Review Article

Transferosomes- A Novel Approach in The Design of Transdermal Drug Delivery System

V. Kalyani* and A. Seetha Devi

Department of Pharmaceutics, Hindu college of Pharmacy,

Guntur – 522 002, Andhra Pradesh, India.

ABSTRACT

The transdermal route of drug delivery has gained interest of pharmaceutical research as it circumvents the number of problems associated with oral route of administration. It improves patient acceptability, avoids first pass metabolism, minimizes the side effects, improves the physiological and pharmacological response by avoiding fluctuations in drug levels. 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, ethosomes and transferosomes. In this review the importance of transferosomes in the design of transdermal drug delivery system was discussed in detail with respect to the preparation methods, characterization parameters and their applications.

INTRODUCTION

Skin is the largest human organ and consists of three functional layers: epidermis, dermis, and subcutis. It has a wide variety of functions. One major task of the skin is to protect the organism from water loss and mechanical, chemical, microbial and physical influences. The protective properties are provided by the outermost layer of the skin. Transdermal drug delivery system can be used as an alternative delivery of drug into the systemic circulation. Transdermal drug delivery offers many advantages as compared to traditional drug delivery better alternative to achieve constant plasma levels for prolonged periods of time, which additionally could be advantageous because of less frequent dosing regimens. Advantages claimed are increased patient acceptability, avoidance of first pass metabolism, predictable and extended duration of activity, minimizing side effects and utility of short half life drugs, improving physiological and pharmacological response, avoiding the fluctuation in drug levels. The barrier function govern by stratum coneum is main problem for delivery of drugs across the skin. The stratum corneum consists of corneocytes surrounded by lipid layers, which play an essential role in the barrier properties of the stratum corneum. 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 system like liposomes, niosomes, elastic liposomes such as ethosomes and transfersomes. Among these strategies transferosomes 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 vesicle, which were first introduced in the early 1990s[78-79]. Transfersomes are advantageous as phospholipids vesicles for transdermal drug delivery. Because of their self-optimized and ultra flexible membrane properties, they are able to deliver the drug reproducibly either into or through the skin, depending on the choice of administration or application, with high efficiency. The vesicular transfersomes are more elastic than the standard liposomes and thus well suited for the skin penetration. Transfersomes overcome the skin penetration difficulty by squeezing themselves along the intracellular sealing lipid of the stratum corneum[1, 2].

Advantages of Transfersomes

Transfersomes can deform and pass through narrow constriction without measurable loss.

- They have high entrapment efficiency, in case of lipophilic drug near to 90%.
- 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.
- Transfersomes possess an infrastructure consisting of hydrophobic and hydrophilic moieties together and as a result can accommodate drug molecules with wide range of solubility. They act as depot, releasing their contents slowly and gradually.
- They are biocompatible and biodegradable as they are made from natural phospholipids similar to liposomes.
- They protect the encapsulated drug from metabolic degradation.
- Easy to scale up, as procedure is simple, do not involve lengthy procedure and unnecessary use or pharmaceutically unacceptable additives.

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.

Preparation of Transfersomes[3,4]

A. Thin film hydration technique is employed for the preparation of transfersomes which comprised 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. Organic solvent is then evaporated above the lipid transition temperature using rotary evaporator. Final traces of solvent were removed under vacuum for overnight.
2. A prepared thin film is hydrated with buffer by rotation at 60 rpm for 1 hr at the corresponding temperature. The resulting vesicles were swollen for 2 hr at room temperature.
3. 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.

B. Modified hand shaking, lipid film hydration technique is also founded for the preparation of transfersomes which comprised following steps

1. Drug, lecithin 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 with gentle shaking for 15 minutes at corresponding temperature.

Table 1: Different additives used in formulation of transfersome

Class	Example	Uses
Phospholipids	Soya phosphatidyl choline, Dipalmitoyl phosphatidyl choline, Distearoyl phoshatidyl choline	Vesicles forming component
Surfactant	Sod. Cholate, Sod.deoxycholate, tween-80, Span-80	For providing flexibility
Alcohol	Ethanol, methanol	As a solvent
Buffering agent	Saline phosphate buffer (pH 6.4)	As a hydrating medium
dye	Rhodamine-123, Rhodamine-DHPE, Fluorescein-DHPE Nilered	For CSLM study

Optimization of Formulation containing Transfersomes

There are various process variables which could affect the preparation and properties of the transfersomes. The preparation procedure was accordingly optimized and validated. The process variables are depending upon the procedure involved for manufacturing of formulation. The preparation of transfersomes involves various process variables such as,

1. Lecithin: surfactant ratio
2. Effect of various solvents
3. Effect of various surfactants
4. Hydration medium

Optimization was done by selecting entrapment efficiency of drug. During the preparation of a particular system, the other variables were kept constant[5, 6].

