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BRIEF COMMUNICATION

TRANSFERSOMES: PIVOTAL ROLE IN DRUG DELIVERY

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ABSTRACT

Background and Purposes:*There has been keen interest in the development of a novel drug delivery system. Novel drug delivery system aims to deliver the drug at a rate directed by the needs of the body during the period of treatment, and channel the active entity to the site of action. At present, no available drug delivery system behaves ideally achieving all the lofty goals, but sincere attempts have been made to achieve them through novel approaches in drug delivery. A number of novel drug delivery systems have emerged encompassing various routes of administration to achieve controlled and targeted drug delivery. Encapsulation of the drug in vesicular structures is one such system which can be predicted to prolong the existence of the drug in systemic circulation and reduce the toxicity, if selective uptake can be achieved. Advances have since been made in the area of vesicular drug delivery leading to the development of systems that allow drug targeting and the sustained or controlled release of conventional medicines. The focus of this review is to bring out the application, advantages, and drawbacks of vesicular systems. One of such vesicular system includes Transfersomes.*

Conclusion:*Transfersomes are complex most often vesicular aggregates optimized to attain extremely flexible and self-regulating membranes which make the vesicles very deformable. These systems can be successfully used in animals and humans for the transcutaneous and protein delivery.*

Key Words: *Transdermal, Vesicular, Transfersomes.*

INTRODUCTION

In the past few decades, considerable attention has been focused on the development of new drug delivery system (NDDS). The NDDS should ideally fulfill two prerequisites. Firstly, it should deliver the drug at a rate directed by the needs of the body over the period of treatment. Secondly, it should channel the active entity to the site of action. Conventional dosage forms, including prolonged release dosage forms, are unable to meet these. At present, no available drug delivery system behaves ideally, but sincere attempts have been made to achieve them through various novel approaches in drug delivery (1).

Different types of pharmaceutical carriers are present. They are - particulate, polymeric, macromolecular, and cellular carriers. The particulate type carrier, also known as a colloidal carrier system, includes lipid particles (low and high density lipoproteins-LDL and HDL, respectively), microspheres, nanoparticles, polymeric micelles and vesicular like liposomes, niosomes pharmacosomes, virosomes, etc (2-5). The vesicular systems are a highly ordered assemblies of one or several concentric lipid bilayers formed when certain amphiphilic building blocks are confronted with water. Vesicles can be formed from a diverse range of amphiphilic building blocks. Terms such as synthetic bilayers allude to the non-biological origin of such vesiculogenes. The biologic origin of these vesicles was first reported in 1965 by Bingham(6), and was given the name Bingham bodies. Much water has flown since then.

Transdermal drug delivery systems are topically administered medicaments in the form of patches that deliver drugs for systemic effects at a predetermined and controlled rate. As skin is the most extensive and readily accessible organ in the body, administration of drugs through the skin may have several advantages. But one major limitation of transdermal drug

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delivery is the low penetration rate of substance through the skin.

In order to overcome the poor skin penetration, recently various vesicular carrier systems like Transfersomes, liposomes and ethosomes have been reported to enhance the transdermal delivery of drugs when applied on to the skin non-occlusively. Cevc et.al. (7) first developed the concept of transfersomes as a carrier for transdermal drug delivery in 1992. During the last decade, many investigations have been carried out on Transfersomes and their possible applications as drug carriers.

Transfersomes: Edge over Liposomes & Niosomes

Liposomal as well as niosomal systems are not suitable for transdermal delivery because of their poor skin permeability, breaking of vesicles, leakage of drug, aggregation, and fusion of vesicles (8, 9). To overcome these problems, a new type of carrier system called "transfersome" which is capable of transdermal delivery of low as well as high molecular weight drugs has recently been introduced (10).

Transfersomes are especially optimized by ultradeformable (ultraflexible) lipid supramolecular aggregates which are able to penetrate the mammalian skin intact. Each transfersome consists of at least one inner aqueous compartment which is surrounded by a lipid bilayer with especially tailored properties due to the incorporation of "edge activators" into the vesicular membrane (11, 12).

Surfactants such as sodium cholate, sodium deoxycholate, span 80, and Tween 80, have been used as edge activators (13-15). It was suggested that transfersomes could respond to external stress by rapid shape transformations requiring low energy (16).

These novel carriers are applied in the form of semidilute suspension without occlusion. Due to their deformability, transfersomes are good candidates for the non-invasive delivery of small, medium, and large sized drugs. Multiliter quantities of sterile, well-defined transfersomes containing drug can be and have been prepared relatively easily.

