomes is the successful means of non invasive therapeutic use of such largemolecular weight drugs on the skin. Insulin is generally administered by subcutaneous route that is inconvenient. Encapsulation of insulin into transfersomes (transfersulin) overcomes these entire problems. After transfersulin application on the intact skin, the first sign of systemic hypoglycemia are observed after 90 to 180 min, depending on the specific carrier composition.

Transfersomes 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. 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 interleukin-2 and interferone- α containing transfersomes for potential transdermal application .they reported delivery of IL-2 and INF- α trapped by transfersomes in sufficient concentration for immunotherapy.

Another most important application of transfersomes is transdermal immunization using transfersomes loaded with soluble protein like integral membrane protein, human serum albumin, gap junction protein. These approach offers at least two advantages, first they are applicable without injection and second, they give rise to rather high titer and possibly, to relatively high IgA levels. Transfersomes have also used for the delivery of corticosteroids. Transfersomes

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

Application of anesthetics in the suspension of highly deformable vesicles, transfersomes, induces a topical anesthesia, under appropriate conditions, with less than 10 min. Maximum resulting pain insensitivity is nearly as strong (80%) as that of a comparable subcutaneous bolus injection, but the effect of transfersosomal anesthetics last longer. Transfersomes has also been used for the topical analgesics, anaesthetics agents, NSAIDS and anti-cancer agents.¹⁸

CONCLUSION

Transdermal drug delivery system is frequently used due to its advantage over other routes drug delivery but the penetration of stratum corneum is a rate limiting step, it's major limitations like it can not able to transport the larger size molecule. That is why vesicular system like Transfersomes are developed to overcome these limitations. The elastic vesicles deform themselves to penetrate the skin through pores. It is more efficient & safer in composition then others. In This type of delivery, Drug release can also be controlled according to the requirement. Thus, this approach can overcome the problems which occurs in conventional techniques.

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Table:1. DIFFERENT ADDITIVES USED IN FORMULATION OF TRANSFERSOME¹³

Class	Examples	Uses
Phospholipids	Soya phosphatidylcholine Dipalmitoyl phosphatidylcholine Distearoyl phosphatidylcholine	Vesicles forming component
Surfactants	Sod. Cholate Sod. deoxycholate Tween-80 Span-80	For providing flexibility
Alcohol	Ethanol Methanol	As a solvent
Dyes	Rhodamine-123 Rhodamine-DHPE Fluorescein-DHPE Nilered	For CSLM study
Buffering Agent	Saline phosphate buffer	As a hydrating medium

Table:2. CHARACTERIZATION OF TRANSFERSOMES

Parameters	Methods
1. Vesicle Shape ¹⁴	A. Transmission Electron Microscopy
2. Entrapment Efficiency ¹⁵	B. Mini Column Centrifugation Method
3. Vesicle Size & Size Distribution ¹⁶	C. Dynamic Light Scattering Method
4. Skin Permeation Potential ¹⁰	D. Confocal Laser Scanning Microscopy Florescence Microscopy Transmission Electron Microscopy Thin Layer Chromatography
5. Phospholipid Surfactant Interaction ¹⁰	E. NMR
6. Degree Of Deformatity ¹⁰	F. Differential Scanning Calorimeter
7. Surface Charge & Charge Density ¹⁰	G. Extrusion Method
8. Terbitudy ¹⁷	H. Zeta Meter
9. In Vitro Drug Release Study ¹⁷	I. Nephelometer
10. Effect On The Skin Structure ¹⁷	J. Dialysis Bag Diffusion
11. Stability Study ¹⁷	K. Histological Study Transmission Electron Microscopy Dynamic Light Scattering Method Transmission Electron Microscopy

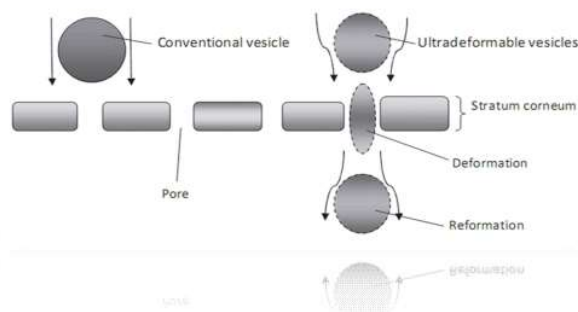


Fig.1.COMPARATIVE DIAGRAM OF TRANSPORT THROUGH CONVENTIONAL AND ULTRADEFORMABLE VESICLES¹²