Characterization of Transfersomes

The characterization of transfersomes is generally similar to liposomes, niosomes and micelles. Following characterization parameters have to be checked for transfersomes.

1. Vesicle size distribution and zeta potential

Vesicle size, size distribution and zeta potential were determined by Dynamic Light Scattering system by Malvern Zetasizer[7].

2. 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 was done by using photon correlation spectroscopy or dynamic light scattering (DLS) measurements. Transfersomes 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.

3. Number of vesicles per cubic mm

This is an important parameter for optimizing the composition and other process variables. Nonsonicated transfersome formulations are diluted five times with 0.9% sodium chloride solution. Haemocytometer and optical microscope can then be used for further study[81]. The Transfersomes in 80 small squares are counted and calculated using the following formula:

Total number of Transfersomes per cubic mm =
(Total number of Transfersomes counted × dilution factor × 4000) / Total number of squares counted

4. Entrapment efficiency

The entrapment efficiency is expressed as the percentage entrapment of the drug added. Entrapment efficiency was determined by first separation of the un-entrapped drug by use of mini-column centrifugation method. After centrifugation, the vesicles were disrupted using 0.1% Triton X-100 or 50% n-propanol[76]. The entrapment efficiency is expressed as:

Entrapment efficiency =
(Amount entrapped / Total amount added) ×100

5. Drug content[8]

The drug content can be determined using one of the instrumental analytical methods such as modified high performance liquid chromatography method (HPLC) using a UV detector, column oven, auto sample, pump, and computerized analysis program depending upon the analytical method of the pharmacopoeial drug.

6. Turbidity measurement

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

7. Degree of deformability or permeability measurement

In the case of transfersomes, the permeability study is one of the important and unique parameter for characterization. The deformability study is done against the pure water as standard. Transfersomes 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.

8. Penetration ability

Penetration ability of Transfersomes can be evaluated using fluorescence microscopy.

9. Occlusion effect

Occlusion of skin is considered to be helpful for permeation of drug in case of traditional topical preparations. But the same proves to be detrimental for elastic vesicles. Hydrotaxis of water is the major driving force for permeation of vesicles through the skin, from its relatively dry surface to water rich deeper regions. Occlusion affects hydration forces as it prevents evaporation of water from skin.

10. Surface charge and charge density

Surface charge and charge density of Transfersomes can be determined using zetasizer.

11. In-vitro drug release

In vitro drug release study is performed for determining the permeation rate. Time needed to attain steady state permeation and the permeation flux at steady state and the information from invitro studies are used to optimize the formulation before more expensive in vivo studies are performed. For determining drug release, transfersomes suspension is incubated at 37^0C and samples are taken at different times and the free drug is separated by mini column centrifugation. The amount of drug released is then calculated indirectly from the amount of drug entrapped at zero times as the initial amount.

12. In-vitro Skin permeation Studies

Modified Franz diffusion cell with a receiver compartment volume of 50ml and effective diffusion area of 2.50 cm2 was used for this study. In vitro drug study was performed by using goat skin in phosphate buffer solution (pH 7.4). Fresh Abdominal skin of goat were collected from slaughterhouse and used in the permeation experiments. Abdominal skin hairs were removed and the skin was hydrated in normal saline solution. The adipose tissue layer of the skin was removed by rubbing with a cotton swab. Skin was kept in isopropyl alcohol solution and stored at 0-40˚C. To perform skin permeation study, treated 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 2.50cm^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 and the top of the diffusion cell was covered. At appropriate time intervals 1 ml aliquots of the receptor medium were withdrawn and immediately replaced by an equal volume of fresh phosphate buffers (pH 7.4) to maintain sink conditions. Correction factors for each aliquot were considered in calculation of release profile. The samples were analyzed by any instrumental analytical technique[9].

13. Physical stability

The initial percentage of the drug entrapped in the formulation was determined and were stored in sealed glass ampoules. The ampoules were placed at 4 ± 2^0C, 25 ± 2^0C, and 37 ± 2^0C for at least 3 months. Samples from each ampoule were analyzed after 30 days to determine drug leakage. Percent drug lose was calculated by keeping the initial entrapment of drug as 100%[5,8].

Applications of Transfersomes[10]

1. 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. After Transfersulin application on the intact skin, the first sign of systemic hypoglare observed after 90 to 180 min, depending on the specific carrier composition.