Salient Features of Transfersomes *(16)*

1. Transfersomes possess an infrastructure consisting of hydrophobic and hydrophilic moieties together and as a result can accommodate drug molecules with a wide range of solubility.
2. They have higher entrapment efficiency that protects the encapsulated drug from metabolic degradation. Thus transfersomes act as depot. Releasing their content slowly and gradually they act as a carrier for low as well as high molecular weight drugs.
3. Transfersomes are biocompatible and biodegradable as they are made from natural phospholipids.
4. Transfersomes can easily pass through narrow constrictions without measurable loss due to their deformable nature. The deformability of vesicles membrane is responsible for its better skin penetration resulting in higher transdermal flux of encapsulated drug.
5. The preparation method for transfersomes is also simple and can be easily scaled up.

Advantages of Transfersomes *(16)*

1. More stable
2. High penetration due to high deformability
3. Biocompatible and biodegradable
4. High entrapment efficiency in case of lipophilic drug near to 90 %
5. Protect the encapsulated drugs from metabolic degradation
6. Can act as depot releasing their contents slowly and gradually
7. Suitable to carry both low / high molecular weight and hydrophilic/lipophilic drugs
8. Can easily reach the deeper skin layer
9. Can deform and pass through narrow constriction (5-10 times less than their own diameter) without measurable loss. This high deformability gives better penetration of intact vesicles.
10. Used for both systemic as well as topical delivery of drugs
11. Easy to scale up as procedure is simple, do not involve lengthy procedures and unnecessary use of pharmaceutically unacceptable additives.

Limitations *(16)*

1. Expensive
2. They are chemically unstable because of their pre-disposition to oxidative degradation.
3. Purity of natural phospholipids is another criteria militating against adoption of transfersomes as drug delivery vehicles.

Proposed Mechanisms of Transfersomes Penetration *(17)*

When a suspension of transfersomes vesicle is placed on the surface of the skin, the water evaporates from the skin surface and the vesicle start to dry out. Due to the strong polarity of major transfersomes ingredients, the vesicles are attracted to the areas of higher water content in the narrow gaps between adjoining cells in the skin barrier. This together with the vesi-

cles, extreme ability to deform, enables transfersomes to temporarily open the pores through which water normally evaporates between the cells. Such newly activated passages can accommodate sufficiently deformable vehicles which maintain their integrity but change their shape reversibly in the regions of higher water content in the deeper skin layers where the vehicle distributes.

Since they are too large to enter the blood locally, they bypass the capillary bed and get into the subcutaneous tissues. Ultimately transfersomes vesicles arrive in the systemic blood circulation via the lymphatic system.

The presence of surface-active agents in the transfersomes enhances the rheological properties and sensitivity to the driving force which results from water concentration gradient across the skin. This enhances the propensity of sufficiently large but deformable pentrant, transfersomes to move across the skin barrier. Such capability combined with the inclination to deform into elongated shapes while maintaining the vehicle integrity can explain the usually high efficiency of transfersomes across the skin.

Formulation of Transfersomes

Materials commonly used for the preparation of transfersomes are phospholipids (soya phosphatidyl choline, egg phosphatidyl choline), surfactant (tween 80, sodium cholate) for providing flexibility, alcohol (ethanol, methanol) as a solvent, dye (Rhodamine-123, Nile-red) for confocal scanning laser microscopy (CSLM), and buffering agent like saline phosphate buffer as a hydrating medium.

Transfersomes are prepared in two steps. First, a thin film, comprising phospholipid and surfactant is prepared, hydrated with buffer (pH 6.5) by rotation, and then brought to the desired size by sonication. The concentration of a surfactant is very crucial in the formulation of transfersomes because at sublytic concentration these agents provide flexibility to vesicles membrane and at higher concentration cause destruction of vesicles. In the second step, sonicated vesicles are homogenized by extrusion through a polycarbonate membrane (18). Various additives commonly employed in the formulation of transfersomes are listed in Table1.