2. 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.

3. Delivery of proteins and peptides

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 bioavaibility obtained from transferosomes is somewhat similar to that resulting from subcutaneous injection of the same protein suspension. The transferosomal preparations of this protein also induced strong immune response after the repeated epicutaneous application.

4. 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, antiproliferive 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. Hafer et al studied the formulation of interleukin-2 and interferone-α containing transferosmes for potential transdermal

application. They reported delivery of IL-2 and INF- α trapped by transferosomes in sufficient concentration for immunotherapy.

5. 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.

6. Delivery of anesthetics

Application of anesthetics in the suspension of highly deformable vesicles, transferosomes, induces a topical anesthesia, under appropriate conditions, within less than 10 min. Maximum resulting pain insensitivity is nearly as strong (80%) as comparable to that of subcutaneous bolus injection, but the effect of transferosomal anesthetics last longer[11].

7. Delivery of NSAIDS

NSAIDS are associated with number of GI side effects. These can be overcome by transdermal delivery using ultra-deformable vesicles. Studies have been carried out on Diclofenac and Ketoprofen. Ketoprofen in a Transfersome formulation gained marketing approval by the Swiss regulatory agency in 2007; the product is expected to be marketed under the trademark Diractin. Further therapeutic products based on the Transfersome technology, according to IDEA AG, are in clinical development.[12]

8. Delivery of Herbal Drugs

Transfersomes can penetrate stratum corneum and supply the nutrients locally to maintain its functions resulting in maintenance of skin. In this connection the Transfersomes of Capsaicin has been prepared which shows the better topical absorption in comparison to pure capsaicin[8].

CONCLUSIONS

Transferosomes are highly significant in the design of transedermal drug delivery system because of their small size, greater penetration through stratum corneum and few systemic side effects. Further research has to be carried out to minimize the side effects of drugs by avoiding fluctuations in drug levels.

REFERENCES

1. Modi CD and Bharadia PD. Transfersomes. New Dominants for Transdermal Drug Delivery. Am J PharmTech Res. 2012;2(3):71-91.
2. Prajapati ST, Patel CG and Patel CN. Transfersomes. A Vesicular Carrier System for Transdermal Drug Delivery. Asian Journal of Biochemical and Pharmaceutical Research. 2011;2 (1):507-524.
3. Kombath RV, Minumula SK, Sockalingam A, Subadhra S, Parre S, Reddy TR and David B. Critical issues related to transfersomes – novel Vesicular system. Acta Sci Pol Technol Aliment. 2012;11(1):67-82.
4. Walve JR, Bakliwal SR, Rane BR and Pawar SP. Transfersomes: A surrogated carrier for transdermal drug delivery system. International Journal of Applied Biology and Pharmaceutical Technology. 2011;2(1):201-214.
5. Pandey S, Goyani M, Devmurari V and Fakir J. Transferosomes. A Novel Approach forTransdermal Drug Delivery. Der Pharmacia Letter. 2009;1(2):143-150.
6. Panchagnula R. Transdermal delivery of drugs. Indian Journal Pharmacology. 1997;29:140-156.
7. Patel R et al. Development and Characterization of Curcumin Loaded Transfersome for Transdermal Delivery. J Pharm Sci Res. 2009;1(4):71-80.
8. Swarnlata S, Gunjan J, Chanchal DK and Shailendra S. Development of novel herbal cosmetic cream with Curcuma longa extract loaded transfersomes for anti-wrinkle effect. African J Pharm Pharmacol. 2011;5(8):1054-1062.
9. Sheo DM, Shweta A, Vijay KT, Ram CD, Aklavya S and Ghanshyam M. Enhanced Transdermal delivery of indinavir sulfate via transfersomes. Pharmacie Globale (IJCP). 2010;1(06):1-7.
10. Sheo DM, Shweta A, Ram CD, Ghanshyam M, Girish K and Sunil KP. Transfersomes-a Novel Vesicular Carrier for Enhanced Transdermal Delivery of Stavudine. Development, Characterization and Performance Evaluation. J Scientific Speculations and Res. 2010;1(1):30-36.
11. Benson HA. Transfersomes for transdermal drug delivery. Expert Opin Drug Deliv. 2006;3(6):727-37.
12. Saeed Ghanbarzadeh and Sanam Aramil. Enhanced Transdermal Delivery of Diclofenac Sodium via Conventional Liposomes, Ethosomes, and Transfersomes. BioMed Research International Volume. 2013;7.