Table 1: Different Additives employed in the Formulation of Transfersomes

Class	Example	Uses
Phospholipids	Soya phosphatidyl choline	Vesicles forming component
	Egg phosphatidyl choline	
	Dipalmitoyl phosphatidyl choline	
	Distearoyl phosphatidyl choline	
Surfactant	Sodium cholate	For providing flexibility
	Sodium deoxycholate	
	Tween-80	
	Span-80	
Alcohol	Ethanol	As a solvent
	Methanol	
Buffering Agents	Saline phosphate Buffer	As a hydrating medium
Dye	Rhodamine-123	
	Rhodamine-DHPE	For confocal scanning laser microscopy
	Fluorescein-DHPE	(CSLM) study
	Nile-Red	

Drugs are incorporated in the formulation according to their nature. Lipophilic drugs are incorporated initially during the thin film preparation step and hydrophilic ones during the hydration step.

Transfersomes are characterized by different physical properties such as vesicle diameter using photon correlation spectroscopy or dynamic light scattering method(19), entrapment efficiency (20), vesicle diameter(21, 22), degree of deformability or permeability (23), *in vitro* drug release (23), confocal scanning laser microscopy (CSLM) study for investigating the mechanism of penetration of transfersomes across the skin for determining the histological organization of the skin, shapes and architecture of the skin penetration pathways, and for comparison and differentiation of the mechanism of penetration of transfersomes with liposomes, niosomes, and micelles.

Other parameters studied are *in vivo* fate (24), pharmacokinetic aspects (25-27), toxicity studies, etc.

Applications of Transfersomes as Drug Carrier Systems

Proteins and other molecules normally do not cross the intact mammalian skin. Despite this, it elicits antibodies against the subcutaneously applied proteins, such as fluorescein-isothiocyanate-labelled bovine serum albumin (FITC-BSA) if these macromolecules are associated with the specially optimized and ultradeformable agent carriers (28).

A judicious combination of the integral membrane proteins and the ultradeformable membrane also provides a solution to the problem of the noninvasive delivery of such molecules. The incorporation of gap junction protein (GJP) into transfersomes for example, results in a maximum immune response to this type of macromolecules (29).

The delivery of peptides by transfersomes provides a very successful means for the noninvasive therapeutic use of such large molecular weight drugs on the skin (30).

Insulin-loaded transfersomes were prepared and evaluated, and it was found out that transfersomes-associated insulin (transfersulinTM) is carried across the skin with an efficacy of >50%, and often >80% if properly optimized.

After each transfersulin application on the intact skin, the first signs of systemic hypoglycemia are observed after 90 to 180 minutes depending on the specific carrier composition (31).

It was reported that the formulation of interleukin-2 and interferon-a containing-transfersomes are able to deliver sufficient concentrations for immunotherapy (32).

The same concept was used for transdermal immunization using transfersomes loaded with soluble protein like integral membrane protein, gap junction protein, bovine serum albumin, etc. Corticosteroids are used topically for a large variety of dermatological conditions, but the dermally administered corticosteroids typically fail to deliver a sufficiently large drug amount into the body. The use of highly concentrated, or even supersaturated drug solution on the skin leads to the problem of drug precipitation and higher chances of the adverse effects (33).

Transfersomes improve the site specificity, overall drug safety, and lower the doses several times than currently available formulations for the treatment of skin diseases. Because of their good penetration power and flexibility, transfersomes formulations are used for the effective delivery of non-steroidal anti-inflammatory agents like ibuprofen (34) and diclofenac (34).

Transfersomes not only increase the penetration of diclofenac through intact skin, but also carry these agents directly into the depth of the soft tissues under the application site. Cevc (34), developed a formulation of tamoxifen, the most common agent for the treatment of all stages of breast cancer, based on ultradeformable vesicles and applied it on the shaved murine back.

Most of the epidermally-applied transfersomes penetrated the skin leaving less than 5% of the drug-derived radioactivity on the body surface. Such delivery of tamoxifen lowers the incident of side effects like depression and thrombosis. Recently, the impact of the combined use of ultradeformable liposomes and iontophoresis on the penetration of tritiated estradiol was compared with saturated aqueous solution (35, 36).

CONCLUSIONS

Vesicular systems have been realized as extremely useful carrier systems in various scientific domains. Over the years, vesicular systems have been investigated as a major drug delivery system due to their

flexibility to be tailored for varied desirable purposes. Transfersomes are specially optimized vesicles which can respond to an external stress by rapid and energetically inexpensive shape transformation. Such highly deformable particles can thus be used to bring drugs across the biological permeability barriers such as the skin.

Transfersomes offer ample opportunities for investigators to explore the unidentified breakthroughs in the field of pharmaceutical technology particularly concerned with the development of Transdermal Drug Delivery Systems. To serve the purpose, the pivotal role of transfersomes as carriers vesicles for TDDS should be well identified and established.

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